



The European Federation for Aging Research (EFAR)

1st EFAR Conference on the Biology of Aging

October 14–16, 2026

Cologne, Germany

Abstract Booklet



Organisation:

CECAD (Cologne Cluster of Excellence on Aging and Aging-associated Diseases)



MAX PLANCK INSTITUTE
FOR BIOLOGY OF AGEING



Max Planck Institute
for Metabolism Research



Venue:

Max Planck Institute for Biology of Ageing & CECAD Research Center, Cologne, Germany

Funded by:



Deutsche
Forschungsgemeinschaft

Sponsored by:



ACADEMY OF
GEROSCIENCE



EVIDENT

Frontiers in
Aging

A journal by  frontiers

SARTORIUS



The power of precision

thermo scientific

Posterprize sponsored by The EMBO Journal:



Program

Wednesday, October 14th

Max Planck Institute for Biology of Ageing – Foyer

From 11:00 Registration

Max Planck Institute for Biology of Ageing – Lecture Hall

12:30 – 13:00 **Welcome Statements**, Björn Schumacher, EFAR President, CECAD, Cologne

Session I: Chair Lene Rasmussen

13:00 – 13:25	Invited speaker: Nathan LeBrasseur Mayo Clinic, Rochester	Cellular Senescence and Skeletal Muscle Aging
13:25 – 13:40	Toluwanimi Victory Afolayan MPI for Biology of Ageing, Cologne	In vivo functional characterisation of a rare protein- altering variant in DEPTOR identified in long-lived families
13:40 – 13:55	Arturo Bujarrabal- Dueso CECAD, Cologne	A Novel H2A.Z-Dependent Mechanism Underlies DREAM Complex Regulation of the DNA Damage Response
13:55 – 14:10	David H. Meyer CECAD, Cologne	Aging clocks delineate neuron types vulnerable or resilient to neurodegeneration and identify neuro- protective interventions
14:10 – 14:25	Haoqun Zhan University of Cam- bridge, UK	Nuclear integrity underpins the dynamic range of inflam- mation regulation
14:25 – 14:40	Aleksandr Dekan University of Copenhagen	Genomic Determinants of Maximum Lifespan in Verte- brates
14:40 – 15:05	Invited speaker: Emma Teeling University College Dublin	The molecular basis of bat's extended healthspans

15:05 – 15:40 COFFEE BREAK

Session II: Chair: Joris Deelen

15:40 – 16:05	Invited Speaker: Uri Alon Weizmann Institute of Science, Rehovot	A physiological cliff at menopause reconstructed from 300 million lab tests
16:05 – 16:20	Peter de Keizer University Medical Center Utrecht	PMLhigh, impaired-p53 scarred cells are a therapeutic target for healthy longevity

16:20 – 16:35	Constantinos Demetriades ERIBA/UMCG, Groningen	mTOR Ubiquitination in Ageing and Disease
16:35 – 16:50	Joris Demmers, CECAD, Cologne	Transcription speed is controlled by mTOR via the super elongation complex
16:50 – 17:05	Nikoleta Nikou Universitat Autònoma de Barcelona	Novel Treatments to Mitigate Ovarian Aging and Follicle Loss
17:05 – 17:20	Taiyu Ge CECAD, Cologne	Vitamin B12 boosts H3K4me2 deposition to promote transcription recovery following DNA damage

17:20 – 17:45 BREAK

Session III: Chair: Morten Scheibye-Knudsen

17:45 – 18:10	Invited Speaker: George Garinis University of Crete	DNA damage and Innate Immune responses in Health and Disease
18:10 – 18:25	Dax Houtkamp Vrije Universiteit Amsterdam	Prolonged bed rest reduces PhenoAge despite marked physiological deconditioning
18:25 – 18:40	Shoma Ishikawa CECAD, Cologne	Non-cell-autonomous control of stress surveillance by telomere deprotection
18:40 – 18:55	Maria Sol Jacome Burbano CECAD, Cologne	A neonatal-like cardiac program underlies adult heart regeneration in the naked mole-rat

CECAD Research Center, Foyers and 1st floor

19:15 – 22:15 Poster Session (with finger food and drinks)

Thursday, October 15th

Session IV: Chair: Helen Morrison

9:00 – 9:25	Invited Speaker: Elsa Logharino University of Porto	The geroprotective role of the transcription factor FOXM1
9:25 – 9:40	Lucia Lorenzo Rodriguez CIMUS-USC, Universidade de Santiago de Compostela	Senomorphic effect of genetic and chemical partial reprogramming
9:40 – 9:55	Helene Martini Mayo Clinic, Rochester	Mitochondrial metabolism and epigenetic crosstalk in senescent cells

9:55 – 10:10	Manuel Collado CIMUS-USC, Universidade de Santiago de Compostela	The Last kiss: Apoptotic Secreted Factors Drive Cellular Senescence
10:10 – 10:25	Julian Mutz King's College London	Do mental disorders accelerate the pace of ageing?
10:25 – 10:50	Invited Speaker: Paul Robbins University of Minnesota	MicroRNA regulation of senescence, rejuvenation and aging
10:50 – 11:30	COFFEE BREAK	

Session V: Chair: Hartmut Geiger

11:30 – 11:45	Invited Speaker: Luca Scorrano University of Padova	Fis1 Loss Drives Endothelial Senescence via Maladaptive Fatty-Acid Metabolism
11:55 – 12:10	Francesco Neri University of Turin	Loss of regeneration and epigenetic drift of the intestinal stem cells during aging
12:10 – 12:25	Katharina Papsdorf Institute of Molecular Biology (IMB) Mainz	Lipid droplets in MUFA mediated longevity
12:25 – 12:40	André Rendeiro CeMM Research Center for Molecular Medicine, Vienna	Histological aging signatures enable inference of tissue-specific disease associations from blood
12:40 – 13:05	Invited Speaker: Sara Hägg Karolinska Institute, Stockholm	Tracking human aging for precision health
13:05 – 14:45	LUNCH BREAK	
13:30 – 14:15	Meeting of poster prize selection committee (Sem. 1, MPI)	

Session VI: Chair: Ira Milosevic

14:45– 15:10	Invited Speaker: Lumir Krejčí Masaryk University, Brno	Regulation of Homologous Recombination
15:10 – 15:25	David Doupe Durham University	The transcription factor Sob maintains intestinal stem cell homeostasis to delay aging
15:25 – 15:40	Della David Babraham Institute, Cambridge	Identification of a novel human extracellular chaperone promoting healthy ageing
15:40 – 15:55	Oliver Tüscher, Martin Luther University Halle-Wittenberg (MLU)	TACR3 variant confers resilience to aging and Alzheimer's disease

15:55 – 16:10	Dongryeol Ryu Gwangju Institute of Science and Technology (GIST)	Discovery of a Circulating Myokine that Improves Systemic Function in Aged Mice
16:10 – 16:25	Markus Schosserer Medical University of Vienna, Austria	The role of the ribosomal RNA methyltransferase Nsun5 in mouse aging and development
16:25 – 16:40	Payel Sen National Institute on Aging, USA	A single-cell multi-omic atlas decodes the regulatory logic of liver aging

16:45 – 18:00 EFAR Members Assembly (MPI Lecture Hall)

Schokoladenmuseum (by invitation only)

19:15 – 22:30 Speakers Dinner

Friday, October 15th

Session VII: Chair: Anne Schäfer

9:00 – 09:25	Invited Speaker: Eija Pirinen University of Oulu	Obesity-related remodeling of NAD ⁺ metabolism in human adipocytes
09:25 – 09:40	Mirre Simons The University of Sheffield	Suppression rather than activation of the integrated stress response (GCN2–ATF4) pathway extends lifespan in the fly
09:40 – 09:55	Yossawat Suwanlikit Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester	DNA Methylation–Based Clonal Hematopoiesis Burden Associates with Structural Brain Atrophy
09:55 – 10:10	Vakil Takhaviev ETH Zürich, Switzerland	The Damage Code – Single-Nucleotide Maps of DNA Lesions Across the Ageing [Epi]Genome
10:10 – 10:25	Danila Voronov Leibniz Institute on Aging – Fritz Lipmann Institute (FLI), Jena, Germany	Shared molecular signatures between diapause II and aging in killifish <i>Nothobranchius furzeri</i> suggest aging during diapause II

10:25 – 11:15 BREAK

Session VIII: Chair: Riekelt Houtkooper

11:15 – 11:40	Invited Speaker: Guido Kroemer Université de Paris Cité	Immunosuppression by the geroprotein ACBP/DBI
---------------	---	---

11:40 – 11:55	Shibo Wei Gwangju Institute of Science and Techno- logy (GIST)	Localized NAD ⁺ Replenishment Restores Metabolic Resilience and Mitigates Cardiac Injury after Myocardial Infarction
11:55 – 12:10	Mauro Corrado CECAD, Cologne	Suppression of T Cell–Driven Type I Interferons in Ageing Reveals Gut–Specific Vulnerability
12:10 – 12:35	Invited Speaker: Eline Slagboom Leiden University Medical Center	Lifestyle intervention effects in middle age monito- red across omics layers and tissues; practical impli- cations
12:35 – 13:00	Concluding remarks, poster prizes	

Invited speakers



Uri Alon (ISRAEL)
George Garinis (GREECE)
Sara Hägg (SWEDEN)
Lumír Krejčí (CZECH)
Guido Kroemer (FRANCE)
Nathan LeBrasseur (USA)
Elsa Longarinho (PORTUGAL)
Laura Niederhofer (USA)

Eijla Pirinen (FINLAND)
Wojciech Pokrzywa (POLAND)
Luca Scorrano (ITALY)
Eline Slagboom (NETHERLANDS)
Emma Teeling (IRELAND)

Abstracts

Talks (page 10 – 43)

Posters (page 44ff)

Talks overview (Alphabetical order of authors)

First Name	Last Name	Titel	Page
Toluwanimi Victory	Afolayan	In vivo functional characterisation of a rare protein-altering variant in DEPTOR identified in long-lived families	12
Arturo	Bujarrabal-Dueso	A Novel H2A.Z-Dependent Mechanism Underlies DREAM Complex Regulation of the DNA Damage Response	13
Manuel	Collado	The Last kiss: Apoptotic Secreted Factors Drive Cellular Senescence	14
Mauro	Corrado	Suppression of T Cell-Driven Type I Interferons in Ageing Reveals Gut-Specific Vulnerability	15
Della	David	Identification of a novel human extracellular chaperone promoting healthy ageing	16
Peter	de Keizer	PMLhigh, impaired-p53 scarred cells are a therapeutic target for healthy longevity	17
Alexandr	Dekan	Genomic Determinants of Maximum Lifespan in Vertebrates	18
Constantinos	Demetriades	mTOR Ubiquitination in Ageing and Disease	19
Joris	Demmers	Transcription speed is controlled by mTOR via the super elongation complex	20
David	Doupé	The transcription factor Sob maintains intestinal stem cell homeostasis to delay aging	21
Taiyu	Ge	Vitamin B12 boosts H3K4me2 deposition to promote transcription recovery following DNA damage	22
Dax	Houtkamp	Prolonged bed rest reduces PhenoAge despite marked physiological deconditioning	23
Shoma	Ishikawa	Non-cell-autonomous control of stress surveillance by telomere deprotection	24
Maria Sol	Jacome Burbano	A neonatal-like cardiac program underlies adult heart regeneration in the naked mole-rat	25
Lucia	Lorenzo Rodriguez	Senomorphic effect of genetic and chemical partial reprogramming	26
Helene	Martini	Mitochondrial metabolism and epigenetic crosstalk in senescent cells.	27
David H.	Meyer	Aging clocks delineate neuron types vulnerable or resilient to neurodegeneration and identify neuroprotective interventions	28

First Name	Last Name	Titel	Page
Julian	Mutz	Do mental disorders accelerate the pace of ageing?	29
Francesco	Neri	Loss of regeneration and epigenetic drift of the intestinal stem cells during aging	30
Nikoleta	Nikou	Novel Treatments to Mitigate Ovarian Aging and Follicle Loss.	31
Katharina	Papsdorf	Lipid droplets in MUFA mediated longevity	32
André	Rendeiro	Histological aging signatures enable inference of tissue-specific disease associations from blood	33
Dongryeol	Ryu	Discovery of a Circulating Myokine that Improves Systemic Function in Aged Mice	34
Markus	Schosserer	The role of the ribosomal RNA methyltransferase Nsun5 in mouse aging and development	35
Payel	Sen	A single-cell multi-omic atlas decodes the regulatory logic of liver aging	36
Mirre	Simons	Suppression rather than activation of the integrated stress response (GCN2-ATF4) pathway extends lifespan in the fly	37
Yossawat	Suwanlikit	DNA Methylation-Based Clonal Hematopoiesis Burden Associates with Structural Brain Atrophy	38
Vakil	Takhaveev	The Damage Code – Single-Nucleotide Maps of DNA Lesions Across the Ageing [Epi]Genome	39
Oliver	Tüscher	TACR3 variant confers resilience to aging and Alzheimer's disease	40
Danila	Voronov	Shared molecular signatures between diapause II and aging in killifish <i>Nothobranchius furzeri</i> suggest aging during diapause II	41
Shibo	Wei	Localized NAD ⁺ Replenishment Restores Metabolic Resilience and Mitigates Cardiac Injury after Myocardial Infarction	42
Haoqun	Zhan	Nuclear integrity underpins the dynamic range of inflammation regulation	43

In vivo functional characterisation of a rare protein-altering variant in DEPTOR identified in long-lived families

Afolayan, T.V.¹; Smulders, L.¹; Pahl, R.¹; Pahl, A.¹; & Deelen, J.^{1,2}

¹Genetics and biomarkers of human ageing, Max Planck Institute for Biology of Ageing, Cologne, Germany

²Section of Molecular Epidemiology, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

Studies of long-lived families suggest that they carry protective rare genetic variants that can delay the onset of age-related diseases and promote healthy ageing. Here, we investigated the in vivo effect of the DEPTORCys102Trp variant identified in long-lived families from the Leiden Longevity Study, which we previously showed to have in vitro effects associated with lifespan across species. Using CRISPR/Cas9 editing, we generated a transgenic C57BL/6N mouse line carrying the variant and performed longitudinal phenotyping and lifespan analyses. We showed that male DEPTORCys102Trp/Cys102Trp mice exhibited an increased lean mass, reduced fat mass, improved glucose tolerance, and lower fasting glucose in middle and/or old age compared with their wild-type littermates. We are currently performing characterisation of tissues from the transgenic mice to identify the molecular effect underlying the observed phenotypes. Our study provides a novel integrative pipeline for in vivo characterisation of rare genetic variants linked to human longevity and provides further evidence for a potential role of the DEPTORCys102Trp variant in healthy ageing.

A Novel H2A.Z-Dependent Mechanism Underlies DREAM Complex Regulation of the DNA Damage Response

Bujarrabal-Dueso, A.^{1,2}; Schumacher, B.^{1,2}

¹*Institute for Genome Stability in Aging and Disease, Medical Faculty, University and University Hospital of Cologne, Cologne, Germany*

²*Cologne Excellence Cluster for Cellular Stress Responses in Aging-Associated Diseases (CECAD), Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany*

The DREAM complex is a conserved transcriptional repressor of cell cycle genes that promotes quiescence. Using *C. elegans* we found that DREAM binds and represses multiple genes involved in the DNA damage response. DREAM-complex-deficient mutants show a remarkable resistance to, and improved repair of various DNA-damage types. The mechanisms of DREAM complex regulation are not fully understood, but emerging evidence shows that this complex interacts with epigenetic modulators that could be driving its repressive function.

Using a forward genetic screen in *C. elegans* we found that a mutation for the gene *ssl-1* (ortholog of SRCAP/EP400), involved in the maintenance and deposition of H2A.Z, confers severe sensitivity to DNA damage. Employing RNA-seq and ChIP-seq analysis on these mutants we observe a broad downregulation of DREAM-associated genes, including repair genes. Repressed genes in *ssl-1* mutants are characterized by a marked reduction of H2A.Z around the promoter area, suggesting a novel function for H2A.Z deposition that regulates the normal expression of DNA repair genes. Furthermore, the capacity to deposit H2A.Z is also required for the DNA damage resistance phenotype of DREAM deficient organisms.

The Last kiss: Apoptotic Secreted Factors Drive Cellular Senescence

Collado, M.^{1,2}

¹Laboratory of Cellular Senescence, Cancer and Aging, Center for Research in Molecular Medicine (CiMUS), University of Santiago de Compostela, Health Research Institute of Santiago de Compostela (IDIS), E15782 Santiago de Compostela, Spain.

²Departament of Immunology and Oncology (DIO), Centro Nacional de Biotecnología (CNB-CSIC), E28049 Madrid, Spain.

Senescence and apoptosis are fundamental safeguards of tissue homeostasis, yet their interplay remains poorly understood. Here, we identify apoptosis-induced senescence (AIS) as a previously unrecognized paracrine mechanism linking cell death to tissue repair. Conditioned media from apoptotic cells, triggered by diverse stimuli, robustly induces senescence in neighboring cells. This effect depends on mitochondrial apoptosis, as BAX inhibition suppresses both cell death and AIS. Strikingly, depletion of mitochondrial DNA or RNA in apoptotic cells blunts this response, uncovering mitochondrial nucleic acids as key mediators. Mechanistically, AIS requires activation of the cGAS–STING and NF- κ B pathways, connecting mitochondrial stress to inflammatory signaling. Together, our findings reveal a mitochondria-driven intercellular program that coordinates elimination and replacement of damaged cells, positioning AIS as a critical regulator of regeneration with broad implications in ageing and disease

Suppression of T Cell–Driven Type I Interferons in Ageing Reveals Gut-Specific Vulnerability

Corrado, M.^{1,2,3}

¹*Institute for Genetics, Faculty of Mathematics and Natural Sciences, University of Cologne, Cologne, DE*

²*Cologne Excellence Cluster on Aging and Aging-associated Diseases (CECAD), University of Cologne, Cologne, DE*

³*Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, DE*

Ageing is associated with chronic sterile inflammation (inflammageing), progressive metabolic fitness impairment and immune function decline. Leveraging transcriptional, proteomic and metabolic profiling of human and mouse T cells isolated from young and elderly donors, we found a prominent Type I interferon (Type I IFN) signature and mitochondrial alterations in the elderly cohort (more prominent in males than females). Notably, mitochondrial deficiencies have been linked to Type I IFN response through a mechanism dependent on mitochondrial DNA (mtDNA) release and its activation of the cGAS–STING pathway. This is commonly considered a targetable pathway to reduce inflammation and improve healthspan in ageing. Nevertheless, the mechanism of mtDNA release in T cells as well as the physiological impact on gut homeostasis of inhibiting Type I IFNs during ageing has not been clarified. We found that T cells during ageing present mitochondrial alterations with reduction of cardiolipin content and that cardiolipin deficiency alone phenocopies T cell ageing with mtDNA release via BAX/BAK pores and cGAS/STING-mediated Type I IFN response activation. While we confirmed this pathway is genetically and pharmacologically treatable, its genetic inhibition in mice with T cell specific cardiolipin deficiency resulted in additional deterioration of gut phenotype with more severe colitis and immune infiltration, leading to a more premature death in mice. This study shows the sex- and tissue-specific evolutionary conserved functional heterogeneity of Type I IFN response in human and mice in different tissues. While Type I IFNs suppression in non-barrier sites could benefit healthspan during ageing, its abrogation at barrier sites impairs control of microbiota thereby accelerating age-associated tissue dysfunction.

Identification of a novel human extracellular chaperone promoting healthy ageing

Choi, Y.H.¹; Olabiyi, B.F.¹; Tataridas-Pallas, N.¹; Thompson, M.¹; Wilde, E.²; Mosonyi, C.²; Taylor, A.I.P.³; Aubrey, L.D.³; Radford, S.E.³; Kumita, J.R.²; & **David, D.C.**¹

¹Signalling, Babraham Institute, Cambridge, UK

²Pharmacology department, University of Cambridge, UK

³Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds, UK

Proteostasis, the maintenance of a functional proteome, declines with age and contributes to organismal dysfunction. The role of the extracellular proteostasis network (exPN) in ageing remains poorly understood. Yet age-associated changes in the extracellular environment promote extracellular protein aggregation. Leveraging the identification of exPN factors in *C. elegans* (Gallotta et al.), we discovered huEC1, a previously uncharacterised human extracellular chaperone associated with human longevity. Remarkably, huEC1 expression in *C. elegans* extends lifespan, enhances stress resistance and delays tissue decline, revealing systemic benefits across the organism. Mechanistically, huEC1 potentially inhibits aggregation of diverse amyloidogenic proteins by blocking fibril elongation and promotes microglial clearance of oligomeric amyloid β . Together, these findings establish huEC1 as a novel, conserved extracellular proteostasis factor that contributes to healthy ageing. Our work highlights exPN as a promising, yet still underexplored, target for future interventions.

References:

1. Gallotta I, Sandhu A, Peters M, Haslbeck M, Jung R, Agilkaya S, Blersch J, Rödelberger C, Röseler W, Huang C, Sommer RJ, David DC. (2020). Extracellular proteostasis prevents aggregation during pathogenic attack. *Nature* 584, pages 410–414.

PMLhigh, impaired-p53 scarred cells are a therapeutic target for healthy longevity

Baar, M.P.^{1,2}; Putavet D.A.^{1,2}; Bigossi G.³; Brand T.¹; Marcozzi S.³; Bouma E.M.^{1,2}; Teifel M.²; Herbst J.²; Sarlis N.J.²; Leyten T.M.F.¹; de Bruin A.⁴; Malavolta M.^{3,4} and **de Keizer P.L.J.**^{1,2}

¹Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

²Cleara Biotech B.V., Utrecht, the Netherlands

³Advanced Technology Center for Aging Research and Geriatric Mouse Clinic, IRCCS INRCA, Ancona, Italy

⁴Department of Biomolecular Health Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands.

⁵Department of Clinical and Molecular Sciences (DISCLIMO), Università Politecnica Delle Marche, Ancona, Italy

Clinical translation of senescence-targeting therapies has been limited by their heterogeneity^{1,2} and uncertainty over potential benefits^{3,4}. Here, we identify a distinct population of irreparably damaged, pro-inflammatory cells characterized by impaired p53 signaling⁵, PML^{high} DNA-SCARS⁶, independent of p16^{ink4a} or p21^{cip1}. As this distinguishes them from classical senescence, we term them “scarred” cells.

Through structural and molecular optimization, we developed CL04183, a peptide that binds open-conformation TAD2-phosphorylated p53 and induces transcription-independent mitochondrial apoptosis.

In geriatric mice (825d at start)⁷, late-life administration of CL04183 increased median lifespan by >27% while preserving cardiac, cognitive, neuromuscular function and multiple WHO Intrinsic Capacity domains, as vitality, locomotion, and strength⁸. CL04183 countered liver disease and impaired-p53 cancer in mice. PK, ADME, GLP-toxicology, and GMP-manufacturing support clinical translation. Together, scarred cells are a therapeutically actionable aging-associated cell state, targeting of which may enhance human healthspan.

References:

1. De Keizer, P. L. J. The Fountain of Youth by Targeting Senescent Cells? Trends in Molecular Medicine 23, 6–17 (2017).
2. Tao, W., Yu, Z. & Han, J.-D. J. Single-cell senescence identification reveals senescence heterogeneity, trajectory, and modulators. Cell Metabolism 36, 1126–1143.e5 (2024).
3. Grosse, L. et al. Defined p16^{High} Senescent Cell Types Are Indispensable for Mouse Healthspan. Cell Metabolism 32, 87–99.e6 (2020).
4. Triana-Martinez, F. et al. p16^{High}-expressing immune cells control disease tolerance as a defense and health span-extending strategy. Immunity S107476132600083X (2026) doi:10.1016/j.immuni.2026.02.013.
5. De Keizer, P. L. J., Laberge, R.-M. & Campisi, J. p53: Pro-aging or pro-longevity? Aging 2, 377–379 (2010).
6. Rodier, F. et al. DNA-SCARS: distinct nuclear structures that sustain damage-induced senescence growth arrest and inflammatory cytokine secretion. Journal of Cell Science 124, 68–81 (2011).
7. Marcozzi, S. et al. Comprehensive longitudinal non-invasive quantification of healthspan and frailty in a large cohort (n = 546) of geriatric C57BL/6 J mice. GeroScience 45, 2195–2211 (2023).
8. Bigossi, G. et al. A Comparative Analysis of Grip Strength Evaluation Methods in a Large Cohort of Aged Mice. J cachexia sarcopenia muscle 16, e70050 (2025).

Genomic Determinants of Maximum Lifespan in Vertebrates

Dekan, A.¹, Scheiby-Knudsen, M.¹

¹*Institute of Cellular and Genetic Medicine, University of Copenhagen, Copenhagen, Denmark*

Maximum lifespan ranges from weeks to centuries across vertebrates, suggesting genomic encoding of lifespan regulation. We present the largest vertebrate comparative genomic analysis of lifespan to date: 3,112 annotated genomes, a human-validated ~10,000-species lifespan database built with AI agents, and effort-corrected lifespan estimates from observation records. Using RERconverge to test relative evolutionary rates (RERs) across ~13,000 orthologs, we identified clade-specific lifespan-associated genes, including ~40 significant hits ($q < 0.05$) in well-powered classes. Enriched programs involved autophagy, DNA damage and inflammatory response, and cell-cycle regulation. PPAR signaling showed reversed lifespan associations in mammals versus other vertebrates. Interpretable ML models further recovered genomic predictors of maximum lifespan. Together, these results suggest that evolutionary tuning of damage production, repair, and tissue renewal determine vertebrate lifespan.

mTOR Ubiquitination in Ageing and Disease

Demetriades, C.¹

¹*European Research Institute for the Biology of Ageing (ERIBA), University of Groningen (RUG), University Medical Center Groningen (UMCG), 9713 GZ Groningen, The Netherlands*

Proper control of mTOR signaling is relevant for health, disease and ageing. Information from intra- and extra-cellular signaling cues is transmitted to mTOR through an intricate signaling network that controls its localization and activity. Interestingly, although mTOR is a heavily ubiquitinated protein, the role of this post-translational modification in regulating its activation status remains poorly understood. In this presentation, I will report our recent findings on the identification and characterization of the first described deubiquitinase (DUB) enzyme that directly acts on mTOR itself to control its activity, and will discuss the role of non-degradative mTOR ubiquitination in cell physiology, ageing and human disease.

Transcription speed is controlled by mTOR via the super elongation complex

Joris J.P.G. Demmers^{1,5}; Jiang Chang¹; Jose M. Heredia-Genestar¹; Barbara Steurer¹; Ziqin Tang²; Sander Barnhoorn¹; Ping Gao¹; Renata M.C. Brandt¹; Y. van Loon¹; Jeroen A.A. Demmers³; Altaf H. Sarker⁴; Serena T. Bruens¹; Arjan F. Theil¹; Priscilla K. Cooper⁴; Jurgen A. Marteijn¹; Jan H.J. Hoeijmakers^{1,2,5}; Joris Pothof¹

¹Department of Molecular Genetics, Erasmus MC Cancer Institute, Erasmus Medical Center, 3000 CA, Rotterdam, The Netherlands

²Princess Maxima Center for Pediatric Oncology, Oncode Institute, Heidelberglaan 25, 3584 CS, Utrecht, The Netherlands

³Proteomics Center, Erasmus Medical Center, 3000 CA, Rotterdam, The Netherlands

⁴Biological Systems and Engineering Division, Lawrence Berkeley National Laboratory, Berkeley, CA, 94720, USA

⁵University of Cologne, Faculty of Medicine, Cluster of Excellence for Aging Research, Institute for Genome Stability in Ageing and Disease, Joseph Stelzmann Strasse 26, 50931 Cologne, Germany

The mechanistic target of rapamycin (mTOR), a kinase whose activity inversely correlates with lifespan 1–3, is a central regulator of cell growth in response to nutrients and growth factors 3,4. Active mTOR promotes general translation 5,6 and synthesis of ribosomal and transfer RNA 7–9 to support protein translation. As transcription precedes translation, we wondered whether mTOR might also affect general transcription of mRNAs. Here, we demonstrate that mTOR regulates transcriptional output by genome-wide control of RNA polymerase II transcription elongation speed via the super elongation complex factor AFF1, a novel mTOR target that is phosphorylated by mTOR in the cytoplasm and subsequently translocates to the nucleus. This transcriptional regulation is mechanistically distinct from mTOR's role in translation. Inhibition of mTOR decreased transcription speed, reducing transcriptional output and cellular mRNA levels in both cells and mice, while simultaneously improving transcriptional accuracy, and reducing R-loops and DNA-damage-driven transcription stress, a recently discovered pro-aging phenotype across organs and species 10. These findings extend mTOR's functional role to include genome-wide RNAPII transcriptional control, thereby tightly balancing mRNA levels and translation, while also enhancing pro-aging transcription-associated phenotypes.

References:

1. Mossmann, D., Park, S., and Hall, M.N. (2018). mTOR signalling and cellular metabolism are mutual determinants in cancer. *Nat Rev Cancer* 18, 744–757. 10.1038/s41568-018-0074-8.
2. Johnson, S.C., Rabinovitch, P.S., and Kaeblerlein, M. (2013). mTOR is a key modulator of ageing and age-related disease. *Nature* 493, 338–345. 10.1038/nature11861.
3. Liu, G.Y., and Sabatini, D.M. (2020). mTOR at the nexus of nutrition, growth, ageing and disease. *Nature Reviews Molecular Cell Biology* 21, 183–203. 10.1038/s41580-019-0199-y.
4. Battaglion, S., Benjamin, D., Walchli, M., Maier, T., and Hall, M.N. (2022). mTOR substrate phosphorylation in growth control. *Cell* 185, 1814–1836. 10.1016/j.cell.2022.04.013.
5. Thoreen, C.C., Chantranupong, L., Keys, H.R., Wang, T., Gray, N.S., and Sabatini, D.M. (2012). A unifying model for mTORC1-mediated regulation of mRNA translation. *Nature* 485, 109–113. 10.1038/nature11083.
6. Philippe, L., van den Elzen, A.M.G., Watson, M.J., and Thoreen, C.C. (2020). Global analysis of LARP1 translation targets reveals tunable and dynamic features of 5' TOP motifs. *Proc Natl Acad Sci U S A* 117, 5319–5328. 10.1073/pnas.1912864117.
7. Mayer, C., Zhao, J., Yuan, X., and Grummt, I. (2004). mTOR-dependent activation of the transcription factor TIF-IA links rRNA synthesis to nutrient availability. *Genes Dev* 18, 423–434. 10.1101/gad.285504.
8. Chan, J.C., Hannan, K.M., Riddell, K., Ng, P.Y., Peck, A., Lee, R.S., Hung, S., Astle, M.V., Bywater, M., Wall, M., et al. (2011). AKT promotes rRNA synthesis and cooperates with c-MYC to stimulate ribosome biogenesis in cancer. *Sci Signal* 4, ra56. 10.1126/scisignal.2001754.
9. Michels, A.A., Robitaille, A.M., Buczynski-Ruchonnet, D., Hodroj, W., Reina, J.H., Hall, M.N., and Hernandez, N. (2010). mTORC1 directly phosphorylates and regulates human MAF1. *Mol Cell Biol* 30, 3749–3757. 10.1128/MCB.00319-10.
10. Gyenis, A., Chang, J., Demmers, J., Bruens, S.T., Barnhoorn, S., Brandt, R.M.C., Baar, M.P., Raseta, M., Derks, K.W.J., Hoeijmakers, J.H.J., and Pothof, J. (2023). Genome-wide RNA polymerase stalling shapes the transcriptome during aging. *Nat Genet* 55, 268–279. 10.1038/s41588-022-01279-6.

The transcription factor Sob maintains intestinal stem cell homeostasis to delay ageing

Shahzad, F.¹; Wei, W.¹; Smith, A.L.M.²; Greaves, L.C.²; & Doupé, D.P.¹

¹Department of Biosciences, Durham University, Durham, UK

²Wellcome Centre for Mitochondrial Research, Biosciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle, UK

Ageing is associated with physiological decline and disrupted tissue homeostasis, often driven by imbalanced stem cell activity. The *Drosophila* midgut serves as a powerful model for studying epithelial homeostasis and ageing as it exhibits many conserved hallmarks of regulation and deteriorating intestinal stem cell function with age. We have identified the transcription factor encoded by Sister of odd and bowl (Sob) as a conserved marker of intestinal stem/progenitor cells in homeostasis whose expression is lost with age (Shahzad et al., 2026). Premature downregulation of *sob* shortens lifespan while overexpression in the intestinal stem/progenitor cells is sufficient to extend lifespan, suggesting a critical role in maintaining homeostasis with age. At the cell and tissue level stem/progenitor knockdown and overexpression reveal that Sob maintains homeostasis by regulating both proliferation and lineage specification. In young guts, Sob restricts intestinal stem cell proliferation and promotes enteroendocrine differentiation while limiting excessive enterocyte differentiation. We have also found that the transcription factor Exex, the Notch pathway inhibitor Numb, and the enterocyte differentiation regulator Dawdle act downstream of Sob to regulate proliferation and differentiation. Our findings position Sob as a critical molecular switch linking stem cell dysfunction to gut ageing.

References:

1. Shahzad, F, Wei, W, Smith, ALM, Greaves, LC, and Doupé, DP (2026). The transcription factor Sob maintains intestinal stem cell homeostasis to delay ageing. bioRxiv 2026.05.29.728682.

Vitamin B12 boosts H3K4me2 deposition to promote transcription recovery following DNA damage

Taiyu Ge^{1,2}; Georgia Chatzinikolaou^{3,4}; Evi Goulielmaki^{3,4}; George A. Garinis^{3,4}; Siyao Wang^{1,2,5}; Björn Schumacher^{1,2,3}

¹*Institute for Genome Stability in Aging and Disease, Medical Faculty, University and University Hospital of Cologne, Cologne, Germany*

²*Cologne Excellence Cluster for Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany*

³*Department of Biology, University of Crete, Heraklion, Greece*

⁴*Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Heraklion, Greece*

⁵*Institute of Molecular Biology (IMB), Mainz, Germany*

DNA lesions impair transcription and contribute to aging, but how nutrient state regulates recovery from this stress is unclear. Here we show that dietary vitamin B12 rescues developmental delay and lifespan shortening amid ultraviolet-induced DNA damage in *Caenorhabditis elegans*. Mechanistically, vitamin B12 benefits upon UV require the methionine cycle, whereas methionine supplementation is sufficient to recapitulate B12 effects. We further demonstrate that vitamin B12 promotes transcription recovery after DNA damage through increased H3K4me2 levels, independently of nucleotide excision repair. Consistently, methionine supplementation in human cells suppresses UV-induced apoptosis and promotes transcription recovery after DNA damage through depositing H3K4me2. Moreover, vitamin B12 supplementation extends lifespan, maintains body weight and improves liver transcription activity with an elevated H3K4me2 in progeroid mice. Together, our study reveals transcription recovery after DNA damage as metabolically regulated and identifies a conserved nutrient-epigenetic axis that promotes organismal resilience to genotoxic stress.

Prolonged bed rest reduces PhenoAge despite marked physiological deconditioning

Houtkamp, Dax¹; Moritz Eggelbusch^{1,2}; Mirjam Pijnappels¹; Richard T Jaspers¹; Pol Grootswagers³; Rob CI Wüst¹

1 Department of Human Movement Sciences, Faculty of Behavioral and Movement Sciences, VU Amsterdam;

2 Professorship of Exercise Biology, TUM School of Medicine and Health, Technical University of Munich, Munich, Germany.

3. Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands.

Ageing clocks are increasingly used to quantify health, but their sensitivity to rapid inactivity-induced functional decline remains unclear. We studied whether 60 days of strict bed rest, a controlled model of accelerated functional ageing, altered PhenoAge. PhenoAge (9 markers) was measured in 24 healthy adults aged 33 ± 9 years, including eight females, before and after 60 days bed rest conducted at German Aerospace Center (Köln). Bed rest induced significant reductions in VO₂max, muscle strength, bone mineral density and lean mass, but mean PhenoAge paradoxically decreased from 23.3 to 21.7 years. This reduction was primarily driven by a 9% decrease in creatinine, a ~4% increase in albumin, and a 3% increase in lymphocyte concentration. Increases in fasting glucose and C-reactive protein only modestly increased PhenoAge. PhenoAge decreased while physiological systems showed a clear accelerated ageing. These findings indicate that mortality-trained clinical biomarker clocks may be insensitive to rapid functional decline. Blood-based aging clocks should be validated against short-term exercise and/or nutritional interventions.

Non-cell-autonomous control of stress surveillance by telomere deprotection

Shoma Ishikawa, Maria Khachatryan, Björn Schumacher

¹*Institute for Genome Stability in Aging and Disease, University of Cologne, Cologne, Germany.*

²*Cologne Excellence Cluster for Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany.*

Loss of telomere end protection triggers cellular senescence or cell death, which functions as a tumor suppressor while also accelerating aging-associated dysfunction and diseases. Although telomere protection is dynamic and responding to various endogenous and environmental insults across lifetime, whether and how early-life telomere instability influences life history trajectories in the organismal context remain unknown. Here, we uncover a previously unrecognized consequence of compromised shelterin-mediated telomere protection in germ cells by employing *C. elegans* as a metazoan model. Counterintuitively, we show that early-adulthood telomere deprotection promotes organismal health and longevity in nematode worms via mechanisms that preserve germline genome stability and integrity, without overt reproductive cost. The somatic longevity response is mediated by the induction of apoptosis and the subsequent engulfment of genomically compromised germ cells by gonadal niche cells. We also demonstrate that intestinal p38-like stress signaling is required to elicit germ cell apoptosis and lifespan extension upon telomere deprotection. Of note, the somatic p38-like signaling is essential to safeguard inheritable euploidy in the descendants amid telomere deprotection, suggesting the engagement of somatic surveillance in the faithful inheritance of genetic materials. Finally, we identify prostaglandin signaling as a hormone-like mechanism through which deprotected germline genomes provoke non-cell-autonomous activation of the p38-like stress response that augments somatic health.

Taken together, our study establishes an unprecedented pro-longevity signaling circuits initiated by early-life telomere deprotection in ovarian germ cells. The state of telomere integrity in youth dictates animal aging trajectories via hormone-like regulation of somatic stress responses that shape adaptive and survival strategies through apoptotic corpse clearance. Given the implication of ovarian hormones in systemic coordination of homeostasis and physiology as well as age-related disease risks in humans, our work may provide a novel paradigm for a better understanding of the effects imparted by age-dependent accumulation of meiotic chromosome errors in human eggs on female fertility and longevity.

A neonatal-like cardiac program underlies adult heart regeneration in the naked mole-rat

Jacome Burbano, M.S.¹; Wagner, E.^{2,3}; Wang, N.¹; Grimm, S.²; Zimmermann, F.³; Geissen, S.³; Lackmann, J-W.⁴; Antczack, P.^{2,4}; Winkels, H.^{2,3}; Mollenhauer, M.³; Reznick, J.¹

¹University of Cologne, Faculty of Medicine and University Hospital Cologne, Cluster of Excellence Cellular Stress Responses in Aging-associated Diseases (CECAD), Cologne Germany

²Centre for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany

³Heart Center, Department of Cardiology, Faculty of Medicine and University Hospital Cologne, University of Cologne, 50937 Cologne, Germany; Center for Molecular Medicine Cologne (CMMC), University of Cologne, 50937 Cologne, Germany

⁴Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany

Cardiac regeneration is severely restricted in most adult mammals, leading to irreversible damage, fibrosis, and loss of function after myocardial infarction (MI). In contrast, neonatal mammals transiently regenerate the heart through cardiomyocyte (CM) proliferation and minimal scarring, but this capacity is rapidly lost after birth.

Here, we identify the naked mole-rat (NMR, *Heterocephalus glaber*) as a striking exception. Adult NMR hearts retain neonatal-like metabolic and structural traits, including reduced fatty-acid oxidation, a subset of mono-nucleated diploid CMs, and fetal-like contractile proteins. Following MI, NMR mount a regenerative response. Despite comparable initial injury to mice, NMR hearts show sustained CM cell-cycle re-entry, progressive scar resolution and up to 30% recovery. ECM proteomics identified a factor enriched in injured NMR hearts. Injection of this factor into adult mice after MI stimulated CM proliferation and reduced fibrosis, suggesting NMR ECM components can reactivate regenerative programs. Overall, these results establish the naked mole-rat as a unique adult mammalian model of heart regeneration.

Senomorphic effect of genetic and chemical partial reprogramming

Lorenzo-Rodríguez, L.¹

¹Laboratory of Cell Senescence, Cancer and Aging, Center for Research in Molecular Medicine and Chronic Diseases (CiMUS), University of Santiago de Compostela, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain.

Partial reprogramming has emerged as a promising strategy to ameliorate aging phenotypes, yet its cellular targets and mechanisms remain poorly defined. Cellular senescence is a central hallmark of aging and a plausible mediator of reprogramming-induced rejuvenation. Here we show that genetic and chemical partial reprogramming act directly on senescent cells without restoring proliferative capacity. OSKM expression or a reduced two-compound regimen, tranylcypromine and RepSox (2c), attenuates senescence-associated secretory activity, restores mitochondrial homeostasis and apoptotic priming, and improves functional and inflammatory parameters in aged mice, establishing senomorphic, identity-preserving reprogramming as a potentially safer aging intervention.

Mitochondrial metabolism and epigenetic crosstalk in senescent cells.

Martini, Helene^{1,2}; Birch, Jodie³; Marques, Francisco⁴; Victorelli, Stella^{1,2}; Lagnado, Anthony^{1,2}; Pirius, Nicholas^{1,2}; Franco, Ana Catarina^{1,2}; Lee, Gung^{1,2}; Han, Yeaen^{1,2}; Rowsey, Jennifer²; Gaspar-Maia, Alexander⁵; Ismail, Mohammed Wazim⁵; Mazzone, Amelia⁵; Hitosugi, Taro⁶; Espe, Tianna M.⁶; Li, Ya⁶; Washington, Alexander⁷; Kostalari, Enis⁷; Havas, Aaron⁸; Murad, Rabi⁸; Lei, Xue⁸; Porritt, Rebecca⁸; Maddocks, Oliver⁹; Jurk, Diana^{1,2}; Khosla, Sundeep²; Adams, Peter D.⁸; Passos, Joao F.^{1,2}

¹Physio&Biomed Engineering Mayo Clinic MN

²Robert&Arlene Kogod Center Aging Mayo Clinic MN

³LMS&ICS Faculty of Medicine Imperial College London UK

⁴Biochemistry Albert Einstein College of Medicine NY

⁵Dpt of Lab Medicine and Pathology & Epigenomics programs Mayo Clinic MN

⁶Dpt Oncology, Division of Oncology Research Mayo Clinic MN

⁷Gastroenterology and Hepatology, Mayo Clinic MN

⁸Sanford Burnham Prebys Medical Discovery Inst CA

⁹School of Cancer Sciences University of Glasgow UK

Chronic low-grade inflammation is a hallmark of aging and a major risk factor for morbidity and mortality in older adults. Senescent cells (SCs) promote tissue dysfunction and organismal aging in part through the senescence-associated secretory phenotype (SASP). However, the mechanisms contributing to the SASP are not fully elucidated. Our team has shown that mitochondrial dysfunction plays a central role in aging and SASP production. Understanding how mitochondrial dysfunction drives the SASP is essential for identifying new therapeutic targets to counteract the detrimental impact of SCs during aging.

Here, we demonstrate that mitochondrial metabolism is a key regulator of the epigenetic regulation of the SASP, where mitochondria-derived metabolites, such as citrate and acetyl-CoA, fuel histone acetylation at SASP gene loci, promoting their expression and inflammation in SCs. Interfering with mitochondrial metabolism, by inhibiting SLC25A1 and citrate export, reduces histone acetylation and SASP expression. Moreover, we show that mtDNA/cGAS/STING signaling cooperates with this metabolic–epigenetic pathway to enable full SASP activation and inflammation. Finally, single-cell multiome analysis in muscle demonstrates that pharmacological inhibition of SLC25A1 in vivo reduces chromatin accessibility at SASP genes, decreases inflammation, and is associated with improved healthspan in aged mice, underscoring its therapeutic potential. Our data support the concept that the SASP is driven by crosstalk between mitochondrial metabolism and epigenetic changes and identify new targets to combat the pro-aging effects of SCs.

Aging clocks delineate neuron types vulnerable or resilient to neurodegeneration and identify neuroprotective interventions

Gallrein, C.^{1,2,3,5,6}; **Meyer, D.H.**^{1,2,5,6}; Woitzat, Y.^{3,4}; Ramirez–Ramirez, V.^{1,2}; Vuong–Brender, T.^{1,2}; Kirstein, J.^{3,4} and Schumacher, B.^{1,2,6}

¹*Institute for Genome Stability in Aging and Disease, Medical Faculty, University and University Hospital of Cologne, Cologne, Germany*

²*Cologne Excellence Cluster for Cellular Stress Responses in Aging–Associated Diseases (CECAD), University of Cologne, Cologne, Germany*

³*Leibniz Institute on Aging – Fritz–Lipmann–Institute (FLI), Jena, Germany*

⁴*Friedrich Schiller University, Institute for Biochemistry and Biophysics, Jena, Germany*

⁵*These authors contributed equally*

⁶*Corresponding authors*

Different neuron types show distinct susceptibility to age-dependent degeneration, yet the underlying mechanisms are poorly understood. Here we applied aging clocks to single neuron types in *C. elegans* and found that distinct neurons differ in their biological age. Ciliated sensory neurons with high neuropeptide and protein biosynthesis gene expression show accelerated aging and degeneration, correlating with loss of function, which could be prevented by pharmacological inhibition of translation. We show that the *C. elegans* neuronal aging transcriptomes correlate with human brain aging patterns and anticorrelate with geroprotective interventions. We performed an in silico drug screen to identify potentially neuroprotective small molecules. We show that the plant metabolite syringic acid and the piperazine derivative vanoxerine delay neuronal degeneration, and propose these compounds as neuroprotective interventions. Furthermore, we identify neurotoxins that accelerate neurodegeneration, indicating that distinguishing aging trajectories between neuron types can inform on protective interventions as well as risk factors.

References:

1. Gallrein, C., Meyer, D.H., Woitzat, Y., Ramirez–Ramirez, V., Vuong–Brender, T., Kirstein, J., and Schumacher, B. (2026). Aging clocks delineate neuron types vulnerable or resilient to neurodegeneration and identify neuroprotective interventions. *Nat. Aging* 6, 849–868. <https://doi.org/10.1038/s43587-026-01067-5>

Do mental disorders accelerate the pace of ageing?

Mutz, J.¹; Whitman, E.T.²; Moffitt, T.E.^{1,2}; Caspi, A.^{1,2}

¹ *Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom.*

² *Department of Psychology and Neuroscience, Duke University, Durham, United States.*

Background: Mental disorders are linked to earlier onset of age-related disease and premature mortality, but whether they accelerate biological ageing is unclear. We tested associations between mental disorders and the pace of ageing, and whether these are causal.

Methods: In UK Biobank and the Dunedin Study, we examined associations of mental disorder diagnoses, psychiatric multimorbidity, dimensional psychopathology and polygenic scores with DunedinPACNI, a neuroimaging measure of the pace of ageing. Two-sample Mendelian randomisation (MR) tested causal effects.

Results: Most mental disorders were associated with faster ageing, with the largest effect for psychotic disorders. Greater psychiatric multimorbidity showed a graded association with faster ageing, replicating in the Dunedin Study. Polygenic score associations were small. MR supported causal effects for substance use, affective and neurotic disorders, but not psychotic disorders.

Conclusions: Mental disorders are associated with, and for several groups causally linked to, a faster pace of ageing, largely reflecting illness rather than genetic liability.

Loss of regeneration and epigenetic drift of the intestinal stem cells during aging

Anna Krepelova^{1,2,3}; Seyed Mohammad Mahdi Rasa^{3,4}; Omid Omrani³; Francesco Annunziata^{3,5}; Jing Lu³; Chiara Giannuzzi^{1,2}; Elisabeth Wyart²; Alberto Minetti³; Alessandro Ori^{3,6}; Ihab Ansari⁷; Dor Bilenko⁷; Yehudit Bergman⁷; Karl Lenhard Rudolph³; Paolo Porporato²; **Francesco Neri**^{1,2,3*}

¹Department of Life Sciences and Systems Biology, University of Turin, Turin, Italy

²Molecular Biotechnology Center (MBC), University of Turin, Turin, Italy

³Leibniz Institute on Aging – Fritz Lipmann Institute (FLI), Jena, Germany

⁴Institute of Immunology, UKSH, Kiel, Germany

⁵Telethon Institute of Genetics and Medicine (TIGEM), Naples, Italy

⁶Genentech Inc., San Francisco, CA, USA.

⁷Institute for Medical Research, Hebrew University Medical School, Jerusalem, Israel.

*Corresponding author. Email: francesco.neri@unito.it

Aging of the intestinal epithelium is associated with impaired stem cell function, reduced regenerative capacity and increased cancer risk. Epigenetic drift, particularly altered DNA methylation, is a hallmark of aging and is frequently observed in intestinal tumorigenesis. However, how age-associated inflammation, metabolic dysfunction and tissue regeneration converge to generate epigenetic drift in intestinal stem cells remains poorly understood. Across three studies, we combined transcriptomic, epigenomic, proteomic and metabolomic profiling of aged intestinal tissues with functional assays in mouse models and analyses of human colon datasets. We identified IFN γ -STAT1 signaling as a driver of age-related stem cell dysfunction, aberrant lineage priming and impaired regeneration. We further showed that aged epithelia develop proteostatic stress, while polyamine metabolism supports regenerative recovery. Finally, we demonstrated that intestinal DNA methylation drift originates in stem cells and expands through crypt clonality and fission, driven by inflammation, reduced Wnt signaling, altered iron metabolism and impaired TET activity. Together, these studies define a mechanistic link between inflammaging, regenerative decline and epigenetic drift, explaining how aging creates a molecular substrate for cancer-associated DNA methylation changes.

References

1. Omrani, O., Krepelova, A., Rasa, S.M.M., Sirvinskaskas, D., Lu, J., Annunziata, F., Garside, G., Bajwa, S., Reinhardt, S., Adam, L., et al. (2023). IFN γ -Stat1 axis drives aging-associated loss of intestinal tissue homeostasis and regeneration. *Nat. Commun.* 14, 6109.
2. Minetti, A., Omrani, O., Brenner, C., Cansiz, F., Imada, S., Rösler, J., Khawaled, S., Allies, G., Meckelmann, S.W., Gebert, N., et al. (2025). Polyamines sustain epithelial regeneration in aged intestines by modulating protein homeostasis. *Nat. Cell Biol.* 1–15.
3. Krepelova, A., Rasa, M., Annunziata, F., Lu, J., Giannuzzi, C., Omrani, O., Wyart, E., Porporato, P.E., Ansari, I., Bilenko, D., et al. (2025). Iron homeostasis and cell clonality drive cancer-associated intestinal DNA methylation drift in aging. *Nat. Aging*, 1–17.

Novel Treatments to Mitigate Ovarian Aging and Follicle Loss

Nikoleta Nikou^{a,b}, Maria López Panadés^{a,b} and Ignasi Roig^{a,b}

^a *Unitat de Citologia i Histologia, Departament de Biologia Cel·lular, Fisiologia i Immunologia, Facultat de Biociències, Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Spain*

^b *Grup d'Inestabilitat i Integritat del Genoma, Institut de Biotecnologia i Biomedicina, Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Spain*

The gradual decline of ovarian reserve, culminating in menopause, is a hallmark of women's reproductive aging. Studies have previously linked the age-related reduction in primordial follicles to the DNA damage response and oxidative stress. Here, we investigate the potential of SKQ1, a mitochondria-targeted antioxidant, in preserving the ovarian reserve.

Using female mice as a model, we administered SKQ1 to evaluate its impact on ovarian health. One group was exposed to ethanol, a known inducer of oxidative stress associated with diminished ovarian reserve, while another group received co-administration of SKQ1 and ethanol. Ethanol exposure resulted in a significant reduction in primordial follicles, confirming its detrimental effect on ovarian reserve. Conversely, SKQ1 treatment effectively increased primordial follicle numbers, restoring them to control levels. Furthermore, proteomic, metabolomic, and lipidomic analyses revealed that SKQ1 treatment protected the ovary from the detrimental effects of ethanol.

Expanding our investigation to natural aging, SKQ1 treatment significantly reduced primordial follicle loss compared to untreated mice, suggesting its potential to slow down the natural aging process. Proteome, metabolome, and lipidome analysis of SKQ1-treated ovaries indicated a rejuvenation effect, suggesting that SKQ1 treatment goes beyond mere preservation of the ovarian reserve.

Together, these findings identify SKQ1 as a promising therapeutic candidate to preserve ovarian reserve and delay ovarian aging, opening new avenues for interventions aimed at extending female reproductive lifespan and improving reproductive health in women.

Key words: Ovarian reserve; SKQ1; DNA repair, Oocyte

Lipid droplets in MUFA mediated longevity

Sebastian Steinmüller; Janine C. Brück; **Katharina Papsdorf**

Institute of Molecular Biology (IMB) Mainz, Germany

Aging is characterized by the gradual decline of tissue function. But age progression can be slowed by interventions such as diet. For example, diets rich in specific lipids such as monounsaturated fatty acids (MUFAs) in the Mediterranean diet, correlate with longevity in humans. Specific MUFAs including oleic acid also causally extend lifespan in the nematode *C. elegans*. This suggests that MUFAs are a powerful target for dietary manipulations in the context of aging. However, the cellular mechanism underlying these benefits remain largely unknown. We find that MUFAs upregulate the number of lipid droplets, key lipid storage organelles, and that an increased lipid droplet number is necessary for MUFA-induced longevity in *C. elegans*. Interestingly, the number of lipid droplets in the intestine of individual worms also predicts their remaining lifespan. Lipid droplets form contacts with the endoplasmic reticulum, peroxisomes and mitochondria for lipid synthesis and degradation. We applied super resolution microscopy to observe the organelle landscape during aging focusing on lipid droplets interaction partners. We find that anabolic lipid droplet processes decline with age and detect a shift towards catabolic pathways. Importantly, lipid droplet interaction sites are modulated in MUFA enriched long-lived worms. This suggest that MUFAs, stored in lipid droplets, induce rearrangements in the organelle landscape, that may be key for longevity.

Histological aging signatures enable inference of tissue-specific disease associations from blood

Abila, E.^{1,2}; Buljan, I.^{1,2}; Zheng, Y.¹; Kleissl, L.^{1,3}; Klotz, S.⁴; Veres, T.¹; Weng, Z.⁵; Nackenhorst, M.⁶; Kamies, R.⁷; Michl, A.⁷; Kadri, S.⁷; Hulla, W.⁸; Perkonigg, M.⁹; Drach, M.³; Tschandl, P.³; Sterniczky, B.³; Heinig, M.^{10,11}; Desadeleer, L.¹²; Wuyts, W.¹²; Vanaudenaerde, B.¹²; Ceulemans, L.J.¹²; Buchanan, D.D.¹³; Fennell, L.¹⁴; Stary, G.^{1,3}; Tolkach, Y.⁵; Wöhrer, A.^{4,9}; Schiller, H.B.^{7,15}; & **Rendeiro, A.F.**^{1,2}

¹ CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Lazarettgasse 14 AKH BT 25.3, 1090, Vienna, Austria

² Ludwig Boltzmann Institute for Network Medicine at the University of Vienna, Augasse 2-6, A-1090 Vienna, Austria

³ Department of Dermatology, Medical University of Vienna, Vienna, Austria

⁴ Division of Neuropathology and Neurochemistry, Department of Neurology, Medical University of Vienna, Vienna, Austria

⁵ Institute of Pathology, University Hospital Cologne, Cologne, Germany

⁶ Department of Pathology, Medical University of Vienna, Vienna, Austria

⁷ Research Unit Precision Regenerative Medicine, Helmholtz Munich, Comprehensive Pneumology Center Munich (CPC-M), German Center for Lung Research (DZL), Munich, Germany

⁸ Institute of Pathology, Landeskrankenhaus Wiener Neustadt, Wiener Neustadt, Austria

⁹ Institute of Neuropathology and Neuromolecular Pathology, Medical University of Innsbruck, Innsbruck, Austria

¹⁰ Institute of Computational Biology, Helmholtz Munich, Neuherberg, Germany

¹¹ Department of Computer Science, TUM School of Computation, Information and Technology, Technical University of Munich, Garching, Germany

¹² Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Department CHROMETA, KU Leuven, 3000 Leuven, Belgium

¹³ University of Melbourne, Parkville Australia

¹⁴ University of Sunshine Coast, Queensland, Australia

¹⁵ Institute of Experimental Pneumology, LMU University Hospital, Ludwig-Maximilians University, Munich, Germany

Aging is characterized by profound structural remodeling of human tissues. Using 25,712 whole-slide images from 40 tissue types across 983 individuals in the GTEx cohort, we leveraged deep learning to quantify morphological alterations and develop “tissue clocks” that predict biological age. These clocks correlate with established molecular aging markers, subclinical pathologies, and comorbidities, while highlighting demographic and lifestyle factors linked to tissue-specific age acceleration. Furthermore, by integrating paired histology and transcriptomic data, we developed a method to predict tissue-specific age gaps directly from blood samples. We validated this approach across independent cohorts for eight prevalent diseases, including Alzheimer’s, stroke, and Crohn’s disease, demonstrating that histopathological imaging provides a robust, scalable framework for monitoring tissue-specific physiological decline.

References:

1. Abila E, Buljan I, Zheng Y, Kleissl L, Klotz S, Veres T, Weng Z, Nackenhorst M, Kamies R, Michl A, Kadri S, Hulla W, Perkonigg M, Drach M, Tschandl P, Sterniczky B, Heinig M, Desadeleer L, Wuyts W, Vanaudenaerde B, Ceulemans LJ, Buchanan DD, Fennell L, Stary G, Tolkach Y, Wöhrer A, Schiller HB, and Rendeiro AF (2026). Histological aging signatures enable inference of tissue-specific disease associations from blood. *Nature Medicine* (in press). Preprint at bioRxiv: <https://doi.org/10.1101/2024.11.14.618081>.

Discovery of a Circulating Myokine that Improves Systemic Function in Aged Mice

Thanh T Nguyen¹; Yeongmin Kim¹; Yunju Jo²; Beom-Jun Kim³; Chang-Myung Oh¹; **Dongryeol Ryu¹**

¹Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology (GIST), Gwangju, Republic of Korea.

²Department of Microbiology, Wonkwang University School of Medicine, Iksan, South Korea

³Department of Internal Medicine, Division of Endocrinology and Metabolism, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background

The global demographic shift toward an aging population has intensified the clinical burden of age-related conditions, such as sarcopenia and cognitive decline. Skeletal muscle is now recognized as a sophisticated endocrine organ that maintains systemic homeostasis through the secretion of myokines. To identify potent therapeutic candidates, we implemented a two-layer analytical framework combining machine learning and human multi-omics data to discover myokines that mitigate age-associated muscle atrophy and restore inter-organ crosstalk.

Methods

We applied XGBoost coupled with SHAP (SHapley Additive exPlanations) to GTEx human muscle transcriptomics, prioritizing genes encoding secreted proteins with age-associated downregulation. These candidates were integrated with plasma proteomic profiling from a Korean sarcopenia cohort (Asan Medical Center), identifying AMPEX (Aged Muscle Protecting Exerkine) as a lead candidate positively correlated with grip strength and gait speed. Recombinant protein was produced in CHO cells and applied to C2C12 myotubes to assess function via RNA-seq and GSEA. In vivo efficacy was evaluated in 19-month-old C57BL/6J mice treated with 2.5 or 5.0 mg/kg for 14 weeks. Assessments included DEXA body composition, hanging and treadmill tests, and a comprehensive behavioral battery (Y-maze, Open Field, Elevated Plus Maze).

Results

To characterize the function of the newly identified myokine, recombinant protein was produced in CHO cells and applied to C2C12 myotubes, followed by RNA sequencing and gene set enrichment analysis (GSEA). GSEA revealed enrichment of gene sets associated with muscle homeostasis, mitochondrial integrity, and exercise capacity. Unbiased human phenotype ontology-based analysis further demonstrated associations with muscle and mitochondrial diseases, supporting therapeutic potential. Based on these findings, we designated this myokine as AMPEX (Aged Muscle Protecting Exerkine). In vitro, recombinant AMPEX induced myotube hypertrophy, indicating anabolic effects. In aged mice, chronic AMPEX administration increased lean mass and fiber cross-sectional area (CSA) in multiple muscles while reducing fat mass and improving bone mineral density. AMPEX-treated mice also exhibited enhanced endurance, spontaneous activity, and cognitive performance, alongside reduced anxiety-related behaviors. These systemic benefits were observed in both sexes and accompanied by improved external signs of aging. Ongoing studies are evaluating circulating AMPEX levels in a 1,000-person cohort and its impact on lifespan.

Conclusion

AMPEX represents a first-in-class recombinant myokine that reverses core features of muscle aging and enhances systemic vitality. By addressing both local muscle wasting and age-related functional deterioration, AMPEX offers a transformative therapeutic strategy for sarcopenia and the promotion of systemic healthy aging.

The role of the ribosomal RNA methyltransferase Nsun5 in mouse aging and development

Liendl, L.¹; Wagner-Schrittwieser, A.²; Apel, A.²; Winter, C. ²; Papp, L.¹; Heissenberger, C.¹; Schmid-Siegel, M.²; Tav, K.²; Hengstschläger, M.²; **Schosserer, M.**^{1,2,3}

¹*Institute of Molecular Biotechnology, Department of Biotechnology, BOKU University, Vienna, Austria*

²*Institute of Medical Genetics, Center for Pathobiochemistry and Genetics, Medical University of Vienna, Vienna, Austria*

³*Max Planck Institute for Biology of Ageing, Cologne, Germany*

We previously showed that the absence of a single m5C modification on 28S rRNA, introduced by NSUN5, increases the lifespan and stress resistance of *S. cerevisiae*, *C. elegans*, and *D. melanogaster*. Here, we investigated the consequences of constitutive whole-body Nsun5 knockout in mice, resulting in the absence of methylation at C3438 of the 28S ribosomal RNA. Indeed, frailty and lifespan assessments indicated that the loss of Nsun5 is beneficial at advanced age, in both male and female animals. However, Nsun5 knockout also caused reduced body weight, partial embryonic lethality, and defects in immune function. Investigations into the underlying mechanisms suggest that the role of Nsun5 in modulating translation is linked to cell growth and differentiation. Given the evolutionary conservation of NSUN5, we are confident that our experiments will help elucidate the contribution of rRNA modifications to organismal fitness and may pave the way for the design of geroprotectors targeting NSUN5.

A single-cell multi-omic atlas decodes the regulatory logic of liver aging

Sen, P.¹; Sarker, N.¹; Yang, N.¹

¹Laboratory of Genetics and Genomics, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

The liver exhibits striking spatial organization and profound age- and sex-dependent functional changes, yet the regulatory mechanisms remain incompletely understood. Prior single-cell studies have described age-related loss of hepatocyte zonation, immune remodeling, and metabolic decline, but lack integrated transcription factor mapping, and systematic sex comparisons. Therefore, we generated a lifespan- and sex-resolved single-cell multi-omic atlas of mouse liver integrating RNA and ATAC modalities. By profiling five age groups, our data reveal continuous and non-linear regulatory dynamics that cannot be inferred from binary young-old contrasts. This resource identifies cell-type-, zone-, age-, and sex-resolved transcription factor regulation, oscillatory metabolic programs, emergence of distinct senotypes, and extensive chromatin plasticity. We further uncover a transient, lineage-inappropriate gene expression pattern in female hepatocytes with age. Together, our study defines the spatiotemporal regulatory logic of hepatic aging in both sexes.

Suppression rather than activation of the integrated stress response (GCN2–ATF4) pathway extends lifespan in the fly

Miriam Götz¹; Dan Hayman¹; Gracie Adams¹; Fumiaki Obata²; **Mirre Simons¹**

¹ *University of Sheffield*

² *RIKEN & University of Kyoto*

Stress response pathways are emerging as conserved modulators of lifespan. The prevailing hypothesis is that activation of stress-responsive pathways, including the amino acid deprivation arm of the integrated stress response (ISR; the GCN2–ATF4 pathway), is pro-longevity. Activation of ATF4 orthologs extends lifespan in *Saccharomyces cerevisiae* and *Caenorhabditis elegans*, but its role in other longer-lived organisms remains unclear. We comprehensively tested the role of the GCN2–ATF4 pathway in longevity in the fly (*Drosophila melanogaster*) for the first time. We used conditional genetic manipulation of dGCN2 and its downstream effector *Drosophila* ATF4 (*crc*; dATF4). In contrast to previous studies, we show that overexpression of dGCN2 and dATF4 significantly reduces lifespan, while knockdown (in vivo RNAi) of dATF4 extends lifespan. We confirmed that dATF4 activity was successfully modulated using a fluorescent dATF4 activation reporter. Borrelidin, a tRNA synthetase inhibitor, significantly reduced lifespan in a both dATF4 and diet-dependent manner, independent of microbial load, showing our modulation of dATF4 altered nutrient to ISR signaling. We further conducted long-read RNA sequencing and found that our manipulation of dATF4 changed global transcription in opposite directions, including known ATF4 target genes. Enrichment analysis revealed that dATF4 overexpression may drive metabolic stress, while dATF4 knockdown may upregulate proteostasis and DNA repair pathways. Our work reveals that ATF4 may exhibit a dual, dose-, and context-dependent role in aging. Chronic dATF4 activation is detrimental in flies, while chronic suppression is pro-longevity. The GCN2–ATF4 pathway thus qualifies as a modifiable control of lifespan with cross-species relevance.

This work is published: <https://doi.org/10.1073/pnas.2518812123>

I will also cover currently unpublished work on this pathway, including a novel connection we have discovered with the spliceosome.

DNA Methylation–Based Clonal Hematopoiesis Burden Associates with Structural Brain Atrophy

Suwanlikit, Y.^{1,2,3,*}; Crofts, S.J.^{1,2,4,*}; Cox, S.^{5,*}; Robertson, N.A.^{1,6}; Marioni, R.⁷; Tan, S.H.^{1,8}; Kirschner, K.^{1,9,#}; Chandra, T.^{1,6,10,#}.

¹ Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester MN, USA

² Mayo Clinic Graduate School of Biomedical Sciences, Rochester MN, USA

³ Department of Pharmacology, Mahidol University, Bangkok, Thailand

⁴ School of Biological Sciences, University of Edinburgh, Edinburgh, UK

⁵ Lothian Birth Cohorts, Department of Psychology, University of Edinburgh, Edinburgh, UK

⁶ Department of Quantitative Health Sciences, Mayo Clinic, Rochester MN, USA

⁷ Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK

⁸ Bioinformatics and Computational Biology, University of Minnesota, Minneapolis MN, USA

⁹ Department of Hematology, Mayo Clinic, Rochester MN, USA

¹⁰ Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester MN, USA

Clonal hematopoiesis (CH) effects on neurodegeneration remain poorly understood¹. Using COMET2, a methylation-based clonality predictor, we examined longitudinal associations between clonal burden and brain structure in the Lothian Birth Cohort 19363 (n = 1,091) across three time points (ages 73–79). Latent growth curve modeling revealed that rising clonality significantly predicted progressive gray matter loss ($\beta = -0.958$, $p < 0.01$), following a left-lateralized cortical atrophy pattern in medial temporal and parietal regions that spatially corresponded with an established Alzheimer's disease (AD) cortical map⁴ ($r = 0.344$, $p = 0.004$). Subcortical analyses showed relative caudate preservation and no significant hippocampal association. A complementary CH burden predictor derived from the EWAS study⁵, capturing systemic epigenetic remodeling across mutant and wild-type immune cells, was associated with global atrophy but showed divergent regional patterns. Together, these findings establish CH burden as a contributor to brain atrophy, with clonality specifically linked to AD-like cortical atrophy in cognitively healthy older adults.

References:

1. Singh, J. et al. Clonal hematopoiesis of indeterminate potential as a prognostic factor: a systematic review and meta-analysis. *Blood Adv.* 8, 3771–3784 (2024).
2. Crofts, S. J. C., Grenko, C. M., Robertson, N. A., Kirschner, K. & Chandra, T. Inference of clonal hematopoiesis using the collective behaviour of DNA methylation states. *bioRxiv* (Preprint). <https://doi.org/10.1101/2025.11.18.689122> (2025).
3. Deary, I. J. et al. The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. *BMC Geriatrics.* 7, 28 (2007).
4. Couvy-Duchesne, B. et al. Grey-Matter Structure Markers of Alzheimer's Disease, Alzheimer's Conversion, Functioning and Cognition: A Meta-Analysis Across 11 Cohorts. *Hum. Brain Mapp.* 46, e70089 (2025).
5. Kirmani, S. et al. Epigenome-wide DNA methylation association study of CHIP provides insight into perturbed gene regulation. *Nat. Commun.* 16, 4678 (2025).

The Damage Code – Single-Nucleotide Maps of DNA Lesions Across the Ageing [Epi]Genome

Aghajani, E.A.¹; Singh, N.K.¹; Hildbrand, N.¹; Andonova, J.¹; Diedrich, S.¹; MacArthur, M.R.²; Ocampo, A.³; Sturla, S.J.¹; **Takhaveev, V.**¹

¹Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland

²Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, NJ, USA

³Department of Biomedical Sciences, University of Lausanne, Lausanne, Switzerland

Genomic instability is a primary hallmark and cause of ageing, yet which DNA-damage types matter, where they accumulate, and how they affect gene regulation remain unclear. We address this using genome-wide, single-nucleotide- and strand-resolved sequencing: click-code-seq for oxidized guanines and abasic sites¹, and enhanced GLOE-seq for strand breaks² – three major types of DNA damage. We mapped guanine oxidation and DNA methylation in 150 human PBMC genomic DNA samples across ageing, in addition to available matched RNA-seq and ATAC-seq data. In male mouse livers across the lifespan, we profiled oxidation, abasic sites, strand breaks, DNA methylation, RNA-seq and ATAC-seq. In both species, we uncovered transcriptional strand asymmetry of all three damage types, yet with different orientations. DNA damage was highly enriched in ATAC-seq peaks. Locus-specific DNA damage correlated with gene expression, methylation and chromatin state, including at tumour-suppressor, genome-maintenance and inflammation genes, and associated with a range of epigenetic-age metrics.

References:

1. Takhaveev, V., Püllen, N.J., Singh, N.K., Lefevre, L., Aghajani, E.A., Huber, S.M., Schauer, S., Gahlon, H.L., Poetsch, A.R. and Sturla, S.J. (2026). Click-code-seq reveals strand biases of DNA oxidation and depurination in human genome. *Nature Chemical Biology* 22, 716–727.
2. Son, K., Takhaveev, V., Mor, V., Yu, H., Dillier, E., Zilio, N., Püllen, N.J., Ivanov, D., Ulrich, H.D., Sturla, S.J. and Schärer, O.D. (2024). Trabectedin derails transcription-coupled nucleotide excision repair to induce DNA breaks in highly transcribed genes. *Nature Communications* 15, 1388.

TACR3 variant confers resilience to aging and Alzheimer's disease

Nicolas Ruffini^{1,2,3,†}; Florian Udo Fischer^{2,3,†}; Robert Subirana Slotos²; Julia Goschke²; Leon Scholz²; Kristel Knaepen⁴; Stefan Hüttelmaier⁵; Helen Morrison^{6,7}; Theresa Steffan²; Ann Sophie Pabst⁸; Jennifer Winter⁸; Bernhard Baier⁹; Andreas Mierau¹⁰; Harald Binder¹¹; Alexander Drzezga^{12,13,14}; Stefan Teipel^{15,16}; Andreas Fellgiebe^{12,17}; Kristina Endres^{2,18,†}; **Oliver Tüscher**^{1,2,3,19,20,†} for the Alzheimer's Disease Neuroimaging Initiative* and on behalf of the German AgeGain study group

¹ Leibniz Institute for Resilience Research Mainz gGmbH, Mainz, Germany

² Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Mainz, Germany

³ Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, University Medical Center Halle, Halle (Saale), Germany

⁴ Institute for Movement and Neurosciences, German Sport University Cologne

⁵ Section for Molecular Cell Biology, Institute of Molecular Medicine, Martin Luther University Halle/Wittenberg, Germany

⁶ Leibniz Institute on Aging, Fritz Lipmann Institute, Jena, Germany

⁷ Faculty of Biological Sciences, Friedrich-Schiller University, Jena, Germany

⁸ Mainz University Medical Center, Institute of Human Genetics, Mainz, Germany

⁹ Department of Neurology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

¹⁰ Department of Exercise and Sport Science, LUNEX, Differdange, Luxembourg

¹¹ Institute of Medical Biometry and Statistics (IMBI), Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany

¹² University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Nuclear Medicine, Cologne, Germany

¹³ Research Centre Juelich, Institute for Neuroscience and Medicine II, Molecular Organization of the Brain, Juelich, Germany

¹⁴ German Centre for Neurodegenerative Diseases, Bonn/Cologne, Germany

¹⁵ German Center for Neurodegenerative Diseases (DZNE) Rostock Greifswald, Rostock, Germany

¹⁶ Department of Psychosomatic Medicine, University Medicine Rostock, Rostock, Germany

¹⁷ Clinic for Psychiatry, Psychosomatics and Psychotherapy, AGAPLESION Elisabethenstift, Darmstadt, Germany

¹⁸ Faculty of Computer Sciences and Microsystems Technology, Kaiserslautern University of Applied Sciences, Zweibrücken, Germany

¹⁹ German Center for Mental Health (DZPG), Site Halle-Jena-Magdeburg, Halle (Saale), Germany

²⁰ Institute of Molecular Biology (IMB) Mainz gGmbH, Mainz, Germany

Genetic factors conferring cognitive resilience in aging remain poorly characterized. The neurokinin-3 receptor (NK3-R), encoded by Tachykinin Receptor 3 (TACR3), modulates cholinergic signaling in memory circuits vulnerable to aging. Previous studies linked the non-WT expression of the TACR3 variant rs2765 with cognitive decline and reduced volume of the hippocampus and basal forebrain. We investigated rs2765 in the preregistered AgeGain cohort of cognitively healthy older adults (n=188) with independent validation in the ADNI cohort (n=809). Analyses integrated structural neuroimaging, longitudinal cognitive assessments, epigenetic aging (PhenoAge), genome-wide methylation profiling, and mechanistic validation through luciferase assays and cross-species protein expression studies. rs2765 WT confers resilience to age- and AD-related cognitive decline through RBMX-dependent regulation of NK3-R expression, with effects of remarkable size cascading from memory to systemic aging. rs2765 genotyping will stratify individuals for NK3-R modulator therapy and complement APOE-based risk assessment in precision geromedicine.

Shared molecular signatures between diapause II and aging in killifish *Nothobranchius furzeri* suggest aging during diapause II

Voronov, D.¹; Akkus, S.^{1,2}; Gravili, I.^{1,2}; Paul, D.¹; Cellerino A.^{1,2}

¹Leibniz Institute on Aging – Fritz Lipmann Institute (FLI), Jena, Germany

²Scuola Normale Superiore (SNS), Pisa, Italy

Nothobranchius furzeri (Cyprinodontiformes) live in seasonal freshwater ponds that are dried out for most of the year. To survive this, these fish can arrest their embryonic development via diapause. It can occur in three developmental stages: during gastrulation (diapause I), at mid-somitogenesis (diapause II) and before hatching (diapause III). Diapause II (DII) state can last up to multiple years. Diapause is a facultative developmental trajectory, and its alternative trajectory is direct development (DD). Time spent in DII does not affect the lifespan of the adult fish after hatching indicating that either the embryos do not age during diapause or the aging signature is erased post diapause. Despite being a state of arrest, DII nonetheless exhibits dynamic regulation of many genes, a significant proportion of which are regulated during aging as well. This leads to the hypothesis that gene regulation patterns selected to enable diapause could have a pleiotropic detrimental effect in adult life reducing lifespan. We leveraged the next generation sequencing (NGS) technologies to generate multiomic transcriptomic RNA-seq and methylomic RRBS datasets spanning from blastula (3-day post fertilization) to sexually mature (3-week post hatching) fish. Using RNA-seq we looked at DEGs resulting from comparison of DII with DD and genes that follow monotonic trajectories after hatching. We used DNA methylation RRBS data to identify DNA regions differentially methylated in DII and to update the methylomic aging clock model to predict the epigenetic age of DII and DD samples. RNA-seq suggests that gene expression in DII is similar to gene expression during maturation and aging. Aging clocks models show that DII samples exhibit higher epigenetic age than DD samples. Our findings point not only to the shared molecular signatures between DII, maturation and aging, but to embryos exhibiting higher molecular age during DII, which is then reversed upon exit from DII.

Localized NAD⁺ Replenishment Restores Metabolic Resilience and Mitigates Cardiac Injury after Myocardial Infarction

Shibo Wei^{1,2}; Yan Zhang^{1,2}; Dongryeol Ryu¹

¹Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology, Gwangju, South Korea

²Department of Medicine, Dalian University of Technology, Dalian, China

Aging is accompanied by a progressive decline in metabolic resilience, characterized by systemic NAD⁺ depletion, mitochondrial dysfunction, and impaired redox homeostasis. These interconnected processes drive increased susceptibility to a broad spectrum of age-associated pathologies, including cardiovascular diseases such as myocardial infarction (MI). Notably, the early phase following MI represents a critical period during which this pre-existing metabolic vulnerability is rapidly amplified, leading to extensive cardiomyocyte loss and setting the trajectory for adverse cardiac remodeling. Although restoration of NAD⁺ metabolism has emerged as a promising strategy to counteract aging-associated metabolic dysfunction, systemic administration of NAD⁺ precursors remains poorly suited for the acute post-MI setting due to limited cardiac bioavailability and delayed tissue exposure. Here, we develop an injectable and adhesive nicotinamide riboside (NR)-conjugated hydrogel, termed iANgel, that enables immediate, localized, and sustained NAD⁺ replenishment directly within the infarcted myocardium. Early post-MI delivery of iANgel effectively restores myocardial NAD⁺ levels, preserves mitochondrial respiratory capacity, and maintains redox homeostasis under ischemic stress, thereby enhancing cardiomyocyte survival. In a murine MI model, this early intervention translates into improved cardiac contractile performance, stabilization of electrophysiological function, reduced inflammatory remodeling, and enhanced neovascularization at later stages. Together, these findings identify age-associated metabolic decline as a critical determinant of post-MI progression and demonstrate that spatiotemporally controlled NAD⁺ delivery can effectively intercept this vulnerability. This work highlights a therapeutic strategy that bridges aging biology with acute cardiovascular intervention.

Nuclear integrity underpins the dynamic range of inflammation regulation

Haoqun Zhan¹; Yoko Ito²; Ioana Olan¹; Masato Kanemaki³; Masashi Narita¹

¹CRUK Cambridge Institute, University of Cambridge, UK

²International University of Health and Welfare, Japan

³National Institute of Genetics, Japan

The nuclear lamina is essential for genome organisation and nuclear structure, yet how nuclear lamin redundancy influences transcriptional programmes and cell identity remains poorly understood. Here we show depletion of A-type lamins induces a “de-capping” phenotype characterised by recurrent nuclear envelope rupture. Live-cell imaging revealed dynamic rupture–repair cycles with transient loss of nuclear compartmentalisation. Surprisingly, such A-type lamin dependency was cell type specific, and we identify the lamin B receptor (LBR) as a key compensatory factor. Dual depletion of lamin A/C and LBR was sufficient to induce de-capping in otherwise resistant cells, whereas LBR overexpression rescued nuclear integrity following lamin A/C loss.

Functionally, de-capping induced a slow-cycling basal inflammatory cell state dependent on dysregulated NF- κ B signalling. Using live imaging, we demonstrate nuclear rupture drives passive bidirectional diffusion of NF- κ B across the nuclear envelope. In basal conditions, rupture promoted NF- κ B influx into nuclei and elevated inflammatory gene expression, whereas during strong activation, rupture facilitated NF- κ B efflux and attenuated cytokine induction. Thus, transient rupture compresses the dynamic range of NF- κ B signalling by disrupting nucleocytoplasmic compartmentalisation. Importantly, we observed similar de-capping phenotypes in naturally aged mice livers. Together, our findings identify nuclear integrity as a dynamic regulator of transcriptional signalling and establish nuclear envelope rupture as a novel mechanism of inflammatory regulation which may contribute to age-related chronic low-grade inflammation.

Poster overview (Alphabetic order of authors)

No	First Name	Last Name	Titel	Page
P1	Isabelle	Ader	Identification of functional cellular markers related to human health, frailty and chronological age	56
P2	Aleksandra	Aizenshtadt	Human liver organoids preserve donor age signatures and reveal inter-individual differences in tissue resilience	57
P3	Danish	Anwer	Cell-Level Disease Scoring Reveals Transcriptional Heterogeneity in Alzheimer's Disease Across 56 Brain Cell types	58
P4	Filippo		A 12-week anabolic lifestyle intervention (VOILA) improves body composition and metabolic health in older adults.	59
P5	Brecht	Attema	A human-like bile acid pool in mice reveals translational insights in BA metabolism and attenuates atherogenesis in female Ldlr-/- mice	60
P6	Yaniel	Ayala	Proteomic characterization of Selinexor-mediated rescue of the healthy phenotype in progeroid fibroblasts	61
P8	Carine	Beaupere	Role of glucocorticoid signaling in cellular senescence related to laminopathic lipodystrophies	62
P9	Lara	Becker	Does taurine supplementation slow down human aging? First results of the randomised, controlled TauAge trial	63
P10	Serafima	Beletskaya	Characterization of Alternative Splicing Programmes in Retinal Aging through Single-Cell Long-Read Sequencing	64
P11	Fatih	Bogaards	Multi-omics profiling adds predictive value to clinical risk stratification in older emergency department patients: the ZNAge cohort	65
P12	Valquiria	Bueno	T and B lymphocytes in Alzheimers' disease	66
P13	Mengyuan	Cai	Epigenetic Aging Indicators are Associated with Bone Mineral Density in a Population-Based Setting	67

Poster overview (Alphabetic order of authors)

No	First Name	Last Name	Titel	Page
P14	Cor	Calkhoven	C/EBP α and C/EBP β as key transcription factors in health and lifespan regulation	68
P15	Alexander David	Carlsson	A Combination Approach to Modulating NAD ⁺ Precursor-Induced Lifespan Extension in <i>C. elegans</i>	69
P16	Alessandro	Cellerino	Ribosome stalling as a new hallmark of brain aging	70
P17	Maria	Conte	Skin Volatilomics Reveals Distinct Metabolic Signatures in Parkinson's Disease and Multiple System Atrophy: A Non-Invasive Approach for Differential Diagnosis	71
P18	Virginia	Cora	An iPSC-Based Platform to Model Astrocyte Senescence in the Human Midbrain	72
P19	Simay	Coskun	Towards non-invasive molecular risk stratification in ADPKD using urinary extracellular vesicle-derived microRNAs	73
P20	Daniela G.	Costa	Tomatidine is a senotherapeutic compound that improves cognitive function and reduces cellular senescence in aged mice	74
P21	Chiara	Dalla Santa	Modeling Biological Age and Physiological Resilience to Predict Surgical Risk in Aging Populations	75
P22	Antigone	Dimas	Short-term animal product restriction reshapes gene expression and genetic regulation of cholesterol metabolism and telomere homeostasis in humans	76
P23	Nicoleta Elena	Dina	Challenges in Detecting Biotoxins and Biomolecules by using Surface-enhanced Raman Scattering Spectroscopy on Nanopatterned Substrates	78
P24	Ariel	Eraso	Aggregate Lifespan Encyclopaedia (ALE) – A new way to record animal lifespans	79
P25	Maria	Ermolaeva	Aging-compatible metabolic modulators that maintain efficacy by circumventing mitochondrial aging	80

Poster overview (Alphabetic order of authors)

No	First Name	Last Name	Titel	Page
P26	Fabian	Finger	Mitochondrial membrane lipid cardio-lipin controls fiber-type adaptations in ageing muscle via ERRy	81
P27	Alessandro	Fontana	A model for the role of transposable elements in evolution and ageing	82
P28	Matteo	Forte	Surviving Deprivations: How responses to Essential Nutrient deprivations uncover the mechanisms of Lifespan, Reproduction and Somatic Maintenance	83
P29	Nicholas S.	Foulkes	Linking Sunlight and ROS -Induced DNA Damage Repair with Longevity: A key role for photolyases.	84
P30	Ana Catarina	Franco	A Spatial Multi-Omic Atlas of Cellular Senescence in Mouse and Human Skin	85
P32	Joelle Noriko	Galang	Effect of aging on neutrophil function in humans	86
P33	Antonio	García-Bernardo Tartiere	FAβ-gal: an automated system for SA-β-gal fluorescence quantification	87
P34	Hartmut	Geiger	Aging of the adaptive immune system affects the gut microbiome and systemic levels of vitamin B6	88
P35	Alessandro	Gialluisi	Investigating the link between physical activity, depressive symptoms and epigenetic aging: findings from the Moli-sani study	89
P36	Chiara	Giannuzzi	Decoding Age-Related Failure of Intestinal Regeneration	90
P37	Irene	Gravili	Transcriptomic clock in the short-lived African Killifish predicts mortality and detects longevity interventions	91
P38	Mélina	Guillon	Rapamycin alleviates estrogen deficiency-induced bone loss in genetically heterogeneous mice	92
P39	Kavya	Gupta	Molecular Determinants of Clonal Fitness in Clonal Hematopoiesis	93
P40	Victor	Guryev	PATH : A Framework for Phenotypic Aging Dimensions and Disease Risk Stratification	94

Poster overview (Alphabetic order of authors)

No	First Name	Last Name	Titel	Page
P41	Ameerali	Hameed	Community-Level Facilitators and Barriers to Physical Activity Among Older Adults in Karachi, Pakistan: A Qualitative Study	95
P42	Dan	Hayman	Manipulating individual spliceosome components to identify pro-longevity treatments	97
P43	Lotta	Hiihtola	Establishing human microglial models of aging and senescence	98
P44	Mark	Hipp	Predicting protein homeostasis collapse in CAG-expansion diseases	99
P45	Dax	Houtkamp	The association between VO ₂ peak, metabolic blood biomarkers, and prefrailty in 327 community dwelling older adults	100
P46	Shraman	Jana	Co-methylation network reorganisation reveals an independent dimension of epigenetic aging along a bidirectional chromatin axis in human blood methylome	101
P47	Yunju	Jo	Machine Learning–Driven Discovery of a Circulating Biomarker and Development of a Sarcopenia Risk Assessment Index with Multi–Ethnic Validation	102
P48	Katarzyna	Jonak	Age-dependent thiol oxidation targets core proteostasis functions	103
P49	Christina	Karagianni	Caloric restriction and its interplay with redox signaling in lifespan and healthspan	104
P50	Sira	Karvinen	Tissue Specific Regulation of Cellular Senescence by Genetic Aerobic Capacity, Aging, and Exercise	105
P51	Agapi	Kavvadia	The Host–Microbe Redox interplay and its role in Aging and Neurodegeneration	106
P52	Kazuto	Kawamura	Restoration of biological age during prolonged fasting–refeeding mediated by a fasting–responsive linker histone	107

Poster overview (Alphabetic order of authors)

No	First Name	Last Name	Titel	Page
P53	Aurelien	Kerever	The optimized stem cell niche: ECM remodeling supports skin aging resistance in the naked mole rat	108
P54	Anton	Khmelinskii	Mechanisms of life span extension by osmolytes	109
P55	Lisa	Kleissl	Interplay of structural changes in skin tissue during aging and the progression of chronic inflammatory skin diseases	110
P56	Konstantin	Kogan	Extract, Stabilize, Measure: Preserving NAD from Collection to Analysis	111
P57	Angelina Job	Kolady	Unravelling the role of H3K4me2 in response to DNA damage and transcription stress during development and ageing	112
P58	Merve	Kutay	Molecular signatures of sex-specific liver aging	113
P59	Amanda	Latham	Characterizing Cellular Drivers of Cognitive Decline Across the Aging Mouse Hippocampus	114
P60	Peter	Lenart	High-throughput measurement of lifespan and fluorescence-based aging markers at single-animal resolution in <i>C. elegans</i>	115
P61	Joelina	Lienau	Old muscle, new rules: muscle derived FGF21 drives systemic resistance to protect failing muscle	116
P62	Martina	Mankarious	Understanding the role of H3K36 methylation in epigenetic aging	117
P63	Sofia	Manzo	Investigating the impact of ageing on 3D genome architecture in adlRD models in the turquoise killifish	118
P64	Agata	Marchi	Cell-type-resolved pseudobulk classification identifies microglial PTPRG as a transcriptional hub in Alzheimer's disease	119
P65	Asya	Martirosyan	Metabolic reprogramming as a quality control strategy in long-lived bats	120

Poster overview (Alphabetic order of authors)

No	First Name	Last Name	Titel	Page
P66	Saara	Marttila	Epigenetic clocks do not capture the ageing-associated cognitive decline in middle-aged individuals	121
P67	Kyriakos	Mavridis	Redox-Regulated BTB/POZ Protein C40A11.2 Mediates Early-Life Stress Adaptation in <i>Caenorhabditis elegans</i>	122
P68	Christos	Mavrommatis	Methylation-associated Gene Expression (MaGE) proxies of cellular senescence: scalable systemic senescence biomarkers in relation to disease severity and 174 incident disease outcomes.	123
P69	Felix	Mayr	SAM depletion by a proline to polyamine shunt is sensed by the elongator complex to promote longevity	124
P70	Alex	Miralles Domínguez	Reversibility of the Senescence Growth Arrest after CDK4/6 Inhibitor Therapy	125
P71	Lucia	Muñoz Gil	Decoding age-related changes on cell-type specific GRNs in the naturally short-lived African turquoise killifish	126
P72	Julian	Mutz	Social disconnection, metabolomic ageing and cardiometabolic outcomes	127
P73	David	Osuna de la Pena	Redox selection in the airway as a blueprint for aging-related stress adaptation	128
P74	Seyma	Öztürk	Short telomeres in the hematopoietic system promote inflammatory signalling and impair regeneration after acute lung injury	129
P75	Tsimafei	Padvitski	Disentangling cellular damage and aging	130
P76	Francesca	Pagliarin	Exploring the effects of estradiol on cellular senescence and its implications for female aging	131
P77	Leon	Peshkin	Aging in the loop: what is missing from the Big Beautiful training data for Foundation Model of aging pharmaco-biology ?	132

Poster overview (Alphabetic order of authors)

No	First Name	Last Name	Titel	Page
P78	Eleanor	Phillips	The Potential Role of Cysteine and Associated Metabolic Pathways in the Dietary Restriction Response in <i>Drosophila</i>	133
P79	Ana Catarina	Ramalho	New D246p53 isoform responds to DNA damage to enhance p53 family functions in cellular senescence and ageing	134
P80	Verena	Rhebaum	Micronutrient and metabolomic profiles associate with specific systemic multimorbidity profiles	135
P81	Luís	Ribeiro	Establishment of an in vitro model of neuronal aging to dissect surface proteome alterations underlying cognitive decline	136
P82	Luisa	Ricciardi	Integrated Longitudinal Metabolic and Proteomic Profiling Reveals Sex-Dependent Trajectories of Aging	137
P83	Sebastien	Riquier	Deciphering the molecular bases of long lifespan in bats by multi-species comparative RNAseq analysis of blood	138
P84	David	Roiz del Valle	The aging modulator miR-29 is essential for adult cardiomyocyte function	139
P85	Baptiste	Sadoughi	Embracing aging complexity from within-individual heterogeneity to non-linear age-associated trajectories	140
P86	Lilian	Sales Gomez	Cellular Senescence in the Aging Liver Contributes to Cognitive Decline – Crosstalk between Liver and Brain	141
P87	Jérôme	Salignon	Pasta, a versatile transcriptomic clock, maps the chemical and genetic determinants of aging and rejuvenation	142
P88	Walter	Sandt	Evolutionary conserved diapause mechanisms of slowed aging and rejuvenation	143

Poster overview (Alphabetic order of authors)

No	First Name	Last Name	Titel	Page
P89	Isabela	Santos Valentim	DREAMing of Healthy Aging: Deciphering the Molecular Links Between Sleep, Circadian Rhythms, and Cellular Repair	144
P90	Tobias T.	Schmidt	Evolution of primary cells through replicative crisis to immortality	145
P91	Attila	Sebe	Lower blood cell mitochondrial DNA amount and inflammation associates with higher all-cause mortality and aging: a 30-year prospective epidemiological study	146
P92	Jaco	Selle	Perinatal obesity causes premature alveolar aging with AT2 depletion through DNA/RNA hybrid formation driven by IL-6-mediated transcriptional stress and genomic instability	147
P93	Hagar	Setty	Naturally recurring embryonic loss reveals a sperm-dependent link between reproduction and aging	148
P94	Aditya	Singh	NO MAJOR BRAIN ALTERATIONS IN AGED SIGLEC-E/F DOUBLE-KNOCK-OUTS	149
P95	Ilze	Skujina	Enhanced Genome Maintenance Through Rapid DNA Double-Strand Break Repair as a Candidate Mechanism of Exceptional Longevity in Myotis myotis	150
P96	Rajalakshmi	Srinivasan	Expanding the list of Hallmarks of Aging: Insights from amino acid dependent regulation of aging	151
P97	Anton	Stamm	Do Senescent Cells Disrupt the Clock? Investigating SASP Effects on Circadian Rhythms	152
P98	Carmen-Jeanette	Stepek	Spatiotemporal Mapping of Neurodegenerative Stress in the Locus Coeruleus in a Cell-type Specific Ercc1 Deficiency Model	153
P99	Dominik	Lucas	Sciex	154

Poster overview (Alphabetic order of authors)

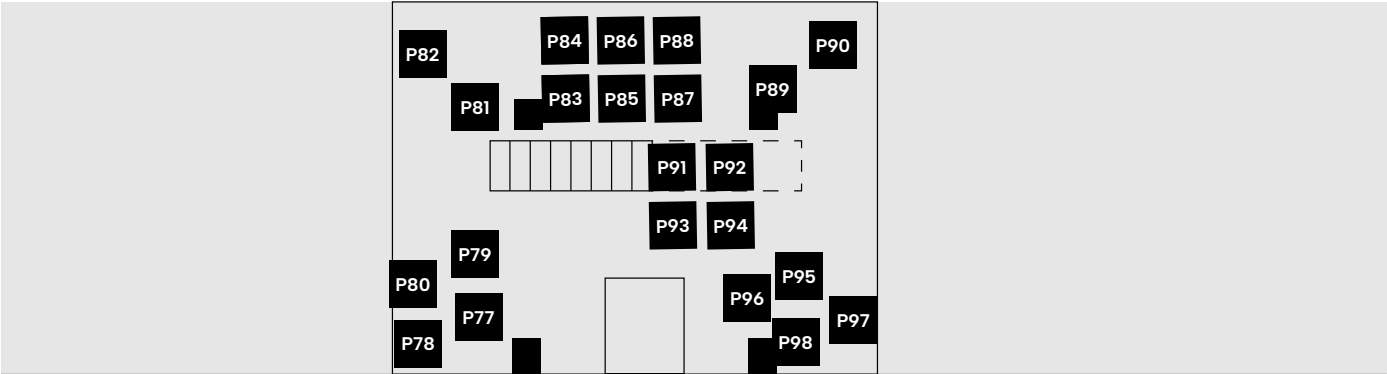
No	First Name	Last Name	Titel	Page
P100	Vassilis	Stratoulas	Neuromelanin drives age-associated lysosomal dysfunction in human dopaminergic neurons	155
P101	Danielle	Taylor	Title: Age-Related Disruption of Circadian Brain-Bladder Communication Reveals a Novel Therapeutic Target for Nocturia	156
P102	Emmanouil	Theodorakis	Endogenous double-stranded RNA links transcription stress to senescence-associated cellular adaptation	157
P103	Ulrike	Topf	Zinc at the crossroads of aging, healthspan, and proteostasis in <i>Caenorhabditis elegans</i>	158
P104	Anne-Ulrike	Trendelenburg	DARe: Decoding the Biology of Aging to Enable Therapeutic Innovation	159
P105	Maria	Tretowicz	Human whole-blood NAD ⁺ levels do not vary with age or lifestyle interventions	160
P106	Lorenzo	Trofarello	The role of PLIN2 during adipogenic differentiation	161
P107	Marek	Uvizl	Comparative analysis of miRNAs and their role in longevity of bats	162
P108	Karla	Valdivieso	Decoding the Role of MIF in Ischemic Brain Injury	163
P109	Ingrid	van der Pluijm	XPG deficiency accelerates vascular aging via VSMC phenotypic switching and metabolic dysfunction, which is mitigated by dietary restriction.	164
P110	Thi Hong Phuong	Vo	Fatty Acids Differentially Drive and Shape Hepatocyte Senescence	165
P111	Nini	Wang	Rewiring of gene regulatory programs underlie regenerative potential of the naked mole-rat heart	166
P112	Margaret	Weber	Estimating Somatic Mutation Rates across Bat Lifespans	167
P113	Luisa	Wensky	Glycation in Vascular Aging is associated with vascular and metabolic Dysfunction	168

Poster overview (Alphabetic order of authors)

No	First Name	Last Name	Titel	Page
P116	Seunghwa	Woo	Telo-CUT: A Telomere-Specific DNA Damage Model Reveals Drivers of Aging	169
P117	Nanxiang	Yin	Experimental β -cell senescence models reveal autophagy defects and altered stimulus-secretion coupling	170

Poster Presentation

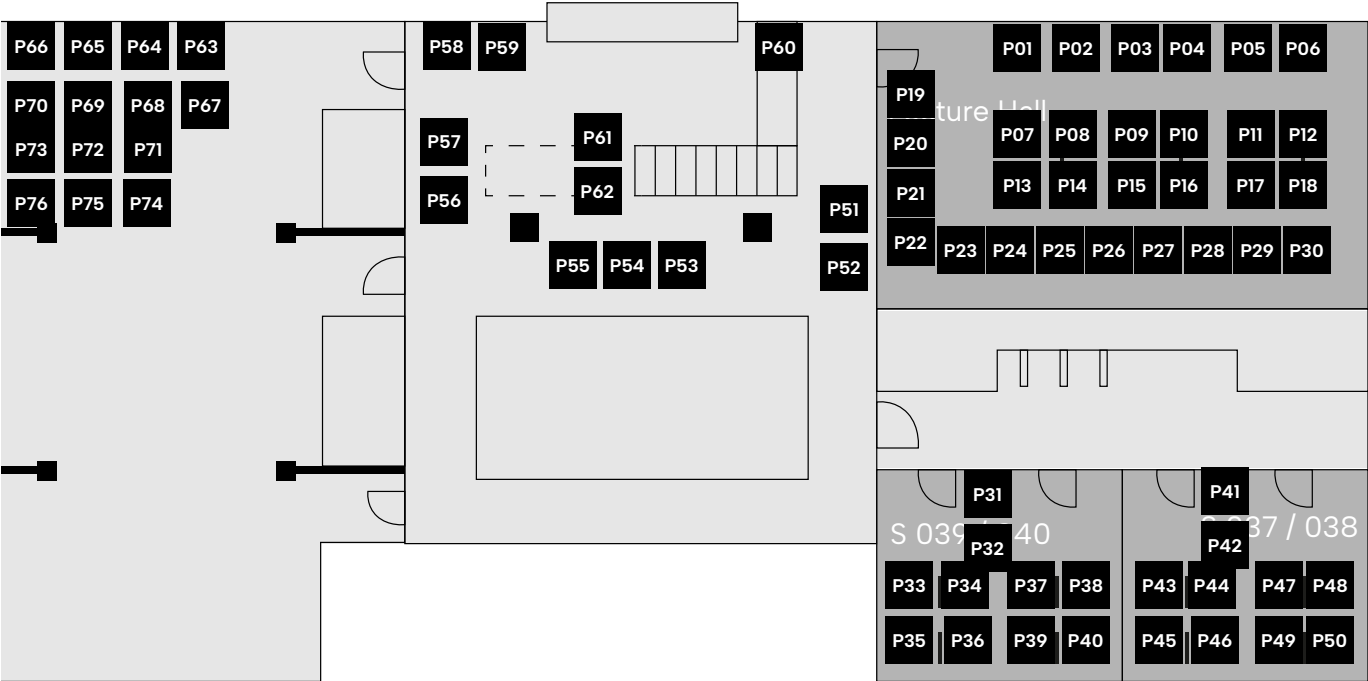
CECAD Ground Floor (P01-P98)



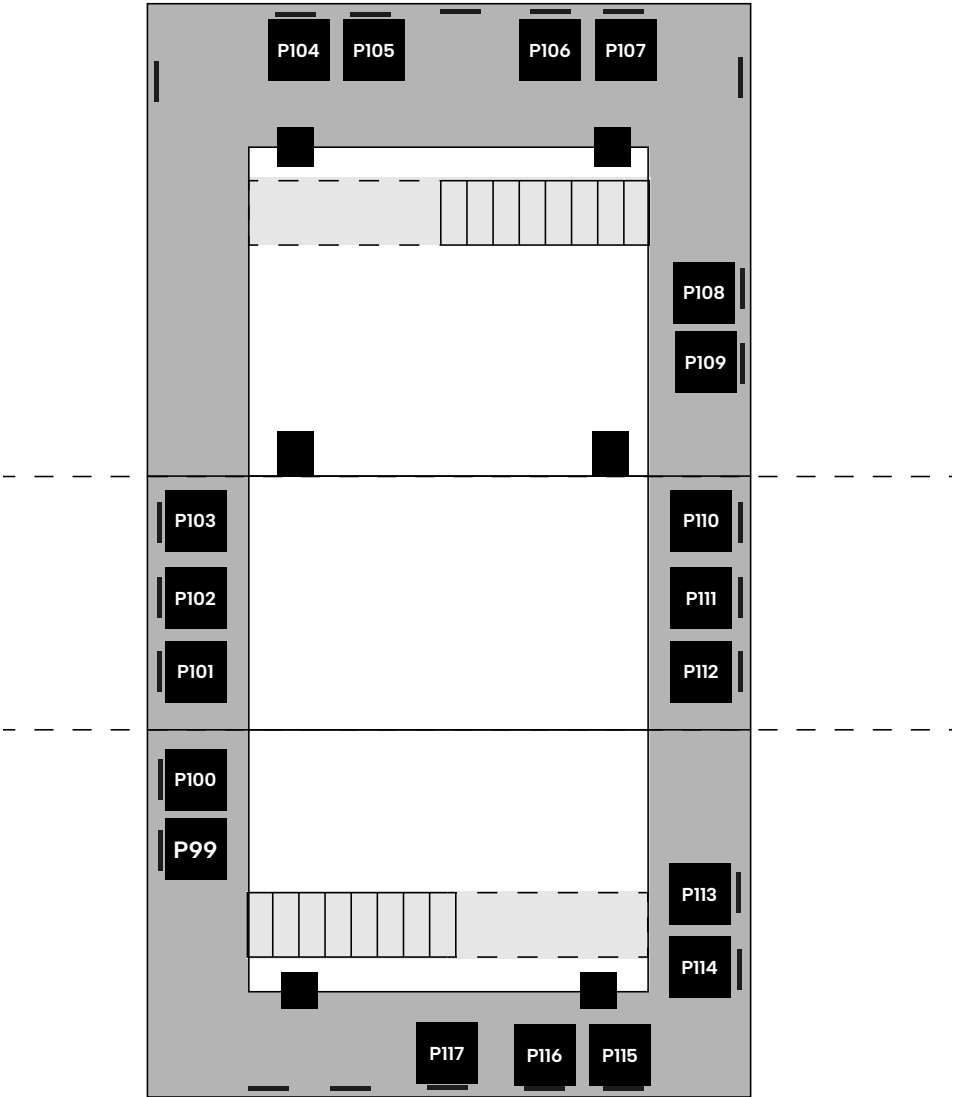
Entrance CECAD

← MPI Building

Entrance CECAD



CECAD First Floor (P98–P119)



Identification of functional cellular markers related to human health, frailty and chronological age

Chloé Brodeau¹, Camille Joly¹, Anaïs Chekroun¹, Jean Nakhle¹, Vincent Blase^{1,2}, Nicolas Espagnolle¹, Cédric Dray^{1,6}, Armelle Yart¹, Valérie Planat¹, Margot Tertrais¹, Julien Fassy³, Sophie Guyonnet^{4,5,6}, Wan-Hsuan Lu^{4,5,6}, Philippe de Souto Barreto^{4,5,6}, Olivier Teste², Marie Tremblay-Franco⁷, Kamaryn T Tanner⁸, Alan A Cohen⁸, Audrey Carrière¹, Louis Casteilla^{1,#}, **Isabelle Ader**^{1,6,#,*}

¹ RESTORE Research Center, Université de Toulouse, INSERM I301, CNRS 5070, EFS, ENVT, 4 bis avenue Hubert Curien, 31100 Toulouse, France

² Université de Toulouse, UT2J, IRIT, (CNRS/UMR 5505), Toulouse, France

³ Université Côte d'Azur, UMR CNRS 7275 Inserm I323, IPMC, Valbonne, France

⁴ Gérontopole of Toulouse, Institute of Aging, Toulouse University Hospital (CHU Toulouse).

⁵ CERPOP UMR 1295, Université de Toulouse, INSERM, UPS, Toulouse, France.

⁶ Institut Hospitalo-Universitaire HealthAge, IHU HealthAge, Toulouse, France

⁷ Toxalim (Research Center in Food Toxicology), Toulouse University, INRAE, ENVT, INP-Purpan, UPS, Toulouse, France.

⁸ Department of Environmental Health Sciences, Butler Columbia Aging Center, Mailman School of Public Health, Columbia University, New York, NY, USA

IHU HealthAge/Open Science group

: contributed equally to the work

*Address for correspondence: Isabelle ADER: RESTORE Laboratory, UMR I301-Inserm 5070-CNRS EFS Univ. P. Sabatier, Université de Toulouse,

4 bis avenue Hubert Curien | 31100 TOULOUSE France.

Email: isabelle.ader-perarnau@inserm.fr

Introduction:

Aging leads to decline in physiological reserves, an increase in age-related diseases, reduced functional ability and a shortened healthspan. While molecular markers of chronological aging exist, their link to general health and intrinsic capacity (IC), a composite measure of physical and mental capacities, remains unclear. This study integrates the WHO's Healthy Aging framework with geroscience to explore fibroblasts as indicators of health.

Methods:

We assessed primary skin fibroblasts from 133 individuals aged 20 to 96, evaluating their ability to maintain tissue Structure, modulate Immune responses, and regulate Metabolism (SIM functions). By combining functional and molecular analyses, we investigated the relationship between fibroblast performance, chronological age, and IC. Results:

Our results demonstrate that fibroblast SIM functions are modified with stressors and age, correlating with IC rather than just chronological age. Notably, fibroblasts from pre-frail and frail individuals exhibited reduced mitochondrial respiration and lower extracellular Periostin levels with Periostin being able to capture IC status, irrespective of age and sex, reflecting a cellular "health memory."

Conclusion:

The SIM paradigm provides a complementary framework to the established hallmarks of aging, advancing our understanding of how cellular aging impacts functional decline. These findings suggest that fibroblast-derived markers could serve as indicators of frailty and reduced IC, enabling early detection of individuals at risk for health deterioration and laying the foundation for early identification of functional decline.

Human liver organoids preserve donor age signatures and reveal inter-individual differences in tissue resilience.

Aleksandra Aizenshtadt^{1,2}; Katharina Ferencevic¹; Carmen Sancho-Serra³; Iva Kelava³; Erick Armingol³; Kristina Sæterdal Kømurcu^{1,4}; Ales Kvasnicka^{4,5}; Madeleine Fandrich⁶; Alex Dulovic⁶; Andrea Dalmao-Fernández¹; Hanne Røberg-Larsen^{1,4}; Sheraz Yaqub^{7,10}; Espen Melum^{1,8-11}; Peter Loskill^{6,12}; Stefan Krauss^{1,2}

¹Hybrid Technology Hub – Centre of Excellence, Institute of Basic Medical Sciences, University of Oslo;

²Department of Immunology and Transfusion Medicine, Oslo University Hospital, Oslo, Norway.

³Wellcome Sanger Institute, Cambridge, UK;

⁴Department of Chemistry, University of Oslo, Norway;

⁵Core Facility for Global Metabolomics and Lipidomics, Oslo University Hospital;

⁶NMI Natural and Medical Sciences Institute at the University of Tübingen, Reutlingen, Germany;

⁷Department of Gastrointestinal and Paediatric Surgery, Oslo University Hospital;

⁸Norwegian PSC Research Center, Department of Transplantation Medicine, Division of Surgery and Specialized Medicine;

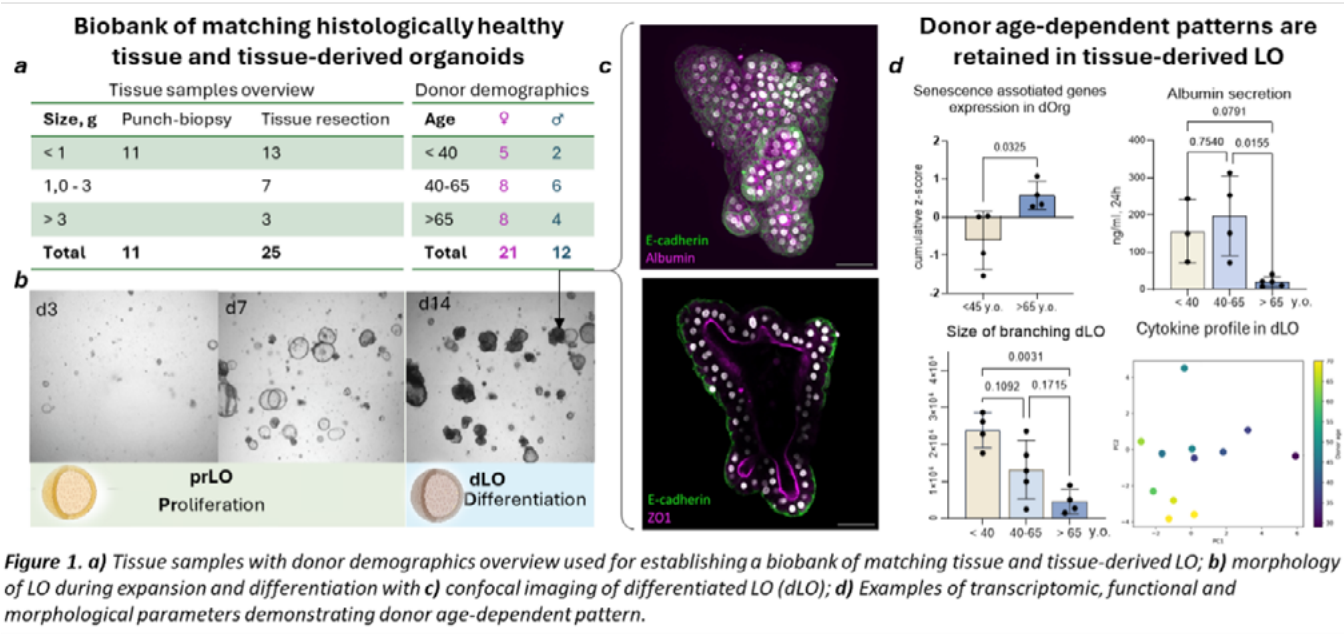
⁹Research Institute of Internal Medicine, Division of Surgery and Specialized Medicine, Oslo University Hospital;

¹⁰Institute of Clinical Medicine, University of Oslo;

¹¹Section of Gastroenterology, Department of Transplantation Medicine, Division of Surgery and Specialized Medicine, Oslo University Hospital, Rikshospitalet, Norway;

¹²Department of Microphysiological Systems, Institute of Biomedical Engineering, Faculty of Medicine of the Eberhard Karls University of Tübingen, Germany

Age-related processes contribute to chronic liver and metabolic diseases, major causes of mortality worldwide. However, modeling donor-specific hallmarks of ageing and liver resilience remains challenging. We generated human liver organoids (LO) from limited tissue samples and established matched LO-tissue biobank (Fig.1). To investigate resilience, LO were subjected to chronic (fatty acid, FFA) and acute (doxorubicin) injury models, followed by recovery assessment. Multi-omics approach (snRNAseq, lipidomics, cytokines) and functional readouts defined donor-specific stress-response and recovery trajectories. LO retained donor age-associated molecular and functional features: increased senescence markers, altered cytokine profiles, reduced albumin secretion in LO of older donors. LO captured inter-individual differences in response and recovery after FFA treatment, whereas recovery following doxorubicin was limited. Recovery capacity was modulated by metformin and sex hormones, showing preserved tissue plasticity. This platform enables mechanistic studies of liver resilience, ageing, and therapeutic responsiveness.



Cell-Level Disease Scoring Reveals Transcriptional Heterogeneity in Alzheimer's Disease Across 56 Brain Cell types

Anwer, D.¹; Ke, Y.¹; & Polster, A.^{1,2}

¹ *Department of Biology and Biological Engineering, Division of Systems and Synthetic Biology, Chalmers University of Technology, Gothenburg, Sweden*

² *Department of Microbiology, Oslo University Hospital and University of Oslo, Oslo, Norway*

Alzheimer's disease (AD) is characterized by profound cellular heterogeneity in the brain, yet most transcriptomic studies rely on bulk or aggregated comparisons that obscure disease-affected cell subpopulations and leave the process of cellular degeneration poorly characterized. We developed a cell-level disease score based on transcriptional similarity to AD transcriptomic profiles to enable systematic identification of disease-affected cells. ScRNA-sequencing from post-mortem prefrontal cortex of AD and non-cognitively impaired (NCI) donors was analyzed, with scores computed across 56 annotated cell subtypes as the difference in cosine similarity to AD and NCI pseudobulk profiles. AD subjects showed significantly elevated scores in 30 of 56 cell-types (FDR<0.05), with the strongest signals in microglia and astrocytes. Scores correlated with plaque burden, tangle counts, and cognitive decline, most strongly in microglia, oligodendrocyte precursor cells, and astrocytes. Differential expression between AD-like and NCI-like cells within the same donors revealed extensive molecular heterogeneity within cell-subtypes, establishing a generalizable framework for cell-state-resolved analyses in future scRNAseq studies.

A 12-week anabolic lifestyle intervention (VOILA) improves body composition and metabolic health in older adults.

Artoni, F.¹; Bogaards, F.¹; Morwani-Mangnani, J.¹; Monsegue, A. P.²; Kramer, C. S.³; Verdijk, L. B.²; de Groot, L. C. P. G. M.³; Deelen, J.¹; Slagboom P. E.¹

¹ *Molecular Epidemiology, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands.*

² *Maastricht University Medical Center+, Department of Human Biology, NUTRIM Institute of nutrition and translational research in metabolism, Maastricht, The Netherlands.*

³ *Wageningen University, Agrotechnology and Food Sciences Group, Division of Human Nutrition and Health, Wageningen, The Netherlands.*

Older adults experience a gradual decline in muscle mass and metabolic health. The VOILA intervention study is a 12-week lifestyle intervention in three groups of Dutch older adults (>60 years) with compromised mobility (n=38), compromised metabolic health (n=33) or recovering from total knee replacement surgery (n=21). All participants underwent supervised high-intensity resistance training, nutritional counseling and supplementation. We used linear mixed models to estimate the physical and metabolic changes experienced by VOILA participants. Over the three groups combined, total lean mass % and BMI significantly increased, while total fat %, circulating total and LDL cholesterol, omega-6 and poly-unsaturated fatty acids, as well as apolipoprotein B significantly decreased (PFDR < 0.05). Whereas women started with a lower health at baseline, no significant differences in response were observed between sexes. Interestingly, participants who were unhealthiest at baseline, based on our composite metabolomics-based overall health score (Personal-MetaboHealth), showed the largest improvements in body composition and metabolic health.

A human-like bile acid pool in mice reveals translational insights in BA metabolism and attenuates atherogenesis in female *Ldlr*^{-/-} mice

Attema, B.¹; Yntema, T.²; Eijgenraam, T.R.^{2,3}; Weersing, E.¹; Hovingh, M.V.²; Mulder, N.L.²; Fu, J.^{2,4}; Riksen, N.⁵; van de Sluis, B.²; de Boer, J.F.^{2,6}; Koonen, D.P.Y.²; & Kuipers, F.^{1,6}

¹European Research Institute for the Biology of Ageing (ERIBA), University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

²Department of Pediatrics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

³Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

⁴Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

⁵Department of Internal Medicine, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

⁶Department of Laboratory Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

Bile acids (BA) are implicated in ageing and age-related pathology including cardiovascular disease (CVD), but translation of murine models is limited by interspecies differences in BA metabolism. We studied the impact of a human-like BA pool in mice, with a focus on atherogenesis.

To induce a human-like BA pool, liver-specific *Cyp2a12/Cyp2c70* knockdown (DKD) was generated using CRISPR/Cas9. DKD mice received glycolithocholic acid (GLCA) to further humanize secondary BA levels. In parallel, *Ldlr*^{-/-} DKD mice were fed a LF, cholesterol-rich diet for 12 weeks to study atherogenesis.

In both models, DKD resulted in a human-like BA pool with increased hydrophobicity and levels of secondary BAs. GLCA further elevated secondary BAs but had no further physiological effects. In *Ldlr*^{-/-} mice, a human-like BA pool reduced atherogenesis in females, but not males, reflected by smaller lesions, necrotic cores, lower plasma total and VLDL cholesterol but no changes in inflammatory mediators.

All in all, DKD in mice results in a human-like BA pool, establishing a translationally relevant model to study BAs in age-related disease and revealing a protective role of BAs in CVD.

Proteomic characterization of Selinexor-mediated rescue of the healthy phenotype in progeroid fibroblasts

Ayala, Y.¹; Encarnación, S.²; Navarro-Garcia, F.¹; & Cisneros, B.³

¹Department of Cell Biology, Center for Research and Advanced Studies (Cinvestav), Mexico City, Mexico

²Center for Genomic Sciences, National Autonomous University of Mexico (UNAM), Cuernavaca, Morelos, Mexico

³Department of Genetics and Molecular Biology, Center for Research and Advanced Studies (Cinvestav), Mexico City, Mexico

Hutchinson–Gilford Progeria Syndrome (HGPS) is a genetic disorder that mimics physiological aging. HGPS is caused by a mutation in the LMNA gene that produces progerin, a toxic lamin A variant that triggers nuclear disorganization, DNA damage, and premature senescence. Progerin upregulates exportin XPO1, disrupting nucleocytoplasmic proteostasis. Although the XPO1 inhibitor Selinexor reverses the progeroid phenotype, its molecular mechanism remains unclear. To elucidate it, we assessed the effect of Selinexor on nucleocytoplasmic proteome distribution in healthy and HGPS cells. Mass spectrometry of these subcellular fractions showed that Selinexor globally attenuates protein synthesis while selectively increasing nuclear localization of proteasome subunits. In silico analysis linked these nuclear-enriched subunits to p62, an XPO1 cargo. We experimentally validated Selinexor-mediated nuclear relocalization of p62, which accumulates as biomolecular condensates in the nucleoplasm. We are currently investigating how nuclear p62 and proteasome activation restore cellular homeostasis in HGPS.

Role of glucocorticoid signaling in cellular senescence related to laminopathic lipodystrophies

P. Tandabany¹; M. Nouvel^{1,2}; M. Auclair¹; A. Murali¹; B. Fève^{1,2}; C. Vigouroux^{1,2*}; **C. Beaupere^{1*}**

¹ Sorbonne University, Inserm UMR_S 938, Saint-Antoine Research Centre, Cardiometabolism and Nutrition University Hospital Institute (ICAN), Paris, France

² Assistance Publique-Hôpitaux de Paris (AP-HP), Saint-Antoine University Hospital, Coordinating Reference Centre for Rare Diseases of Insulin Secretion and Insulin Sensitivity (PRISIS), Endocrinology Department, Paris, France

Genetic lipodystrophies are rare disorders, characterized by abnormal distribution of adipose tissue. They predispose individuals to insulin resistance, hepatic steatosis, and cardiovascular disease. The most frequent monogenic form is linked to mutations in the LMNA gene, encoding nuclear lamins. Premature aging is a hallmark of laminopathies, often associated with early cellular senescence, defects in nuclear envelope integrity and functions, due to the abnormal accumulation of prelamin A, either farnesylated (progerin) e.g. in the Hutchinson Gilford Progeria syndrome (HGPS), or non-farnesylated e.g. in the Dunnigan lipodystrophy.

Recently, we observed that prolonged glucocorticoid (GC) exposure can reduce senescence in fibroblasts from patients carrying the LMNA p.R482W (Dunnigan) or the LMNA p.G608G (HGPS) variants. Interestingly, these cells exhibit a reduction in prelamin A or progerin accumulation and partial restauration of nuclear defects. These findings point to GC signaling as a potential therapeutic target in laminopathies. However, further investigation is needed to fully understand the mechanisms involved.

Does taurine supplementation slow down human aging? First results of the randomised, controlled TauAge trial

Becker, L.K.¹; Starzynska, K.²; Al Sadat, L.²; Murr, A.²; Wackerhage, H.¹; Hauner, H.²

¹Professorship of Sport Biology, TUM School of Medicine and Health, Technical University Munich

²Clinical Nutrition Medicine, TUM School of Medicine and Health, Technical University Munich

INTRODUCTION: Taurine extends healthspan and lifespan in animals, but whether it has similar effects in humans is unknown [1]. To investigate this, we performed a randomised, double-blind, placebo-controlled taurine intervention trial.

METHODS: 83 apparently healthy participants (42 women, 41 men; age=62.9 ± 5.7 years; BMI=25.2 ± 2.9 kg/m²) received either 4 g/day taurine or placebo for six months (NCT06613542). We then measured cardiometabolic biomarkers and muscle function (grip-strength, knee-extensor torque) pre and post intervention and calculated the time×group interaction using linear mixed-effects models in a per-protocol analysis.

RESULTS: Participants tolerated taurine well. For all outcomes analysed so far, model-estimated time×group interactions were not significant (all p>0.05).

DISCUSSION: Taurine supplementation does not affect cardiometabolic health or muscle function in healthy older participants. Aging biomarker (i.e., proteomic clocks, DNA-methylation patterns) analyses to answer the main research question are ongoing.

References:

1. Singh, P., Gollapalli, K., Mangiola, S., Schraner, D., Yusuf, M.A., Chamoli, M., Shi, S.L., Bastos, B.L., Nair, T., Riermeier, A., et al. (2023). Taurine deficiency as a driver of aging. *Science* 380, eabn9257.

Characterization of Alternative Splicing Programmes in Retinal Aging through Single-Cell Long-Read Sequencing

Beletskaya, S.^{1,2}; Ciampi, L.³; Fusté, B.²; Köhler, F.²; Zehnsdorf, M.²; Iñiguez, L. P.^{1,2}; Irimia, M.^{1,2,4}

¹ Department of Medicine and Life Sciences, Universitat Pompeu Fabra, Barcelona, Spain

² Centre for Genomic Regulation, Barcelona Institute of Science and Technology, Barcelona, Spain

³ Centro Andaluz de Biología del Desarrollo, CSIC-Universidad Pablo de Olavide-Junta de Andalucía, Seville, Spain

⁴ ICREA, Barcelona, Spain

In an increasingly aged population, identifying the molecular bases of vision loss is of growing urgency. Alternative splicing (AS) dysregulation is a hallmark of aging, yet its role in retinal aging remains largely uncharacterized. Importantly, given retinal cellular complexity, changes in AS require a cell-type-specific investigation to avoid cell type composition artifacts. While addressing the cell type specificity issue, most conventional single-cell short-read sequencing cannot resolve full-length isoforms, hampering characterization of functionally critical sequences such as the microexons, whose retina-specific inclusion is essential for outer segment integrity, necessary for healthy vision. Using deep-coverage single-cell long-read RNA sequencing combined with AS quantification pipelines developed in-house, we resolve splicing dynamics at high cellular granularity. This enables us to quantify and characterize cell-type-specific as well as shared AS events in the vertebrate retina. Together, this work establishes a cell-type-resolved isoform atlas linking age-associated splicing programs to retinal neurodegeneration.

References:

1. Bhadra, M., Howell, P., Dutta, S., Heintz, C., and Mair, W.B. (2019). Alternative splicing in aging and longevity. *Human Genetics* 139, 357–369.
2. Ciampi, L., Mantica, F., López-Blanch, L., Permanyer, J., Rodríguez-Marín, C., Zang, J., Damiano Cianferoni, Senda Jiménez-Delgado, Bonnal, S., Miravet-Verde, S., et al. (2022). Specialization of the photoreceptor transcriptome by Srm3-dependent microexons is required for outer segment maintenance and vision. *Proceedings of the National Academy of Sciences* 119.

Multi-omics profiling adds predictive value to clinical risk stratification in older emergency department patients: the ZNAge cohort

Bogaards, F.A.^{1,2,3,4}; Affeldt¹, A.M.; Steiner^{1,5}; J., Meyer, D.^{2,6}; Schumacher, B.^{2,6}; Deelen, J.^{2,4,5}; Polidori, M.C.^{1,2,3}; Müller, R-U^{1,2,7}; Antczak, P.^{1,2,3}

¹Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany.

²Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany.

³Center for Molecular Medicine Cologne (CMMC), Cologne, Germany.

⁴Molecular Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

⁵Max Planck Institute for Biology of Aging, Cologne, Germany.

⁶Institute for Genome Stability in Aging and Disease, Medical Faculty, University and University Hospital of Cologne, Cologne, Germany.

⁷Center for Rare Diseases Cologne, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany.

Timely risk stratification is critical for older adults visiting the emergency department (ED). Yet the Multi-dimensional Prognostic Index (MPI) and other conventional clinical tools capture only part of the biological processes underlying ageing, frailty, and mortality risk. Multi-omics data and integrative analyses may improve prognostic precision in this group. The ZNAge cohort comprises 492 older adults recruited at ED presentation, with clinical characterization including the MPI and multi-omics (methylome, transcriptome, proteome, metabolome) blood profiling. With 3 years follow-up and 210 mortality events, ZNAge is a unique resource to study molecular rehospitalization and mortality determinants. We show that the Personal-MetaboHealth score improves 3-year mortality risk estimation on top of the MPI ($\Delta\text{AUC} = +0.053$, $p = 0.003$). Currently, we are investigating additional omics-based biomarkers and have identified mortality associated factors shared across the four omics layers. These analyses position ZNAge as a resource to identify biomarkers that offer added value to clinical markers in estimating health and frailty in older adults at clinical risk.

References:

1. Van den Berg N, et al. (2026). Personal-MetaboHealth, an actionable health check in middle age, is improved by an effective lifestyle intervention in those at risk. MedRxiv.

T and B lymphocytes in Alzheimers' disease

Valquiria Bueno; Marli Leite de Moraes

UNIFESP Federal University of São Paulo – BRAZIL

Alzheimer's disease is characterized by loss of memory, impairment in daily-life activities and language, motor skills disorders, and loss of perception. The pathology includes the deposition of extracellular amyloid-beta ($A\beta$) peptide, intracellular tau protein tangles and neuronal loss. Cytokines, chemokines and inflammatory molecules are expressed by microglia, astrocytes and neurons. The blood-brain barrier's integrity is impaired causing efflux of inflammatory mediators and attraction of myeloid and lymphoid cells. Since immune cells can migrate from periphery to the brain's lesions contributing to neuronal death, and in circulation, lymphocytes (T and B) shift from naive toward late differentiated cells, we hypothesized that immune cells could be used as early biomarkers of cognitive impairment, provide knowledge for early interventions, and be targets for new therapies. Our aim was to investigate circulating immune cells in mild cognitive impairment (MCI) and with subjective cognitive impairment (SCI) individuals.

We included 76 individuals from Brazilian Alzheimer's Research Center – UNIFESP with mild cognitive impairment (MCI, n=58) or subjective cognitive impairment (SCI, n=18). 4mL of blood from MCI or SCI was collected to isolate peripheral blood mononuclear cells. Cells were stained for flow cytometry analysis using: CD3 (FITC), CD4 (PECy7), CD8 (APCCy7), CD45RA (PE), CD27 (APC), CD19 (PE), IgD (PerCPCy5.5), IgM (APCCy7), CD33 (PerCPCy5.5). Intracellular cytokines (anti-TNF- α and anti-IL-6) were identified by flow cytometry after 24 hours of cells culture in the presence or absence of phytohemagglutinin and using a cytofix/cytoperm kit. Plasma was used to identify the presence of autoantibodies against amyloid-beta ($A\beta$ 40) peptide via immunosensor. Student T-test was used and statistical significance was considered when $p < 0.05$. Groups: MCI (22 men and 35 women, 56–79 years) and SCI (6 men and 12 women, 56–78 years). Subsets of CD4+ and CD8+ T lymphocytes (naïve, central memory, effector memory, emra) and double negative T lymphocytes were not statistically different between MCI and SCI. However, B lymphocytes IgM memory were higher in SCI whereas B lymphocytes double negative were higher in MCI. In addition, B lymphocytes from the MCI group produced higher levels of TNF- α and this group also displayed autoantibodies against $A\beta$ 40. CD33 was not different between the groups. In conclusion, B cells are activated in MCI individuals and could be targeted for diagnosis and treatment.

Epigenetic Aging Indicators are Associated with Bone Mineral Density in a Population-Based Setting

Mengyuan Cai^{1,2}, Evert F S van Velsen¹, Lieke Kuiper¹, Jinluan Chen^{1,2}, Katerina Trajanoska^{1,2}, Joyce B J van Meurs¹, Fernando Rivadeneira¹, M Carola Zillikens¹

¹Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.

²Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.

Background. Epigenetic ageing markers capture biological ageing, but their links to bone mineral density (BMD) and trabecular bone score (TBS) remain inconsistent across measures.

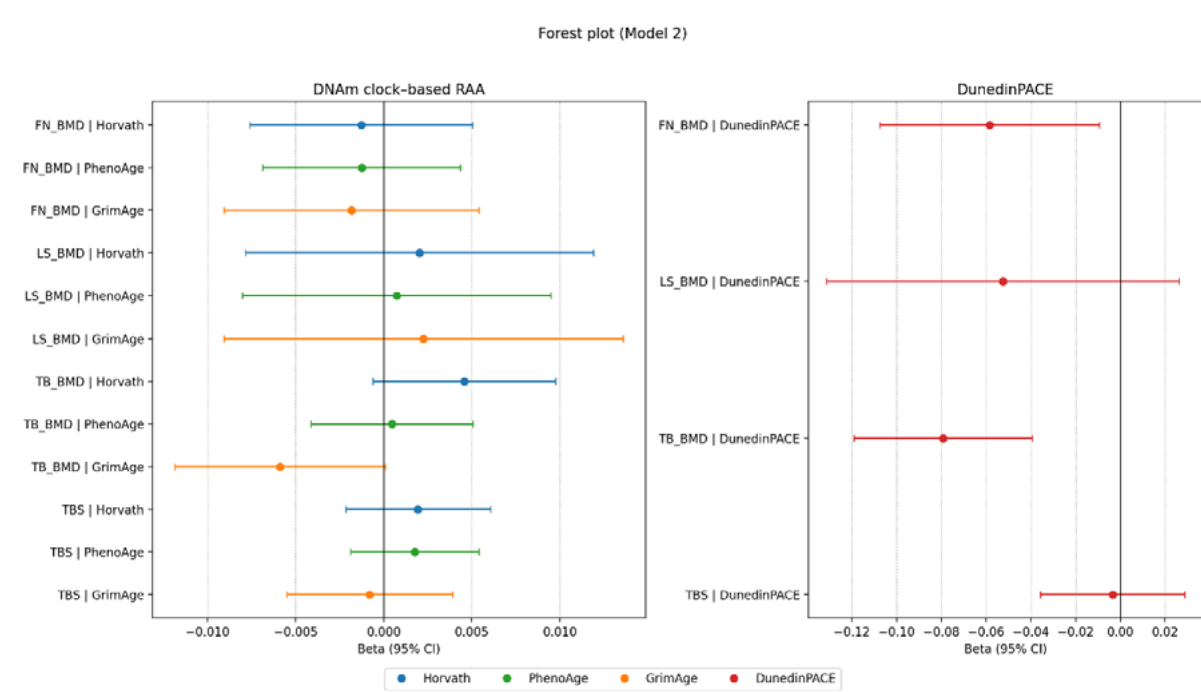
Objectives. To examine associations of epigenetic ageing indicators with site-specific BMD and TBS.

Methods. We examined four DNA methylation-based aging indicators: three epigenetic clocks (Horvath, GrimAge, and PhenoAge) that focus on relative age acceleration (RAA), and one that measures the pace of aging (DunedinPACE). RAA was defined as residuals from regressing DNAm age on chronological age (z-scored). Outcomes were femoral neck (FN), lumbar spine (LS), total body (TB) BMD, and TBS. Linear regression models were fitted with technical and blood cell composition covariates, with additional adjustment for lifestyle and clinical covariates. False discovery rate (FDR) was controlled across 16 primary tests (Benjamini-Hochberg).

Results. In the full sample (n=2,246), higher DunedinPACE was associated with lower TB BMD in the fully adjusted model ($\beta = -0.08$, 95% CI -0.12 to -0.04; FDR $q < 0.05$). Before multiple-testing correction, DunedinPACE also showed an inverse association with FN BMD ($\beta = -0.06$, 95% CI -0.11 to -0.01). In the basic model, DNAm clock-based RAAs were associated with TB BMD (Horvath: $\beta = 0.006$; GrimAge: $\beta = -0.006$), but these associations did not remain significant after FDR correction. No associations were observed for LS BMD or TBS.

Conclusion. A faster pace of ageing was associated with lower BMD, most consistently for TB BMD, whereas DNAm clock-based RAA measures showed no robust associations with BMD or TBS after multiple-testing correction.

Keywords: DNA methylation; DunedinPACE; bone mineral density; trabecular bone score; biological aging



C/EBP α and C/EBP β as key transcription factors in health and lifespan regulation

Müller C.¹, Muck, J.S.¹, Ustyantsev, K.¹, Berezikov, E.¹ & Calkhoven, C.F.¹

¹European Institute for the Biology of Ageing (ERIBA) University Medical Centre Groningen (UMCG), University of Groningen, Groningen, The Netherlands

The related transcription factors CCAAT/enhancer binding proteins alpha (C/EBP α) and beta (C/EBP β) play crucial roles in metabolic regulation and stress signaling across a wide range of tissues. In rats, mice, humans, and chickens, CEBPA and CEBPB mRNAs undergo alternative translation initiation, giving rise to three protein isoforms of C/EBP α and C/EBP β , respectively. Two isoforms function as full-length transcription factors, containing N-terminal transactivation domains and a C-terminal dimerization and DNA-binding domain. The third isoforms are N-terminally truncated variants translated from downstream AUG codons, which compete with full-length isoforms for DNA binding and thereby antagonizing their activity. Expression of these truncated isoforms depends on the translation of a short upstream open reading frame (uORF) in CEBPA and CEBPB mRNAs, followed by re-initiation at a downstream AUG codon, a process stimulated by mTORC1 signaling. In mice, the role of C/EBP β in regulating health and lifespan involves both protein isoform regulation as well as epigenetic DNA methylation. We now investigated the C/EBP α -mediated regulatory mechanisms in the evolutionarily distant, short-lived African turquoise killifish (*Nothobranchius furzeri*). Our findings demonstrate that the uORF-mediated regulation of C/EBP isoforms expression is conserved across species. Disruption of the uORF selectively abolishes expression of the truncated isoforms expression, resulting in unrestrained activity of the full-length isoforms. Notably, this genetic modification significantly extended both the median and maximal lifespan and improved healthspan in mice (C/EBP β) and killifish (C/EBP α). Comparative transcriptome analysis revealed upregulation of genes and pathways associated with healthspan and lifespan regulation. Together, these results identify a conserved mechanism of CEBP gene regulation with a key role in modulating longevity across species.

References:

1. Müller, C., Muck, J.S., Ustyantsev, K., Kortman, G., Hartung, J., Berezikov, E. and Calkhoven, C.F. (2025) Enhanced C/EBP α function extends healthspan and lifespan in the African turquoise killifish. *Aging Cell*, DOI: 10.1111/ace.70211
2. Niehrs, C. and Calkhoven, C.F. (2020) The emerging role of C/EBP β and epigenetic DNA methylation in ageing. *Trends Genet*, 6, 71–80 DOI: 10.1016/j.tig.2019.11.005
3. Müller, C., Zidek, L.M., Ackermann, T., de Jong, T. Liu, P., Kliche, V., Zaini, M.A., Kortman, G., Harkema, L., Verbeek, D.S., Tuckermann, J.P., von Maltzahn, J., de Bruin, A., Guryev, V., Wang, Z-Q and Calkhoven, C.F. (2018). Reduced expression of C/EBP β -LIP extends health- and lifespan in mice. *eLife* 2018;7:e34985 DOI: 10.7554/eLife.34985

A Combination Approach to Modulating NAD⁺ Precursor–Induced Lifespan Extension in *C. elegans*

Alexander D. Carlsson¹; He-Ling Wang^{1,*}; Evandro F. Fang^{1,2,*}

¹ Department of Clinical Molecular Biology, University of Oslo and Akershus University Hospital, Lørenskog, Norway

² The Norwegian Centre on Healthy Ageing (NO-Age) and The Norwegian National Anti-Alzheimer's Disease (NO-AD) Networks, Oslo, Norway

* Correspondence

Lead correspondence: E.F.F. e.f.fang@medisin.uio.no

NAD⁺ metabolism has become a central theme in aging research over the past decade^{1,2}. Yet recent evidence shows that animals can tolerate a large reduction in NAD⁺ without overt loss of fitness³, suggesting that its role in aging is not explained by bulk levels alone. Supplementation with the precursor nicotinamide riboside (NR) extends lifespan in some aging models⁴, albeit modestly. Because NAD⁺ is consumed by enzymes with opposing effects on aging, we hypothesize that raising NAD⁺ while simultaneously inhibiting a detrimental NAD⁺-consuming enzyme, PARP1, will extend lifespan more than either intervention alone. Our preliminary data in *C. elegans* show a trend toward lifespan extension following PARP1 inhibition. We next aim to directly compare the lifespan effects of NR, the PARP1 inhibitor olaparib, and their combination.

References:

- 1 Lautrup, S., Hou, Y., Fang, E.F., and Bohr, V.A. (2024). Roles of NAD⁺ in Health and Aging. *Cold Spring Harb Perspect Med* 14, a041193. <https://doi.org/10.1101/cshperspect.a041193>.
- 2 Zhang, J., Wang, H.-L., Lautrup, S., Nilsen, H.L., Trebak, J.T., Watne, L.O., Selbæk, G., Wu, L.E., Omland, T., Pirinen, E., et al. (2025). Emerging strategies, applications and challenges of targeting NAD⁺ in the clinic. *Nat Aging* 5, 1704–1731. <https://doi.org/10.1038/s43587-025-00947-6>.
- 3 Chubanava, S., Karavaeva, I., Ehrlich, A.M., Justicia, R.M., Basse, A.L., Kulik, I., Dalbram, E., Ahwazi, D., Heaselgrave, S.R., Trošt, K., et al. (2025). NAD depletion in skeletal muscle does not compromise muscle function or accelerate aging. *Cell Metabolism* 37, 1460–1481.e17. <https://doi.org/10.1016/j.cmet.2025.04.002>.
- 4 Zhang, H., Ryu, D., Wu, Y., Gariani, K., Wang, X., Luan, P., D'Amico, D., Ropelle, E.R., Lutolf, M.P., Aebbersold, R., et al. (2016). NAD⁺ repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science* 352, 1436–1443. <https://doi.org/10.1126/science.aaf2693>.
- 5 Fang, E.F., Scheibye-Knudsen, M., Brace, L.E., Kassahun, H., SenGupta, T., Nilsen, H., Mitchell, J.R., Croteau, D.L., and Bohr, V.A. (2014). Defective Mitophagy in XPA via PARP-1 Hyperactivation and NAD⁺/SIRT1 Reduction. *Cell* 157, 882–896. <https://doi.org/10.1016/j.cell.2014.03.026>.

Ribosome stalling as an upstream driver of multiple brain aging hallmarks

Di Fraia, D.^{1,2}; Marino, A.^{1,3}; Jae H.L.⁴; Gravili I.^{1,5}; Frydman, J.⁶; Ori A.^{1,7}; **Cellerino, A.**^{1,5}

¹ *Leibniz Institute on Aging – Fritz Lipmann Institute, Jena Germany*

² *Institute for Genetics, University of Cologne, Cologne, Germany*

³ *Proteomics Research Infrastructure, University of Copenhagen, Copenhagen, Denmark,*

⁴ *Biochemistry and Cell Biology, Stony Brook University, New York NY, USA,*

⁵ *Scuola Normale Superiore, Pisa, Italy*

⁶ *Dept. of Biology, Stanford University Stanford CA, USA*

⁷ *Genetech, South San Francisco, CA, USA*

A notable phenomenon in brain aging is a loss of concordance between mRNA and protein levels, whereby age-linked changes in mRNA do not necessarily lead to proportional changes in protein levels. Using the killifish as a model of compressed lifespan, we showed that protein-transcript uncoupling correlates with aging-associated increase in ribosome stalling on codons coding for basic aminoacids. Stalling causes increased aggregation on one hand and reduced biosynthesis of DNA- and RNA-binding proteins on the other hand affecting critical proteins involved in DNA repair, transcription, splicing and translation suggesting a causal role for ribosome stalling in multiple aging hallmarks.

To experimentally test this hypothesis, we experimentally induced ribosome stalling in brain organotypic cultures using anisomycin and observed a significant increase in transcriptomic age as measured by a killifish transcriptomic clock we developed. Our results indicate that induction of ribosome stalling is sufficient to induce a global aging-like phenotype.

Skin Volatilomics Reveals Distinct Metabolic Signatures in Parkinson's Disease and Multiple System Atrophy: A Non-Invasive Approach for Differential Diagnosis

Conte, M.¹; Conte, G.²; Casarosa, L.²; Trofarello, L.¹; Devigili, G.³; Mazzetti, S.³; Leta, V.³; Eleopra, R.³; Tagliavini, F.³; Franceschi, C.⁴; Briganti, S.⁵; Camera, E.⁵; & Salvioli, S.^{1,6}

¹Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy;

²Department of Agriculture, Food and Environment, University of Pisa, Pisa, Italy;

³Parkinson and Movement Disorders Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy;

⁴Lobachevsky State University of Nizhny Novgorod, Nizhny Novgorod, Russia;

⁵Laboratory of Cutaneous Physiopathology, San Gallicano Dermatological Institute IRCCS, Rome, Italy;

⁶IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.

Volatile organic compounds (VOCs) are emerging biomarkers of neurodegeneration and aging, reflecting metabolic, oxidative, and microbiota-related alterations [1–2]. While VOCs have been widely investigated in Parkinson's disease (PD), no studies are available for Multiple System Atrophy (MSA). We analyzed skin VOCs collected through non-invasive swabs from PD and MSA patients and healthy subjects (HS) using SPME–GC/MS. Canonical discriminant analysis clearly separated MSA from PD and HS. MSA showed increased aldehydes, aromatic hydrocarbons, and cyclic oxidation products associated with severe oxidative stress, lipid peroxidation, and neuroinflammation, suggesting profound metabolic instability. In contrast, PD displayed branched hydrocarbons and fatty alcohols linked to chronic sebaceous dysregulation, enhanced lipid turnover, and altered microbiota–sebum interactions. These results indicate distinct metabolic signatures between PD and MSA, with MSA characterized by a stronger oxidative–inflammatory burden. Overall, skin VOCs may represent a promising non-invasive tool for early differential diagnosis and identification of disease-specific therapeutic targets.

References

1. Conte M, Conte G, Martucci M, Monti D, Casarosa L, Serra A, Mele M, Franceschi C, Salvioli S (2020). The smell of longevity: a combination of Volatile Organic Compounds (VOCs) can discriminate centenarians and their offspring from age-matched subjects and young controls. *Geroscience*. 42, 201–216.
2. Conte M, Conte G, Salvioli S (2021). VOCs profile can discriminate biological age. *Aging (Albany NY)*. 13, 9156–9157.

An iPSC-Based Platform to Model Astrocyte Senescence in the Human Midbrain

Cora, Virginia¹; Lu Yang, Nika¹; Bolognin, Silvia¹

¹ *University of Maastricht, MERLN Institute, Maastricht, The Netherlands*

Emerging evidence suggests that astrocyte senescence may contribute to age-related neuronal dysfunction, but progress in the field is limited by the lack of human-relevant models. To address this challenge, we induced senescence-like features in astrocyte monocultures and astrocyte-containing midbrain organoids derived from healthy and Parkinson's disease donors. This was achieved through repeated passaging of stem-cell-derived midbrain precursors, an approach that avoids artificial stressors and genetic manipulation. Astrocytes derived from high-passage precursors exhibited increased SA- β -Gal activity and altered mitochondrial morphology. Both high-passage-derived astrocytes and organoids showed reduced LMNB1/Lamin-B1 levels and increased accumulation of DNA damage response markers. Lipidomic analysis of high-passage-derived organoids revealed broad reductions across multiple lipid classes. These findings establish repeated passaging as a simple strategy to model senescence-like features in human midbrain systems and provide a platform to investigate age-related neurodegeneration.

Towards non-invasive molecular risk stratification in ADPKD using urinary extracellular vesicle-derived microRNAs

Yaren Simay Coskun^{1,2,3}; Roman-Ulrich Müller^{1,3}; Reza Esmailie²

¹*Institute of Biology, Faculty of Mathematics and Natural Sciences, Heinrich Heine University Düsseldorf, Düsseldorf, Germany*

²*Detechgene GmbH, Cologne, Germany*

³*Department of Nephrology, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany*

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by highly heterogeneous disease progression and remains a major cause of chronic kidney disease and renal failure. Current prognostic models, including imaging-based risk stratification, incompletely capture interindividual disease trajectories, highlighting the need for non-invasive molecular biomarkers. Urinary extracellular vesicles (uEVs) represent a promising biomarker source, as they reflect kidney-derived molecular alterations and contain stable microRNA (miRNA) cargo implicated in renal injury and fibrosis.

Different uEV isolation strategies were comparatively evaluated to establish a robust workflow for downstream molecular profiling. Following vesicle isolation, miRNA extraction and quantitative PCR (qPCR) assays were optimized for the detection of candidate miRNAs associated with renal pathophysiology, including miR-30e-5p, miR-17-5p, and miR-192-5p. In parallel, pre-analytical variables and assay reproducibility were assessed to support standardized translational biomarker analyses. Based on this framework, large-scale sequencing of approximately 300 patient samples is planned to identify multimodal and ratio-based miRNA signatures associated with ADPKD progression.

Preliminary analyses demonstrated reproducible isolation of uEVs and successful downstream detection of all investigated candidate miRNAs by qPCR. Comparative evaluation of isolation approaches revealed differences in assay compatibility and miRNA yield, emphasizing the importance of standardized pre-analytical workflows for robust molecular profiling.

These findings support the feasibility of uEV-derived miRNAs as non-invasive molecular biomarkers in ADPKD. Ongoing large-scale sequencing and multimodal biomarker integration may improve molecular risk stratification and facilitate personalized monitoring of disease progression.

Tomatidine is a senotherapeutic compound that improves cognitive function and reduces cellular senescence in aged mice

Costa, Daniela G.^{1,2,3,4*}; Gee, Lucy M.^{1,2*}; Lee, Gung^{1,2}; Sales Gomez, Lilian^{1,2}; Franco, Ana Catarina^{1,2}; Vizioli, Maria Grazia^{1,2}; Valdivieso, Karla^{1,2}; Zhang, Lei J.^{5,6}; Pirius^{1,2}; Martini, Helene^{1,2}; Porritt, Rebecca A.⁷; Saul, Dominik⁸; Cavadas, Claudia^{3,4}; Ebert, Scott⁹; LeBrasseur, Nathan K.^{1,2}; Khosla, Sundeep^{1,2,9}; Passos, João F.^{1,2}; Adams, Christopher M.⁹; Robbins, Paul D.⁶; Jurk, Diana^{1,2}

¹Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN 55905, USA

²Robert and Arlene Kogod Center on Aging, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

³Center for Neuroscience and Cell Biology (CNC-UC), University of Coimbra, Portugal; Center for Innovation in Biomedicine and Biotechnology (CIBB), University of Coimbra, Coimbra, Portugal.

⁴Faculty of Pharmacy, University of Coimbra, Portugal.

⁵Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, University of Georgia, Athens, GA, USA

⁶Masonic Institute on the Biology of Aging and Metabolism, Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, MN, USA.

⁷Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA

⁸Robert Bosch Center for Tumor Diseases, Stuttgart

⁹Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, MN, USA.

*Contributed equally

Cellular senescence is a key driver of aging and age-related dysfunction across tissues, including the brain. Through a high-content phenotypic screen of natural compounds in senescent cells, we identified tomatidine, a tomato-derived aglycone of tomatine, as a previously unrecognized senotherapeutic agent. In vitro, tomatidine selectively suppressed senescence-associated secretory phenotype (SASP) expression in senescent human brain microvascular endothelial cells and fibroblasts without altering p16Ink4a or p21Cip1 levels, consistent with a senomorphic mechanism. In aged mice, tomatidine treatment reduced frailty and improved motor coordination and cognitive performance. These functional improvements were accompanied by decreased markers of senescence (p16Ink4a, p21Cip1, and telomere-associated DNA damage foci) in multiple tissues, including liver, skin, and hippocampal neurons. In the brain, tomatidine reduced endothelial cell senescence, increased tight junction protein expression, and attenuated neuroinflammation and microglial activation, suggesting improved blood-brain barrier integrity. Together, these findings identify tomatidine as a promising senescence-targeting compound with systemic and neuroprotective effects in aging, supporting translational development for age-related disorders.

Tentative Title: Modeling Biological Age and Physiological Resilience to Predict Surgical Risk in Aging Populations

Dalla Santa, C.^{1,2}; Kleve, G.^{2,3}; Normand, V.A.¹; Polster, A.^{4,5}; Ougland, R.^{3,4}; & Nilsen, H. L.⁴

¹ *Ambr Institute, Oslo, Norway*

² *Department of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway*

³ *Department of Surgery, Bærum Hospital Vestre Viken Hospital Trust, Gjetsum, Norway*

⁴ *Department of Microbiology, Oslo University Hospital, Oslo, Norway*

⁵ *Department of Life Sciences, Chalmers University of Technology, Gothenburg, Norway*

Abstract (1000 characters without spaces)

Older adults exhibit substantial variability in their capacity to tolerate physiological stressors such as major surgery. While chronological age is commonly used to assess risk, it fails to capture the biological heterogeneity underlying frailty, functional decline, and resilience. We developed a machine learning framework to improve prediction of postoperative complications, such as prolonged hospital stays in older patients undergoing cancer surgery.

Our approach integrates clinical measurements, blood biomarkers, lifestyle factors, and proteomic data. Using gradient-boosted models, we estimate biological age (BA) and evaluate its association with postoperative outcomes and recovery trajectories. Clinical validation will be performed using data from an ongoing trial evaluating home-based prehabilitation. Model interpretability methods are used to identify key systems and biomarkers associated with resilience and adverse outcomes. In addition, organ-specific BA estimates derived from proteomic aging clocks will be explored in relation to postoperative complications. By linking BA signatures to clinical outcomes, this work aims provide a robust framework for personalized risk stratification and targeted interventions.

Short-term animal product restriction reshapes gene expression and genetic regulation of cholesterol metabolism and telomere homeostasis in humans

Alexandros Simistiras^{1*}; Georgia Katsoula^{2,3*}; Christina Emmanouil¹; Ozvan Bocher^{2,4}; Maria Koufaki^{1,5}; Stavros Glentis⁶; Theodosios Kyriakou⁷; Konstantinos Rouskas⁸; Eleftheria Zeggini^{2,3}; Pantelis Hatzis⁹; **Antigone S. Dimas^{1,2#}**

¹ Institute for Bioinnovation, Biomedical Sciences Research Center 'Alexander Fleming', Fleming 34, 16672, Vari, Greece

² Institute of Translational Genomics, Helmholtz Zentrum München – German Research Center for Environmental Health, 85764 Neuherberg, Germany

³ Technical University of Munich (TUM) and Klinikum Rechts der Isar, TUM School of Medicine and Health, Munich, Germany

⁴ Univ Brest, Inserm, EFS, UMR 1078, GGB, F-29200 Brest, France

⁵ Cancer Inflammation and Immunity, Cancer Research UK Manchester Institute, The University of Manchester, Manchester, UK

⁶ Pediatric Hematology/Oncology Unit (POHemU), First Department of Pediatrics, University of Athens, Aghia Sophia Children's Hospital, Athens

⁷ Centre for Medicines Discovery, Nuffield Department of Medicine, University of Oxford, Oxford, UK

⁸ Institute of Applied Biosciences, Centre for Research & Technology Hellas, Thessaloniki, Greece

⁹ Institute for Basic Research, Biomedical Sciences Research Center 'Alexander Fleming', Fleming 34, 16672, Vari, Greece

* equal contribution

corresponding author dimas@fleming.gr

Dietary intake affects all physiological processes, including risk for age-related diseases, yet the molecular mechanisms underlying these effects remain incompletely understood in humans. To address this gap, we leveraged a unique natural model of dietary restriction by profiling 200 Greek individuals who alternate between omnivory and dietary restriction of animal products for religious reasons, in a highly structured manner, alongside 211 continuously omnivorous control individuals (FastBio study). Extensive molecular profiling was performed at two time points: during a period of omnivory in both groups, and following ~4 weeks of animal product restriction for the dietary restriction group or two periods of omnivory for controls. The restriction period is characterized by near-complete dietary depletion of animal-derived protein and fat, as well as reduced intake of other nutrients, including calcium. We have previously demonstrated that ~4 weeks of animal product restriction induces widespread immunometabolic remodeling, with most changes being in a direction suggesting positive effects on health, and results in metabolic profiles associated with lower risk of all-cause mortality. We have revealed diet-dependent genetic effects on protein abundance, involving proteins implicated in cholesterol biosynthesis, energy regulation, and protein repair, and demonstrated rapid and extensive remodeling of the gut microbiome.

In the present study we performed RNA sequencing on whole blood (quantifying 16,484 genes) to characterize the effects of animal product restriction on gene expression. We identified 1,221 and 548 differentially expressed genes (DEGs) between time points in the dietary restriction and the control groups respectively, with nearly four times as many unique discoveries in the restriction group compared to controls (909 vs 236 DEGs). Top diet-responsive upregulated DEGs were cholesterol efflux genes ABCA1 and ABCG1, whose increased expression is associated with a reduction in atherosclerosis risk, as well as lipid homeostasis transcriptional regulators SREBF1, SREBF2, and PPARG. Diet-responsive DEGs were also enriched for biological processes, including telomere maintenance, VEGFA-VEGFR2 signaling, and CCT/TRiC protein folding. Using matched genotype and gene expression data from the same individuals (4,542,821 SNPs and 14,945 genes following QC), we mapped steady-state cis expression quantitative trait loci (cis-eQTLs) for each dietary group and time point (context), detecting an average of 6,114 cis-eQTLs per context, with ~74% replication in eQTLGen. eQTLs detected during dietary restriction were enriched in transcription factor binding sites, with the largest diet-induced enrichment shift found for CBX5 ($\Delta \log OR = 0.43$, FDR = 0.031), an epigenetic regulator of silenced heterochromatin that is essential for telomere stability maintenance. Although ~98% of eQTLs were shared between contexts, using a Bayesian meta-analysis framework, we identified 74 diet-responsive eQTLs (corresponding to 74 eGenes) displaying differential effects on gene regulation. Of these, 11 eGenes have links to telomere biology, and include TERF2, TNKS2, PARN, NAF1, and NRIP. Using publicly available genome-wide association studies (GWAS) from the GWAS Catalog we found strong evidence for colocalization of the TERF2 diet-responsive eQTL with abundance of SPARC1, a calcium binding protein with a likely role in bone formation, and of the NRIP1 diet-responsive eQTL with weight, body fat mass, BMI and systolic blood pressure. Additionally, we found that a diet-responsive eQTL identified for DVL1, colocalizes

strongly with telomere length. This gene is a WNT signaling gene and has been suggested to associate with leukocyte telomere length through GWAS. Mendelian randomization analysis suggested that increased DVL1 expression contributes to greater telomere length ($\beta=0.052$, $se=0.009$, $p=3.21e-8$), supporting a role for this gene in telomere homeostasis. Finally, using a transcriptomic age score as a proxy for biological age, we found that individuals following animal product restriction presented with an estimated 4.42-year lower biological age compared to control individuals (linear mixed model, $df=402$, $se=1.057$, $p=0.000$). Taken together, these findings suggest that animal product restriction induces widespread transcriptional reprogramming in whole blood and influences biological pathways linked to ageing, in part through effects on cholesterol metabolism and telomere maintenance.

Challenges in Detecting Biotoxins and Biomolecules by using Surface-enhanced Raman Scattering Spectroscopy and Nanopatterned Substrates

N. E. Dina^{1*}, A. Colniță¹, D. Marconi¹, I. A. Brezeștean¹, A. S. Tatar¹

¹ Department of Isotopic and Molecular Technologies, National Institute for Research and Development of Isotopic and Molecular Technologies, Cluj-Napoca, Roman

The incorporation of nanopatterned substrates with plasmonic properties into surface-enhanced Raman spectroscopic (SERS) sensing platforms is a crucial part of the development of new miniaturized detection devices with on-site applications. We employed nanoimprint lithography (NIL) and magnetron sputtering to fabricate plasmonic nanostructures able to detect environmental contaminants and toxins. Thus, networks of tunable nanopillars were imprinted in thermoplastic polymers and metallized with Ag/Au thin films using magnetron sputtering technique. The structural and topographical properties were assessed by SEM and AFM techniques (Figure 1). The nanostructured sensing platforms were very suitable for SERS detection of crystal violet, for example, reaching a limit of detection of 10 pM [1] and of 1 μ M in case of nodularin [2]. After assessing these figures of merit for the fabricated SERS-active substrates, relevant biotoxins from natural acquifers or biomolecules present as biomarkers in chronic non-communicative diseases [3] and neurodegeneration diseases [4] were considered as analytes for testing their performance in practice.

Keywords: nanopatterning, biomedical applications, biotoxins, SERS, nanoimprint lithography, sensing.

Acknowledgements: This work was supported by a grant of the Ministry of Research, Innovation and Digitization, CCCDI – UEFISCDI, project number PN-IV-P7-7.1-PED-2024-0052, within PNCDI IV and the “Nucleu” Program within the National Research Development and Innovation Plan 2022–2027, Romania, supported by MEC, project no. 27N/03.01.2023, component project PN 23 24 01 02.

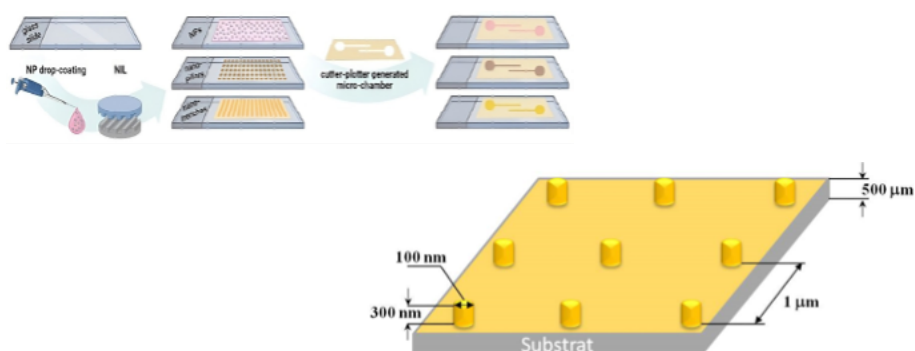


Figure 1: Flexible substrates: a network of periodical pillars (width: 100 nm, pitch: 1 μ m, height: 300 nm) fabricated by thermal nanoimprint lithography (NIL) and their envisioned integration in a miniaturized device.

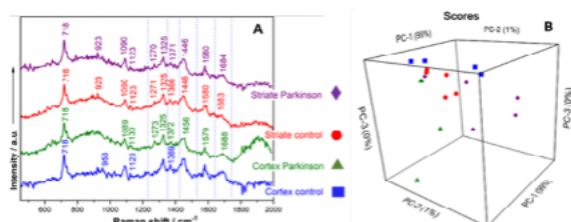


Figure 2: SERS spectra of neural tissue and their integrated chemometric analysis showing clear discrimination between in vivo healthy models and neurodegenerated models [4].

References:

1. A. Colniță, D. Marconi, N. E. Dina, I.A. Brezeștean, et al. Spectrochim. Acta A, 276, 121232, 2022.
2. I. A. Brezeștean, A.M.R. Gherman, ..., N.E. Dina, Int J Mol Sci, 23, 15741, 2022.
3. N.E. Dina et al. Biosens. Bioelectron, 219, 114843, 2023.
4. A. Colniță, D. Marconi, Vlad Al. Toma, I. Brezeștean, .., N.E. Dina, Microchemical. J., 206, 111589, 2024.

Aggregate Lifespan Encyclopaedia (ALE) – A new way to record animal lifespans

Eraso, A.

Senckenberg, Translational Biodiversity Genomics, Frankfurt

Lifespan differs by orders of magnitude across mammals. Differences in lifespan are often attributed to the positive correlation between mass and lifespan. Though humans live five times longer than expected for their mass, there are mammals that live proportionately longer still. To better understand the genetic factors that underpin human longevity, we can leverage a wealth of newly available genomics data. Unfortunately, longevity records are currently limited to maximum recorded lifespans. These data can bias analysis as maximum lifespan records correlate with population size.

Here we present the Aggregate Lifespan Encyclopaedia (ALE), a resource expanding current lifespan records in three key ways: 1) Updated records, 2) New metrics, and 3) Transparency. ALE provides maximum lifespan data for 1,383 mammalian species, 300 more than AnAge. New individual-level lifespan data from zoos and recent publications enabled us to update existing maximum lifespan records. We also leveraged these individual-level lifespan data to calculate new metrics: Q90, E90, and bootstrapped maximum. Q90 and E90 represent the 90th percentile and average of the top 10% lifespans, respectively. Bootstrapped maximum lifespan was calculated averaging the maximum lifespan of 1000 subsets of the individual data. These metrics substantially reduce correlations between lifespan and sample size, thus enabling comparative genomics analysis to identify molecular underpinnings of natural lifespan differences. For each metric we also curated a final value, and provided informative curation rationales. Altogether we hope our updated records, new metrics, and transparency will make ALE the new gold standard for lifespan estimation and unbiased genomics.

Aging-compatible metabolic modulators that maintain efficacy by circumventing mitochondrial aging.

Eberechukwu Okoli¹, Ulas Isildak¹, Handan Melike Dönertaş^{1,2} and Maria **Ermolaeva**^{1,2,*}

¹Leibniz Institute on Aging – Fritz Lipmann Institute (FLI), Beutenbergstrasse 11, 07745 Jena, Germany.

²Cluster of Excellence Balance of the Microverse, Friedrich Schiller University Jena, Jena, Germany.

*-corresponding author: maria.ermolaeva@leibniz-fli.de

Preclinical and clinical studies consistently demonstrate that lifestyle interventions such as dietary restriction (DR), DR mimetics, and exercise remain the most effective strategies to extend lifespan and healthspan. However, their efficacy is substantially reduced in older populations, primarily due to age-associated mitochondrial dysfunction, as shown by us and others. Here, we used metformin as a prototype DR mimetic to perform a genetic screen in *C. elegans*, aiming to identify molecular pathways mediating DR-like metabolic remodeling downstream of mitochondria. This approach revealed key regulators that link mitochondrial nutrient stress sensing to downstream metabolic adaptation. We then identified pharmacological agents targeting these pathways and found that a combination of two compounds, NORM1 and NORM2, directly activates a DR-like program independently of mitochondria, maintaining efficacy even in late life. Together, these compounds represent a first-in-class approach for DR-like interventions optimized for aged organisms and are currently being validated in the short-lived vertebrate model *N. furzeri*, with early results forthcoming.

Mitochondrial membrane lipid cardiolipin controls fiber-type adaptations in ageing muscle via ERR γ

Fabian Finger^{1,2,*}, Mikkel Frost¹, Shinya Watanabe³, Tao Ma^{1,2}, Katsuhiko Funai³, Steen Larsen^{4,5,6}, Zachary Gerhart-Hines^{1,2}

¹Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, DK

²ADIPOSIGN, Center for Adipocyte Signaling, Department of Biochemistry and Molecular Biology, University of Southern Denmark, Odense, DK

³Diabetes and Metabolism Research Center, University of Utah, Salt Lake City, Utah, USA

⁴Department of Biomedical Sciences, University of Copenhagen, Copenhagen, DK

⁵Clinical Research Centre, Medical University of Bialystok, Bialystok, PL

⁶Institute of Sports Medicine Copenhagen, Department of Orthopedic Surgery M, Copenhagen University Hospital – Bispebjerg and Frederiksberg, DK

*Correspondence to: Fabian Finger; email: fabian.finger@sund.ku.dk

Ageing paradoxically leads to both a decline in skeletal muscle mitochondrial function and a shift in muscle composition that favors fibers rich in mitochondria. Yet the biological rationale and mechanism underlying this phenomenon remain largely unknown. Here we show that synthesis of the mitochondrial membrane lipid, cardiolipin, causally links mitochondrial dysfunction to fiber-type adaptations. By mimicking the ageing decline of skeletal muscle cardiolipin levels in young mice, we could reproduce numerous ageing hallmarks, including the shift from glycolytic to oxidative fibers. This shift is mediated by mitochondria-to-nucleus signalling through the nuclear receptor, ERR γ , which equips muscle fibers with ROS-sensitive glucose uptake and enhanced glycolytic rerouting to sustain antioxidant defenses. These findings reveal how changes in a mitochondrial membrane lipid can cell-autonomously orchestrate protective fiber-type adaptations in ageing and myopathies.

A model for the role of transposable elements in evolution and ageing

Alessandro Fontana (National Gerontology Centre, Cyprus)

The Devo-Evolvable Soma Theory of Ageing (DESTA) frames ageing as the cumulative outcome of genetically orchestrated, late-acting epigenetic modifications serving as somatic „experiments“, through which evolution explores phenotypic variation. Protein-coding sequences constitute only a small and highly conserved fraction of the genome, suggesting a role for noncoding DNA in evolutionary processes. A substantial portion of noncoding DNA is represented by transposable elements (TEs), increasingly recognised as important contributors to gene regulation. We propose that TEs facilitate the expansion and diversification of gene regulatory networks by providing transcription factor binding sites. To minimise disruption, in early development TEs are tightly repressed by epigenetic marks, which may be progressively released by genetically driven, age-associated epigenetic changes in later life, thereby contributing to transcriptional pseudo-randomness and ageing-associated phenotypes. This model places TEs within the context of DESTA and offers a conceptual basis for interpreting their role in evolution and ageing.

Relevant publications

1. Fontana, A. (2026) Evolvable Soma Theory of Ageing: observations from the natural world. *Geroscience*.
2. Fontana, A. and Kyriazis, M. (2025) Evo-devo computational comparison of Evolvable Soma Theory of Ageing and Standard Evolutionary Ageing Theories. *GECCO '25 Companion*:979–982.
3. Fontana, A. and Kyriazis, M. (2025) Evolvable Soma Theory of Ageing: insights from computer simulations. *Biogerontology* 26(2):87.
4. Fontana, A. and Wrobel, B. (2025) Evolvability in artificial development of large, complex structures and the principle of terminal addition. *Artificial Life* 31(3):276–288.
5. Fontana, A. and Kyriazis, M. (2024) How evolution makes us age: introducing the Evolvable Soma Theory of Ageing. *Biosystems* 243:105271.
6. Fontana, A. (2023) Unravelling the nexus: Towards a unified model of development, ageing, and cancer. *Biosystems* 231:104966.
7. Fontana, A. and Wrobel, B. (2014) Pseudorandomness of gene expression: a new evo-devo theory of ageing. *Current Aging Science* 7(1):48–53.

Surviving Deprivations: How responses to Essential Nutrient deprivations uncover the mechanisms of Lifespan, Reproduction and Somatic Maintenance

Forte, M.¹; Mirth, C.¹; Piper, M.¹

¹*Faculty of Biological Sciences, Monash University, Melbourne, Australia*

Ageing is a conserved feature of metazoan life, yet its rate is sensitive to environmental conditions, most powerfully, to food. Organisms possess evolutionary conserved, highly specific nutrient sensors that distribute resources to competing biological needs. These nutrient-sensing programs are compelling candidates for cellular mechanisms that modulate ageing, because they can affect somatic maintenance and reproduction in a coordinated way. However, the way individual dietary components engage such programs is not fully understood. We have been subjecting adult fruit flies (*Drosophila melanogaster*) to combinations of essential nutrient deprivations in an attempt to dissect these programs. This has revealed surprising effects of deprivation combinations that produce non-additive, often antagonistic effects on life histories that cannot be predicted a priori from textbook knowledge of their physiological roles. For example, we have found that deprivation of the essential amino acid phenylalanine can rescue the lethal cost of methionine deprivation on lifespan, an effect that is temporally gated and partially dissociable from a classic lifespan-reproduction reallocation model. Such observations are indicative of amino acid-specific sensing programs that can gate whole-organism survival outcomes. In further work, we are investigating several nutrient combinations to investigate the possibility that precise dietary manipulations can reveal more about the minimal set of processes required to sustain life.

Linking Sunlight and ROS –Induced DNA Damage Repair with Longevity: A key role for photolyases.

Foulkes, N.S.¹; Li, H.¹; Vallone, D.¹ & Bertolucci, C.²

¹*IBCS-BIP, Karlsruhe Institute of Technology, Eggenstein-Leopoldshafen, Germany.*

²*University of Ferrara, Ferrara, Italy.*

Using zebrafish, medaka, and blind cavefish, we have explored the impact of sunlight on cellular physiology. Direct exposure of fish cells to light triggers elevated ROS levels and MAPK signalling that in turn activates transcription factors binding to the D-box enhancer. Thereby sunlight-induced changes in the transcriptome have profound effects on circadian clock entrainment, redox homeostasis and the maintenance of genome integrity. We have focused on a class of flavoproteins which play a central role in photic cellular responses, namely the photolyases. As well as mediating the repair of UV-induced DNA damage via light-dependent photoreactivation, the conservation of photolyases in blind cavefish has revealed that these flavoproteins also contribute to the light-independent repair of ROS-induced DNA damage. Loss of photolyase function is associated with elevated levels of DNA damage as well as significantly reduced longevity. Thereby our findings reveal an intricate interconnection between sunlight exposure, redox regulation, genome integrity and ultimately the aging process.

A Spatial Multi-Omic Atlas of Cellular Senescence in Mouse and Human Skin

Ana Catarina Franco^{1,2}; Yaeun Han^{1,2}; Anthony Agudelo^{4,5}; Dominik Saul^{1,3}; Anthony Lagnado^{1,2}; Yukang Li^{1,2}; Ines Sturmlechner^{1,6}; Saranya Wyles⁷; James Kirkland⁸; Luigi Ferrucci⁹; Nathan LeBrasseur^{1,10}; Nicola Neretti^{4,5}; João F Passos^{1,2}

¹Robert and Arlene Kogod Center on Aging Mayo Clinic, Rochester, MN, USA;

²Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA;

³Department of Trauma and Reconstructive Surgery, Eberhard Karls University Tübingen, Germany;

⁴Department of Molecular Biology, Cell Biology, and Biochemistry, Brown University, Providence, RI, USA.

⁵Center on the Biology of Aging, Brown University, Providence, RI, USA.

⁶Department of Immunology, Mayo Clinic, Rochester, MN, USA

⁷Department of Dermatology, Mayo Clinic Rochester, MN, USA;

⁸Center for Advanced Gerotherapeutics, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

⁹Translational Gerontology Branch, Intramural Research Program, National Institute on Aging, Baltimore, Maryland, USA.

¹⁰Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, Minnesota 55905, United States

The skin, the body's outermost barrier, is continuously exposed to environmental stressors, making it particularly susceptible to aging and senescence accumulation—a key driver of tissue decline. Here, we present the first spatially-resolved atlas of senescence in mouse and human skin, revealing its cell type specificity, and functional impact during aging. We first analyzed skin from young and aged mice. Preliminary spatial proteomics revealed age-related increase in senescence markers, and cell type-specific expression of cyclin-dependent kinase inhibitors. Using the p16-Ink-ATTAC mouse model, we observed a significant reduction of p16 protein levels in the dermis, where it is predominantly expressed, accompanied by increased epidermal thickness, indicating that clearance of p16-positive cells rescues epidermal thinning, a key hallmark of skin aging.

We then profiled sun-protected human skin from young and aged individuals using spatial multi-omics, including iterative indirect immunofluorescence imaging (4i), Akoya Phenocycler (CODEX), and Xenium spatial transcriptomics, with custom protein and RNA panels targeting senescence-associated features.

To define senescence, we implemented a combinatorial framework in which cells were classified as senescent if they were positive for three core hallmarks: cell cycle arrest markers, negative for proliferation markers, and positive for senescence-associated secretory phenotype (SASP). This approach revealed a significant age-related increase in senescent cells across the different platforms, with keratinocytes and fibroblasts showing the highest proportions.

Spatial analyses demonstrated that senescent cells form clusters both at protein and transcriptomic levels. These clusters were enriched for Notch and TGF- β signaling, consistent with secondary senescence. Aged skin showed increased immune infiltration, with immune cells—including cytotoxic CD8 T cells and FOXP3-positive CD4 T cells—also scoring positively for senescence based on the criteria. Senescent clusters were located proximally to immune cells, suggesting immune surveillance and recruitment.

Together, these findings provide a spatially resolved framework for understanding senescence in skin aging across species.

Effect of aging on neutrophil function in humans

Galang, J.N.¹; Schlüter, T.¹; Sumpster, N.¹; Asmann, N.¹; Merlo Pich, L.¹; Sarlea, A.¹; van de Veerdonk, F.¹; Ziogas, A.^{1,2}; & Netea, M.G.^{1,3}

¹*Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, the Netherlands*

²*Laboratory of Biological Chemistry, Department of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece*

³*Department for Immunology and Metabolism, Life and Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany*

Neutrophils are the most abundant immune cell type in circulation, acting as an early responder to infections. However, because of the difficulty to assess their function in vitro, the impact of aging on their function is poorly known. We performed a study to determine how aging affects neutrophil function. Participants belonged to three age groups: young adults (20–30 y.o.), older adults (55–65 y.o.), and octo/nonagenarians (> 88 y.o.). Neutrophils of older adults and octo/nonagenarians had a higher percentage of immature CD10–neutrophils, and increased expression of CD66b compared to young adults. Neutrophil function such as phagocytosis and NETosis were not affected by aging. Interestingly, ROS production at baseline was increased only for older adults, but not in young adults and octo/nonagenarians. Furthermore, PMA stimulation assays showed an increased IL–8 expression in older adults and octo/nonagenarians. RNA–sequencing of neutrophils revealed an increased expression of interferon response genes in older adults and octo/nonagenarians, accompanied by an increased expression of retrotransposons.

FA β -gal: an automated system for SA- β -gal fluorescence quantification

Antonio G. Tartiere^{1,2}; David Roiz-Valle^{1,2,3}; Yaiza Español¹; Gabriel Bretones¹; José M. P. Freije^{1,2,3} and Alejandro P. Ugalde^{1,2}

¹*Departamento de Bioquímica y Biología Molecular, Instituto Universitario de Oncología (IUOPA), Universidad de Oviedo, Oviedo, Spain*

²*Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain*

³*Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain*

The prominent role of cellular senescence in aging and cancer has promoted the development of a wide variety of methods to quantify it. Among them, the Senescence-Associated β -galactosidase (SA- β -gal) assay remains the gold standard. This method is based on the processing of the substrate X-gal by β -galactosidase of senescent cells to produce a colored precipitate commonly referred to as indigo. However, this technique presents several limitations related to its color-based readout. In this context, we have developed FA β -gal (Fluorescence Analysis of β -gal), a method that exploits the intrinsic far-red fluorescence of indigo to circumvent these limitations. In this sense, our approach demonstrates a strong linear correlation with senescence levels as well as a high sensitivity. In addition, FA β -gal is suitable for quantifying different types of cellular senescence in different cell lines, as well as in tissue sections. Finally, we have developed workflows and informatic tools that standardize and automate its quantification, rendering it easily introducible in the routine of any laboratory using the classical assay.

Aging of the adaptive immune system affects the gut microbiome and systemic levels of vitamin B6

Selina Stahl¹, Hanna Widmaier², Vadim Sakk¹, Kodandaramireddy Nalapareddy³, Ann-Kathrin Kissmann⁴, Frank Rosenau⁴, Medhanie A. Mulaw⁵, David B. Haslam⁶, **Hartmut Geiger^{1,*}**

¹*Institute of Molecular Medicine, Ulm University, Ulm, Baden-Württemberg, 89081, Germany.*

²*Department of Internal Medicine I, University Hospital of Ulm, Ulm, Baden-Württemberg, 89081, Germany.*

³*Division of Experimental Hematology and Cancer Biology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45229, USA.*

⁴*Institute of Pharmaceutical Biotechnology, Ulm University, Ulm, Baden-Württemberg, 89081, Germany.*

⁵*Unit for Single-Cell Genomics, Ulm University, Ulm, Baden-Württemberg, 89081, Germany.*

⁶*Microbial Genomics and Metagenomics Laboratory, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45229, USA.*

Age-associated immune remodeling (AAIR) is a hallmark of aging and may contribute to age-related alterations in the gut microbiome. We investigated whether mucosal AAIR acts as an upstream host factor shaping microbiome composition during aging. The ileal lamina propria of aged mice exhibited characteristic features of AAIR, including reduced naïve CD4⁺ and CD8⁺ T cell populations and expansion of memory and regulatory T cells. Using a hematopoietic stem cell (HSC) transplantation model, we demonstrated that young RAG1^{-/-} recipients reconstituted with aged HSCs developed key features of mucosal AAIR despite residing in a young host environment, indicating that these changes are driven, at least in part, by intrinsic hematopoietic aging. Shotgun metagenomic sequencing revealed that AAIR was associated with a reduced abundance of microbial taxa encoding vitamin B6 (VB6) biosynthesis and salvage pathways, accompanied by lower circulating VB6 levels. These findings identify a link between immune aging, microbiome functional capacity, and systemic VB6 availability, suggesting an immune-microbiome-VB6 axis that may represent a novel target for interventions aimed at improving health during aging.

Investigating the link between physical activity, depressive symptoms and epigenetic aging: findings from the Moli-sani study

Gialluisi, A.^{1,2}; Bracone, F.¹; Pepe, A.¹; Limone, A.G.¹; Di Castelnuovo, A.¹; Costanzo, S.^{1,3}; Tirozzi, A.⁴; Bonaccio, M.¹; Morelli, M.¹; Licastro, D.⁵; Cerletti, C.¹; Donati, M.B.¹; de Gaetano, G.¹; Iacoviello, L.^{1,2}

¹*Epidemiology and Prevention Research Unit, IRCCS Neuromed, Pozzilli, Italy*

²*Department of Medicine and Surgery, LUM University, Casamassima, Italy*

³*Research Center in Epidemiology and Preventive Medicine (EPIMED), Department of Medicine and Surgery, University of Insubria, Varese, Italy*

⁴*Medical Genetics Unit, Department of General and Emergency Pediatrics, AORN Santobono-Pausilipon, Naples, Italy*

⁵*Area Science Park, Trieste, Italy*

Objective: To investigate the link between physical activity (PA), depressive symptoms and DNA methylation (DNAm) aging clocks.

Methods: In an Italian cohort (N=1,098 subjects recruited at 2005–10 and 2017–20; mean (SD) age 58.8 (5.6) y, 51.3% women; median (IQR) follow-up 12.6 (1.1) y), we tested associations of PA levels (MET-h/day in sport activities) with depressive symptoms (standardized PHQ-9 scale) and DNAm aging (Hannum, Horvath, GrimAge, DNAmPhenoAge, DunedinPACE) clocks, through multivariable linear mixed models.

Results: PA was associated with lower depressive symptoms (Beta (SE): -0.16 (0.05)), including both somatic (-0.12 (0.05)) and cognitive domains (-0.15 (0.05)). DNAm aging clocks revealed significant inverse associations of PA with the Horvath (-0.31 (0.13)) and the DunedinPACE clock (-0.01 (0.004)).

Conclusions: These findings suggest that ~3.3 additional MET-h/day of sport PA (equivalent to ~50 min/day of brisk walking), would correspond to a 2-point lower PHQ-9 score, a change that may be relevant at the population level. A potential mediation of DNAm clocks in this link is currently under investigation.

Decoding Age-Related Failure of Intestinal Regeneration

Chiara Giannuzzi¹; Alberto Minetti²; Anna Krepelova¹; Francesco Neri¹

¹ *Molecular Biotechnology Center (MBC), Turin, Italy*

² *Leibniz institute on Aging, Jena, Germany*

Chemotherapy-induced intestinal injury is a major dose-limiting toxicity that disproportionately affects older patients, the population most frequently receiving anticancer treatments. While the young intestine rapidly restores epithelial integrity after injury, tissue repair is markedly impaired with aging, resulting in prolonged epithelial damage and reduced resilience. However, the mechanisms responsible for this age-dependent regenerative failure remain poorly understood.

Here, we investigated the response to 5-fluorouracil-induced intestinal injury in young and aged mice by integrating transcriptomic, proteomic, single-cell, and functional organoid approaches.

We found that aging profoundly reshapes the regenerative landscape of the intestine, impairing epithelial plasticity and limiting the activation of injury-induced repair programs. Integrative single-cell analyses identified a conserved pro-regenerative tuft cell population as a major target of this age-dependent remodeling. While these cells display regenerative features in young animals, aging drives a marked shift toward inflammatory programs, suggesting a loss of their regenerative potential. Functional studies further support the concept that preserving this tuft cell population enhances epithelial resilience following chemotherapy-induced damage.

Together, our findings identify age-dependent tuft cell reprogramming as a previously unappreciated mechanism contributing to impaired intestinal regeneration. These results provide new insight into why the aged intestine responds poorly to injury and highlight pro-regenerative tuft cells as a promising target to improve tissue repair and treatment tolerance in older cancer patients.

Transcriptomic clock in the short-lived African Killifish predicts mortality and detects longevity interventions

Gravili, I.^{1,2}; Debdas, P.²; Caterino, C.²; Baumgart, M.²; Carli, F.³; Raimondi, F.¹; Cellerino, A.^{1,2}

¹ *Scuola Normale Superiore, Pisa, Italy*

² *Leibniz Institute on Aging – Fritz Lipmann Institute, Jena, Germany*

³ *University of Pisa, Pisa, Italy*

Age predictors (aging clocks) based on different -omics data represent attractive biomarkers for translational aging research. We developed a transcriptomic clock to predict the age of the short-lived killifish (*Nothobranchius furzeri*) from RNA-seq data. This clock relies on a Selective Adversarial-Deep Neural Network (SA-DNN) coupled with a binary stochastic filter. This architecture brings three key advantages: minimal pre-processing, minimization of confounder effects (e.g. sex, strain, sequencing batch etc..) on prediction, and interpretable biological feature selection. The clock was trained on 241 biological samples and tested on a held-out set of 17 samples as well as on different external datasets. First, the clock demonstrates generalizability, discerning young and old fish in tissues not included in the training set. Second, transcriptomic age of fin biopsies predicts mortality from longitudinal data. Finally, the clock detected the effect of late-onset low temperature exposure, a known longevity intervention, in *N. furzeri*.

Rapamycin alleviates estrogen deficiency–induced bone loss in genetically heterogeneous mice

Guillon, M.¹; Harford, M.P.¹; Ding, M.²; Kassem, M.^{1,3,4}; & and Figeac F.¹

¹Odense University Hospital & University of Southern Denmark, Department of Molecular Endocrinology (KMEB), Odense, Denmark

²Odense University Hospital & University of Southern Denmark, Department of Orthopedic Surgery and Traumatology, Odense, Denmark

³Khalifa University, Faculty of Medicine and Health Sciences, Abu Dhabi, United Arab Emirates

⁴University of Copenhagen, Department of Cellular and Molecular Medicine, Copenhagen, Denmark

Background: Rapamycin (RAPA) extends lifespan and healthspan in mice, but its effects on musculoskeletal health remain largely unknown.

Purpose: To evaluate the effects of dietary RAPA on bone loss after ovariectomy (OVX) in genetically heterogeneous HET3 mice.

Methods: Sixteen-week-old female HET3 mice underwent OVX or sham surgery and received either control diet (ND) or 14 ppm RAPA for 8 weeks. Bone microarchitecture, strength, histology, and bone RNA-seq were assessed. In vitro experiments were performed using human bone marrow mesenchymal stem cells to examine osteogenic differentiation and human osteoclasts to assess bone resorptive behavior following RAPA treatment.

Results: RAPA diet markedly protected against OVX-induced bone loss (–19.1% in OVX–RAPA vs –36.4% in OVX–ND). RAPA reversed OVX transcriptional signature, with increased bone formation pathways and reduced inflammation. RAPA boosted bone formation and decreased bone resorption in vitro.

Conclusion: RAPA preserved trabecular bone and reversed OVX-driven molecular changes in HET3 mice, a model with greater human relevance. Human cell data support its translational potential.

Molecular Determinants of Clonal Fitness in Clonal Hematopoiesis

Kosebent, E. G.^{1,2,3}; Havranek, N.⁴; Doma, E.⁴; **Gupta, K.**^{5,6}; Kollman, K.⁴; Kirschner, K.^{1,2,3,5,6}

¹ Cancer Research UK Scotland Institute, Glasgow, UK

² School of Cancer Sciences, University of Glasgow, UK

³ Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN, USA

⁴ Department of Biomedical Sciences, Institute of Pharmacology and Toxicology, University of Veterinary Medicine Vienna, Vienna, Austria.

⁵ Department Internal Medicine, Division of Hematology, Mayo Clinic, Rochester, MN, USA

⁶ Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, MN, USA

Clonal hematopoiesis (CH) is driven by age-associated expansion of mutant hematopoietic stem and progenitor cell clones and is linked to hematologic malignancy, cardiovascular disease, and mortality, yet why different mutations expand in vivo remain unclear. We hypothesized that CH associated mutations reshape intrinsic cellular programs in distinct ways that determine clonal fitness and evolutionary success. To test this, we developed a murine hematopoietic progenitor platform enabling systematic comparison of recurrent CH mutations. We found that each mutation imposes a unique balance of stress adaptation, inflammatory signaling, and survival capacity with some shared and others highly divergent effects. Splicing factor mutations predominantly impair fitness through apoptosis while epigenetic regulator mutations broadly rewire inflammatory and stress response pathways with TET2 uniquely coupling senescence and defective DNA repair. These mutation specific programs converge on altered inflammatory signaling and competitive fitness providing a mechanistic framework for how diverse CH mutations drive clonal selection and disease risk.

PATH: A Framework for Phenotypic Aging Dimensions and Disease Risk Stratification

Ghorbani, F.¹; Nollen, E.¹; & Guryev, V.¹

European Research Institute for the Biology of Ageing (ERIBA), Groningen, The Netherlands
Abstract

Aging is a multidimensional process, yet most aging models reduce it to a single score. We developed PATH (Phenotypic Ageing Transitions for Health), a data-driven framework, to identify distinct phenotypic aging dimensions and assess their relevance to age-related disease risk. Using baseline data from 152,241 participants in the Dutch Lifelines cohort and 1,177 behavioral, psychological, social, physical, environmental, and biomedical variables, we identified seven aging-associated phenotypic dimensions. These dimensions were significantly associated with the future onset of cancer, diabetes, COPD, heart failure, stroke, and Parkinson's disease. The dimensions captured domains related to cumulative life stress, psychological resilience, physical functioning, respiratory symptoms, and smoking behavior and exposure. Notably, the cumulative life stress dimension predicted disease risk as strongly as, or more strongly than, traditional biomedical factors. These findings support a multidimensional model of aging and demonstrate that accessible phenotypic data can be used to stratify individuals by disease risk and inform targeted prevention strategies.

Community-Level Facilitators and Barriers to Physical Activity Among Older Adults in Karachi, Pakistan: A Qualitative Study

Ameerali Abdul Hameed^{1,2}; Mohammad Asim²; Sonia Sameen; Saniya Sabzwari^{1,3} & Bilal Ahmed Usmani²

¹ Department for Educational Development, Aga Khan University, Karachi, Pakistan

² Department of Community Health Sciences, Aga Khan University, Karachi, Pakistan

³ Department of Family Medicine, Aga Khan University, Karachi, Pakistan

Background: The global older adult population is expanding rapidly, with projections indicating it will reach two billion by 2050. Pakistan, a low- and middle-income country (LMIC), has approximately 15 million individuals aged 60 and above, constituting 7% of its total population a figure expected to nearly double by 2050. Physical inactivity is highly prevalent among this population group, with WHO data indicating a 50% prevalence among females and 30% among males aged 70 and above. Physical inactivity is closely linked to chronic non-communicable diseases (NCDs) and mental health disorders. NCDs currently account for 58% of total mortality in Pakistan, placing an enormous burden on an already strained healthcare system. Despite the well-documented health benefits of physical activity (PA), the community-level determinants shaping PA participation among older adults in Pakistan remain poorly understood. This study specifically focuses on community-level facilitators and barriers to physical activity among older adults living in urban Karachi.

Methods: A qualitative exploratory study was conducted in two of Karachi's most densely populated districts District Central (Gulberg Town) and District East (Gulshan Town) selected to capture socioeconomic diversity and urban density. A total of 24 community-dwelling older adults aged 60 and above, with no known cognitive disorders and able to move independently without assistive devices, were recruited using maximum variation purposive sampling. This approach ensured diversity across age, gender, physical activity behavior, presence of comorbidities, socioeconomic status, and living arrangements. Semi-structured, in-depth interviews guided by the Socio-Ecological Model (SEM) were conducted at participants' residences. Data were analyzed using Braun and Clarke's six-step thematic analysis framework with inductive-deductive open coding, and findings were organized according to the four levels of the SEM. The current abstract focuses specifically on the community level.

Results: Thematic analysis at the community level identified one overarching theme: Environmental and Social Influences, with distinct subthemes capturing both facilitators and barriers.

Community Level Facilitators – Availability of Community Resources: The presence of community-based recreational centers, senior citizen centers within residential societies, and peer groups emerged as key facilitators for physical activity. Participants reported that these spaces not only provide structured opportunities for exercise, but also serve as important venues for social interaction and peer encouragement. Such centers were described as significant sources of motivation that support an active lifestyle in old age. Participants specifically highlighted informal peer networks formed in neighborhood streets, outside apartment buildings, and in communal gathering spots as substitutes where formal spaces were lacking. The social dimension of these community spaces was seen as equally important as the physical infrastructure, as group participation enhanced social capital and reduced feelings of isolation.

Community Level Barriers – Norms and Attitudes: Prevailing sociocultural norms and attitudes emerged as the most prominent community-level barrier. Physical activity is not culturally normalized as a priority for older adults in Karachi; instead, ageing is widely associated with rest and reduced physical exertion. This 'sedentary ageing' norm was reported by participants as a pervasive cultural expectation that discourages physical effort in later life. The barrier was particularly pronounced for women, who face gendered social restrictions on outdoor participation. Female participants described experiencing discomfort, staring, and social judgment when attempting to engage in activities such as morning walks, even in traditional attire. Safety concerns, including street harassment and crime, further restricted women's access to public spaces for physical activity.

Community Level Barriers – Infrastructure, Safety, and Accessibility: Poor physical infrastructure was consistently identified as a significant barrier. In both study districts, public parks were few, poorly maintained, overcrowded, and lacking age-friendly features such as even walking surfaces, adequate benches, shaded seating, and accessible pathways. The absence of dedicated pedestrian walkways, zebra crossings, and side-walks created safety hazards from road traffic, particularly for older adults concerned about falls. Private gyms and recreational facilities, where available, were financially inaccessible to most participants due to high membership fees. Community-based recreational centers in gated housing schemes were restricted to residents,

further limiting broader participation. Participants also noted the absence of any formal older adult clubs or peer support groups in either study district, reflecting a systemic gap in community infrastructure tailored to the needs of aging populations.

Conclusion: This study is among the first to provide an in-depth, qualitative examination of community-level facilitators and barriers to physical activity among older adults in urban Pakistan. Community-based senior citizen centers and peer group networks were identified as key facilitators, while restrictive sociocultural norms, especially for women – poor infrastructure, limited safe public spaces, and safety and security concerns were the major barriers. The strong interdependence between community-level factors and broader individual and policy-level dynamics highlights the need for multi-level, context-sensitive interventions. Findings underscore the urgent need for culturally responsive community environments that are inclusive, age-friendly, and gender-sensitive. Municipal authorities and health departments in Karachi should prioritize investment in accessible public spaces, community-based programs, and culturally appropriate awareness campaigns to promote physical activity and support healthy aging among the growing older adult population in urban Pakistan.

References:

1. World Health Organization (2022). Physical Activity. WHO Fact Sheet. Available from: <https://www.who.int/news-room/fact-sheets/detail/physical-activity>
2. Braun V, Clarke V, and Weate P (2016). Using thematic analysis in sport and exercise research. In: Routledge Handbook of Qualitative Research in Sport and Exercise. London: Routledge.
3. Mahmood B, Cox S, Ashe MC, Nettlefold L, Deo N, Puyat JH, et al. (2022). 'We just don't have this in us...': understanding factors behind low levels of physical activity in South Asian immigrants in Metro-Vancouver, Canada. PLoS One 17, e0273266.
4. Barnett DW, Barnett A, Nathan A, Van Cauwenberg J, and Cerin E (2017). Built environmental correlates of older adults' total physical activity and walking: a systematic review and meta-analysis. International Journal of Behavioral Nutrition and Physical Activity 14, 103.

Manipulating individual spliceosome components to identify pro-longevity treatments

Hayman, D.J.¹; Simons, M.J.P.¹

¹ School of Biosciences, University of Sheffield, Sheffield, United Kingdom

Alternative splicing regulates which exons of a protein-coding gene are spliced into a translatable mRNA, undertaken by a dynamic complex called the spliceosome. Alternative splicing occurs in most human genes (Wang et al., 2008), but requires tight regulation to produce the correctly spliced mRNA for the specific context. During ageing, dysregulation in splicing is observed, leading to aberrant protein production (Latorre and Harries, 2017). Furthermore, treatments such as dietary restriction and mTOR suppression induced wide-spread changes in spliceosome expression and splicing. To date, it has been unclear if individual spliceosome components can affect longevity and how splicing is related to ageing on a mechanistic level. To test this we downregulated 6 individual spliceosome components in vivo in *Drosophila* using a globally expressed conditional driver. We identified that the knockdown of some spliceosome components rapidly induce mortality, whereas others extend lifespan (full results shown in Hayman et al., 2026). These pro-longevity spliceosome genes offer promise as pro-longevity targets.

References:

1. Hayman, D.J. and Simons, M.J.P. (2026). Knockdown of the fly spliceosome component Rbp1 (orthologue of SRSF1) extends lifespan. *GeroScience*, pp.1–10.
2. Latorre, E. and Harries, L.W. (2017). Splicing regulatory factors, ageing and age-related disease. *Ageing research reviews*, 36, pp. 165–170.
3. Wang, E.T., Sandberg, R., Luo, S., Khrebtkova, I., Zhang, L., Mayr, M., Kingsmore, S.F., Schroth, G.P., Burge, C.B. (2008). Alternative isoform regulation in human tissue transcriptomes. *Nature*, 456(7221), pp. 470–476.

Establishing human microglial models of aging and senescence

Hiihtola, L.¹, Kostian, N.¹, Korhonen, M.¹, Stratoulas, V.¹

¹*Faculty of Pharmacy, University of Helsinki, Helsinki, Finland*

Aging is a major risk factor for neurodegenerative diseases and cancer. Senescent cells accumulate with age and contribute to the inflammatory environment through senescent associated secretory phenotype. Microglia, the resident macrophages of the brain, serve as its primary line of immune defence. Aging is connected with dysregulated microglial responses, including exaggerated inflammatory activation. Common in vitro models, including cell lines and human iPSC-derived microglia, fail to preserve age-associated features. In this study, we use a recently described chemical cocktail to induce senescence and aging in continuous and human monocyte derived microglia-like cells. We characterize resulting cellular and functional changes associated with microglial aging. This work provides the basis for incorporating an aging angle into our ongoing neurodegeneration and cancer research projects.

Predicting protein homeostasis collapse in CAG-expansion diseases

Nobari, P.¹, Mauthe, M.¹, Kampinga, H.H.¹, & Hipp, M.S.^{1,2}

¹Department of Biomedical Sciences, University Medical Centre Groningen, the Netherlands

²School of Medicine and Health Sciences, Carl von Ossietzky University Oldenburg, Oldenburg, Germany

CAG-expansion diseases, including Huntington's disease (HD) and spinocerebellar ataxia type 1 and 3 (SCA1 and 3), arise from expansions in the genomic CAG repeat sequence, resulting in the production of aggregation-prone proteins containing expanded polyglutamine (polyQ) stretches. While a longer CAG-repeat length correlates with increased polyQ aggregation propensity and earlier disease onset, substantial inter-individual variability suggests that repeat length alone is insufficient to predict the age of disease onset. Moreover, detection of aggregation would be too late as a predictive measurement. Loss of protein homeostasis, a hallmark of aging and neurodegenerative diseases, is thought to precede polyQ aggregation. We hypothesize that the cellular protein homeostasis capacity can partially explain the variability in age of onset. Therefore, we aim to assess the decline in protein homeostasis before it collapses with reporters for different aspects of protein homeostasis.

The association between $\dot{V}_{O_{2peak}}$, metabolic blood biomarkers, and prefrailty in 327 community-dwelling older adults

Houtkamp, D.^{1,2}; Wüst, R.C.I.²; Bongers, B.C.^{1,3}; Pijnappels, M.²; Chettouf, S.¹; van de Wiel, A.^{1,4}; Bautmans, I.^{1,5,6,7}; & Pool-Goudzwaard, A.L.^{1,2}

¹ *SOMT University of Physiotherapy, Amersfoort, The Netherlands*

² *Department of Human Movement Sciences, Vrije Universiteit, Amsterdam, The Netherlands*

³ *Institute of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands*

⁴ *Department of Radiation Science and Technology, Delft University of Technology, Delft, The Netherlands*

⁵ *Rehabilitation Research group, Vrije Universiteit Brussel, Brussel, Belgium*

⁶ *Gerontology Department, Vrije Universiteit Brussel, Brussel, Belgium*

⁷ *Geriatrics Department, Universitair Ziekenhuis Brussel, Brussel, Belgium*

$\dot{V}_{O_{2peak}}$ and metabolic biomarkers are strong predictors of morbidity and mortality^{1,2}. We examined the associations between CPET-derived $\dot{V}_{O_{2peak}}$, 250 NMR-based metabolic biomarkers, and prefrailty in 327 community-dwelling older adults aged 55–75 years. $\dot{V}_{O_{2peak}}$ was lower in prefrail compared to robust older adults according to the Frailty Index (FI) and Groningen Frailty Indicator (GFI), but not the Fried Phenotype (FP). Logistic LASSO models combining age, sex, $\dot{V}_{O_{2peak}}$, and metabolic biomarkers showed excellent discrimination for GFI-defined prefrailty (AUC = 0.97), moderate discrimination for FI (AUC = 0.78), and lower discrimination for FP (AUC = 0.70). 95 biomarkers were independently associated with $\dot{V}_{O_{2peak}}$ (mL.kg.⁻¹.min⁻¹), yet provided minimal additional predictive value beyond age, sex, and $\dot{V}_{O_{2peak}}$, suggesting overlapping biological pathways. Associations between $\dot{V}_{O_{2peak}}$, biomarkers, and prefrailty were markedly stronger for the multidimensional FI and GFI than for FP, highlighting their different frailty constructs. Overall, $\dot{V}_{O_{2peak}}$ was more strongly associated with prefrailty than a panel of metabolic biomarkers.

References:

1. Lang JJ, Prince SA, Merucci K, Cadenas-Sanchez C, Chaput JP, Fraser BJ, Manyanga T, McGrath R, Ortega FB, Singh B, Tomkinson GR (2024). Cardiorespiratory fitness is a strong and consistent predictor of morbidity and mortality among adults: an overview of meta-analyses representing over 20.9 million observations from 199 unique cohort studies. *British journal of sports medicine*, 58(10), 556–566.
2. Deelen J, Kettunen J, Fischer K, van der Spek A, Trompet S, Kastenmüller G, Boyd A, Zierer J, van den Akker EB, Ala-Korpela M, Amin N, Demirkan A, Ghanbari M, van Heemst D, Ikram MA, van Klinken JB, Mooijaart SP, Peters A, Salomaa V, Sattar N, Spector TD, Tiemeier H, Verhoeven A, Waldenberger M, Würtz P, Davey Smith G, Metspalu A, Perola M, Menni C, Geleijnse JM, Drenos F, Beekman M, Jukema JW, van Duijn CM, and Slagboom PE (2019). A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals. *Nature Communications* 10, 3346.

Co-methylation network reorganisation reveals an independent dimension of epigenetic aging along a bidirectional chromatin axis in human blood methylome

Jana, S.; Shalev, I.

Department of Biobehavioral Health, The Pennsylvania State University, University Park, USA

Epigenetic clocks quantify aging at individual CpGs. However, whether coordinated co-methylation between CpGs is reorganised with age remains uncharacterised. We analysed co-methylation networks from age-associated CpGs in whole blood across two population cohorts (total n = 1385, age 14–101) classifying CpG pairs by correlation change between young and old individuals. We identified genome-wide loss of existing co-methylation alongside gain of new co-methylation, indicating bidirectional network remodelling decoupled from CpG methylation changes. Disconnected CpG pairs co-localised to active chromatin and enriched for transcription factors linked to immunosenescence and inflammation, while newly connected pairs co-localised to repressed chromatin and enriched for Polycomb repressive complexes. Bipartite rewiring profile clustering revealed modules enriched for ECM reorganisation, developmental patterning, and mitochondrial metabolism. Co-methylation rewiring scores were strongly age-associated and independent of epigenetic clocks, establishing co-methylation reorganisation as a distinct dimension of epigenetic aging.

References:

1. Seale K, Horvath S, Teschendorff A, Eynon N, and Voisin S (2022). Making sense of the ageing methylome. *Nat. Rev. Genet.* 23, 585–605.

Machine Learning–Driven Discovery of a Circulating Biomarker and Development of a Sarcopenia Risk Assessment Index with Multi–Ethnic Validation

Yunju Jo^{a,b,†}; Shibo Wei^{a,†}; Juewon Kim^{a,c,†}; Zhuo Li^d; Hee–Won Jung^e; Tam Dao^a; Seung–Jun Jeong^a; Sun–gyeon Kim^f; Baeki E. Kang^f; Seungyeon Nam^{f,g}; Karim Gariani^{h,i}; Andrea Trombetti^j; Emmanuel Biver^j; Thanh T. Nguyen^{a,k}; Hung V. Nguyen^{l,m}; Yen T. N. Nguyen^{l,m}; Dung C. Vu^{k,n}; Beom–Jun Kim^{o,*}; Dongryeol Ryu^{a,*}

^a Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology (GIST), Gwangju 61005, South Korea. yunjujo1029@wku.ac.kr, yj.eunice.jo@gmail.com

^b Department of Microbiology, Institute of Wonkwang Medical Science, Sarcopenia Total Solution Center, Wonkwang University School of Medicine, Iksan 54538, South Korea

^c Department of Physiology, Konkuk University College of Medicine, Chungju 27478, South Korea.

^d Department of Nephrology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, 250021, China

^e Division of Geriatrics, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, South Korea.

^f Department of Genome Medicine and Science, AI Convergence Center for Medical Science, Gachon Institute of Genome Medicine and Science, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon 21936, South Korea.

^g Department of Health Sciences and Technology, Gachon Advanced Institute for Health Sciences and Technology (GAIHST), Gachon University, Incheon 21936, South Korea.

^h Division of Endocrinology, Diabetes and Metabolism, Department of Medical Specialties, Geneva University Hospitals, Geneva 1205, Switzerland

ⁱ Faculty Diabetes Center, University of Geneva Medical Center, University of Geneva, Geneva 1205, Switzerland

^j Division of Bone Diseases, Department of Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva 1205, Switzerland

^k Center of Endocrinology, Metabolism, Genetic/Genomics and Molecular Therapy, Vietnam National Children's Hospital, Hanoi 100000, Vietnam.

^l Department of Internal Medicine, Hanoi Medical University, Hanoi 100000, Vietnam

^m Department of Rheumatology, Bach Mai Hospital, Hanoi 100000, Vietnam

ⁿ Department of Pediatrics, University of Medicine and Pharmacy – Vietnam National University, Hanoi 100000, Vietnam

^o Division of Endocrinology and Metabolism, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul 44610, South Korea.

[†] These authors contributed equally to this work and shared first authorship.

^{*} Corresponding authors

Introduction: Sarcopenia, the age–related decline in skeletal muscle mass and function, poses significant health risks in elderly populations, yet current diagnostics rely on costly imaging and region–specific criteria, with no universally accepted biomarker to harmonize assessment.

Objectives: We aimed to identify a minimally invasive, mechanistically relevant, and clinically translatable circulating biomarker for sarcopenia and to develop a computationally optimized Sarcopenia Risk Assessment (SRA) Index for global clinical applications.

Methods: An XGBoost–driven pipeline integrated skeletal muscle transcriptomics (GTEx, GSE111017) with secretome profiles. Candidate biomarkers were validated in multi–center cohorts (Korean Seoul, $n = 324$; Chinese Shandong, $n = 230$; Vietnamese Hanoi, $n = 91$; and Swiss Geneva, $n = 94$). Genetically inferred causal effects were estimated using two–sample Mendelian randomization. Mechanistic insights were derived from sc/snRNA–seq and recombinant protein–based gain–of–function assays, alongside cross–species models.

Results: A circulating endothelial–derived secreted protein was identified as a shared biomarker of muscle aging. In the primary Korean Seoul cohort, circulating levels of this protein tracked with appendicular skeletal muscle mass and functional decline, enabling an SRA Index with an AUROC of 0.8723. External validation confirmed robust performance in Chinese (AUROC = 0.890) and Vietnamese (AUROC = 0.922) cohorts; the Swiss cohort (AUROC = 0.708) further demonstrated reproducibility despite ethnicity–specific FNIIH criteria. Notably, circulating levels of this protein remained unchanged in pediatric patients with spinal muscular atrophy, Duchenne muscular dystrophy, and Pompe disease, indicating specificity for age–related sarcopenia rather than generalized muscle degeneration. Mechanistically, sc/snRNA–seq localized this protein to aged endothelial cells, where it promoted activation of the NF– κ B signaling axis, inducing cytoskeletal contraction, MMP–mediated remodeling, and cellular senescence. Loss of its ortholog in *C. elegans* extended lifespan and mobility, while high skeletal muscle expression in BXD mice predicted reduced survival.

Conclusion: This circulating biomarker is clinically accessible, highly specific, and supported by genetic and functional evidence, providing a translational framework for sarcopenia risk stratification and therapeutic targeting.

Age-dependent thiol oxidation targets core proteostasis functions

Katarzyna Jonak¹; Hrudya Mohan^{1,2}; Wiktoria Trynkos^{1,3}; & Ulrike Topf¹

¹Laboratory of Molecular Basis of Aging and Rejuvenation, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland

²Doctoral School of Molecular Biology and Biological Chemistry, Warsaw, Poland

³Faculty of Chemistry, University of Warsaw, Poland

Many age-related disorders are associated with an imbalance in cellular proteostasis and elevated ROS. While ROS-induced proteome damage is studied extensively, less is known about ROS as an endogenous stress signal during aging. Recent evidence suggests that redox-sensitive proteins regulate protein synthesis during early oxidative shifts. We explore how the early aging oxidation modulates stress defenses potentially safeguarding proteostasis and extending health and lifespan.

We developed a dataset on the *Saccharomyces cerevisiae* thiol oxidation investigating the kinetics of yeast proteome oxidation on a large scale at different stages of chronological aging. By combining this with existing data, we created the OxiAge Database (<http://oxiage.ibb.waw.pl>) to track how thiol oxidation changes across different species and biological processes over time. Our large-scale analysis identified reversible thiol oxidation targets in key proteostasis processes during the early stages of aging, particularly among conserved zinc-binding proteins. As zinc homeostasis is known to be imbalanced during aging, we performed a meta-analysis of known zinc-binding proteins across three domains of life, emphasizing the evolutionarily conserved importance of redox regulation of these proteins and their response to zinc deficiency. Notably, we found that conserved zinc-binding proteins involved in protein synthesis are among the early oxidation targets in aging. Currently, we are analyzing mutant variants of the selected proteins to understand translation regulation mechanisms in response to age-dependent stress, with potential implications for health and lifespan prolongation.

References:

1. Jonak, K., & Topf, U. (2026). Integrated analysis of the redoxome and zinc proteome links ribosomal protein oxidation to zinc homeostasis. *Redox Biology*, 104152.
2. Jonak, K., Suppanz, I., Bender, J., Chacinska, A., Warscheid, B., & Topf, U. (2024). Ageing-dependent thiol oxidation reveals early oxidation of proteins with core proteostasis functions. *Life Science Alliance*, 7(5).

Funding:

This work is supported by the National Science Centre, Poland, under the grant no. 2022/47/D/NZ3/01740 (SONATA) for KJ and grant no. 2022/45/B/NZ1/03714 (OPUS) for UT. KJ is additionally supported by the EMBO Postdoctoral Fellowship ALTF 82-2022.

Caloric restriction and its interplay with redox signaling in lifespan and healthspan

Christina Karagianni¹; Archonta Traikou¹; Nikoleta Tavernarakis¹; Maria Ermolaeva³; Daphne Bazopoulou^{1,2}

¹ Department of Biology, University of Crete, ² Institute of Molecular Biology & Biotechnology, FORTH, Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) ³

Reactive oxygen species (ROS) are increasingly recognized as key signaling molecules that regulate stress responses and promote survival. We previously demonstrated that a transient increase in ROS levels during early *Caenorhabditis elegans* development modulates the activity of the COMPASS complex, resulting in reduced H3K4 methylation and persistent improvements in lifespan and stress resistance (Bazopoulou et. al, 2019). Here, we identify developmental caloric restriction (CR) as a physiological stimulus that elevates ROS levels and induces the transgenerational inheritance of enhanced longevity and stress resilience. We further investigate the mechanisms underlying these effects, including the redox-sensitive COMPASS complex and pathways capable of transmitting longevity-associated traits across generations. Together, our findings reveal how redox-sensitive pathways bridge the gap between early-in-life nutritional stress and transgenerational resilience.

References:

1. Bazopoulou, D., Knoefler, D., Zheng, Y., Ulrich, K., Oleson, B. J., Xie, L., Kim, M., Kaufmann, A., Lee, Y. T., Dou, Y., Chen, Y., Quan, S., & Jakob, U. (2019). Developmental ROS individualizes organismal stress resistance and lifespan. *Nature*, 576(7786), 301–305. <https://doi.org/10.1038/s41586-019-1814-y>

Tissue Specific Regulation of Cellular Senescence by Genetic Aerobic Capacity, Aging, and Exercise

Damskägg, S.¹; Lautaoja-Kivipelto, J.²; Koch, L.G.³; Britton, S.L.⁴; Kainulainen, H.⁵; **Karvinen, S.**^{6,7}

1 Department of Biological and Environmental Science, University of Jyväskylä, Jyväskylä, Finland

2 Research Unit of Biomedicine and Internal Medicine, Faculty of Medicine, University of Oulu, Oulu, Finland

3 Department of Physiology and Pharmacology, University of Toledo, Toledo, USA

4 Department of Molecular and Integrative Physiology and Department of Anesthesiology, University of Michigan, Ann Arbor, USA

5 Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

6 Gerontology Research Center (GEREC) and Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

7 Department of Molecular and Integrative Biosciences, Faculty of Biological and Environmental Sciences, University of Helsinki, Helsinki, Finland

A key mechanism for healthy aging is decreasing cellular senescence, a state of irreversible cell cycle arrest leading to senescent cell accumulation and tissue dysfunction. Exercise may attenuate senescence, while genetic aerobic capacity influences metabolic health and lifespan. This study evaluated the effects aging and exercise on cellular senescence in liver, skeletal muscle, and adipose tissue in rats selectively bred for low vs. high genetic aerobic capacity. Sixty female Low-Capacity runners (LCR) and High-Capacity Runners (HCR) were studied in three groups: young, inactive; aged, inactive; aged with access to running wheels for one-year. Senescence markers were analysed using qPCR, Western blot, and β -galactosidase assay. Compared to HCR, LCR rats had higher p21Cip1 expression in muscle and adipose tissue ($p \leq 0.049$) and aging associated with higher p21Cip1 in liver and muscle ($p \leq 0.039$). Exercise associated with higher levels of p16Ink4a in muscle and p21Cip1 in adipose tissue ($p \leq 0.033$). Our results suggest that genetic aerobic capacity has more profound effect on tissue senescence than long-term exercise.

The Host–Microbe Redox interplay and its role in Aging and Neurodegeneration

Agapi Kavvadia¹, Orestis Kontogiannis¹, Ellen A. A. Nollen², Daphne Bazopoulou^{1,3}

¹Department of Biology, University of Crete, Heraklion, Greece

²European Research Institute for the Biology of Ageing, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

³Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology Hella, Heraklion, Greece

Reactive Oxygen Species (ROS) are produced at host barrier sites in response to bacterial contact in every eukaryote host studied. Those highly reactive molecules play a dual role: excessive ROS induce oxidative stress and, therefore, contribute to human diseases, while low levels of ROS act as signaling molecules and regulate biological processes physiologically. Previous studies showed that treatments that elevate endogenous ROS during developmental stages have life-altering effects on *C. elegans* i.e., in lifespan and neuroprotection (1,2). We now find that dietary bacteria are important for these redox-altering treatments to elicit their effects in the *C. elegans* host. We also show that the timing of application and redox state of the dietary bacteria are both critical factors. These findings will advance our understanding on host–bacteria interactions and, in particular, on redox-regulated events triggered by dietary bacteria that impact the health and lifespan of the host.

References:

1. Bazopoulou, Daphne, et al. "Developmental ROS Individualizes Organismal Stress Resistance and Lifespan." *Nature*, vol. 576, no. 7786, Dec. 2019, pp. 301–305.
2. Oleson, Bryndon J, et al. "Early Life Changes in Histone Landscape Protect against Age-Associated Amyloid Toxicities through HSF-1-Dependent Regulation of Lipid Metabolism." *Nature Aging*, vol. 4, no. 1, 6 Dec. 2023, pp. 48–61.

Restoration of biological age during prolonged fasting–refeeding mediated by a fasting–responsive linker histone

Kazuto Kawamura¹; Anna R. Diederich¹; Birgit Gerisch¹; Roberto Ripa¹; Christian Latza¹; Joachim D. Steiner^{1,4}; Stephanie Fernandes²; Filippo Artoni²; David H. Meyer³; Damini Sant¹; Simon Oehm⁴; Franziska Grundmann⁴; Roman-Ulrich Müller⁴; Constantinos Demetriades²; Adam Antebi¹

¹ *Molecular Genetics of Ageing Department, Max Planck Institute for Biology of Ageing, Cologne, Germany*

² *Cell Growth Control in Health and Age-related Disease Research Group, Max Planck Institute for Biology of Ageing, Cologne, Germany*

³ *Institute for Genome Stability in Aging and Disease, University of Cologne, Cologne, Germany*

⁴ *Department II of Internal Medicine and Center for Molecular Medicine Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany*

Reversal of biological age can occur in the immortal germline during early embryogenesis or during Yamanaka factor reprogramming. Whether there are other contexts that promote restoration of biological age, especially in an adult organism, is largely unknown. Here we describe an experimental paradigm in which we observe remarkable somatic restoration and significant reduction of predicted biological age in an aged adult organism. We observe progressive degeneration and increases in predicted biological age during prolonged periods in fasting-induced adult reproductive diapause of *Caenorhabditis elegans*. When recovery is initiated by refeeding, germline regeneration, somatic repair and regrowth occur, accompanied by a reduction in predicted biological age. Interestingly, transcriptomic changes that ensue during refeeding-induced recovery are inversely correlated with ad libitum age-related transcriptomic changes, suggesting restoration of the transcriptome to a more youthful state. Through an RNAi screen we identify the linker histone *hil-1* as a key mediator of resilience during fasting and restoration during refeeding. *hil-1* mutation leads to reduced lifespan during adult reproductive diapause while having no effect on ad libitum lifespan. During refeeding, repression of *hil-1* facilitates somatic regrowth and recovery of locomotor function. Accordingly, HIL-1 is a fasting-responsive linker histone whose expression is strongly upregulated during adult reproductive diapause and downregulated during refeeding, suggesting chromatin plasticity is important for starvation survival and restoration. Induction of HIL-1 is dependent on DAF-16/FOXO and HLH-30/TFEB, two key transcription factors that promote longevity. Regulation of HIL-1/H1.0 may be evolutionarily conserved as we also observe an increase in H1.0 expression in response to amino acid starvation in human cell culture. Furthermore, H1.0 knockout cells are less resilient to prolonged amino acid starvation. Our study reveals refeeding-induced recovery from adult reproductive diapause as a time window of biological age plasticity in adult tissues, and identifies *hil-1*/H1.0 as part of an epigenetic switch of resilience and restoration during prolonged fasting–refeeding.

The optimized stem cell niche: ECM remodeling supports skin aging resistance in the naked mole rat

Aurelien Kerever¹, Kazuto Tsuji², Justine Flipo³, Melanie Viltard⁴, Kyohei Higashi², Eri Arikawa-Hirasawa¹, Romain Fontaine³.

¹ Juntendo University Graduate School of Medicine, Tokyo, Japan.

² Tokyo University of Science, Tokyo, Japan.

³ Université Paris Cité, CNRS, INSERM, Institut Cochin, Paris, France.

⁴ Fondation pour la Recherche en Physiologie, Brussels, Belgium.

The extracellular matrix (ECM) of epithelial stem cell niches regulates homeostasis through two axes: the biomechanical scaffold of the basement membrane, and the heparan sulfate (HS) reservoir that binds and presents growth factors. Both deteriorate in aging niches. The naked mole rat (NMR), an exceptionally long-lived rodent, preserves skin integrity across its lifespan, yet its skin ECM is poorly characterized. We asked whether NMR runs its niche ECM as an optimized baseline: distinctly configured and stable with age. Comparing NMR and mouse by confocal morphometry, RNA-sequencing, glycosaminoglycan analysis, and structural modelling, we find NMR HS preloaded with the 2SNS motif that binds FGF2 and FGF7 (11.5% vs 1.4% in mouse). NMR basal keratinocytes engage a geometrically elaborated dermo-epidermal junction (1.9-fold tortuosity, 4-fold digitation density) above an adhesion program that is constitutively distinct and nearly constant across keratinocyte states, while mouse shifts it markedly. These features remain stable across the NMR lifespan, suggesting the niche is built on an ECM baseline optimized for sustained stem cell support.

Mechanisms of life span extension by osmolytes

Heerschop, S.^{1,*}; Ivanova, E.^{2,*}; Arz, V.^{2,*}; Gameiro, E.²; Maliavko, A.³; Danalatos, I.R.¹; Roithner, F.¹; Charvin, G.³; Padeken, J.^{2,#}; **Khmelniskii, A.^{2,#}**; Luke, B.^{1,2,#}

¹*Institute of Developmental Biology and Neurobiology (IDN), Johannes Gutenberg Universität, Mainz, Germany*

²*Institute of Molecular Biology (IMB), Mainz, Germany*

³*GMGM UMR 7156, Université de Strasbourg, Strasbourg, France*

* *These authors contributed equally to this work*

Co-corresponding authors

Osmolytes are small organic molecules that accumulate across all domains of life in response to stress, and have been linked to aging. Yet the mechanisms through which osmolytes influence the aging process and organismal longevity remain poorly defined.

We address this question by systematically examining links between osmolyte action and the primary hallmarks of aging. Using genetically tractable aging systems that allow proteostasis to be monitored at single-protein resolution, we demonstrate that osmolytes extend lifespan through their activity as chemical chaperones, suppressing age-dependent protein aggregation and maintaining proteostasis. Critically, this chemical chaperone activity, rather than upstream stress signaling, is the proximal driver of longevity. Our findings resolve a long-standing gap between the biochemical literature on protein stabilization and the biology of aging, establish proteostasis maintenance as a conserved function of the osmolyte class and provide a unifying mechanistic explanation for previously reported but poorly understood pro-longevity effects of specific osmolytes.

Interplay of structural changes in skin tissue during aging and the progression of chronic inflammatory skin diseases

Kleissl, L.^{1,2}; Veres, T.¹; Buljan, I.^{1,3}; Sterniczky, B.²; Dingelmaier-Hovorka, R.²; Kopf, A.^{1,2}; Drach, M.²; de Rooij, L.¹; Sary, G.^{1,2} & Rendeiro, A.F.^{1,3}

*1 CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences,
Lazarettgasse 14 AKH BT 25.3, 1090, Vienna, Austria*

2 Department of Dermatology, Medical University of Vienna, Vienna, Austria

3 Ludwig Boltzmann Institute for Network Medicine at the University of Vienna, Vienna, Austria

Aging induces profound structural and cellular changes that compromise tissue integrity and increase susceptibility to chronic inflammatory disorders such as psoriasis (Pso) and atopic dermatitis (AD). However, it remains unclear how such alterations contribute to disease onset.

We study age-related changes in healthy individuals (n=80), and disease-associated changes in Pso (n=90) and AD (n=70) patients. Combining AI-powered biological age prediction from histopathological images with gene-expression analysis, reveals mechanisms linking skin aging to chronic inflammation. We uncover disease-specific morphological signatures, allowing us to grade disease severity. By integrating transcriptomic profiles, we identify pathways driving histological scores, including gap junction assembly and distinct immune programs for each inflammatory state.

This comprehensive morphological and molecular framework provides an unbiased view of how age-related changes trigger disease onset. Together with spatial transcriptomics and immune phenotyping, it will reveal how these changes drive the onset and progression of inflammatory skin diseases.

Extract, Stabilize, Measure: Preserving NAD from Collection to Analysis

Kogan, K.; Euro, L.; Haimilahti, K.; Jansson, S.; Forsström S.; Buzkova, J.; Suomalainen, A

NADMED Ltd, Helsinki, Finland

Accurate measurement of NAD-related redox metabolites is essential for reliable biological interpretation and clinical decision-making. Yet these metabolites are highly sensitive to pre-analytical conditions arising during blood collection, storage, transport, and freeze-thaw cycles. At NADMED, we have observed that such factors can substantially alter measured redox states and compromise data quality, regardless of the analytical platform used.

Drawing on accumulated experimental data, we address common challenges in clinical and research laboratories, focusing on how sample handling affects NAD-metabolite stability. We identify steps that promote redox degradation and outline practices that preserve biological signal integrity from collection to analysis. These principles apply broadly to LC-MS, cyclic enzymatic assays, and NMR spectroscopy.

We propose a practical workflow for redox-focused analysis: extract, stabilize, measure. Rapid extraction, effective stabilization, and controlled measurement conditions help ensure that analytical readouts reflect true physiological states rather than pre-analytical artifacts.

References:

1. Euro, L., Haimilahti, K., Jansson, S., Forsström S., Buzkova, J., Suomalainen, A (2025). Dynamics of blood NAD and glutathione in health, disease, aging and under NAD-booster treatment. bioRxiv 2025.02.24.639825; doi: <https://doi.org/10.1101/2025.02.24.639825>

Unravelling the role of H3K4me2 in response to DNA damage and transcription stress during development and ageing

Angelina Job Kolady^{1,3}; Walter Sandt³; David H. Meyer^{1,3}; Anna Eva Koch^{1,4}; Robert Hänsel – Hertsch^{1,3,4}, Björn Schumacher^{1,3,4}; Siyao Wang^{1,2,3}

¹*Institute for Genome Stability in Ageing and Disease, Medical Faculty, University of Cologne, Germany*

²*Institute of Molecular Biology, Mainz, Germany*

³*Cologne Excellence Cluster for Aging and Aging-Associated Diseases (CECAD), Cologne, Germany*

⁴*Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany*

Cells are continuously exposed to DNA damage that can stall RNA Pol II, threatening genome stability^{1,2} and contributing to diseases such as cancer, neurological disorders, and cardiovascular disease. We investigated the role of histone H3 lysine 4 dimethylation (H3K4me2) in transcription recovery after transcription-blocking stress using *C.elegans* and mouse dermal fibroblasts. H3K4me2 levels increased during recovery and correlated with productive transcription elongation. Reduced H3K4me2 delayed development and impaired recovery, while elevated levels accelerated recovery, indicating a conserved role in restoring transcription. Temporal analyses showed that RNA Pol II Ser2P reappears before H3K4me2 accumulation, suggesting H3K4me2 sustains rather than initiates elongation. CUT&Tag profiling revealed coordinated H3K4me2 and RNA Pol II Ser2P regulatory patterns during transcription recovery. Ongoing IP-MS studies are examining how the H3K4me2 is recruited during transcription recovery. These findings identify H3K4me2 as a conserved chromatin feature that promotes transcription recovery and genome stability during ageing.

References:

1. Kolady, A.J., and Wang, S. (2026). The role of histone modifications in transcription regulation upon DNA damage. *FEBS Letters* 600, 418–438. <https://doi.org/10.1002/1873-3468.70241>.
2. Wang, S., Meyer, D.H., and Schumacher, B. (2020). H3K4me2 regulates the recovery of protein biosynthesis and homeostasis following DNA damage. *Nat Struct Mol Biol* 27, 1165–1177. <https://doi.org/10.1038/s41594-020-00513-1>.

Molecular signatures of sex-specific liver aging

Merve Kutay; Andreas Beyer

Cologne Excellence Cluster for Aging and Aging-Associated Diseases (CECAD), Cologne, Germany

Chronic liver diseases and liver ageing are global health issues that trigger complex transcriptomic pathways at the cellular level. Recent studies have demonstrated that transcriptomic responses to liver damage and ageing processes exhibit significant biological variations between female and male organisms. However, existing research using murine models has been strongly biased towards using male animals only, which poses a major barrier towards elucidating sex-dependent effects of age on liver health. To investigate sex-specific liver aging at the molecular level, this study identified transcriptional marker genes that facilitate an unbiased quantification of cellular damage to hepatocytes. The resulting hepatocyte damage score was subsequently used to analyze how male versus female transcriptional aging trajectories distinctly impact on liver health. To avoid sex bias, diverse liver damage datasets were split into two training groups: 13 female and 21 male. In each group, genes that were statistically significant in at least 50% of the datasets and up- or down-regulated in the same direction in at least 75% of them were filtered. The 165 common genes identified from the intersection of the female and male groups were tested using 13 independent datasets and selected as the “top 101 global marker genes” with the most robust transcriptomic signal. In the next step, age-related genes will be identified using the female and male age datasets. The accuracy of these genes in predicting hepatocyte damage scores (HDS) will be modelled using Elastic Net regression analysis, and the sex-specific changes in damage profiles with aging will be analysed.

Ultimately, this sex-unbiased bioinformatics approach establishes a robust framework for identifying universal hepatocyte diagnostic markers while opening new ways to untangle how aging dynamics drive liver pathology with sex.

Keywords: Liver Aging, Hepatocyte Damage Score (HDS), Bioinformatics, Sex Bias, Elastic Net Regression

Characterizing Cellular Drivers of Cognitive Decline Across the Aging Mouse Hippocampus

Amanda Latham^{1,2}; Sonia Rodriguez^{1,2}; Ethan Leitschuh^{1,2}; Marissa Schafer^{1,2,3,4}

¹Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA

²Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, MN, USA

³Department of Neurology, Mayo Clinic, Rochester, MN, USA

⁴Department of Neuroscience, Mayo Clinic, Rochester, MN, USA

As global life expectancy increases, the prevalence of age-related cognitive impairment and dementia continues to rise, affecting more than 50 million people worldwide. The hippocampal formation and adjacent corpus callosum and fimbria-fornix white matter tracts are particularly vulnerable to age-associated structural and functional decline linked to cognitive dysfunction. Emerging evidence suggests that inflammatory cell populations contribute to brain aging; however, the cellular and molecular mechanisms driving hippocampal dysfunction remain incompletely understood. To define the cellular niches associated with brain aging and cognitive decline, we performed comprehensive behavioral phenotyping and brain analyses across the murine lifespan in male and female C57Bl/6N mice aged 6 – 29 months. Across multiple cognitive and behavioral domains, aging was associated with impairments in spatial memory, recognition memory, executive function, exploratory behavior, and anxiety-related behaviors. To define the cellular states, transcriptional changes, and microenvironment-specific interactions linked to domain-specific cognitive dysfunction with age, we generated spatial transcriptomic and whole-transcriptome single-nucleus RNA sequencing datasets from the hippocampal formation and surrounding white matter. Our analyses reveal the emergence of senescent and inflammatory immune and glial populations with age, particularly within white matter-associated microenvironments. By leveraging these datasets, we aim to provide mechanistic insight into the cell-mediated processes underlying cognitive decline in the aging brain.

High-throughput measurement of lifespan and fluorescence-based aging markers at single-animal resolution in *C. elegans*

Lenart, P.¹; Arangelova, I.¹; Towbin, B.¹

¹*Institute of Cell Biology, University of Bern, Bern, Switzerland*

Genetically identical individuals can vary several-fold in lifespan even under identical conditions. Understanding the origin of this heterogeneity requires longitudinal measurement of individual aging trajectories, yet conventional approaches either sample population averages or, when following individuals, sacrifice throughput or resolution.

We present an automated *C. elegans* assay that fills this gap. By trapping animals in arrayed microchambers, we track up to 1,000 individuals by hourly live imaging at cellular resolution across their entire lifespan. An automated pipeline extracts per-animal survival, motility, and trajectories of fluorescence-based aging markers, yielding both population statistics and single-animal aging dynamics. We validated the platform using *daf-2(e1368)* and *eat-2(ad1116)* mutants, reproducing published lifespan extensions while revealing sub-population structure and aging marker-to-lifespan covariation within isogenic cohorts.

Old muscle, new rules: muscle derived FGF21 drives systemic resistance to protect failing muscle

Lienau, J.^{1,3}; Gillum, M.P.¹; Gerhart-Hines, Z.²; & Finger, F.¹

¹Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

²Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark

³joelina.lienu@sund.ku.dk

Aging creates a paradox for FGF21: while analogous are therapeutics showing efficacy in metabolic disease, endogenous FGF21 is chronically elevated in aging. As homeostatic control declines with age, stress pathways become activated, leading to increased circulating FGF21. Skeletal muscle – a major source of FGF21 under mitochondrial stress and aging – remains poorly understood as a driver of systemic signaling stress. We used a muscle-specific mitochondrial myopathy model that accelerates skeletal muscle aging and drives circulating muscle-derived FGF21 to near-pharmacological levels. We found no canonical response of FGF21, consistent with an actively induced resistance state safeguarding failing muscle in aging. Together, these findings sharpen the paradox of FGF21 biology in aging: sustained endogenous elevation does not yield productive signaling. Instead, FGF21 responsiveness is shaped by tissue context and chronic stress. Defining when FGF21 is adaptive and when resistance emerges will be critical for identifying biomarkers, stratifying patients, and guiding personalized FGF21-based therapies for aging and age-related disease.

Understanding the role of H3K36 methylation in epigenetic aging

Martina Mankarious^{a,b}; Anna Hansknecht^{a,b}; Kira Zeevaert^{a,b}; Monica Varona-Baranda^{a,b}; Mina Shaiganc;
Deepika Puri^{a,b}; Wolfgang Wagner^{a,b}

^a Helmholtz-Institute for Biomedical Engineering, Medical Faculty of RWTH Aachen University, 52074 Aachen, Germany

^b Institute for Stem Cell Biology, University Hospital of RWTH Aachen, 52074 Aachen, Germany

^c Institute for Computational Genomics, RWTH Aachen, 52074 Aachen, Germany

Aging is associated with robust and reproducible changes in DNA methylation (DNAm), however the upstream chromatin mechanisms governing these methylation patterns are poorly understood. Histone 3 lysine 36 (H3K36) methylation, specifically H3K36me2/me3, recruit DNA methyltransferases, DNMT3A/B, to target regions. Therefore, we aimed to elucidate whether H3K36 methylation patterns change with aging and if this contributes to age-associated DNAm. H3K36me2 and H3K36me3 profiles were investigated in peripheral blood derived mononuclear cells of 5 old and 5 young donors. We observed significant changes in both marks, with particularly loss of H3K36me2 and gain of H3K36me3. Notably, these genomic regions were enriched in genes associated with leukocyte and immune function. We observed that subsets of both patterns overlap with each other, suggesting a shift toward H3K36me3 in aging. However, genomic regions with age-associated DNAm did not reveal clear changes with H3K36 marks drift in aging. To better understand how the H3K36 marks interact with DNAm, we generated CRISPR-Cas9 knockout of the histone methyltransferases, NSD1 and SETD2, which are responsible for depositing H3K36me2 and H3K36me3, respectively, in induced human pluripotent stem cells. In fact, NSD1 and SETD2 knockout clones showed marked decrease in H3K36me2 and H3K36me3 patterns. NSD1 knockout resulted in a significant hypomethylation, but it was not considerably impacting age-associated DNAm. On the other hand, we did not see any evident DNAm changes in SETD2 knockout lines. Collectively, our work demonstrates an age-associated shift from H3K36me2 to H3K36me3, but these changes appear to be independent from age-associated DNAm.

Investigating the impact of ageing on 3D genome architecture in adIRD models in the turquoise killifish

Manzo, S.¹; Muñoz Gil, L.¹; Ardila García, L.¹; Hernández-Perez, M.V.¹; Naranjo-Durán, S.¹; Macho Rendón, J.²; Ciampi, L.¹; Tena, J.¹; & Martínez-Morales, J.R.¹

¹Centro Andaluz de Biología del Desarrollo (CSIC/UPO), Seville, Spain

²CABIMER, Seville, Spain

The retina enables vision and is highly vulnerable to ageing and neurodegeneration. Inherited Retinal Diseases (IRDs) are leading causes of blindness worldwide, affecting >5 million people. However, epigenomic complexity and limited human retinal samples hinder mechanistic studies. Since ageing and neurodegeneration may converge on shared molecular pathways, we use the turquoise killifish, a short-lived vertebrate model that recapitulates the hallmarks of human ageing, to investigate chromatin regulation in both physiological and neurodegenerative contexts. We generated a transgenic killifish model carrying the human rhodopsin mutation, resulting in photoreceptor degeneration. Using bulk RNA-seq, ATAC-seq and HiC, we identified transcriptional and chromatin accessibility changes linked to loss of retinal identity, immune activation and stress pathways. Furthermore, alternative splicing analyses revealed conserved ageing programs also observed in zebrafish. Ultimately, our study reveals mechanisms driving retinal ageing and degeneration.

Cell-type-resolved pseudobulk classification identifies microglial PTPRG as a transcriptional hub in Alzheimer's disease

Agata Marchi¹; Danish Anwer¹; Eduard Kerkhoven¹; Nicola Pietro Montaldo^{2,3}; Jeroen Gilis¹; Annikka Polster^{1,2}

¹ *Division of Systems and Synthetic Biology, Department of Life Sciences, Chalmers University of Technology, Gothenburg, Sweden.*

² *Department of Microbiology, Oslo University Hospital and University of Oslo, 0424 Oslo, Norway.*

³ *Cresco Centre for Embryology and Healthy Development, Oslo, Norway.*

Alzheimer's disease (AD) involves complex cell-type-specific pathology. Using supervised machine learning on pseudobulk single-nucleus RNA-seq data from the ROSMAP cohort, we evaluated combinations of six brain cell types for AD classification. Microglia and astrocytes were the most informative. A logistic regression model trained on 228 highly variable genes achieved strong performance in ROSMAP (balanced accuracy 87%, AUC 0.89) and generalized to an independent Seattle AD Brain Cell Atlas cohort (balanced accuracy 86%, AUC 0.92). Among 72 selected genes, microglial PTPRG showed the strongest contribution. Enrichment and network analyses linked microglial genes to inflammatory signaling and astrocyte genes to protein homeostasis stress. PTPRG occupied distinct co-expression networks in AD and cognitively normal microglia, reflecting inflammatory dysregulation versus immune homeostasis. Cell-cell communication analysis identified APOE, GRN, PSEN1, and CLU as predicted neuronal regulators of microglial PTPRG. These findings identify PTPRG as a central hub integrating neuronal signaling and inflammatory dysregulation in AD.

Martirosyan

Metabolic reprogramming as a quality control strategy in long-lived bats

Bats (Chiroptera) exhibit extraordinary longevity relative to their body size, yet the cellular mechanisms underlying this phenomenon remain poorly understood. Using primary fibroblasts from *Myotis myotis* (long-lived, ~37 years), *Rousettus aegyptiacus* (shorter-lived, ~20 years), and *Homo sapiens* as a reference, we investigated species-specific responses to UVC-induced genotoxic stress through an integrated multi-omics approach encompassing quantitative proteomics, phosphoproteomics, Seahorse respirometry, live-cell apoptosis profiling, and mitochondrial functional assays.

Under genotoxic stress, *Myotis* fibroblasts mounted a pronounced upregulation of TCA cycle and fatty acid oxidation enzymes, accompanied by increased mitochondrial OXPHOS activity and remodelling of mitochondrial dynamics. This metabolic shift was coupled with apoptotic priming — evidenced by pro-apoptotic protein phosphorylation and live-cell caspase activation — suggesting that *Myotis* preferentially eliminates damaged cells through a metabolically-fuelled quality control program. *Rousettus*, despite its comparatively shorter lifespan, showed a markedly different metabolic and bioenergetic stress response, pointing to divergent cellular strategies even within the same order. Human fibroblasts displayed robust ATM-mediated DNA damage signalling with comparatively muted metabolic engagement.

Together, these findings support a model in which the longevity of *Myotis* is underpinned by a metabolic-first quality control strategy: rapid energetic commitment to mitochondrial function primes efficient apoptotic clearance of genotoxically damaged cells, potentially limiting the accumulation of senescent or mutagenised cells over a long lifespan. This work positions bat comparative biology as a productive framework for identifying actionable metabolic nodes in healthy ageing.

Epigenetic clocks do not capture the ageing-associated cognitive decline in middle-aged individuals

Ciantar, J.¹; Rovio, S.^{2,3,4}; Elovainio, M.⁵; Pahkala, K.^{2,3,6}; Mykkänen, J.^{2,3}; Lehtimäki, T.^{7,8,9}; Raitakari, O.^{2,3,10}; Raitoharju, E.^{1,8,9} & **Marttila, S.**^{1,11,12}

¹ *Molecular Epidemiology (MOLE), Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland*

² *Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland*

³ *Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland*

⁴ *Department of Public Health, University of Turku and Turku University Hospital, Turku, Finland*

⁵ *Department of Psychology, Faculty of Medicine, University of Helsinki, Helsinki, Finland*

⁶ *Paavo Nurmi Centre, Unit for Health and Physical Activity, University of Turku, Turku, Finland*

⁷ *Department of Clinical Chemistry, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.*

⁸ *Finnish Cardiovascular Research Center Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.*

⁹ *Fimlab Laboratories, Tampere, Finland*

¹⁰ *Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland*

¹¹ *Tampere University Hospital, Wellbeing Services County of Pirkanmaa, Tampere, Finland*

¹² *Gerontology Research Center, Tampere University, Tampere, Finland*

Epigenetic clocks are biomarkers of ageing that associate with various ageing-related phenotypes, morbidity and mortality. Ageing-associated non-pathological cognitive decline can be observed from mid-life onwards. As cognitive phenotypes have not been included in the construction of the various epigenetic clocks, our aim was to study whether the epigenetic clocks capture the ageing-associated cognitive decline. In the YFS cohort (aged 34–49 years at baseline, n=1250), cognitive performance was measured twice (follow-up of 7 to 9 years) using the CANTAB® test battery. We included overall cognitive performance and four specific cognitive domains in the analysis. The epigenetic clocks were PhenoAge, GrimAge and DunedinPACE. In our cohort, epigenetic clocks did not comprehensively capture the ageing associated cognitive decline. Only one association, between GrimAge and information processing, was statistically significant in the fully adjusted model. In a middle-aged cognitively healthy population, biological aging estimated using epigenetic clocks does not seem to be associated with cognitive decline.

Redox-Regulated BTB/POZ Protein C40A11.2 Mediates Early-Life Stress Adaptation in *C. elegans*

Kyriakos Mavridis¹; Agapi Kavvadia¹ & Daphne Bazopoulou¹

¹ *Department of Biology, University of Crete & Institute of Molecular Biology and Biotechnology FORTH, Heraklion, Greece*

Early-life interventions, such as mild oxidative stress, have been shown to alter lifespan trajectories and enhance healthspan in *Caenorhabditis elegans* [1,2]. However, the molecular mechanisms facilitating long-term resilience remain elusive. Transcriptomic analyses of developing worms, which are intrinsically more oxidized than the population mean and live longer, identified several upregulated yet uncharacterized genes encoding BTB/POZ domain-containing proteins [1]. These proteins are predicted to function as substrate adaptors for Cullin-RING E3 ubiquitin ligases, suggesting a potential role of selective protein degradation in cellular adaptations accompanying mild stress in development. My research focuses on one such protein, encoded by C40A11.2, which is predicted to be regulated by the heat shock factor HSF-1, based on promoter analysis and de novo motif discovery. Interestingly, knockdown of C40A11.2 confers heat tolerance on control worms but increases sensitivity in the otherwise stress-resistant Insulin/IGF-deficient mutants. Using RNAi, dietary interventions, and stress reporter strains, I study C40A11.2's role in stress adaptation within characterized longevity pathways. This work aims to provide mechanistic insights into how genetics and diet influence long-term fitness.

References:

Bazopoulou, D.; Knoefler, D.; Zheng, Y.; Ulrich, K.; Oleson, B. J.; Xie, L.; Kim, M.; Kaufmann, A.; Lee, Y. T.; Dou, Y.; Chen, Y.; Quan, S.; Jakob, U. (2019) Developmental ROS Individualizes Organismal Stress Resistance and Lifespan. *Nature*, 576, 301–305.

Hall, S. E.; Beverly, M.; Russ, C.; Nusbaum, C.; Sengupta, P. (2010) A Cellular Memory of Developmental History Generates Phenotypic Diversity in *C. Elegans*. *Curr. Biol.* 20, 149–155

Methylation-associated Gene Expression (MaGE) proxies of cellular senescence: scalable systemic senescence biomarkers in relation to disease severity and 174 incident disease outcomes.

Daniel Simpson^{1,2,*}, Samuel Crofts^{1,2,3,*}; **Christos Mavrommatis**^{1,4,*}; Kirstyn Loyva^{1,5}; Yossawat Suwanlikit^{1,2,6}; Thomas White¹; Riccardo Marioni⁷; Kristina Kirschner^{1,5}; Nathan Lebrasseur^{1,8,†}; Tamir Chandra^{1,9,†}

* These authors contributed equally to this work

† These authors jointly supervised this work

¹ Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester MN, USA

² Mayo Clinic Graduate School of Biomedical Sciences, Rochester MN, USA

³ School of Biological Sciences, University of Edinburgh, Edinburgh, UK

⁴ Graduate School for Biological Sciences, University of Cologne, Cologne, Germany

⁵ Department of Hematology, Mayo Clinic, Rochester MN, USA

⁶ Department of Pharmacology, Faculty of Science, Mahidol University, Thailand

⁷ Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK

⁸ Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, Minnesota, USA

⁹ Department of Quantitative Health Sciences, Mayo Clinic, Rochester MN, USA

Cellular senescence is a key hallmark of aging, yet its measurement remains limited by invasive, tissue-specific techniques — unsuitable for large-scale cohort research. We present MaGE (Methylation-associated Gene Expression predictors) — the first DNA methylation-based proxies of senescence gene expression, providing a whole-blood-derived, systemic measure of senescence burden, establishing a new class of tool via DNAm-based RNA prediction. MaGE was developed via Elastic Net on paired DNAm and qPCR for p16INK4A, p14ARF and p21CIP1 (n=514). MaGE scores associated with COVID-19 severity and Crohn's disease. Across 174 incident disease outcomes and all-cause mortality (10-year follow-up; n=18,859), MaGE generated 49 Bonferroni-significant associations across 18 unique diseases and mortality ($P < 0.05/174$), with strongest associations for MaGE-p16/Pulmonary Fibrosis ($HR=2.10$, $P=1.99 \times 10^{-5}$) and MaGE-p21/Alcoholic Liver Disease ($HR=2.64$, $P=1.94 \times 10^{-5}$) — outperforming 14 epigenetic clocks and standard clinical risk factors, including FEV1 and smoking. MaGE transforms a specialized assay into a scalable senescence biomarker.

SAM depletion by a proline to polyamine shunt is sensed by the elongator complex to promote longevity

Felix A.M.C. Mayr^{1,2,3,*}; Maxime J. Derisbourg^{2,3}; Anchal Srivastava³; Naomi Park²; Sebastian Uhrig²; Gabriel A. Guerrero³; Dennis S. Gadalla³; Sebastian Grönke³; Linda Partridge^{1,3}; John Labbadia¹; Martin S. Denzel^{2,3,4,5}

¹*Institute of Healthy Ageing, Department of Genetics, Evolution and Environment, Division of Biosciences, University College London, London, United Kingdom*

²*Cambridge Institute of Discovery, Altos Labs, Cambridge, United Kingdom*

³*Max Planck Institute for Biology of Ageing, Cologne, Germany*

⁴*Cologne Excellence Cluster Cellular Stress Response in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany*

⁵*Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany*

* Correspondence: f.mayr@ucl.ac.uk

Metabolic state, mRNA translation, and the tuning of stress response pathways become deregulated with aging, and their modification can prolong survival. Their coordinated interaction, however, remains poorly understood. In a forward genetic screen in *Caenorhabditis elegans* for resistance to the ribosomal toxin gentamicin (G418), we discovered a mutation in the gene encoding pyrroline-5-carboxylate reductase 1 (*pycr 1*), responsible for the last step in de novo proline biogenesis. *pycr 1* mutant worms were long-lived, but had only slightly reduced proline levels. Instead, we observed a strong depletion of S adenosyl methionine (SAM) in *pycr 1* mutants due to an increased proline to polyamine shunt, and dietary supplementation of methionine fully suppressed their lifespan extension. Thus, *pycr 1* mutants model a state of methionine restriction, which is associated with longevity. SAM is required for tRNA maturation and thus essential for accurate and efficient mRNA translation. Protein synthesis dysregulation activates heat shock transcription factor HSF 1, and a transcriptome analysis of *pycr 1* mutants revealed significant HSF 1 target gene expression. As expected, *pycr 1* longevity was *hsf 1* dependent, however, G418 resistance was partially *hsf-1* dependent. G418 occupies and constricts the ribosomal decoding center, which results in loss of tRNA selection and accommodation. Loss of elongator complex function depletes tRNA wobble base modifications and we observed that this was sufficient to alleviate G418 toxicity. Moreover, we found that reduced elongation complex function induces longevity in WT but not in *pycr-1(wrm22)* worms. Our observations indicate that the elongator complex is a sensor for SAM depletion and mediates an HSF-1 independent hormetic stress response.

Reversibility of the Senescence Growth Arrest after CDK4/6 Inhibitor Therapy

Miralles-Dominguez, A.¹; Pérez-Sánchez, I.¹; Prados, M.-A.¹; Failde-Fiestras, A.¹; Paredes-Paredes, R.¹; Lorenzo-Rodríguez, L.¹; Da Silva-Álvarez, S.^{1,2}; Collado, M.^{1,3}

¹Laboratory of Cell Senescence, Cancer and Aging, Center for Research in Molecular Medicine and Chronic Diseases (CiMUS), University of Santiago de Compostela, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain.

²Center for Research in Biological Chemistry and Molecular Materials (CiQUS), Department of Biochemistry and Molecular Biology, University of Santiago de Compostela, Santiago de Compostela, Spain.

³Department of Immunology and Oncology (DIO), Centro Nacional de Biotecnología (CNB-CSIC), Madrid, Spain.

Cellular senescence is a hallmark of aging characterized by a stable cell cycle arrest triggered by stressors such as anticancer therapies. In aging, senescent cell accumulation contributes to age-associated diseases, such as cancer. CDK4/6i induces a senescence-like phenotype in HR+/HER2- breast cancer cells, although relapses after treatment withdrawal are frequent.

Here, we investigated the reversibility of CDK4/6i-induced senescence in human and murine tumor cell lines and immortalized primary cells. Across all models analyzed, cells resumed proliferation after drug withdrawal, indicating that this state is reversible. Importantly, regrown cells remained sensitive to subsequent treatment, arguing against resistant clone expansion and suggesting that senescent-like cells can re-enter the cell cycle. In addition, SA- β -gal-positive sorted cells were able to proliferate.

These findings support the concept that therapy-induced senescence is a dynamic cellular state. Understanding the mechanisms underlying senescence escape may help prevent tumor relapses and support strategies targeting senescent cell persistence in aging.

Decoding age-related changes on cell-type specific GRNs in the naturally short-lived African turquoise killifish

Muñoz-Gil, L.¹; Hernández, V.¹; Manzo, S.; Ardila-García, L.; Naranjo, S. & Tena, J.J.¹

¹Andalusian Center for Developmental Biology (CABD), Consejo Superior de Investigaciones Científicas/Universidad Pablo de Olavide/Junta de Andalucía, Sevilla, Spain)

Aging reshapes gene expression through epigenetic dysregulation and chromatin remodeling, yet the cell-type-specific regulatory logic driving this process remains largely unknown. Here we present a multi-omic approach to decode gene regulatory network (GRN) dynamics across the lifespan using the turquoise killifish, a naturally short-lived vertebrate model. Using snMultiome (snRNA-seq + snATAC-seq), we will profile three aging-relevant tissues — brain, liver and heart — in both males and females, and reconstruct age- and cell-type-specific GRNs by identifying key transcription factors, target genes and cis-regulatory elements. This physiological aging atlas will then serve as a reference to assess how age-driven GRN reorganizations are conserved, accelerated or fundamentally altered in three age-related disease models: diet-induced steatohepatitis, cardiac arrhythmia and a Parkinson's disease-like model. Together, this work aims to identify the key regulatory modules driving aging and their role in pathological contexts, potentially revealing novel therapeutic targets.

Social disconnection, metabolomic ageing and cardiometabolic outcomes

Mutz, J.¹; Gilchrist L.²; Fancourt, D.³

¹ *Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom.*

² *Centre for Preventive Neurology, Wolfson Institute of Population Health, Queen Mary's University of London, London, United Kingdom.*

³ *Department of Behavioural Science and Health, University College London, London, United Kingdom.*

Background: Social isolation and loneliness raise cardiometabolic risk, but the metabolic pathways are unclear. We tested whether isolation, loneliness and their combination relate to metabolomic ageing and incident cardiometabolic disease, using Mendelian randomisation (MR) for causality and mediation.

Methods: In UK Biobank adults, we examined cross-sectional links of isolation/loneliness with two metabolomic ageing measures (MileAge delta; Metabolomic Mortality Profile Score). Cox models tested prospective links with incident disease. Two-sample MR (UK Biobank, FinnGen, MVP) assessed causality.

Results: In up to 239,411 adults (mean age 56.9; 54.1% female; 13.7-year follow-up), both exposures showed dose-response links with metabolomic ageing, strongest when combined. All deficits and scores predicted higher cardiometabolic hazards. MR supported causal effects on coronary atherosclerosis, MI and type 2 diabetes; mediation was non-significant.

Conclusions: Isolation and loneliness relate to metabolic dysregulation and cardiometabolic risk, MR supporting causal effects, though mediation via metabolomic ageing was unsupported.

Redox selection in the airway as a blueprint for aging-related stress adaptation

Osuna de la Peña, D.¹; Laidlaw, S.²; Przybilla, M. J.²; Ding, C.²; Alhendi, A.¹; Stoichkova, Z.¹; Zheng, H.¹; Gowers, K. H. C.¹; Campbell, P. J.²; Nangaila, J.²; & Janes, S. M.¹

¹*Lungs for Living Research Center, UCL Respiratory, University College London, London, UK*

²*Wellcome Sanger Institute, Hinxton, United Kingdom*

Tobacco smoking is a major source of morbidity and mortality which involves several proximal causes of aging: oxidative stress, DNA damage, somatic selection and epigenetic alterations. Genomic studies in cancer have shown that smoking is strongly associated with redox adaptation, especially in the respiratory tract, but whether this phenotype arises in normal tissues is unclear. Here, we leveraged functional screens of primary bronchial epithelial cultures exposed to tobacco smoke and characterized their genomic, epigenomic and transcriptomic signatures. We found that smoke exposure increases basal cell fitness in a smoking status-dependent manner. This was not associated with specific driver mutations but with demethylation of the redox master regulator NFE2L2 and several of its target genes. Accordingly, basal cells from smokers exhibited enhanced antioxidant responses, survival, senescence resistance and buffering of mutagenesis. These findings suggest that tobacco smoke establishes a functional landscape characterized by oxidative stress resistance at the cost of increased cancer risk. Such a trade-off may be a generalizable feature of proliferative tissues under stress.

Short telomeres in the hematopoietic system promote inflammatory signalling and impair regeneration after acute lung injury

Öztürk, S.^{1,2}; Kopatscheck, J. S.^{1,2}; Ye, J. L.³; Büchler, G.³; Blume, J.³; Hildebrand, C. B.^{1,2}; Pich, A.⁴; Mühlfeld, C.^{5,6}; Bär, C.^{3,7}; Brandenberger, C.^{1,2,5}

¹Institute of Functional Anatomy, Charité – Universitätsmedizin Berlin, Berlin, Germany,

²German Centre for Lung Research (DZL), Associated Partner, Berlin, Germany,

³Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Hannover, Germany,

⁴Institute of Toxicology, Core Facility Proteomics, Hannover Medical School, Hannover, Germany,

⁵Institute of Functional and Applied Anatomy, Hannover Medical School, Hannover, Germany,

⁶Biomedical Research in End-stage and Obstructive Lung Disease Hannover (BREATH), Member of the German Centre for Lung Research (DZL), Hannover, Germany,

⁷Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), Hannover, Germany

Aging hematopoietic cells may contribute to severity of acute lung injury (ALI) in elderly. To test this, development of ALI was studied in an aging model of telomerase reverse transcriptase (Tert) knockout (KO) mice with short telomeres in the lung or bone marrow (BM), achieved by BM transplantation (Fig 1).

In the acute phase, ALI was most severe in mice with KO BM, indicated by lung mechanics, inflammatory cytokines and increased recruitment of neutrophils. Transcriptomics confirmed findings of enhanced inflammatory signaling and impaired heat shock stress response (HSR) in mice with KO BM. In the regenerative phase, mice with KO BM still showed increased recruitment and activation of macrophages. Ongoing inflammation and deregulated HSR was confirmed by proteomics analysis. Phosphoproteomics further implied that PIM kinases, which are degraded via HSR proteins, contributed to continued macrophage activation during regeneration^{1,2}.

Our data show that hematopoietic cells play a crucial role in development and regeneration of ALI in aging. An impaired HSR could be driving persistent inflammation in macrophages and delaying regeneration.

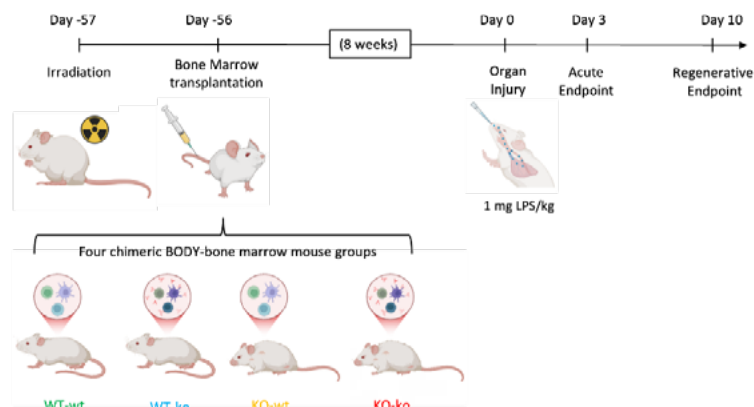


Figure 1: Experimental layout.

References

- Xu, X., Xu, P., Shen, G., Peng, X., Liu, Z., Chen, C., Yu, W., Su, Z., Lin, J., Zheng, G., et al. (2025). Targeting macrophage polarization by inhibiting Pim2 alleviates inflammatory arthritis via metabolic reprogramming. *Cell. Mol. Immunol.* 22, 418–436.
- Shay, K.P., Wang, Z., Xing, P.-X., McKenzie, I.F.C., and Magnuson, N.S. (2005). Pim-1 Kinase Stability Is Regulated by Heat Shock Proteins and the Ubiquitin-Proteasome Pathway.

Disentangling cellular damage and aging

Tsimafei Padvitski¹; Andreas Beyer¹

¹CECAD, University of Cologne, Cologne, Germany

Aging and cellular damage are closely linked across multiple scales, but details of their relationship are not fully resolved. In particular, it remains unclear how much of the aging-associated transcriptional state reflects damage-like programs, how much remains distinct, and how both processes relate to erosion of differentiated cell identity. Here, we addressed this question in podocytes and hepatocytes by comparing independently derived transcriptomic signatures of cellular damage, chronological aging, and cell-type identity, and applied them as single-cell scores in aging and damage datasets.

In summary, aging and damage signatures were highly collinear within each cell type and converged on shared stress-associated pathways, while retaining organ-specific components. In both cell types, increased damage and aging scores were accompanied by reduced cell-type identity. Our results suggest that aging and damage converge on a shared transcriptomic trajectory shaped by progressive erosion of differentiated cellular identity.

Exploring the effects of estradiol on cellular senescence and its implications for female aging

Pagliarin,F.¹; Veeningen,N.¹; Wang,B.¹; & Demaria,M.¹

¹European Research Institute for the Biology of Ageing (ERIBA), University Medical Center Groningen, 9713AV Groningen, The Netherlands

Sex differences are a hallmark of human aging, with women and men following distinct biological trajectories across the lifespan. A key divergence emerges during midlife, when women undergo a relatively rapid decline in circulating estrogens as a consequence of menopause, whereas in men sex hormone levels decrease more gradually. This abrupt endocrine transition in women coincides with the loss of the early-life cardiometabolic advantage and with increased vulnerability to metabolic, musculoskeletal, and degenerative conditions in later life.

Estrogens are central regulators of homeostasis, coordinating energy metabolism, tissue maintenance, and structural integrity across multiple organs. Their decline at menopause is associated with broad physiological remodeling, including increased adiposity, reduced bone strength, and impaired skeletal muscle performance. Collectively, these changes highlight the importance of estrogen signaling in preserving tissue function during aging, although the underlying cellular mechanisms remain incompletely understood.

Cellular senescence is increasingly recognized as a driver of organismal aging. It is characterized by stable cell-cycle arrest and the acquisition of a pro-inflammatory secretory phenotype (SASP), which promotes tissue dysfunction and chronic inflammation when senescent cells accumulate. Senescence arises in response to different types of cellular stress and is shaped by signals from the organism, including hormonal cues. In this context, the loss of estradiol at menopause may contribute to conditions that enhance senescence accumulation and tissue decline, although the relationship remains to be clarified.

In this study, we investigate the role of estradiol in regulating cellular senescence and age-related functional changes. Using aged female mice treated with chronic estradiol supplementation, we assess body composition and motor performance. Treated animals show improved motor function, reduced fat mass, and increased lean mass compared to controls. In parallel, in vitro experiments evaluate whether estradiol affects the establishment of senescent phenotypes and related inflammatory outputs.

Preliminary results suggest that estradiol may attenuate age-associated functional decline and influence senescence-associated features, supporting a link between estrogen deficiency and cellular senescence processes. Understanding how estradiol shapes both cellular and organismal aging will be essential for developing targeted, safe, and personalized interventions to promote healthy aging in women.

Aging in the loop: what is missing from the Big Beautiful training data for Foundation Model of aging pharmaco-biology?

Leon Peshkin (peshkin@gmail.com)

Beth Israel Deaconess Medical Center, Boston, MA 02115, USA

A Foundation Model of aging pharmaco-biology would predict how an aging organism responds to pharmacological intervention—from molecules to cells to tissues—by integrating multi-species single-cell expression models with life-span data across interventions. Thousands of published experiments in dozens of species seem a natural starting point, and curated databases already exist. Yet our work on control standardization and community curation (ALEC&COLLIDA) reveal, this data is too heterogeneous and incomplete to train such a model. Questionable quality survival curves are buried in figures, controls are incomparable across labs, dosing and timing are inconsistently reported, and negative results are systematically absent. We argue that realizing this vision requires not merely aggregating existing data but building specialized, scalable experimental and curation workflows — and systematically re-investigating hundreds of compounds. We outline how such workflows could be organized.

References:

1. Spiridonova O, Kriukov D, Nemirovich-Danchenko N, and Peshkin L (2024). On standardization of controls in lifespan studies. *Aging* 16, 3047–3055.

The Potential Role of Cysteine and Associated Metabolic Pathways in the Dietary Restriction Response in *Drosophila*

Phillips, E.J.¹; Simons, M.J.P.¹

¹ School of Biosciences, University of Sheffield, Sheffield, United Kingdom

Dietary Restriction (DR) extends lifespan across diverse taxa. Amino acid availability and its metabolism are thought to be key in this process although it may not provide a universal mechanistic explanation (Gautrey and Simons, 2021). The contribution of individual amino acids in the diet to ageing remains understudied. While the thiol containing amino acid, cysteine, is a vital antioxidant precursor and has been shown to extend life-span (Ma et al., 2025), it has also been shown to induce mitochondrial ageing by disrupting iron homeostasis (Hughes et al., 2020). We find that dietary cysteine supplementation suppresses the longevity benefits of DR in *Drosophila*. Comparative transcriptomics across six species revealed differential expression of a number of cysteine metabolism genes under DR and conditional RNAi knockdown of these genes also reduced mortality risk under DR. The addition of cysteine to DR diets significantly increased mortality when the cysteine clearance gene CDO-1 was knocked down, suggesting that an inability to clear cysteine has a detrimental effect on lifespan. In addition, we show that iron supplementation rescues toxicity caused by cysteine, suggesting that previously characterised cysteine-iron interactions present a physiological limitation that may constrain DR. These results indicate longevity outcomes are sensitive to fluctuations in specific metabolic pathways and amino acid balances, rather than broad macronutrient restriction alone.

References:

1. Gautrey, S.L. and Simons, M.J., 2022. Amino acid availability is not essential for life-span extension by dietary restriction in the fly. *The Journals of Gerontology: Series A*, 77(11), pp.2181–2185.
2. Hughes, C.E., Coody, T.K., Jeong, M.-Y., Berg, J.A., Winge, D.R., Hughes, A.L., 2020. Cysteine Toxicity Drives Age-Related Mitochondrial Decline by Altering Iron Homeostasis. *Cell* 180, 296–310.e18.
3. Ma, Y., Chen, M., Huang, K., Chang, W., 2025. The impact of cysteine on lifespan in three model organisms: A systematic review and meta-analysis. *Aging Cell* 24, e14392.

New $\Delta 246p53$ isoform responds to DNA damage to enhance p53 family functions in cellular senescence and ageing

Shrutee N. Parkar¹; **Ana Catarina Ramalho**^{2,3} & Marco M. Candeias^{1,2,3,4,*}

¹ Building E-108, Graduate School of Medicine, Kyoto University, Kyoto 606-8501, Japan

² Department of Human Genetics, National Institute of Health Doutor Ricardo Jorge, Lisbon 1649-016, Portugal

³ BioISI-Biosystems & Integrative Sciences Institute, Faculty of Sciences, University of Lisbon, Lisbon 1749-016, Portugal

⁴ MARCO-Molecular Ageing, RNA Chemistry & Oncogenesis lab, MIA-Portugal-Multidisciplinary Institute of Ageing, University of Coimbra, Coimbra 3004-504, Portugal

* Correspondence: candeias@gmail.com

p53 is with little doubt one of the most powerful genes in our genome, as it makes growth vs arrest, repair vs replacement, catabolism vs anabolism, life vs death decisions in the cell. An alteration or malfunction in p53 may lead to cancer, degeneration or premature ageing. So, it is not surprising that p53 is also one of the most complex and tightly regulated genes, encoding for at least 10 RNA variants and 12 widely accepted protein forms. Here we identify one new p53 protein isoform of approximately 18 kDa that we termed $\Delta 246p53$. $\Delta 246p53$ is translated from an alternative translation initiation site (TIS) in codon 246. TIS-246 is preceded by a strong Kozak sequence and appears conserved in vertebrates, from sea lamprey to humans. $\Delta 246p53$'s origin and expression in cells were confirmed by frameshift and start codon mutations; five different antibodies against several epitopes from its N-terminus down to its C-terminus and one against the DNA binding domain region just upstream of its initiator methionine working as negative control; as well as siRNAs and an antisense oligo targeting TIS-246, which knocked-down $\Delta 246p53$ with little or no effect on full-length (FL) p53 protein levels. $\Delta 246p53$ was induced by DNA damage and triggered senescence and impaired tumour formation/growth in colony formation assays. Mechanistically, $\Delta 246p53$ interacted with FLp53, leading to a decrease in the expression of downstream target genes HDM2 and p21. Concurrently, it also interacted with $\Delta Np63$, leading to p53-independent p63-mediated activation of p21, a known senescence activator. Our results unveil a new naturally occurring and tightly controlled factor with specific functions in p21 regulation and senescence. Future studies on $\Delta 246p53$ are likely to help us better understand and control the processes of tumour suppression and ageing.

Micronutrient and metabolomic profiles associate with specific systemic multimorbidity profiles

Anna M. Affeldt^{1,3°}; Verena Rhebaum^{1°}; Wilhelm Stahl²; Thomas Benzing^{1,3}; Roman-Ulrich Müller⁴; Maria Cristina Polidori^{1,3,5~}; Philipp Antczak^{5,6*}; Joris Deelen^{5,7,8*}

¹Ageing Clinical Research, Department II of Internal Medicine and Centre for Molecular Medicine Cologne, University of Cologne, Faculty of Medicine and University Hospital Cologne, Kerpener Str. 62, 50937Cologne, Germany;

²Institute for Biochemistry and Molecular Biology I, medical Faculty, Heinrich-Heine-University, Moorenstr. 5 40225 Düsseldorf, Germany

³Department II of Internal Medicine, Cologne, University of Cologne, Faculty of Medicine and University Hospital Cologne, Kerpener Str. 62, 50937Cologne, Germany;

⁴Department of Nephrology, Medical Faculty, University Hospital Düsseldorf, Heinrich-Heine-University, Germany

⁵Cologne Excellence Cluster on Cellular Stress- Responses in Aging- Associated Diseases (CECAD), University of Cologne, Faculty of Medicine and University Hospital Cologne, Joseph-Stelzmann-Str. 26, 50931 Cologne, Germany;

⁶Department II of Internal Medicine and Centre for Molecular Medicine Cologne, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

⁷Section of Molecular Epidemiology, Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, The Netherlands

⁸Max Planck Institute for Biology of Ageing, Cologne, Germany

[°]equal contribution

^{*}equal supervision-

~corresponding

Background: Multimorbidity frequently occurs in distinct clusters, yet its underlying biomolecular and prognostic signatures remain poorly defined.

Methods: We included 195 older patients (median 76 (IQR 8), 49.2% F) who underwent a comprehensive geriatric assessment. Metabolites and carotenoids were quantified in blood using HPLC and NMR metabolomics were quantified in blood. Multivariate associations among clinical, micronutrient and metabolic variables were explored using LASSO and visualised in an interaction network.

Results: Micronutrients were predominantly associated with systemic diagnoses such as sleep apnea (coef -2.77) or chronic kidney disease requiring dialysis (coef - 7.07). Multivariate association of MetaboHealth highlighted diabetes ($p < 0.001$), cancer ($p < 0.01$) and respiratory illness ($p < 0.01$) as key diagnoses driving the score.

Conclusion: These findings suggest that multimorbidity clusters are characterized by specific metabolic profiles with potential prognostic relevance.

Establishment of an in vitro model of neuronal aging to dissect surface proteome alterations underlying cognitive decline

Inês S Santos¹; Ana R Afonso^{1,2}; Jeannette Schmidt^{1,2}; **Luís F Ribeiro**^{1,2}

¹ Multidisciplinary Institute of Aging (MIA-Portugal), University of Coimbra (UC), PT

² Centre for Innovative Biomedicine and Biotechnology (CIBB), UC, PT

Approximately 40% of the healthy population over 60 years of age experiences cognitive decline, underscoring the strong association between aging and cognition. Interconnected brain regions involved in cognitive function, such as the hippocampus and cortex, appear particularly vulnerable to aging, displaying structural and functional alterations in the absence of significant neuronal loss. These alterations may be driven by changes in the neuronal surface proteome; however, detailed characterization of neuronal proteomic alterations during aging remains limited.

This study aims to characterize age-related changes in the neuron-type-specific surface proteome, enabling the identification of intrinsic neuronal aging signatures that would otherwise be masked by other cellular populations. Moreover, because neurons rely on membrane-associated machinery for proper function, focusing on the membrane proteome will help us better understand circuit dysfunction and identify potential druggable targets.

We established an in vitro neuronal aging model using primary mouse hippocampal and cortical cultures maintained for 14, 21, and 28 days in vitro (DIV), corresponding to distinct stages of neuronal maturation and aging. At 28 DIV, neurons exhibited reduced nuclear size, increased endosomal size, and elevated p21 labeling, consistent with an aged neuronal phenotype. Furthermore, we observed a decrease in inhibitory synapse density in both hippocampal and cortical cultures, whereas excitatory synapse density decreased only in cortical cultures. These findings highlight the importance of assessing cell-type-specific and brain-region-specific differences during investigations of neuronal aging.

In addition, we are evaluating the effects of pro-aging and anti-aging compounds to validate our model and characterize novel compounds that prevent neuronal aging. Finally, we are using this translationally relevant aging model to investigate cell-type-specific alterations in the neuronal membrane proteome during aging.

Integrated Longitudinal Metabolic and Proteomic Profiling Reveals Sex-Dependent Trajectories of Aging

Ricciardi, L.¹; Daraki, G.¹; Ohl, C.¹; Reuter, M.¹; & Morrison, H.³

Leibniz Institut für Alternsforschung, Jena – Fritz Lipmann Institute, Germany

Aging is associated with progressive alterations in systemic energy metabolism. We combined longitudinal metabolic phenotyping with stage-matched tissue proteomics to define sex-specific trajectories of metabolic aging in mice at young (6–7 months), adult (14–16 months), and old (22–24 months) life stages. Metabolic cage analyses assessed energy expenditure (EE), respiratory exchange ratio, and voluntary activity, complemented by body composition measurements and μ CT-based quantification of subcutaneous (SAT) and visceral adipose tissue (VAT). Males exhibited a progressive decline in EE across aging, whereas females showed an early reduction followed by stabilization. SAT decreased more markedly than VAT in both sexes, although females retained higher SAT levels at advanced age. Proteomic profiling of liver, skeletal muscle, and adipose tissue revealed tissue- and sex-specific remodeling, including reduced mitochondrial and oxidative phosphorylation pathways in liver. These findings demonstrate distinct sex-dependent metabolic aging trajectories linked to coordinated tissue-specific proteomic adaptations.

Deciphering the molecular bases of long lifespan in bats by multi-species comparative RNAseq analysis of blood

Sebastien Riquier¹; Marek Uvizl¹; Megan Power¹; Margaret Weber¹; Tadhg Lonergan¹; Athanasios Toros¹; Gwennaelle Hurpyl¹; Sébastien Puechmaillé²; Frederic Touzalin¹; Sonja Vernes³; Ine Alvarez van Tussenbroek³; Dina Dechmann⁴; Roger Ransome⁵; Gareth Jones⁵; Emma C. Teeling¹

¹UCD, School of Biology and Environmental Science, Belfield, Dublin 4, Ireland.

²Institut des Sciences de l'Evolution de Montpellier (ISEM), University of Montpellier, France.

³School of Biology, The University of St Andrews, Fife, UK

⁴Department of migration, Max Planck Institute of Animal Behavior, Radolfzell, Germany.

⁵School of Biological Sciences, University of Bristol, Life Sciences Building, 24 Tyndall Avenue, Bristol BS8 1TQ, UK.

Across the animal kingdom, all are not equal against ageing. Some bat species have evolved exceptional ranges of healthspans given their body sizes that distinguish them from other mammals. Understanding the regulatory bases of these lifespan differences and their resistance to diseases remains to be determined to understand precisely how long-lived bats possess such exceptional traits. Our past study (Huang et al. 2019) showed that *M. myotis* bats' blood increases expression of DNA repair genes with age, as a potential mechanism of their lifespan. With updated genome and annotations, bioinformatic pipelines for the detection of coding, long non-coding, circular RNA, added to extended bat known age ranges and the new blood samples from 4 additional bat species, we have the opportunity to 1) investigate if longevity mechanisms of *M. myotis* are similar across Chiroptera phylogeny 2) create a catalog of all RNA molecules associated with bat healthspan independently of their nature.

We analysed five longitudinal RNAseq datasets generated from the non-lethally sampled whole blood from aged individuals of 5 bat species : wild *Myotis myotis* (Britany, France), wild *Rhinolophus ferrumequinum* (Woodchester Mansion, Gloucestershire, UK), wild *Molossus molossus* (Gamboa, Panama), captive *Phyllostomus discolor* (St. Andrews, Scotland) and captive *Rousettus aegyptiacus* (Copenhagen zoo, Denmark). Human and mice whole blood datasets downloaded from public databases are used as an outgroup.

We observed that increase of DNA repair was characteristic of *M. molossus* and *M. myotis*, in association with their relative phylogenetic proximity and their absence of telomere erosion with age. Additionally these two species expressed significantly more basal levels of DNA repair genes compared to other species. In contrast, while *P. discolor* showed decrease of DNA repair with age, *R. aegyptiacus* and *R. ferrumequinum* showed non-linear expression patterns, suggesting alternative mechanisms for their longevity be determined.

WGCNA network analysis shows no clear blood cell marker pattern associated with DNA repair, making the blood cell population expressing this DNA repair to be determined.

Overall, this multi-specie outlook on blood gene expression shows extensive differences of ageing mechanisms in bats and will permit us, in fine, to synthesise a unique and robust knowledge on longevity mechanisms in the Chiroptera order.

The aging modulator miR-29 is essential for adult cardiomyocyte function

Roiz-Valle, D.^{1,2,3}; Folgueira, C.^{4,5,6}; Moledo-Nodar, L.^{1,2}; Tartiere, A.G.^{1,2}; Cicuéndez, B.^{4,7,8}; Romero-Becerra, R.⁴; Rodríguez, F.⁹; He, Y.-W.¹⁰; Freije, J.M.P.^{1,2,3}; Sabio, G.^{4,7}; López-Otín, C.^{1,11,12}; Caravia, X.M.¹³; Ugalde, A.P.^{1,2}

¹Departamento de Bioquímica y Biología Molecular, Instituto Universitario de Oncología del Principado de Asturias (IUOPA), Universidad de Oviedo, Oviedo, Spain

²Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain

³Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain

⁴Department of Myocardial Pathophysiology, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

⁵Department of Physiology, CIMUS, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain.

⁶CIBER Fisiopatología de la Obesidad y Nutrición (CIBERObn), 15706, Spain.

⁷Organ Crosstalk in Metabolic Diseases Group, Molecular Oncology Program, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

⁸Faculty of Experimental Science, Universidad Francisco de Vitoria, 28223 Madrid, Spain

⁹Unidad de Transgénicos, Bioterio e Imagen Preclínica, Servicios Científico-Técnicos, Universidad de Oviedo, Oviedo, Spain

¹⁰Department of Integrative Immunobiology, Duke University School of Medicine, Durham, NC, USA

¹¹Facultad de Ciencias de la Vida y la Naturaleza, Universidad Nebrija, Madrid, Spain

¹²Centre de Recherche des Cordeliers, Université de Paris Cité, Sorbonne Université, INSERM, Paris, France

¹³Instituto de Biomedicina y Biotecnología de Cantabria, Departamento de Biología Molecular, Universidad de Cantabria, Santander, Spain.

Aging is the main risk factor for cardiovascular diseases, underscoring the need to identify molecular regulators that sustain cardiac function during aging.

The microRNA miR-29 is a well-established aging-associated regulator as its expression increases with age, and its overexpression promotes premature aging. Here, we define the role of miR-29 in the adult cardiomyocyte (CM) by generating an inducible, CM-specific miR-29-deficient mouse model (Heart-iKO). Heart-iKO mice develop dilated cardiomyopathy (DCM) with reduced ejection fraction, leading to premature death.

Mechanistically, Heart-iKO CMs exhibit alterations in mitochondrial structure and function. Transcriptomics of bulk heart and isolated CMs revealed a downregulation of oxidative phosphorylation and electron transport chain gene programs. A similar mitochondrial impairment was also observed in miR-29-deficient human CMs derived from induced pluripotent stem cells. Together, these findings highlight the context-dependent role of miR-29 in the aging heart: although its upregulation promotes premature aging, basal expression is required to maintain mitochondrial function and prevent heart failure.

Embracing aging complexity from within-individual heterogeneity to non-linear age-associated trajectories

Sadoughi, B.^{1,2}; Petersen, R.³; Mundry, R.^{4,5,6}; Ruiz Lambides, A.V.⁷; Brent, L.⁸; Platt, M.^{9,10}; Montague, M.⁹; Melin, A.D.^{11,12,13}; Higham, J.^{14,15}; Lea, A.³; Snyder-Mackler, N.^{1,2}

¹ School of Life Sciences, Arizona State University, Tempe, USA

² Center for Evolution and Medicine, Arizona State University, Tempe, USA

³ Department of Biological Sciences, Vanderbilt University, Nashville, USA

⁴ Leibniz ScienceCampus Primate Cognition, German Primate Center, Göttingen, Germany

⁵ Department for Primate Cognition, Georg-August-Universität Göttingen, Göttingen, Germany

⁶ Cognitive Ethology Laboratory, German Primate Center, Göttingen, Germany

⁷ Caribbean Primate Research Center, University of Puerto Rico, Punta Santiago, Puerto Rico

⁸ Centre for Research in Animal Behaviour, University of Exeter, Exeter, United Kingdom

⁹ Department of Neuroscience, University of Pennsylvania, Philadelphia, USA

¹⁰ Department of Psychology, University of Pennsylvania, Philadelphia, USA

¹¹ Department of Anthropology and Archaeology, University of Calgary, Calgary, Canada

¹² Department of Medical Genetics, University of Calgary, Calgary, Canada

¹³ Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Canada

¹⁴ Department of Anthropology, New York University, New York, USA

¹⁵ New York Consortium in Evolutionary Primatology, New York, USA

Aging varies across tissues and the lifespan, yet the extent and temporal structure of this heterogeneity remain poorly characterized. DNA methylation provides a powerful molecular readout of biological aging, enabling comparisons of age-associated dynamics across tissues. Using rhesus macaques, we analyzed DNA methylation profiles from 14 tissues to ask how epigenetic aging trajectories differ across tissues and if they follow linear or non-linear patterns over time. We identify substantial within-individual heterogeneity in aging, with some tissues exhibiting markedly stronger age-associated methylation changes than others¹. To characterize these dynamics, we developed an R package for scalable non-linear modeling of omics data. Applied to >100,000 genomic regions in thymus and liver, our framework revealed strikingly distinct aging trajectories: the thymus showed widespread non-linear decreases in methylation, whereas the liver exhibited a mixture of linear increases and decreases. We further identify a period of maximal epigenetic remodeling in the thymus in early adulthood. Together, these findings reveal pronounced cross-tissue heterogeneity in epigenetic aging and highlight the importance of modeling non-linear dynamics in studies of aging biology.

References:

1. Sadoughi, B., Petersen, R., Patterson, S.K., Slikas, E., Adjandba, C., Ryan, N., Costa, C.E., Newman, L.E., Watowich, M.M., Kelsey, C.R., et al. (2026). Age and early life adversity shape heterogeneity of the epigenome across tissues in macaques. Science, in press.

Cellular Senescence in the Aging Liver Contributes to Cognitive Decline Crosstalk between Liver and Brain

Lilian Gomez¹; Gung Lee¹; Ana Catarina Franco¹; Seunghwa Woo¹; Sundeep Khosla¹, Diana Jurk¹

¹ *Mayo Clinic, Department of Physiology and Biomedical Engineering, Robert and Arlene Kogod Center on Aging, Rochester, MN USA*

Aging is characterized by the accumulation of senescent cells in multiple tissues, including liver and brain. Previous work from our group showed that clearance of p16⁺ senescent cells alleviates brain inflammation, improves cognition, and reduces liver steatosis in aging and obesity. Clinical studies further link liver diseases with cognitive decline, suggesting a liver–brain axis, although the underlying mechanisms remain unclear. We hypothesize that hepatic senescence accelerates brain dysfunction during aging. Using p16–LOX–ATTAC;Alb–Cre mice, we show that aged mice exhibit memory impairment, while targeted elimination of senescent hepatocytes improves learning and memory. This is accompanied by reduced inflammatory markers in liver, brain, and plasma, as well as decreased hippocampal senescence. Our data suggest the existence of a liver–brain senescence signaling axis mediated by a secreted factor. Finally, we use the mouse model TRF1–FokI to demonstrate that hepatocyte telomere dysfunction contributes to learning and memory decline. Overall, these findings support a functional liver–brain crosstalk in aging, where senescent hepatocytes have a key role in cognitive outcomes, although further studies are needed to define the mechanisms involved.

Pasta, a versatile transcriptomic clock, maps the chemical and genetic determinants of aging and rejuvenation

Salignon J.^{1,2#}; Tsiokou M.^{3&}; Marqués P.^{3&}; Rodríguez-Díaz E.³; Ang H.^{1,†}; Pietrocola F.^{3#}; Riedel C.G.^{1,2#}

¹ Department of Medicine Huddinge, Karolinska Institute, Huddinge, Sweden

² Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, Stockholm, Sweden

³ Department of Cell and Molecular Biology, Karolinska Institute, Solna, Sweden

Corresponding authors: jerome.salignon@ki.se, federico.pietrocola@ki.se, and christian.riedel@su.se

& Equal contribution

† Present address: Institute of Molecular and Cell Biology, Agency of Science, Technology and Research, Singapore

Human transcriptomic aging clocks (TACs) can track biological age but remain limited by platform dependence, tissue specificity, or restricted accessibility. To address this, we developed Pasta, a robust and broadly applicable human TAC, built using a novel 'age-shift' learning framework. Pasta accurately predicted relative age across diverse tissues and data types, including bulk and single-cell RNA-Seq as well as microarray data. Its predictions aligned with senescent and stem-like cellular states and relied on model coefficients enriched for p53 and DNA damage response pathways. Applied to the Connectivity Map L1000 dataset, Pasta identified both established and previously unrecognized age-modulatory compounds and genetic perturbations, highlighting mitochondrial translation and mRNA splicing as key determinants of cellular propensity for aging and rejuvenation, respectively. Experimental validation confirmed pralatrexate as a potent senescence inducer and piperlongumine as a rejuvenating agent in human cells. Together, these findings establish Pasta as a versatile and accessible tool for aging research and therapeutic discovery.

Evolutionary conserved diapause mechanisms of slowed aging and rejuvenation

Sandt W., Meyer,D.; Schumacher, B.

¹*CECAD, University of Cologne, Cologne, Germany*

Aging is associated with a general decrease in physiological functionality, susceptibility to injury and increased risk of mortality as a function of time. Different species show a distinct plasticity of lifespan and ability to reset their biological age depending on their evolutionary adaptations. Diapause stages can be assumed in invertebrate and vertebrate species to allow individuals an extended survival under adverse environmental conditions. Here, we determine evolutionary conserved patterns of the slowed aging process in diapause and the rejuvenating exit programs. We show that Diapause is not simply youthful stasis but instead is characterized by a general co-expression-relationship between diapause and adult aging across species, as indicated by aging clocks and gene expression signatures that include the attenuation of metabolic processes. However, diapause entry triggers distinctive stress response programs that might explain the slowed aging trajectory. Diapause exit reactivates the metabolic processes and induces repair programs that might support the re-setting of the biological age. Our findings reveal conserved gene expression programs that in distinct species ranging from nematodes to mammals could slow aging and naturally rejuvenate cells and even organisms during diapause exit.

DREAMing of Healthy Aging: Deciphering the Molecular Links Between Sleep, Circadian Rhythms, and Cellular Repair

Valentim, I. S.¹; Romero-Expósito, F. J.²; Schwab, K.¹; Bayar, M.¹; Riege, K.¹; Lange, L.³; Engmann, O.³; Fisher, M.¹; Olmedo, M.²; Hoffmann, S.¹; & Ermolaeva, M. A.¹

¹*Leibniz Institute on Aging – Fritz Lipmann Institute (FLI), Beutenbergstrasse 11, 07745 Jena, Germany*

²*Department of Genetics University of Sevilla, Av. Reina Mercedes s/n, 41012 Sevilla, Spain*

³*Friedrich-Schiller-Universität Jena, Hans-Knöll-Str. 2, 07745 Jena, Germany*

Chronic sleep restriction and circadian disruption contribute to metabolic, cardiovascular, and neurocognitive decline. Using multi-omics, molecular, biochemical, and pharmacological approaches in *C. elegans*, human retinal cells, and mouse brain tissue, we identified the DREAM complex as a conserved regulator of sleep-dependent homeostasis. DREAM levels oscillate with circadian time and increase during wakefulness, promoting chromatin compaction that limits DNA damage. Sustained DREAM activation suppresses translation, oxidative phosphorylation, and stress responses, whereas sleep-associated DREAM decline enables chromatin relaxation and repair. Chronic sleep or circadian disruption maintained elevated DREAM activity, causing persistent chromatin closure, impaired repair, mitochondrial dysfunction, reduced resilience, and accelerated aging. DREAM inhibition restored repair pathways and improved cellular function despite continued circadian disruption. These findings identify DREAM as a molecular link between sleep, circadian rhythms, and aging, and a potential sleep-mimetic therapeutic target.

Evolution of primary cells through replicative crisis to immortality

Schmidt, T.T.^{1,*}; Cosenza, M.R.^{2,*}; Popay, T.³; Przetocka, S.¹; Haggblom, C.¹; Allsing, N.⁴; Lande, K.⁴; Grimstead, J.⁵; Williams, A.⁴; Baird, D.⁵; Dixon, J.³; Korbel, J.O.^{2,#}; Karlseder, J.^{1,#}

¹ *Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA, USA*

² *Genome Biology, European Molecular Biology Laboratory, Heidelberg, Germany*

³ *Gene Expression Laboratory, Salk Institute for Biological Studies, La Jolla, CA, USA*

⁴ *Integrative Genomics and Bioinformatics Core, Salk Institute for Biological Studies, La Jolla, CA, USA*

⁵ *Division of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, UK*

^{*,#} *These authors contributed equally*

Shortening of telomeres, the repetitive, protective ends of eukaryotic chromosomes, restrict the proliferation capacity of human somatic cells by inducing replicative senescence and crisis. During malignant transformation, premalignant cells must overcome these barriers and acquire replicative immortality. Here, we investigate this fundamental step during tumorigenesis using a spontaneous crisis escape model. Single-cell DNA strand-sequencing of crisis cells revealed high genome instability characterized by complex structural variants (SVs). Unexpectedly, spontaneous emerging postcrisis clones showed relative few and simple SVs, suggesting that crisis evolved to stringently counterselect against cells with high genomic instability. However, with accumulating divisions post crisis escape, the immortal postcrisis clones' genomes evolve and amass genomic alterations, including tetraploidization events with subsequent losses and gains of individual chromosomes. Thus, our data indicate that the highly rearranged genomes found in some cancers are not originating from crisis but are acquired after crisis escape and immortalization.

Lower blood cell mitochondrial DNA abundance associates with higher all-cause mortality and aging: a 30-year prospective epidemiological study

Sebe, A.¹; Lautaoja-Kivipelto, J.¹; Jokelainen, J.²; Skarp, S.¹; Kerkelä, R.¹; Pirinen, E.^{1,3,4,5}; & Ukkola, O.^{1,3}

¹Research Unit of Biomedicine and Internal Medicine, Faculty of Medicine, University of Oulu, Oulu, Finland;

²Northern Finland Birth Cohorts, Arctic Biobank, Infrastructure for Population Studies, Faculty of Medicine, University of Oulu, Oulu, Finland;

³Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland;

⁴Biocenter Oulu, University of Oulu, Oulu, Finland;

⁵Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland

Recent epidemiological studies suggest blood cell mitochondrial DNA (mtDNA) abundance as a promising biomarker for aging and disease, though findings remain inconsistent and pathomechanisms unclear. We investigated blood mtDNA abundance in our OPERA cohort (n=1045), assessed in the 1990s and followed for over 30 years, with a second visit in the 2010s. We quantified mtDNA abundance in blood samples from both time points with RT-qPCR. RNA sequencing was performed in 452 follow-up samples. At both time points, lower mtDNA levels were associated with higher overall morbidity and mortality. MtDNA abundance showed a small, but significant decline over two decades. Transcriptomic analyses linked lower mtDNA levels to enhanced inflammatory pathways in immune cells. Our findings highlight blood mtDNA as a potential biomarker for aging and morbidity, with lower levels possibly linked to inflammatory processes. With three decades of follow-up, these results support its use in preventing morbidity and mortality of diverse etiology. Additionally, blood mtDNA emerges as a promising inflammatory biomarker, warranting further exploration in future studies.

PERINATAL OBESITY INDUCES PREMATURE ALVEOLAR AGING BY AT2 CELL DEPLETION VIA IL-6-DRIVEN TRANSCRIPTIONAL STRESS AND GENOME INSTABILITY

Jaco Selle¹; Oleksiy Klymenko²; Bastian Abend¹; Tobias Trojan^{1,3}; Chrysa Nikopoulou⁶; Stephanie Stephan²; David Meyer⁹; Christina Vohlen^{1,4}; Susanne Herold⁷; Ana-Ivonne Vazquez-Armendariz⁸; Peter Tessarz^{5,6}; Stefan Rose-John¹⁰; Werner Seeger^{2,11}; Jörg Dötsch³; Leo Kurian^{4,5,12}; Björn Schumacher^{4,5,9}; Miguel A. Alejandre Alcazar^{1,2,4,5}

¹ University of Cologne, Faculty of Medicine and University Hospital Cologne, Translational Experimental Pediatrics – Experimental Pulmonology, Department of Pediatric and Adolescent Medicine, Cologne, Germany. (jaco.selle@uk-koeln.de).

² Universities of Giessen and Marburg Lung Center (UGMLC), Institute for Lung Health (ILH), Cardio-Pulmonary Institute (CPI), Member of the German Center for Lung Research (DZL), Giessen, Germany.

³ University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Pediatric and Adolescent Medicine, Cologne, Germany.

⁴ University of Cologne, Faculty of Medicine and University Hospital Cologne, Center for Molecular Medicine Cologne (CMMC), Cologne, Germany.

⁵ University of Cologne, Faculty of Medicine and University Hospital Cologne, Cluster of Excellence – Cellular Stress Response in Aging-associated Diseases (CECAD), Cologne, Germany.

⁶ Max Planck Research Group „Chromatin and Ageing“, Max Planck Institute for Biology of Ageing, Cologne, Germany.

⁷ Department of Internal Medicine, Universities of Giessen and Marburg Lung Center, member of the DZL and CPI, Justus Liebig University, Gießen, Germany.

⁸ Cardio-Pulmonary Institute (CPI) and Department of Pulmonary and Critical Care Medicine and Infectious Diseases, Universities of Gießen and Marburg Lung Center (UGMLC), Member of the German Center for Lung Research (DZL), Justus-Liebig University Gießen, Gießen, Germany.

⁹ Institute for Genome Stability in Aging and Disease, Medical Faculty, University Hospital and University of Cologne, Cologne, Germany.

¹⁰ Biochemical Institute, Christian-Albrechts Universität zu Kiel, Kiel, Germany;

¹¹ Department of Lung Development and Remodeling, Max-Planck-Institute for Heart and Lung Research, Member of the German Center for Lung Research (DZL), Bad Nauheim, Germany.

¹² University of Cologne, Faculty of Medicine and University Hospital, Institute for Neurophysiology, Cologne, Germany.

Background: Obesity is strongly linked to meta-inflammation and cardiopulmonary diseases. Although obesity and aging share overlapping pathways, their effects on genomic stability, translational stress and the interplay between these factors in lung development remain poorly understood.

Aims: Does perinatal obesity induce premature alveolar aging and arrest of alveolarization via meta-inflammation-triggered genomic instability in alveolar epithelial type 2 cells (AT2).

Methods and Results: In murine models, perinatal obesity caused a life-long emphysema-like lung structure. These changes were associated with a depletion of AT2. Mechanistically, we identified increased DNA damage response (DDR) and elevated RNA/DNA hybrids, ultimately resulting in impaired RNA synthesis and loss of AT2. Lung ATAC-Seq and AT2-specific RNA-Seq identified DDR and repair processes together with aging-associated pathways. Gen-length and AT2 sub-population analysis revealed an obesity-induced aging phenotype. IL-6 knock-out and pharmacological IL-6-inhibition protected from these changes and emphysema. In human AT2, serum from lean and obese children, as well as in murine AT2 and alveolospheres we confirmed WAT-secretome and IL-6 as drivers of DDR, which is reversible by RNaseH or IL-6 inhibition.

Conclusion: Perinatal obesity drives premature alveolar aging through AT2-depletion via IL-6 mediated genomic instability and increases susceptibility to chronic lung disease.

Naturally recurring embryonic loss reveals a sperm-dependent link between reproduction and aging

Hagar Setty^{1,2} and Björn Schumacher^{1,2}

¹*Institute for Genome Stability in Aging and Disease, Medical Faculty, University and University Hospital of Cologne, Cologne, Germany*

²*Cologne Excellence Cluster for Cellular Stress Responses in Aging-Associated Diseases (CECAD), Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany*

The reproduction–aging trade-off has been proposed to maximize reproductive output at the expense of somatic maintenance, thereby accelerating aging. Although reproductive costs are known to vary among individuals, the mechanisms underlying this variation remain poorly understood. Using wild-type *C. elegans* populations, we isolated rare individuals exhibiting increased embryonic lethality, which we term naturally recurring embryonic loss (NREL) mothers. We found that embryonic lethality could be transgenerationally inherited across multiple generations under selective propagation of NREL populations, but gradually diminished in the absence of selection, suggesting an epigenetic component to the regulation of embryonic loss. Embryonic lethality in NREL mothers was rescued by mating with healthy males, whereas unhealthy males derived from NREL lineages induced increased embryonic lethality in females, indicating a sperm-dependent effect. Germline analysis of NREL animals revealed abnormalities in sperm DNA organization in both hermaphrodites and males, while oocytes appeared unaffected. Similar sperm DNA abnormalities were observed in aged healthy males and were substantially more pronounced in aged NREL males, raising the possibility that NREL animals undergo premature reproductive aging. Together, our findings suggest that variation in sperm chromatin organization may serve as an indicator of organismal health, with consequences for reproductive success and aging trajectories.

NO MAJOR BRAIN ALTERATIONS IN AGED SIGLEC-E/F DOUBLE-KNOCKOUTS

Aditya Singh^{1,*}, Ioannis Foukarakis^{1,*}, Yiduo Min^{1,*}, Tawfik Abou-Assale¹, Charlotte Wadewitz², Ulrike Steffen³, Lars Nitschke², and Harald Neumann¹

** authors contributed equally*

¹*Institute of Reconstructive Neurobiology, Medical Faculty and University Hospital of Bonn, University of Bonn, Bonn, Germany*

²*Department of Biology, Division of Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany*

³*Department of Internal Medicine 3, Friedrich-Alexander-University Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany*

CD33-related Siglecs are linked to human brain aging and neuroinflammatory disease. In mice, Siglec-E and Siglec-F have been proposed to limit age-related microglial activation, oxidative damage, and neurodegeneration. We analyzed the brains of Siglec-E knockout and Siglec-E/F double-knockout compared to wild-type control mice by bulk RNAseq and immunohistochemistry at 12 and 18 months, respectively. Differential gene expression and pathway enrichment analyses showed no relevant transcriptomic changes in knockout versus age-matched control mice. Immunohistochemistry of the neuron-specific marker NeuN across all the knockout mice showed no change in hippocampal and substantia nigra neuronal density. Interestingly, while Siglec-E and Siglec-F showed negligible brain transcript levels of inhibitory CD33-related Siglecs in young and old wild-type mice, human datasets showed substantial higher expression levels of inhibitory CD33-related Siglec transcript relative to microglial markers, respectively. Together, these findings suggest no evidence for a major role of Siglec-E or Siglec-F in physiological murine brain aging, and highlight potential species-specific brain differences between mice and humans in CD33-related Siglec biology.

Rapid DNA double-strand break repair as a candidate mechanism of exceptional longevity in the bat *Myotis myotis*

Ilze Skujina^{1,2}, Noel Lowndes¹, J. Luessing¹, Xuanjing Li², Frédéric Touzalin², Sebastien Riquier², Asya Martirosyan³, Björn Schumacher³, Emma C. Teeling²

¹Centre for Chromosome Biology, University of Galway, Galway, Ireland

²Laboratory of Molecular Evolution and Mammalian Phylogenetics (BatLab), School of Biology and Environmental Science, University College Dublin, Dublin, Ireland

³Cologne Excellence Cluster for Cellular Stress Responses in Aging-Associated Diseases (CECAD), Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany

DNA is continuously challenged by endogenous and environmental insults that generate DNA lesions, including highly cytotoxic DNA double-strand breaks (DSBs). The progressive accumulation of DNA damage and the resulting genomic instability are recognised as central hallmarks of ageing and major contributors to age-related functional decline. Long-lived species provide valuable models for identifying mechanisms that promote resilience against molecular damage and support extended lifespan. Bats are particularly intriguing in this regard, as many species exhibit exceptional longevity despite the substantial metabolic demands associated with powered flight.

We hypothesised that exceptionally long-lived bats possess enhanced DNA damage response (DDR) mechanisms that contribute to sustained genome maintenance and longevity. To investigate this, we performed a comparative multi-omics analysis of DDR pathways in primary fibroblasts derived from the long-lived bat *Myotis myotis*, the shorter-lived bat *Rousettus aegyptiacus*, *Mus musculus*, and *Homo sapiens* following exposure to ionising gamma radiation.

Preliminary results reveal an exceptionally rapid response to DNA double-strand breaks in *M. myotis*, characterised by near-immediate DSB resolution following irradiation. Integrative transcriptomic and proteomic analyses suggest that this phenotype may be driven by accelerated activation of non-homologous end joining (NHEJ), although the precise molecular mechanisms remain to be determined. These findings identify enhanced DSB repair as a candidate longevity-associated mechanism and reveal early divergence in cellular stress-response and genome-maintenance programmes between long-lived and shorter-lived mammals. Our work highlights comparative biology as a powerful approach for uncovering conserved pathways that promote genome stability and may contribute to healthy lifespan extension.

Expanding the list of Hallmarks of Aging: Insights from amino acid dependent regulation of aging

Sampreeth Gowda^{1,2}; Sharvari Shet^{1,2}; Saujanya Nagendra¹; Abinaya Elango¹; Mounika Yadugani¹ and **Rajalakshmi Srinivasan¹**

¹*Institute of Bioinformatics and Applied Biotechnology, Bangalore, India – 560100*

²*Manipal Academy of Higher Education and Research, Manipal, India*

Email: rajalakshmi@ibab.ac.in

Aging is a process regulated by complex mechanisms. New biological processes are being added to the hallmarks of aging and novel genes are identified to be having a role aging. Amino acid availability is one of the signals that regulate aging. For instance, methionine restriction is a well-known dietary intervention known to elongate aging. On the other hand, glycine supplementation elongates longevity. In this study, we investigate the role of an individual and combination of amino acids in regulating aging processes using *Saccharomyces cerevisiae* model system. Using genomics and cell biology-based approaches, we shed lights on the mechanism through which different amino acid mediates longevity. Our age-dependent analysis of transcriptional and phenotypic responses to different amino acid supplemented conditions revealed a dynamic change in different cellular pathways during aging. By integrating the transcriptomics and microscopy-based analysis, we found that the dynamic mitochondrial architecture and compromised network integrity is one of the contributing factors of aging phenotypes. In addition, we found a novel role of amino acid dependent alteration of extrachromosomal nucleic acids abundance and expression in regulating aging. We also discovered a role of a protein that play a crucial role in mediating these age dependent alterations. The finding from this study will open the scope for adding a new keyword to the existing list of “Hallmarks of Aging”.

Do Senescent Cells Disrupt the Clock? Investigating SASP Effects on Circadian Rhythms

Stamm, A.¹, Demaria M.¹

¹ERIBA, UMCG, Groningen, Netherlands

The circadian clock orchestrates daily gene expression programs that coordinate cellular processes with environmental rhythms and support tissue homeostasis. The pro-inflammatory cytokine IL-1 β has been shown to disrupt circadian rhythms, raising the possibility that senescent cells may exert similar effects through the senescence-associated secretory phenotype (SASP). As senescent cells accumulate with age and contribute to chronic inflammation, understanding their impact on circadian regulation may provide new insights into age-related tissue dysfunction. To investigate this, we culture human fibroblasts in vitro and expose them to conditioned media from either senescent or proliferating fibroblasts. Temporal expression of core circadian clock genes is analyzed to assess changes in circadian period, amplitude, and phase. This study explores a poorly understood interaction between cellular senescence and circadian regulation and may reveal novel mechanisms linking aging, inflammation, and circadian dysfunction.

Spatiotemporal Mapping of Neurodegenerative Stress in the Locus Coeruleus in a Cell-type Specific *Ercc1* Deficiency Model

Steppek C.¹; Chennavajula, K.²; Carey, J.¹; & Niedernhofer, L.J.¹

¹ *Masonic Institute on the Biology of Aging and Metabolism and the Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota, Minneapolis, Minnesota, United States*

² *Institute of Translational Neuroscience, University of Minnesota, Minneapolis, Minnesota, United States*

The locus coeruleus (LC) is a noradrenergic brain nucleus that is particularly vulnerable in age-related neurodegenerative diseases such as Alzheimer's and Parkinson's, showing early neuronal tau and α -synuclein pathology leading to neuronal loss. In this study, we used mice in which the DNA repair gene *Ercc1* was deleted specifically in tyrosine hydroxylase-expressing cells, leading to accelerated degeneration of LC noradrenergic neurons due to failure to repair endogenous DNA damage. To identify the mechanism behind the unique vulnerability of LC neurons to stress, the LC and surrounding microenvironments were profiled by GeoMx[®] Digital Spatial Profiler for whole-transcriptome analysis. Expression profiles were compared to controls at timepoints representing pre- and post- neurodegeneration. A tissue microarray was utilized to reduce batch effects and to accommodate scan-area and reagent constraints, providing a scalable workflow across genotypes and ages. Transcriptomic signatures were identified that may predispose noradrenergic neurons to protein aggregation and loss in LC circuits, which underlie neurodegenerative disease.

References:

1. Mather M, and Harley C W. (2016). The Locus Coeruleus: Essential for Maintaining Cognitive Function and the Aging Brain. *Trends Cogn Sci* 20, 214–226.
2. Frutuoso M, et al. (2025). Disease-specific neuropathological alterations of the locus coeruleus in Alzheimer's disease, Down syndrome, and Parkinson's disease. *Alzheimer's & Dementia* 21, e70262.

A potential R-loop–stress granule axis

Holst, C.M.; Tesauro, C.; Jensen, A.Ø.; Svendsen, S; Damgaard, C.K.; Nielsen, E.H.; **Stevnsner, T.**

Department of Molecular Biology and genetics, Aarhus University, Aarhus, Denmark

Upon oxidative stress, cells must coordinate spatially distinct stress responses to promote survival. In the cytoplasm, stress granules (SGs) transiently assemble to reprogram translation. In the nucleus, multiple DNA repair pathways are activated to resolve diverse forms of genomic damage, including unscheduled R-loops formed during transcription. In certain contexts, R-loops are processed through nucleolytic cleavage of the DNA–RNA hybrid, generating nucleic acid species that may be released into the cytoplasm.

Here, we show that deficiency in key factors, including CSB, XPG, and RAD52, involved in this R-loop processing pathway, leads to reduced SG formation during acute oxidative stress, suggesting a functional link between nuclear genome maintenance and cytoplasmic stress responses. We are further investigating whether cytoplasmic DNA–RNA hybrids act as signalling molecules that promote SG assembly, potentially via nucleic acid-sensing pathways such as cGAS–STING.

Collectively, our findings suggest a previously unrecognized R-loop–SG axis that connects nuclear genome stability with cytoplasmic stress adaptation mechanisms.

References:

1. Åhrén B, and Holst JJ (2001). The cephalic insulin response to meal ingestion in humans is dependent on both cholinergic and noncholinergic mechanisms and is important for postprandial glycemia. *Diabetes* 50, 1030–1038.

cancelled

Neuromelanin drives age-associated lysosomal dysfunction in human dopaminergic neurons

Sandelin, A.¹; Hewapathirana, S.¹; Jämsä, A.¹; Airavaara, M.¹; & **Stratoulis, V.**^{1,2}

¹*Faculty of Pharmacy, University of Helsinki, Helsinki, Finland*

²*Institute of Environmental Medicine, Karolinska Institute, Sweden*

Parkinson's disease is characterized by the progressive degeneration of dopaminergic neurons. During normal aging, human dopaminergic neurons gradually accumulate neuromelanin, a feature absent in rodents. This species-specific accumulation has long implicated neuromelanin in aging and neuronal vulnerability. However, whether neuromelanin exerts protective or detrimental effects remains unclear.

We established a human stem cell-derived dopaminergic neuron model that recapitulates neuromelanin accumulation and enables investigation of its role in neuronal vulnerability. Neuromelanin-positive neurons displayed aging-associated nuclear alterations, concentration-dependent neuronal loss, spontaneous α -synuclein aggregation, and impaired autophagic degradation with p62-positive inclusions. These findings identify neuromelanin as a potential contributor to aging-related lysosomal dysfunction in Parkinson's disease.

Age-Related Disruption of Circadian Brain–Bladder Communication Reveals a Novel Therapeutic Target for Nocturia

Taylor, D.S.^{1,2}; Solem, K.R.²; Gerdes, W.H.²; Veauthier, E.J.²; Vandendoren, M.^{1,3}; & Beford, N.L.^{1,2}

¹Neuroscience Interdisciplinary Program, University of Wyoming, Laramie, USA

²Department of Zoology & Physiology, University of Wyoming, Laramie, USA

³Department of Biomedical Sciences, Creighton University, Omaha, USA)

Nocturia, defined as waking two or more times per night to urinate, affects over 70% of adults over 65 and significantly impacts overall quality of life and well-being. Despite its prevalence, the mechanistic basis of nocturia remains poorly understood. We established the aging mouse as a translational model for nocturia and uncovered circadian disruption in bladder–brain signaling that may drive age-associated mistiming of urination. In healthy adult mice, Piezo1 expression in the bladder and c-Fos expression in the brain exhibit opposing diurnal patterns. We propose that this relationship becomes dysregulated with age, contributing to mistimed urination. Using a Piezo1 agonist and antagonist, we have preliminarily demonstrated induction and reversal of the nocturia phenotype. Together, these findings aim to identify a novel age-related disruption in bladder–brain communication, suggesting that targeting peripheral sensory mechanisms may represent a new chronotherapeutic avenue for reversing the nocturia phenotype and other age-associated urinary disorders.

References:

1. Taylor et al (2001). Diurnal regulation of urinary behavior and gene expression in aged mice. J Gerontol A Biol Sci Med Sci 80, glaf208.

Endogenous double-stranded RNA links transcription stress to senescence-associated cellular adaptation

Theodorakis, E.^{1,2}; Siametis, A.^{2,3}; Stratigi, K.²; Tsaglioti, E.²; Pasparakis, M.^{2,4} & Garinis, G.A.^{1,2}

¹Department of Biology, University of Crete, Heraklion, Crete, Greece

²Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Heraklion, Crete, Greece

³Department of Biochemistry and Molecular Biology, University of Southern Denmark, Odense, Denmark

⁴Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

Accumulating cellular damage can disrupt transcription and RNA homeostasis, triggering stress signals that shape inflammatory and senescence-associated cell states. Endogenous double-stranded RNA (dsRNA) is increasingly recognized as one such signal, yet its origin, immunogenicity and biological consequences in damaged cells remain unclear. It is not known how self-derived dsRNA arises from persistent transcriptional perturbation driven by intrinsic genome instability or how cells respond to its presence during senescence. To address this, we use murine cellular models lacking *Tcea1*, which encodes the transcription elongation factor TFIIS, a key regulator of RNA polymerase II recovery after elongation arrest and oxidative damage. Loss of *Tcea1* impairs transcriptional elongation, causing chronic transcription stress and genome instability. Using this model, we examined the consequences of endogenous dsRNA accumulation in a senescence-associated context. We observed increased intracellular dsRNA together with activation of stress response pathways, including translational stress and stress granule formation. However, despite robust dsRNA accumulation, canonical cytosolic sensing pathways, including MDA5 and RIG-I, were not activated, suggesting that endogenous dsRNA in this setting may be immunologically silent or spatially restricted. Instead, persistent dsRNA was associated with altered RNA processing and increased sequestration within stress granules, pointing to RNA homeostasis mechanisms that may shape cellular stress responses and fate decisions. These findings position endogenous dsRNA as a mediator of transcriptional dysfunction and senescence-associated adaptation, with potential relevance to aging and disease.

Zinc at the crossroads of aging, healthspan, and proteostasis in *Caenorhabditis elegans*

Kumar, A.¹; Liput, K. P.¹; Jonak, K.¹; **Topf, U.**¹

¹*Laboratory of Molecular Basis of Aging and Rejuvenation, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland*

Zinc is an essential micronutrient required for numerous biological processes, including enzymatic catalysis, gene regulation and cellular stress responses. We characterized the dynamics of metal abundance in wild-type *C. elegans* during development and aging, and found that, in contrast to other analyzed metals, zinc levels progressively decline in post-reproductive animals. As zinc levels decrease with age in humans and zinc supplementation is recommended to improve immune function, we investigated the molecular role of zinc in promoting life and healthspan during *C. elegans* aging. While excessive zinc levels are detrimental to lifespan, optimal zinc supplementation is beneficial to life and health. Our data showed that optimal zinc supplementation improves locomotion and antioxidant activity and protects against toxic protein aggregation in aged worms. Proteomic analysis revealed the upregulation of ribosomal and stress-related proteins compared to zinc-depleted worms, suggesting a zinc-responsive adaptation in proteostasis pathways.

This research is funded by the National Science Centre Poland (grant number 2022/45/B/NZ1/03714).

DARe: Decoding the Biology of Aging to Enable Therapeutic Innovation

Sophie Song¹; Tracee Kamunya¹; Angelika Meyer²; Yufei Li²; Liqing Luo²; Luca Borsatti²; Adrian Moliere²; Christopher Plunkett³; Joshua Barbara³; Kanan Choquette³; Scott Hammack³; Andrew Brady⁴; John Eash¹; Sherry Chin¹; Cristian Abarca-Reyes¹; Julian Rothen²; Oleksandr Dergai²; **Anne-Ulrike Trendelenburg**¹

Novartis Biomedical Research,

¹*Diseases of Aging and Regenerative Medicine, Cambridge, US,*

²*Diseases of Aging and Regenerative Medicine, Basel, CH,*

³*Discovery Sciences, San Diego, US,*

⁴*Data and Digital, Cambridge, US*

By 2050, the global population aged 60+ is expected to reach 2.1 billion, with age-related diseases accounting for more than half of the global disease burden. Targeting fundamental mechanisms of aging represents a promising strategy to address multiple chronic diseases simultaneously.

The Diseases of Aging and Regenerative Medicine (DARe) group at Novartis focuses on uncovering the biological drivers of aging to enable therapeutic innovation across neurodegenerative, cardiometabolic, cardiorenal, and immunologic disorders. Our approach integrates human-centric datasets, translational biomarkers, and preclinical models to interrogate core cellular pathways, including energy metabolism, DNA repair, and mitochondrial function.

My group focuses on two key hallmarks of aging with direct translational relevance: declining energy expenditure and impaired DNA repair. Reduced energy expenditure contributes to age-related obesity and associated diseases such as heart failure, while compromised DNA repair is a central driver of multiple age-associated pathologies.

To enable mechanistic insights and target discovery, we developed a 3D bioartificial human skeletal muscle (sBAM) platform that allows capturing both molecular and functional aspects of aging, including contractility and oxygen consumption. Aging is modeled through primary cells from aged donors or γ -irradiation, complemented by in vivo paradigms such as ovariectomy (OVX) combined with disease-relevant stressors and exercise interventions. Importantly, this approach bridges human biology and preclinical modeling, enabling identification and validation of novel targets while strengthening translational alignment between discovery and clinical relevance.

Together, this work establishes a mechanistically grounded and translationally focused framework for targeting aging biology, with the potential to impact multiple chronic diseases through shared underlying pathways.

Whole-blood NAD⁺ does not decline across age and lifestyle interventions in humans

Maria M. Trętowicz^{1,2}; Angelique M.L.; Scantlebery¹; Bauke V. Schomakers^{1,3}; Kaan D. Eroğlu^{1,3}; Michel van Weeghel^{1,2,3,4}; Vera Spek¹; Kasper T. Vinten^{1,2}; Luc Legon¹; Evrim Coskun¹; Fernando Millan-Domingo⁵; Gloria Olaso-Gonzalez⁵; Maria Carmen Gomez-Cabrera⁵; Silvia Montoro-García⁶; Clara Noguera-Navarro⁶; André B. P. van Kuilenburg^{2,7}; Sofia Moco⁸; Juliette C. van Hattum⁹; Harald T. Jørstad⁹; Mohammed Benali¹⁰; Jantine van der Helder¹⁰; Esmee J. M. Biersteker¹⁰; Maheswary Muniandy¹¹; Kirsi H. Pietiläinen¹¹; Eija Pirinen^{11,12,13,14}; P. Eline Slagboom¹⁵; Marian Beekman¹⁵; Joris Deelen¹⁵; Rubén Zapata-Pérez¹⁶; Peter Weijs¹⁰; Michael Tieland^{10,17}; Georges E. Janssens^{1,2*}; Riekelt H. Houtkooper^{1,2,4,18*}

¹ Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, The Netherlands.

² Amsterdam Gastroenterology, Endocrinology, Metabolism Institute, Amsterdam, The Netherlands.

³ Core Facility Metabolomics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.

⁴ Amsterdam Cardiovascular Sciences Institute, Amsterdam, The Netherlands.

⁵ Freshage Research Group, Department of Physiology, Faculty of Medicine, University of Valencia, CIBERFES, Fundación Investigación Hospital Clínico Universitario/INCLIVA, 46010, Valencia, Spain.

⁶ Preclinical Research of Bioactive Compounds and Drugs (PREBIOF), Izpisúa Lab HiTech, Faculty of Health Sciences, Universidad Católica de Murcia (UCAM), Campus los Jerónimos, 30107 Murcia, Spain.

⁷ Laboratory Genetic Metabolic Diseases, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

⁸ Chemistry and Pharmaceutical Sciences Department, Amsterdam Institute of Molecular and Life Sciences (AIMMS), Vrije Universiteit (VU) Amsterdam, De Boelelaan 1108, 1081 HZ, Amsterdam, the Netherlands.

⁹ Department of Cardiology, Amsterdam UMC, University of Amsterdam. Amsterdam Movement Sciences Institute, Amsterdam Cardiovascular Sciences Institute, Amsterdam, The Netherlands.

¹⁰ Department of Nutrition and Dietetics, Faculty of Health, Sport and Physical Activity, Amsterdam University of Applied Sciences, Amsterdam, the Netherlands.

¹¹ Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland.

¹² Research Unit for Biomedicine and Internal Medicine, Faculty of Medicine, University of Oulu, Oulu, Finland.

¹³ Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland.

¹⁴ Biocenter Oulu, Faculty of Medicine, University of Oulu, Oulu, Finland.

¹⁵ Section of Molecular Epidemiology, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands.

¹⁶ Group of Metabolism and Gene Regulation, UCAM HiTech Sport & Health Innovation Hub, Universidad Católica de Murcia, 30107, Guadalupe de Macíascoque, Murcia, Spain.

¹⁷ Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, Victoria, Australia.

¹⁸ Emma Center for Personalized Medicine, Amsterdam UMC, Amsterdam, The Netherlands.

Nicotinamide adenine dinucleotide (NAD⁺), a central redox cofactor linked to multiple hallmarks of aging, has been reported to decline with age, yet its stability and relevance as an aging biomarker in human whole blood remain unclear. To assess this, we developed and validated a quantitative ultra-high-performance liquid chromatography–high-resolution mass spectrometry (UHPLC–HRMS) assay for whole-blood NAD⁺ and applied it to samples from seven independent cohorts, including three cross-sectional aging cohorts, one extreme-phenotype cohort and two exercise and nutrition trials in older adults. Accounting for empirically determined, real-world analytical variability, we defined the sample sizes required to detect age-related differences and then evaluated both age- and intervention-related effects. Whole-blood NAD⁺ remained remarkably stable with age and across lifestyle interventions, while responding to nicotinamide riboside supplementation as expected, challenging its utility as a biomarker of aging or lifestyle factors.

References:

1. Trętowicz MM, Scantlebery AML, Schomakers BV, et al. (2026). Human whole-blood NAD⁺ levels do not vary with age or lifestyle interventions. *Nat Metab*.
2. Vinten KT, Trętowicz MM, Coskun E, et al. (2025). NAD⁺ precursor supplementation in human ageing: clinical evidence and challenges. *Nat Metab* 7, 1974–1990.

The Role of PLIN2 during Adipogenic differentiation

L. Trofarello¹, G. Storci², A. Chiariello¹, S. Valente¹, G. Pasquinelli¹, S. Salvioli¹, M. Conte¹

¹Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy.

²IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.

Correspondence to stefano.salvioli@unibo.it

Perilipin 2 (PLIN2) is a lipid droplet (LD)-associated protein that regulates lipid storage and LD dynamics¹. It also exists in vivo as a circulating form (cPLIN2) that correlates with body adiposity and reduced lean mass². During adipogenesis, PLIN2 is associated with early LDs in preadipocytes, while its expression decreases in mature adipocytes. However, whether PLIN2 downregulation is required for adipogenic differentiation (AD) or rather represents a consequence of this process remains unclear. To address this question, we modulated PLIN2 expression during AD of human primary dermal fibroblasts (DFs). We found that PLIN2 silencing accelerates AD, whereas its accumulation, significantly delays this process, suggesting that its early downregulation is required for AD. Interestingly, despite a strong reduction of Plin2 mRNA during AD, cPLIN2 increases in time up to 15 days and is at least partially associated with extracellular vesicles provisionally indicated as lipidosomes³. Notably, this process is not observed in undifferentiated DFs, suggesting that PLIN2 secretion is an acquired feature of pre-adipocytes and cPLIN2 can be a marker of fat mass.

References:

1. Conte M, Franceschi C, Sandri M, Salvioli S. Perilipin 2 and Age-Related Metabolic Diseases: A New Perspective. *Trends Endocrinol Metab.* 2016 Dec;27(12):893–903. doi: 10.1016/j.tem.2016.09.001.
2. Conte M, Santoro A, Collura S, Martucci M, Battista G, Bazzocchi A, Morsiani C, Sevini F, Capri M, Monti D, Franceschi C, Salvioli S. Circulating perilipin 2 levels are associated with fat mass, inflammatory and metabolic markers and are higher in women than men. *Aging (Albany NY).* 2021 Mar 17;13(6):7931–7942. doi: 10.18632/aging.202840.
3. Karbanová J, Deniz IA, Wilsch-Bräuninger M, de Sousa Couto RA, Fargeas CA, Santos MF, Lorico A, Corbeil D. Extracellular lipidosomes containing lipid droplets and mitochondria are released during melanoma cell division. *Cell Commun Signal.* 2024 Jan 19;22(1):57. doi: 10.1186/s12964-024-01471-7.

Comparative analysis of miRNAs and their role in longevity of bats

Uvizl M.^{1,2}; Riquier S.¹; Huang Z.¹; Lonergan T.¹; Power M.¹; Hurpy G.¹; van Tussenbroek I. A.^{3,4}; Touzalin F.¹; Puechmaillie S. J.^{5,6}; Ransome R.⁷; Jones G.⁷; Vernes S.⁴; Teeling E. C.¹

¹ *School of Biology and Environmental Studies, University College Dublin, Dublin, Ireland*

² *Department of Zoology, Charles University, Prague, Czechia*

³ *Institute of Biology, Leiden University, Leiden, Netherlands*

⁴ *School of Biology, University of St Andrews, St Andrews, United Kingdom*

⁵ *Institut des Sciences de l'Evolution, University of Montpellier, Montpellier, France*

⁶ *Institut Universitaire de France, Paris, France*

⁷ *School of Biological Sciences, University of Bristol, Bristol, United Kingdom*

Longevity and healthspan vary profoundly across mammals, yet the molecular mechanisms that modulate healthy ageing remain poorly understood. Most current knowledge originates from short-lived laboratory species and thus, studying naturally long-lived species offers a complementary and powerful strategy for ageing research. Among mammals, bats are exceptional because many species exhibit extended healthspans relative to their body size as well as limited senescence, and remarkably low tumorigenesis. MicroRNAs (miRNAs) are key post-transcriptional regulators of gene expression implicated in many cellular processes, including ageing and longevity, yet their role in the longevity of bats remains unexplored. Here, we present the first comparative analysis of age-associated miRNA expression in wild bat species spanning a longevity spectrum. We sampled known-aged individuals from three phylogenetically distinct species (long-lived *Myotis myotis* and *Rhinolophus ferrumequinum*, and shorter-lived *Phyllostomus discolor*), collecting whole blood from aged individuals in each population. miRNA profiles were generated using miRNA-seq, and we identified miRNAs whose expression changed significantly across age cohorts within each species before comparing trajectories across species to detect conserved and lineage-specific ageing signatures. Preliminary analyses revealed miRNA that are differentially regulated with age but most of the regulatory patterns are species-specific. These findings highlight miRNA regulation as a potentially important component of bat longevity. Simultaneously, the predominantly species-specific patterns likely reflect the pronounced evolutionary diversity across bat lineages. Ongoing work will integrate these results with genomic and comparative mammalian datasets to elucidate the evolutionary and functional significance of bat miRNA ageing signatures.

Decoding the Role of MIF in Ischemic Brain Injury

Karla Valdivieso¹, Hannah Miserre¹, Maria E. Bernis², Elke Maes², Yijing Wang³, Hao Ji³, Buket Bulut³, Lu Liu³, Luisa Howainksy¹, Qian Liu¹, Zeyi Wang¹, Sudhagar Babu¹, Cem Bugra Kaboglu¹, Xihui Chen¹, Katrin Perez Anderson¹, Hemmen Sabir², Jürgen Bernhagen³, Ozgun Gokce^{1,2}

¹ Department of Neurodegenerative Disease and Geriatric Psychiatry, University Hospital Bonn, Bonn, Germany

² German Center for Neurodegenerative Diseases, Bonn, Germany

³ Institute for Stroke and Dementia Research, LMU Munich, Germany

Macrophage Migration Inhibitory Factor (MIF) is a multifunctional cytokine and intracellular stress effector implicated in neuroinflammation, DNA damage signaling, and cell fate determination. Beyond its established immunoregulatory functions, MIF has recently been identified as a PARP-1-dependent nuclease capable of promoting neuronal cell death following DNA damage in experimental stroke models. These findings position MIF as a potential central mediator linking neuroinflammation, DNA damage responses, and neurodegeneration, key hallmarks of both ischemic injury and brain aging. In this study, we reassessed the role of MIF in ischemic brain injury by generating a novel CRISPR/Cas9-generated *Mif* knockout rat model, a clinically relevant model that recapitulates major pathological mechanisms shared with age-related neurological disorders, including oxidative stress, mitochondrial dysfunction, excitotoxicity, and chronic neuroinflammatory signaling. Using longitudinal magnetic resonance imaging (MRI), we evaluated lesion development and structural brain injury following hypoxic-ischemic insult. In parallel, immunohistochemical analyses were performed to characterize neuronal loss, inflammatory responses, and cellular stress-associated pathways, including markers associated with senescence and tissue remodeling. Single-cell RNA sequencing was additionally performed to dissect cell-type-specific transcriptional responses to MIF loss. These approaches allowed us to investigate how the loss of MIF intervenes in ischemic brain injury and modulates downstream neuroinflammatory responses. This work highlights MIF as a promising candidate at the intersection of inflammation, cellular stress responses, and neurodegeneration, with potential translational relevance for aging-related brain disorders.

XPG deficiency accelerates vascular aging via VSMC phenotypic switching and metabolic dysfunction, which is mitigated by dietary restriction.

Sanne J. M. Stefens¹; José María Heredia-Genestar¹; Martine de Boer²; Nicole van Vliet¹; Renata M. C. Brandt¹; Sander Barnhoorn¹; Merel Batenburg¹; Dirk J. Duncker²; Jan H. J. Hoeijmakers^{1,3,4,5}; Roland Kanaar^{1,3}; Jeroen Essers^{1,6,7}; **Ingrid van der Pluijm**^{1,6}

¹Department of Molecular Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands,

²Department of Cardiology, Erasmus University Medical Center, Rotterdam, The Netherlands,

³Onco Institute, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands,

⁴Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands ,

⁵Institute for Genome Stability in Aging and Disease, Cologne Excellence Cluster for Cellular Stress Responses in Aging- Associated Diseases (CECAD), University of Cologne, Cologne, Germany,

⁶Department of Vascular Surgery, Cardiovascular Institute, Erasmus University Medical Center, Rotterdam, The Netherlands,

⁷Department of Radiotherapy, Erasmus University Medical Center, Rotterdam, The Netherlands

Aging is the strongest risk factor for cardiovascular disease, but mechanisms linking molecular damage to vascular decline remain unclear. Persistent DNA damage contributes to aging, yet its vascular impact is underexplored. We studied Xpg^{-/-} mice lacking the DNA repair enzyme XPG, resulting in DNA damage accumulation and premature aging. Their aortas showed elastin degradation, a shift in vascular smooth muscle cell (VSMC) identity from a contractile to osteogenic and macrophage-like phenotypes, and lipid droplet buildup. Bulk RNA sequencing revealed increased inflammation and reduced lipid and mitochondrial metabolism, demonstrating a link between genomic instability, immune activation, and metabolic disruption. In vitro, Xpg^{-/-} VSMCs exposed to the transcription-blocking DNA-damaging agent Illudin S accumulated lipid droplets, unlike wild-type cells. Dietary restriction restored metabolic gene expression, reduced inflammation, and improved vascular structure. These findings show that DNA damage drives vascular aging via VSMC re-programming and metabolic imbalance, while dietary restriction may counteract these effects.

Fatty Acids Differentially Drive and Shape Hepatocyte Senescence

Vo, T.H.P.; Nier, A.; & Stangl, G.I.

Institute of Agricultural and Nutritional Sciences, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

Hepatic aging is linked to steatosis and fibrosis, yet how dietary fatty acids (FAs) modulate hepatocyte senescence remains unclear. This study established a robust Menadione-induced HepG2 senescence model (45 μ M, 1 h), confirmed by SA- β -gal staining, increased p21/p16 expression, elevated SASP factors (IL-6, IL-8, MMP9, TNF- α , TGF- β 1), and activation of oxidative stress regulators (Nrf2, NQO1). Subsequently, the effects of FAs (25 μ M, 72 h)—palmitate (PA), linoleate (LA), γ -linolenate (GLA), docosahexaenoate (DHA), and erucic acid (EA)—were assessed in both proliferating and Menadione-induced senescent cells. This approach allowed us to distinguish FA-induced senescence from FA-mediated pre-existing senescence.

Menadione robustly induced senescence, as evidenced by significant upregulation of p21/p16 and a pronounced SASP response. EA exhibited context-dependent effects: inducing senescence and pro-inflammatory factors (IL-8, TNF- α , PDGFA) in proliferating cells, while modulating metabolic signaling ANGPTL4 in senescent cells. Notably, all FAs except PA further upregulated p16 in senescent cells, suggesting reinforcement of the irreversible senescence phenotype.

Rewiring of gene regulatory programs underlie regenerative potential of the naked mole-rat heart

Nini Wang^{1,2}; Maria Sol Jacome Burbano^{1,2}; Lukasz Kaczmarczyk^{1,2}; Paulina López Carrasco^{1,2}; Asli Nur Akaydin^{1,2} and Jane Reznick^{1,2}

¹ *Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany*

² *Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany*

The naked mole-rat (NMR) is a eusocial subterranean mammal with exceptional longevity and remarkable adaptation to hypoxia and hypercapnia. Beyond environmental stress tolerance, the NMR heart displays neonatal-like features in metabolism, mitochondrial morphology, and myofilament organization, together with regenerative ability after injury. These traits suggest that evolutionary adaptation to the NMRs hostile habitat may have shaped cardiac features relevant to hypoxia- and ischemia-associated human disease. However, the regulatory mechanisms underlying these unique cardiac properties remain poorly understood. By integrating RNA-seq and ChIP-seq profiling of histone modifications, we explored the genetic and epigenetic architecture which results in metabolic rewiring and fetal-like transcriptional programs in the NMR heart. Motif enrichment and DNA footprinting further identified estrogen-related receptor transcription factors as key regulators of this metabolic rewiring. In addition, injury-induced activation of ERBB2 may serve as a key driver promoting cardiac regeneration in the NMR heart.

Maggie Weber

27-04-2026

Gordon – Systems Aging Conference 2026

Sunday River, Maine

Estimating Somatic Mutation Rates across Bat Lifespans

Margaret Weber, Sebastien Riquier, Gwenaëlle Hurpy, Megan Powers, Tadhg Lonergan, Fred Touzalin, Marek Uvizl, Xuanjing Li, Ines Jover Bravo, Alex Maslov, Jan Vijg, Bjoern Schumacher, Emma Teeling

University of Dublin

Somatic mutations accumulate with age and are linked to cancer, as cells tip into malignancy when a mutational threshold is reached or tumor suppressors are critically impacted. Therefore, species with extraordinarily long lifespans – those with low substitution rates overtime – are deemed “cancer resistant.” In 2022, Cagan et al. demonstrated a strong inverse correlation between lifespan and somatic mutation rate across multiple mammalian species. For example, the house mouse (maximum lifespan = 4 years) experiences 8.5x more mutations per year than the hyperlongevous naked mole rat (maximum lifespan = 39 years). This landmark study did not include bats, one of the greatest lifespan outliers and a metabolically extreme mammalian clade. Bats exhibit lifespans that far exceed those predicted by their body sizes, with some species living over 40 years. Understanding how bats maintain genomic stability over their long lifespans could reveal novel anti-aging or anti-cancer mechanisms that translate into human therapies. Although we assume that bats have evolved specialized mechanisms to maintain genomic stability and cancer-resistance, this has yet to be empirically demonstrated.

This research quantifies somatic mutation accumulation in three bat species and non-bat outgroups. Two primary hypotheses exist: (1) bats may have evolved highly efficient intrinsic DDR machinery that limits mutation accumulation, or (2) they may rely on extrinsic surveillance systems that remove genomically unstable cells. Measuring the rate and nature of somatic mutations across species of varying lifespans offers an opportunity to test these hypotheses directly.

Glycation in Vascular Aging is associated with vascular and metabolic Dysfunction

Wensky, L.¹; Scheijen, J.L.J.M.¹; Waarenburg, M.P.H.¹; Ikebuiro, J.¹; Schalkwijk, C.G.¹; Vangrieken, P.^{1,2}

¹ *Department of Internal Medicine, Maastricht University, School for Cardiovascular Diseases (CARIM), Maastricht, The Netherlands.*

² *Department of Pharmacology and Toxicology, Maastricht University, School for Cardiovascular Diseases (CARIM), Maastricht, The Netherlands.*

Cardiovascular disease (CVD) remains the leading cause of death, with aging representing a key non-modifiable risk factor. Methylglyoxal (MGO), a glycolytic byproduct and precursor of advanced glycation endproducts (AGEs), has been implicated in CVD and is investigated here for its contribution to vascular aging.

Male C57BL/6J mice aged 8 and 72 weeks (n=16/group) underwent cardiac and vascular ultrasound assessment, and a terminal contrast-enhanced ultrasound experiment under basal & insulin-stimulated conditions following a hyperinsulinemic–euglycemic clamp. Aortic AGE levels were quantified by mass spectrometry and tissue glyoxalase 1 (Glo1) activity was assessed.

Aged mice showed increased pulse-wave velocity ($p<0.0001$) and elevated aortic (MGO-derived) AGEs ($p<0.01$), with reduced Glo1 activity in aorta ($p<0.01$) and perivascular adipose tissue ($p<0.001$). Aging was also associated with pronounced insulin resistance (reduced glucose infusion rate, $p<0.0001$).

Vascular AGE accumulation and reduced Glo1 activity are associated with age-related vascular and metabolic dysfunction and MGO-derived AGEs are a potential therapeutic target.

Telo-CUT: A Telomere-Specific DNA Damage Model Reveals Drivers of Aging

Seung-Hwa Woo^{1,2}; Anthony Lagnado^{1,2}; Diana Jurk^{1,2}; Nicholas Pirius^{1,2}; Yaeun Han^{1,2}; Helene Martini^{1,2}; Stacia P. A. Evert^{1,2}; Runqing Huang²; Carolyn M. Roos²; Thomas A. White^{1,2}; Jessica J. Brekke^{1,2}; Jenny L. Rowsey^{1,2}; Nathan K. LeBrasseur^{1,2}; Jordan D. Miller²; Sundeep Khosla^{1,2}; David G. Monroe^{1,2}; João F. Passos^{1,2}

1 Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, MN, USA

2 Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA

Telomere-associated DNA damage drives persistent DNA damage response (DDR) signaling and formation of telomere-associated foci (TAF), a hallmark of cellular senescence. However, whether chronic telomere-specific DDR is sufficient to promote organismal aging in vivo remains unclear. Here we develop TeloCUT, a tamoxifen-inducible mouse model in which telomeric double-strand breaks are generated through expression of a TRF1-FOKI fusion protein. Systemic activation of TeloCUT induced widespread TAF formation together with increased senescence and inflammatory signatures across multiple organs. Despite their young chronological age, TeloCUT mice developed progressive multi-system functional decline, reduced health span and shortened lifespan. Pharmacological inhibition of ATM signaling attenuated these effects, indicating that persistent telomeric DDR signaling through the ATM-p53 pathway is a key driver of the phenotype. These findings provide direct in vivo evidence that sustained DNA damage at telomeres is sufficient to drive systemic aging and establish a tractable model to investigate telomere-specific mechanisms and therapeutic targeting of persistent DDR.

Experimental β -cell senescence models reveal autophagy defects and altered stimulus–secretion coupling

Yin, N.¹; Takahashi, T.^{1,2}; Hayashi, H.³; Hara, A.¹; Takami, Y.¹; Nakagami, H.³; & Yamamoto, K.¹

¹Department of Geriatric and General Medicine, Osaka University Graduate School of Medicine,

²Department of Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada.

³Department of Health Development and Medicine, Osaka University Graduate School of Medicine

Aging contributes to β -cell dysfunction in type 2 diabetes, with senescence recognized as a key mechanism. We established a doxorubicin (DOX)-induced senescence model in MIN6 β -cells to examine how senescence affects organelle homeostasis and insulin secretion. Senescence was confirmed by SA- β -gal positivity, p16INK4a/p21/p53 upregulation, and cell cycle arrest. Using MitoTimer, COX8-EGFP-mCherry, and Insulin-Timer reporters with functional assays, we found that senescent β -cells accumulated aged mitochondria and insulin granules, indicating defective clearance. Upon glucose stimulation, these cells showed exaggerated mitochondrial hyperpolarization, altered Ca²⁺ influx, and increased ROS production. Although insulin content was reduced, secretion normalized to storage was enhanced, suggesting remodeled stimulus–secretion coupling. Similar findings were observed in a p16INK4a/p21/p53 overexpression model. Thus, DOX-induced β -cell senescence provides a tractable model linking DNA damage to autophagy defects, organelle retention, and altered β -cell function.

Impressum:

Publisher

Alliance for Healthy Aging /

Cologne Cluster of Excellence on Aging and Aging-associated diseases (CECAD)

<https://agingfederation.eu/>

<https://www.cecad.uni-koeln.de/outreach/events/2026-1st-efar-conference-on-the-biology-of-aging>

Editorial & Design

CECAD Office

Image credits

Respective PIs, companies and their corresponding websites.