ERIBA

European Research Institute
for the Biology of Ageing

Annual Report

2025

ERIBA

GRONINGEN

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Table of contents

1. Our Mission

At the European Institute for the Biology of Ageing, we are driven by a fundamental question: why do we age? Through rigorous, curiosity-led basic research, we investigate the molecular mechanisms underlying cellular decline and loss of tissue function over a lifetime, from the stability of long-lived cells in the heart and brain to the self-renewal of stem cells that sustain us throughout life.

We pursue this science with ambition and collaboration at our core. Our multidisciplinary teams combine cutting-edge technologies including next-generation sequencing, live cell imaging, and advanced genetic model systems to accelerate discoveries that would be impossible alone. We set the bar high: world-class science, published for its quality and not its quantity, with the courage to take on high-risk questions that can yield transformative breakthroughs.

Beyond the lab, we are committed to training the next generation of life scientists, engaging the public, advising policymakers, and translating fundamental insights into strategies that promote healthy ageing for society at large.

Our ultimate goal is a world in which the burden of age-related disease is reduced and where people everywhere can live longer, healthier lives.

2. Foreword by the director

It is a great pleasure to present to you the Annual Report 2025 of the European Research Institute for the Biology of Ageing. We are proud to share with you our achievements, and the progress that has been made in 2025. Also in 2025 all ERIBIANS have contributed to notable publications, advanced education and several outreach activities to inform the general public.

At ERIBA, we keep marching forward to elucidate the mechanisms that drive ageing, with a view to develop strategies to combat unhealthy ageing and age-related diseases. We published excellent papers in 2025 showing our commitment to ageing research. These publications were the result of important scientific collaborations within ERIBA, with colleagues from the UMCG and with laboratories around the world . We thank all of our colleagues for this continuous collaboration. Looking forward to the future, we anticipate continuing and expanding our collaborations aimed at the advancement of ageing research. In 2025, ERIBA contributed to the launch of the European Federation to Ageing Research (EFAR) to provide a platform for ageing research in Europe in the years to come.

We are committed to talent development in the field of ageing research. In 2025 again, excellent PhD students, undergraduates, and postdocs joined the institute and others left the institute to embark on future endeavours. It is great to see that numerous students have a keen interest in ageing research, and they carry out rotations in our institute.

Also in 2025, our scientists were once again successful in the acquisition of research funding, which includes prestigious and competitive national and global grants. Our scientists have also collaborated with biotech companies, leading to financed collaborative research projects in public-private partnerships. These collaborations have led to finding solutions for age-related diseases and such collaborations also show our commitment to prevention, delay, or reversal of the ageing process.

Knowledge sharing with society is of utmost importance, and I am delighted to share that our scientists were involved in many of the outreach activities. We hosted many outreach events for high school students and the public. Our presence on social media is also one of the many outreach efforts important for sharing our knowledge and findings with society.

Since 2024, ERIBA is part of cluster Biomedical Science & Technology within the UMCG organization. In 2025, we have welcomed a new Manageing Director of the cluster, Mr Hayo Schultink, as well as a new cluster manager, Mr. Marnix Labberté. The cluster is aimed at fostering collaborations, nurturing talents to showcase, achieve our ambition to become a global leading ageing institute for innovative research. I greatly appreciate the efforts and contributions of all the staff involved in paving the way for creating a global, highly reputed ageing institute with state of art facilities. I wish everybody all the best for future endeavours.

Folkert Kuipers
Scientific Director, ERIBA

3. Ageing Research at ERIBA

ERIBA, a renowned European research center, specializes in the study of ageing. The institute delves into fundamental biology to uncover the underlying causes of ageing. Research at ERIBA is dedicated to understanding the mechanisms that lead to cell loss and the deterioration of function in aged cells and tissues. Within the following sections, each research team at ERIBA is introduced, including their research focus, future endeavours, and a selected publication.

STEM CELL REGULATION AND MECHANISMS OF REGENERATION

Eugene Berezikov

Introduction

Our laboratory pursues two synergistic research directions. First, we study mechanisms of resilience using the flatworm Macrostomum lignano – an animal with remarkable regenerative capacity, longevity, and resistance to radiation. Second, we develop novel next-generation sequencing methodologies. Our improved Smart-3SEQ protocol enables cost-efficient gene expression profiling, while SmartComplete captures complete transcriptomes including small and circular RNAs. Recently, we expanded into DNA methylation profiling using FML-seq. These methods are now offered as services at iPsomics, a UMCG company where part of our team is involved, and have opened collaborative opportunities with clinicians in liquid biopsy diagnostics and organ transplantation.

Research focus

Flatworm Biology and Regeneration

The flatworm Macrostomum lignano possesses impressively advanced resilience (Fig. 1). Besides regeneration, it can de-grow during starvation and regrow when food becomes available. It lives several years without increased mortality hazard with age, and sustains very high doses of ionizing radiation (120 Gy) and ultraviolet C (100 mJ/cm²). These remarkable properties are likely conferred primarily by stem cells (neoblasts), which continuously replace damaged cells.

We established a comprehensive genetic toolbox for M. lignano, including stem cell transcriptional signatures, a sequenced and annotated genome, and robust in situ hybridization and transgenesis methods. M. lignano remains the only flatworm species with available transgenesis, enabling the generation of stem-cell-specific transgenic lines. Using these tools, we investigate the molecular mechanisms underlying regeneration, radiation resistance, and the apparent absence of ageing in this organism.

NGS Methodology Development and Clinical Applications

We developed and optimized several sequencing approaches now implemented at iPsomics. Smart-3SEQ provides cost-efficient gene expression profiling for large sample numbers. SmartComplete captures complete transcriptomes – coding and non-coding, polyadenylated and non-polyadenylated RNAs, small and circular RNAs – in a single reaction from minimal input material. FML-seq enables affordable whole-genome DNA methylation profiling. We are currently developing improved FML-seq for cell-free DNA applications.

These methods enabled clinical collaborations:

- **Cell-free RNA for Cancer Diagnostics:** With UMCG oncologists and the OncoLifeS biobank, we apply SmartComplete for profiling cell-free RNA from plasma of lung cancer patients to develop AI-driven prognostic models for survival prediction.
- **Genomic Profiling of Donor Livers:** With the UMCG liver transplantation team, we use SmartComplete for gene expression and FML-seq for DNA methylation profiling to develop classifiers predicting transplantation outcomes from pre-perfusion biopsies.

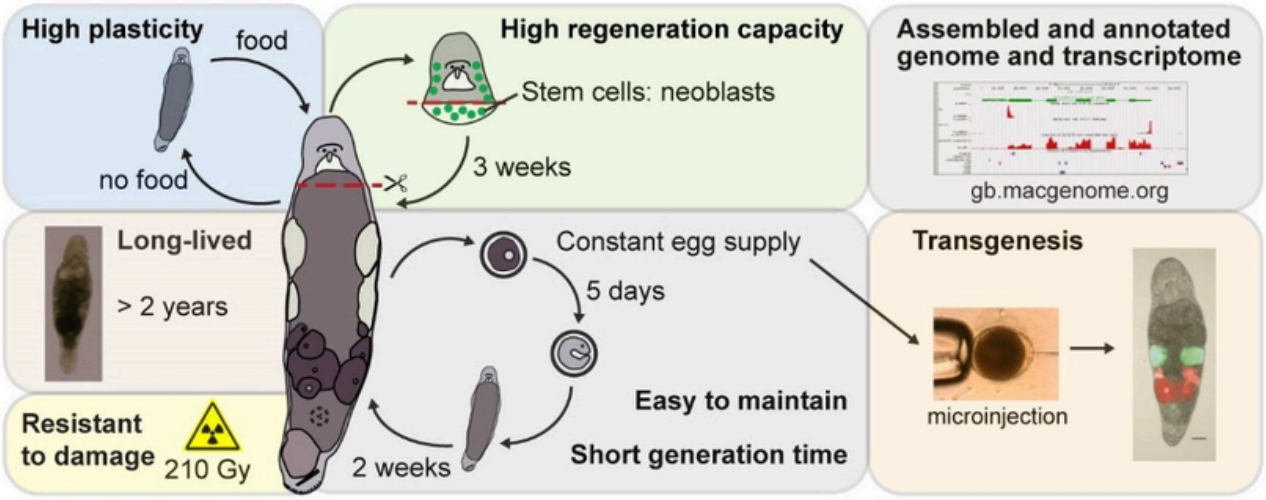


Figure 1. The flatworm Macrostomum lignano is a versatile model organism to study stem cells, regeneration, ageing and resilience mechanisms. Adapted from Wudarski et al., EvoDevo 11:5 (2020).

The future

In flatworm biology, we will use transgenesis combined with single-cell sequencing and comparative genomics to characterize regulatory programs driving cell fate specification during regeneration. We will investigate how M. lignano survives high radiation doses and test whether resilience-associated genes can confer similar properties in other organisms.

For NGS methodology, we are expanding SmartComplete and FML-seq applications to additional clinical indications. The improved FML-seq for cfDNA will enable liquid biopsy applications combining transcriptomic and epigenomic readouts. The liver transplantation project will validate our genomic classifiers prospectively and explore ex situ treatments to improve organ viability.

Selected publication

One probe fits all: a highly customizable modular RNA in situ hybridization platform expanding the application of SABER DNA probes

Kirill Ustyantsev, Mattia Stranges, Filippo Giovanni Volpe, Jan Freark de Boer, Folkert Kuipers, Stijn Mouton, Eugene Berezikov

Development. 2025 Jun 1;152(11):dev204775. doi: 10.1242/dev.204775

RNA in situ hybridization (ISH) is a key method for visualizing gene expression patterns in complex samples. ISH is indispensable for research in development, disease, gene function, and validation of novel cell types identified using single-cell sequencing methods. In non-mammalian models lacking accessibility to a broad spectrum of antibodies, ISH remains a major research tool. Available ISH protocols require different custom hybridization probe types, designs and/or proprietary signal detection chemistry. This makes it difficult for a beginner to navigate and increases research costs when multiple methods need to be applied. Here, we describe OneSABER, a unified open platform connecting commonly used canonical and recently developed single- and multiplex, colorimetric and fluorescent ISH approaches. OneSABER uses a single type of DNA probes adapted from the signal amplification by exchange reaction (SABER) method. We demonstrate the applications, versatility and efficiency of the OneSABER framework in whole-mount samples of the regenerative flatworms Macrostomum lignano and Schmidtea mediterranea and formalin-fixed, paraffin-embedded mouse intestinal sections. Comprehensive comparison of the most suitable ISH signal development techniques is discussed.

Group members

Lisa Glazenburg Technician	**Stijn Mouton** Research Associate	**Kirill Ustyantsev** Research Associate	**Mattia Stranges** PhD student

GENE REGULATION IN AGEING AND AGE-RELATED DISEASES

Cor Calkhoven

Introduction

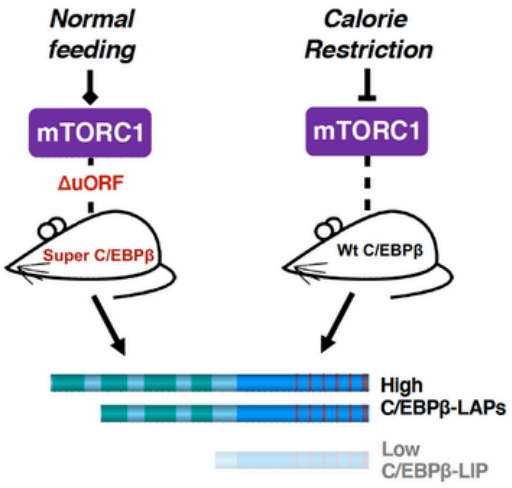
Our research aim is to identify and understand the role of regulatory networks that control the function of C/EBPα and C/EBPβ transcription factors in ageing and age-related diseases. We showed that mRNA-translational regulation of C/EBPβ expression through the mTORC1 nutrient and energy signaling pathway are linked to ageing and health- and lifespan determination. Others showed that deficiency of DNA-demethylation factors that regulate access of C/EBPβ to its genome binding sites result in premature ageing. In addition, the NAD+-SIRT1 pathway controls the function in mitochondrial biogenesis and respiration through regulation of C/EBPα protein-deacetylation. Apart from its physiologic metabolic functions, we study the oncogenic functions of C/EBPβ in promoting cancer metabolism, cell migration and immune evasion, particular in breast cancer. In another line of research, we study the pro-tumorigenic role of TSC-mTORC1 regulation in small cell lung cancer and its potential value as a therapeutic target.

Research focus

The CEBPA- and CEBPB-mRNAs are translated into full length, active transcription factors, C/EBPβ-LAP and C/EBPα-p42, as well as shorter inhibitory isoforms, C/EBPβ-LIP and C/EBPα-p30. A single upstream open reading frame (uORF) in these mRNAs functions as a cis-regulatory element necessary for translation into C/EBPβ-LIP and C/EBPα-p30, making them sensitivity to specific translational regulation pathways, particularly mTORC1 nutrient signaling. We have shown that disrupting mTORC1-mediated regulation of C/EBPβ-LIP by removing the uORF leads to significant delays in a wide range of age-related conditions in mice. These effects are comparable to those observed with calorie restriction or other mTORC1-inhibitory interventions (Figure 1). This $Cebpb^{\Delta uORF}$ mutation confers “C/EBPβ super-function”, as only the transactivating LAP isoform is expressed, remaining unaffected by the inhibitory C/EBPβ-LIP. Similarly, we showed that C/EBPα-p30 expression is regulated in the same way, and removal of the uORF results in “C/EBPα super-function” and extended health and lifespan in the short-lived African Turquoise Killifish (Figure 2).

In addition to mTORC1, we identified other pathways that regulate C/EBPβ-LIP, such as eIF2α-kinases and the RNA demethylase FTO. Another significant regulation of C/EBPα function occurs through lysine acetylation. The acetylation status of C/EBPα is modulated through deacetylation by SIRT1, in response to changes in NAD^+ homeostasis. Hypoacetylated C/EBPα enhances the transcription of mitochondrial genes, leading to increased mitochondrial function and identifying C/EBPα as a key mediator of SIRT1-controlled adaption of energy homeostasis. Preliminary data of studies deciphering the molecular mechanisms behind the differential gene regulation by hypo- versus hyperacetylation C/EBPα suggest the involvement of cofactor switching.

In a separate line of research, we discovered that oncogenic MYC restrains mTORC1 signaling in Burkitt's lymphoma by safeguarding the expression of the tuberous sclerosis complex (TSC). Disruption of MYC-TSC1-mTORC1 regulation leads to increased mitochondrial respiration, accumulation of toxic reactive oxygen species, and cell death. Our current studies reveal that TSC expression is also elevated in small cell lung cancer, and we currently investigate its tumor promoting role and involved regulatory and pathological mechanisms.



Metabolic trait	C/EBPβ −ΔuORF	Calorie restricted
Body weight	↓	↓
Fat content	↓	↓
Steatosis	↓	↓
Adiponectin	↑	↑
Glucose	↓	↓
Insulin	↓	↓
Glucose tol.	↑	↑
Ins. sensitivity	↑	↑
GH/IGF-1	↓	↓

Ageing phenotypes	C/EBPβ −ΔuORF	Calorie restricted
Rotarod	↑	↑
Beam walking	↑	↑
Wire hang	↑	↑
naïve/memory T-cells	↑	↑
Better maintained during ageing (4 vs. 20 months)		
Cancer	↓	↓

Figure 1. The table shows a compilation of phenotypes induced by the Cebpb$^{\Delta uORF}$ mutation resulting in C/EBPβ super-function through loss of LIP expression. Similar metabolic phenotypes and delay in age-related conditions can be achieved by calorie restriction.

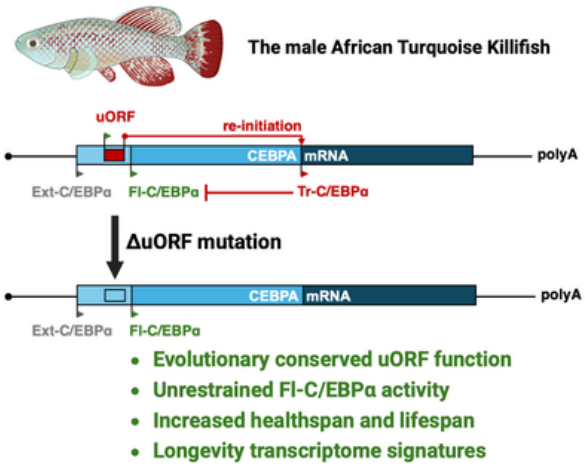


Figure 2. Mutation of the upstream open reading frame (uORF) in the CEBPA gene in short-lived killifish, resulting in unrestrained activity of the C/EBPα transcription factor, is associated with increased healthspan and lifespan.

The future

Triple-negative breast cancer (TNBC) cells express high levels of C/EBPβ-LIP, which is independent of mTORC1 signaling. This upregulation contributes to TNBC cell proliferation, migration, and immune evasion. Our research aims to identify the oncogenic pathways driving C/EBPβ-LIP overexpression and uncovering the mechanisms underlying TNBC development and immune escape. In the context of ageing, we are further investigating the role of mTORC1- and SIRT1-mediated regulation of C/EBPs health and lifespan determination.

Furthermore, we have identified RNA methylation as a new regulatory mechanism for C/EBPs, along with other factors involved in metabolism and cancer, which will require further investigation. Finally, we have uncovered tumor-maintenance functions of TBC1D7 in small cell lung cancer (SCLC) as part of the tuberous sclerosis complex (TSC1/TSC2/TBC1D7). The involved mechanisms and therapeutic potential will be further investigated. As part of both the C/EBP and TSC projects, we aim to develop drug screening strategies to identify new therapies for metabolic disorders and cancer.

Selected publication

Christine Müller, Joscha S. Muck, Kirill Ustyantsev, Gertrud Kortman, Josephine Hartung, Eugene Berezikov and Cornelis F. Calkhoven (2025). Enhanced C/EBPα function extends healthspan and lifespan in the African turquoise killifish. ageing Cell, **https://doi.org/10.1111/acel.70211.**

Objective: The transcription factor CCAAT/enhancer binding protein alpha (C/EBPα) regulates cell differentiation, proliferation, and function in various tissues. Studies in rats, mice, humans, and chickens have shown that CEBPA mRNA undergoes alternative translation initiation, producing three C/EBPα isoforms. Two of these isoforms act as full-length transcription factors with N-terminal transactivation domains and a C-terminal dimerization and DNA-binding domain. The third isoform is an N-terminally truncated variant, which antagonizing the full-length isoform. Expression of the truncated C/EBPα isoform depends on the initial translation of a short upstream open reading frame (uORF) in CEBPA mRNA and subsequent re-initiation at a downstream AUG codon, a process stimulated by mTORC1 signaling.

We investigated whether the ortholog of the CEBPA gene in the evolutionarily distant, short-lived African turquoise killifish (Nothobranchius furzeri) is regulated by similar mechanisms and whether this regulation contributes to health and lifespan determination.

Methods: We performed a bioinformatic cross-species analysis of CEBPA transcript sequences, followed by cloning of NfCEBPA and comparative expression analysis of wild-type and mutant NfCEBPA alleles to investigate mechanisms of CEBPA mRNA translation into distinct C/EBPα protein isoforms. Mutation of the CEBPA uORF was introduced in killifish using CRISPR/Cas9 genome editing. uORF-mutant and wild-type fish were analysed for several age-related phenotypes and subjected to lifespan assessment.

Results: Disruption of the uORF selectively eliminates the truncated isoform, leading to unrestrained activity of the full-length C/EBPα isoforms. This genetic modification significantly extended both the median and maximal lifespan and improved the healthspan of male N. furzeri. Furthermore, comparative transcriptome analysisrevealed an upregulation of genes and pathways that are associated with healthspan and lifespan regulation in other species.

Conclusion: The study highlight a conserved mechanism of CEBPA gene regulation across species and its potential role in modulating the lifespan and ageing phenotypes.

Group members

Christine Müller Senior scientist	**Clément G. Karch** PhD student	**Ying Zhang** PhD student	**Abid Eduardo Bernal Palacios** PhD student

MOLECULAR NEUROBIOLOGY OF AGEING

Ellen Nollen

Introduction

Maintenance of protein homeostasis is essential for cellular health but during ageing cellular maintenance mechanisms become less effective. Due to this loss of protein homeostasis, aggregation-prone proteins accumulate, which are toxic to cells and can cause disease. The biological mechanisms that drive such age-related protein toxicity are still incompletely understood. Our aim is to uncover these mechanisms and identify targets for biomedical interventions that prevent or delay age-related protein toxicity in ageing and age-related diseases.

Research focus

Our research focusses on aggregation-prone proteins that are characteristic of proteinopathies like Parkinson, Alzheimer's and ALS, which include alpha-synuclein, amyloid-beta, and TDP-43, and the mechanisms that drive their toxicity. Using genetic and phenotypic screens in C. elegans models, we have identified several evolutionary conserved mechanisms that, when inhibited, suppress the toxicity of such disease proteins. These include cellular factors like MOAG-4/SERF that drives toxicity through direct, charge-driven, interactions with aggregation-prone proteins. In addition, we identified metabolic factors, such as the tryptophan di-dioxygenase TDO, for which we currently aim to understand how its inhibition protects against protein toxicity. We have recently developed a phenotypic screening pipeline and tools to monitor the consequences of aggregation-prone proteins for health and behavior. We are using this pipeline to uncover and understand the mechanisms involved in protein toxicity. Furthermore, we take advantage of our technology to explore how other systemic and environmental factors, such as neuronal circuits and microbiome-host interactions converge at such proteotoxic mechanisms.

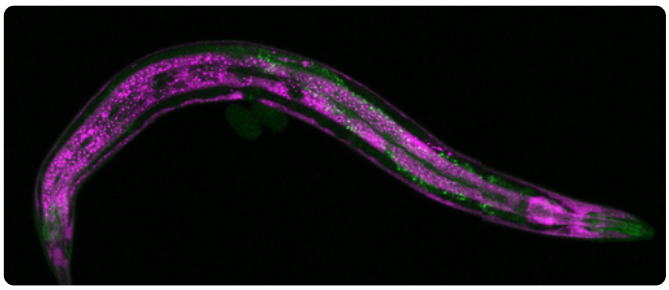


Figure 1. A C. elegans worm expressing TDO tagged with a fluorescent marker (visible in pink)

The future

We will continue our search for biological modifiers and their modes of action and, together with clinical and industrial partners, hope to find targets for interventions that protect or increase resilience to age-related protein toxicity.

Selected publication

Zhang T, Goya ME, Herron-Bedoya A, van der Weerd JC, Tsagkari D, Couzijn S, Güngördü L, Seinstra RI, Heiner Fokkema MR, Chang M, Tavernarakis N, Kuipers F, Nollen EAA. Condensate-Driven Triglyceride Depletion Links α-Synuclein to Mitochondrial Dysfunction. bioRxiv [Preprint]. 2025 Nov 18:2025.10.22.682553. doi: **10.1101/2025.10.22.682553**. PMID: 41278972; PMCID: PMC12633352.

Inclusions of α-Synuclein (αSyn) characterize multiple age-related neurodegenerative diseases, including Parkinson's disease (PD) and Multiple System Atrophy (MSA). While interactions between αSyn and lipids are known to contribute to αSyn pathobiology, the precise cellular mechanisms that link lipids to αSyn toxicity have yet to be elucidated. Through lipidomic profiling of Caenorhabditis elegans, we found that αSyn progressively alters lipid metabolism in ageing worms. αSyn strongly reduces overall content of triacylglycerols (TAG) and disrupts the structure of lipid droplets (LD). These pathological changes depend on αSyn's properties to condensate and form inclusions. Apart from lowering TAG levels, αSyn also increases the proportion of long-chain unsaturated fatty acids (LCUFAs). Consequently, genetic inhibition of LCUFA biosynthesis alleviates αSyn-induced loss of C. elegans motility. Strikingly, bypassing lipid metabolic defects by supplementing Medium Chain Fatty Acids (MCFAs) restores the αSyn-impaired mitochondrial response and rescues motility. These results link αSyn condensation to impaired TAG metabolism, which reduces mitochondrial function and enhances overall toxicity. Together with the finding that plasma TAGs are lowered in Parkinson patient cohorts, these results suggest that restoring TAG metabolism could alleviate αSyn-induced toxicity in Parkinson's and other age-related synucleinopathies.

Group members

Anna Ainslie Postdoc	**Bram Boon** Technician	**Suzanne Couzijn** PhD student	**Eugenia Goya** Postdoc
Lale Güngördü PhD student	**Alejandro Herron** PhD student	**Renée Seinstra** Technician	**Dave Tabb** Senior Scientist

LAB OF GUT-LIVER AXIS IN HEALTHY AGEING

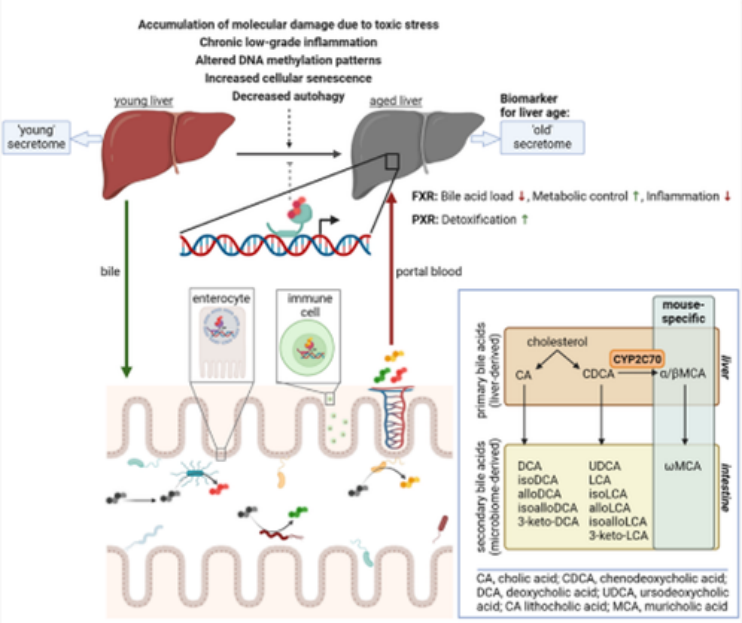
Folkert Kuipers

Introduction

Heterogeneity in ageing processes that are manifest between individuals as well as between organs of an individual represents a very challenging aspect of ageing research that complicates design of healthspan promoting interventions. This challenge is further increased by the recognition of the gut microbiome as a highly dynamic metabolic and immunogenic 'organ' that strongly affects host health and resilience to environmental challenges. Disturbances in gut microbiome-host communication are now known to contribute to a variety of age-related pathological conditions, such as type 2 diabetes and cardiovascular diseases, i.e., conditions with an inflammatory component. It is now well-established that the composition of the microbiome gradually changes during human ageing leading to a decrease in ecological diversity, referred to as dysbiosis. The recent addition of dysbiosis to the list of hallmarks of ageing emphasizes its perceived importance for the biology of ageing. My research program "Gut-Liver Axis in Healthy Ageing" deals with molecular (dys)regulation of cholesterol, bile acid (BA) and lipid metabolism and transport in liver and intestine in inherited and age-related chronic metabolic diseases, including the various roles of the gut microbiome.

Research focus

We propose that the gut microbiome decisively impacts ageing processes in intestine and liver, at least in part through production of secondary BA species (see Figure) with specific physico-chemical characteristics and signaling functions and by modulating their flux within the enterohepatic circulation. The identification of multiple nuclear and membrane-bound receptors that are differentially activated by primary and secondary BAs, the identification of hitherto unknown secondary BAsand the discovery that primary and secondary BAs have different immune-modulating functions warrants further evaluation of their roles in ageing processes. Of great importance in this context are our findings that the composition of the circulating BA pool shows a very large intraindividual variations in healthy subjects, in elderly obese subjects, and in obese subjects with type 2 diabetes. The (patho)physiological relevance of this divergence is currently unknown. A common denominator of conditions associated with liver ageing phenotypes is the well-known age- and dysbiosis-associated impaired intestinal barrier function (leaky gut): increased intestinal permeability results in an enhanced flow of bacterial products (e.g., LPS) towards the liver to induce an inflammatory status that will accelerate liver ageing. Intriguingly, the BA-activated receptor FXR has been identified as a modulator of intestinal barrier function[28], delineating the importance of strong inter-organ communication within the gut-liver axis.



The future

- **Exploration -** To identify nuclear receptor-mediated signaling pathways via which microbiome-derived secondary BAs modulate hallmarks of ageing in the liver and define the roles of BA-activated nuclear receptors in ageing phenotypes in intestine and liver of C57Bl6 mice with a human-like BA pool composition.
- **Modulation -** To assess the impact of interventions that prolong healthspan on microbial BA metabolism and on BA-activated nuclear receptor-mediated signaling pathways in intestine and liver the host.
- **Translation –** To assess the relevance of BA signaling pathways identified as putative ageing-modulating pathways in the human liver.

Selected publication

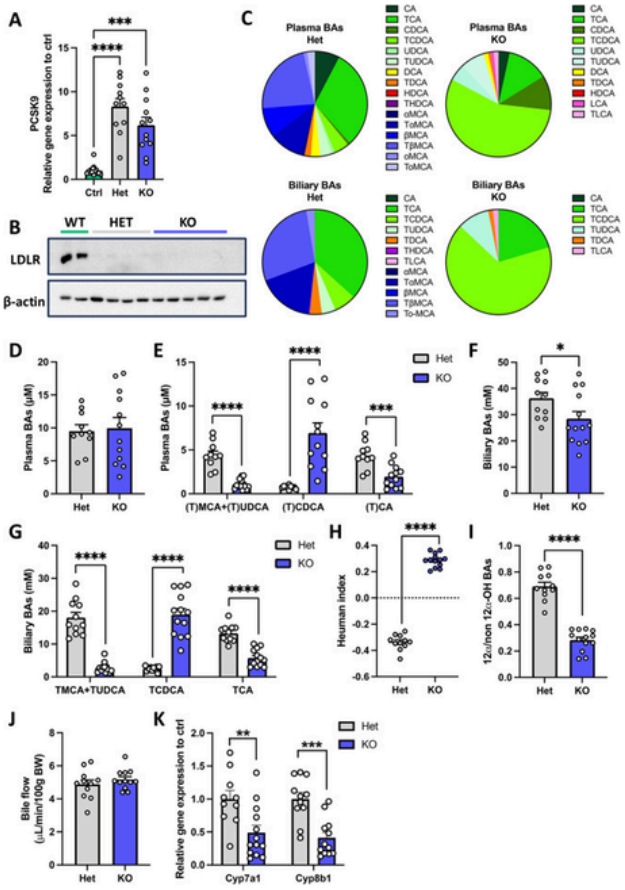
The impact of a humanized bile acid composition on atherosclerosis development in hypercholesterolaemic Cyp2c70 knockout mice

Tess Yntema, Tim R Eijgenraam, Niels J Kloosterhuis, Rick Havinga, Mirjam H Koster, Milaine V Hovingh, Jan Freark de Boer, Debby P Y Koonen, Folkert Kuipers

Abstract

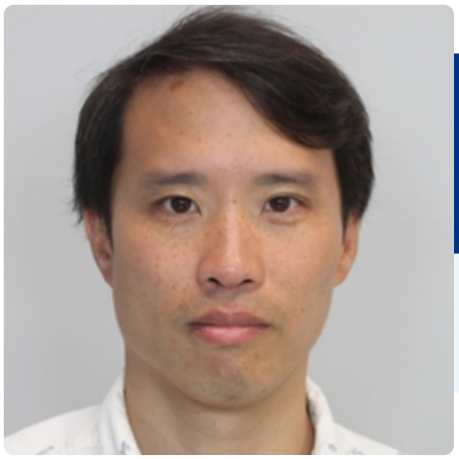
Bile acids (BAs) play important roles in the context of lipid homeostasis and inflammation. Based on extensive preclinical mouse studies, BA signaling pathways have been implicated as therapeutic targets for cardiovascular diseases. However, differences in BA metabolism between mice and humans hamper translation of preclinical outcomes. Recently, we generated Cyp2c70$^{-/-}$ mice with a human-like BA composition lacking mouse/rat specific muricholic acids. We employed this model to assess the consequences of a human-like BA pool on atherosclerosis and heart function in hypercholesterolaemic mice. We overexpressed a PCSK9 gain-of-function (GOF) mutation in the liver of male Cyp2c70$^{-/-}$ and Cyp2c70$^{+/-}$ control mice, and fed these mice a Western-type diet (WD) for 12 weeks. Cyp2c70$^{-/-}$ mice displayed a hydrophobic BA pool rich in chenodeoxycholic acid. Cyp2c70$^{-/-}$ mice showed reduced hepatic total cholesterol and triglycerides ($p < 0.05$) combined with lower plasma total cholesterol ($p < 0.05$) and triglycerides ($p = 0.05$) due to lower VLDL levels.

Circulating white blood cells remained largely unaffected in Cyp2c70$^{-/-}$ mice. Interestingly, we found a trend (p = 0.08) towards smaller atherosclerotic lesions in the aortic root of Cyp2c70$^{-/-}$ mice, but no effect on cardiac morphology or function was observed. To conclude, a human-like BA composition ameliorated PCSK9-GOF-induced hypercholesterolaemia in WD-fed mice which translated into a tendency towards smaller atherosclerotic lesions.



Group members

Brecht Attema Postdoc	**Ellen Weersing** Technician	**In collaboration with Laboratory of Pediatrics**



TELOMERES AND GENOME INTEGRITY

Micheal Chang

Introduction

The overall goal of our lab is to characterize the mechanisms used by a cell to protect its genome from becoming mutated or inappropriately altered or rearranged. The genome is duplicated in a process called DNA replication. If DNA becomes damaged, either as a consequence of normal cellular processes or due to exposure to DNA damageing agents, DNA repair pathways are employed to fix the damage. Defective DNA replication or repair results in genome instability, which is a hallmark of both cancer and ageing.

Research focus

Research in our lab is currently focussed on understanding how cells deal with DNA sequences—in particular, short tandem DNA repeat sequences—that are particularly challenging to replicate or repair. Short tandem DNA repeat sequences account for approximately 7% of the human genome. These sequences are often difficult to replicate, are prone to expansion and contraction, and can cause gross chromosomal rearrangements. Expansion of 15 different short tandem repeat sequences is linked to approximately 70 diseases, including Huntington's disease, Friedreich's ataxia, and fragile X syndrome, while chromosomal rearrangements are a source of genetic diseases and cancer. Misregulation of telomeric repeats, the best-studied example of a short tandem repeat sequence, is a hallmark of both cancer and ageing.

We examine how such sequences are replicated and repaired in the budding yeast **Saccharomyces cerevisiae**, which is an ideal model organism given the highly conserved nature of DNA replication and repair processes and the experimental advantages of the yeast system. We aim to identify relevant genes, and to determine their function and relationship with one another.

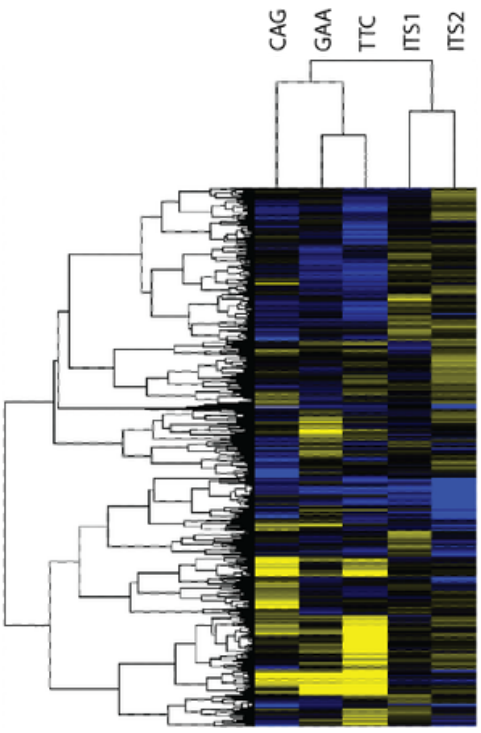


Figure 1. Two-dimensional hierarchical clustering analysis of the interstitial telomeric sequence (ITS) and short tandem DNA repeat (STR) gross chromosomal rearrangement (GCR) screens. The screens are plotted on the horizontal axis. Identified genes (5463 in total) are plotted on the vertical axis. The cluster trees organize the screens and genes based on profile similarity. Yellow and blue indicates GCR rate increase and decrease, respectively, with colour intensity reflecting the strength of the effect. ITS1 and ITS2 refer to two separate ITS screens, optimized to detect genes that either decrease (ITS1) or increase (ITS2) the rate of ITS-induced GCR (Rosas Bringas, Yin et al., 2024; doi: 10.1073/pnas.2407314121). The GAA/TTC repeats were screened in both orientations (with 'GAA' or 'TTC' referring to the strand used as the template for lagging strand DNA synthesis). CTG repeats (reverse complement of CAG) on the lagging strand template were too unstable to be used in a screen.

The future

Our lab will continue to study how cells protect their genome from mutagenic alterations. In particular, we are focussed on understanding how repetitive DNA sequences, which pose unique obstacles for the DNA replication machinery, are dealt with by genome maintenance mechanisms.

Selected publication

Berardi, P., Martinez-Fernandez, V., Rat, A., Rosas Bringas, F.R., Jolivet, P., Langston, R., Mattarocci, S., Maes, A., Aspert, T., Zeinoun, B., Casier, K., Kazemier, H.G., Charvin, G., Doumic, M., Chang, M., and Teixeira M.T. (2025) Both Genome Instability and Replicative Senescence Stem from the Shortest Telomere in Telomerase-Negative Cells. bioRxiv. doi: 10.1101/2025.01.27.635053

In the absence of telomerase, telomere shortening triggers replicative senescence, a tumor suppressor mechanism that is also associated with oncogenic genomic instability. Yet, the precise mechanism that connects these seemingly opposing forces remains poorly understood. To directly study the complex interplay between senescence, telomere dynamics, and genomic instability, we developed a system in Saccharomyces cerevisiae to generate and track telomeres of precise length in the absence of telomerase.

Using single-telomere and single-cell analyses combined with mathematical modeling, we identify a threshold length at which telomeres switch into dysfunction. A single shortest telomere below the threshold length is necessary and sufficient to trigger the onset of replicative senescence in a majority of cells. At population level, fluctuation assays establish that rare genomic instability arises predominantly in cis to the shortest telomere as Pol32-dependent non-reciprocal translocations that result in re-elongation of the shortest telomere and likely transient escape from senescence. The switch of the shortest telomere into dysfunction and subsequent processing in telomerase-negative cells thus serves as the mechanistic link between replicative senescence onset, genomic instability and the initiation of post-senescence survival.

Group members

Micheal Chang Principa Investigator	**Lisa Cabooter** Masters Student	**Inge de Groote-Kazemier** Technician	**Ziqing Yin** PhD Student
Daniele Novarina Research Associate	**Mirjam Piekema** Technician	**Sandra Ollivaud** PhD Student	**Yue Yao** PhD Student

CELLULAR SENESCENCE AND AGE-RELATED PATHOLOGIES

Marco Demaria

Introduction

Our research focuses on the mechanisms that regulate the induction, progression, and functional diversity of cellular senescence, as well as the physiological and pathological consequences of senescent cell accumulation in vivo. Cellular senescence is a dynamic stress response characterized by stable cell-cycle arrest and is widely recognized for its tumor-suppressive role. However, with advancing age or persistent damage, senescence can also impair tissue maintenance by depleting functional cell populations and reshaping tissue microenvironments in ways that promote degeneration and disease.

A defining hallmark of senescent cells is the senescence-associated secretory phenotype (SASP), a complex and heterogeneous secretome composed of cytokines, growth factors, proteases, lipids, and metabolites. While the SASP plays essential roles in tissue remodeling, regeneration, and immune-mediated clearance of damaged cells, accumulating evidence shows that persistent senescent cells contribute to chronic inflammation, aberrant remodeling, and the progression of age-related pathologies. Understanding how the composition and function of the SASP change across contexts remains a central challenge in the field.

The growing recognition of senescence as a driver of ageing and disease has catalyzed intense interest in therapeutic strategies targeting senescent cells, including senolytics and senomorphics. A major goal of our work is to identify when and where senescence should be eliminated, modulated, or transiently induced to maximize tissue health while preserving its beneficial functions.

Research focus

Our laboratory has been at the forefront of establishing senescence heterogeneity as a fundamental biological principle. We and others have shown that senescence is not a uniform cell state, but rather encompasses multiple phenotypically and functionally distinct subsets that coexist within tissues. These subsets are shaped by intrinsic programs, tissue context, sex, immune surveillance, and environmental cues. However, the molecular features that distinguish beneficial from detrimental senescent cells have remained poorly defined.

To address this gap, we integrate multi-omics approaches with genetically engineered senescence-reporter and ablation models to map senescent cell states in vivo. We recently reported a comprehensive integrative transcriptomic and proteomic analysis of p16^{+} senescent cells during ageing (Advanced Science, 2025), revealing pronounced sex-specific differences in senescent cell composition, signaling pathways, and functional consequences.

Complementing this work, we continue to contribute to community-wide efforts to standardize senescence research, including international consensus initiatives defining senescence-associated pathologies and experimental criteria. In parallel, we investigate how pharmacological interventions, metabolic stress, and cancer therapies reshape senescent cell phenotypes, with recent work linking CDK4/6 inhibition to altered senescent vulnerabilities in cancer models (EMBO Journal, 2025).

Beyond senescent cell clearance, our research also explores controlled induction of senescence as a regenerative strategy. Building on our earlier discovery that inhibiting PARP1 redirects oxidative stress–induced cell death toward transient senescence, we showed that this switch reduces fibrosis and improves functional recovery following ischemic kidney injury (Nature ageing, 2024). This work underscores the therapeutic potential of manipulating senescence timing and fate rather than indiscriminate elimination.

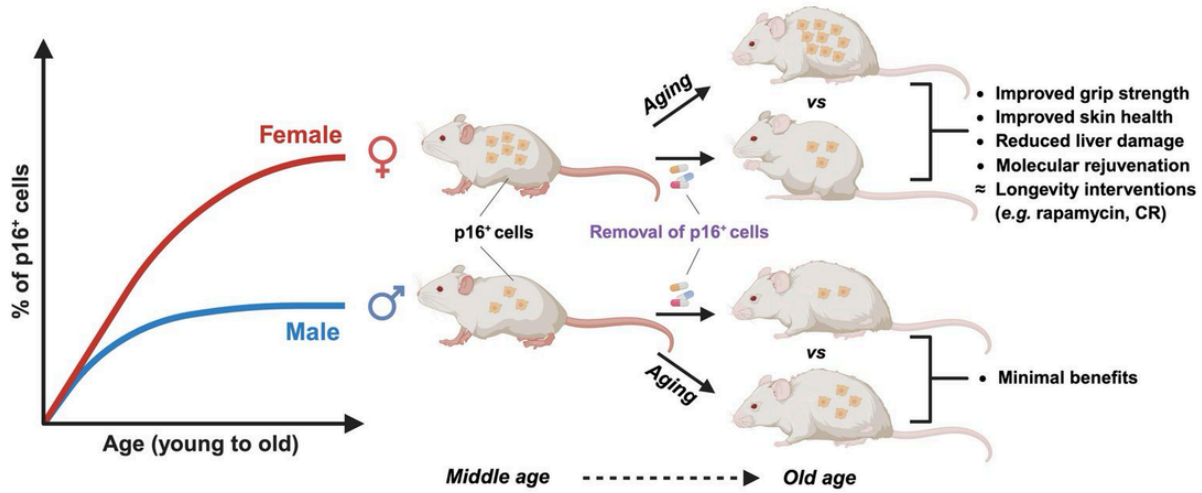


Figure 1. ageing leads to the accumulation of p16⁺ senescent cells, which drive inflammation and tissue dysfunction. Using transcriptomic, proteomic, and functional analyses, we reveal marked sex-specific differences in senescent cell burden and clearance during ageing. Female mice accumulate more p16⁺ cells, particularly in the liver, and selective elimination of these cells restores youthful molecular and functional profiles only in females. Multi-omics integration uncovers conserved mitochondrial–immune regulatory networks underlying these effects. These findings highlight sex as a critical biological variable in the response to senolytic interventions and support the development of precision senotherapeutics tailored to male and female ageing.

The future

Looking forward, our research aims to systematically define senescence subsets across tissues, disease states, and ageing trajectories using unbiased, multi-layered molecular profiling. A major priority is to understand how sex-specific, tissue-specific, and context-dependent senescence programs influence immune surveillance, regeneration, and long-term tissue function.

We are particularly interested in translating these insights into strategies that tailor senescence-targeting interventions to specific biological contexts, thereby improving efficacy while minimizing adverse effects. By integrating fundamental ageing biology with disease-focused and translational models, our overarching goal is to advance a more precise and responsible strategy for targeting senescence in ageing and age-related disease.

Selected publication

Lin Y, Wang B, Huang M, Wolters J, Demaria M. Integrative Omics Reveal Female-Specific Benefits of p16+Cell Clearance in ageing Mice. 2025. Advanced Science. **13:e09444**

Abstract

ageing is marked by the accumulation of cells expressing the cyclin-dependent kinase inhibitor p16Ink4a. These p16⁺ cells, largely senescent, contribute to inflammation and tissue dysfunction. While eliminating p16⁺ cells improves healthspan, sex-specific differences in their burden and clearance remain unclear. Through combined transcriptomic, proteomic, and functional analyses, we reveal distinct sex-dependent dynamics of p16⁺ cells during ageing. Female mice accumulate significantly more p16⁺ cells across multiple tissues, particularly in the liver. In the p16-3MR model, selective ablation of these cells enhances grip strength, promotes skin regeneration, and reduces liver damage exclusively in females. Multi-omics profiling shows that p16⁺ cell removal shifts female liver expression toward youthful, health-associated profiles, marked by improved mitochondrial activity and reduced inflammatory signaling-molecular patterns resembling those induced by longevity interventions such as calorie restriction, rapamycin, and acarbose. Integrative analysis of our and independent datasets identifies a conserved transcriptional network involving Srm, Cd36, and Lrrfip1, suggesting shared mitochondrial-immune regulatory mechanisms. Overall, our findings establish p16⁺ cells as critical yet heterogeneous drivers of tissue ageing, uncover sex-specific differences in their abundance and senolytic responsiveness, and support the development of precision senotherapeutics that consider sex as a key biological variable in ageing and rejuvenation.

Group members

Martijn Rutten Postdoc	**Pilar Picallos** Postdoc	**Sjors Maassen** Postdoc	**Boshi Wang** Scientist
Naomi Veeningen Postdoc	**Jamil Nehme** Postdoc	**Abdullah Altulea** PhD student	**Alessio Piccolantonio** PhD student
Anton Stamm PhD Student	**Chen Ge** PhD Student	**Chi Zhang** PhD Student	**Francesca Pagliarin** PhD Student
Mengling Huang PhD Student	**Myrthe Klaver** PhD Student	**Sebastian Mackedenski** PhD Student	**Teodora Gheorghe** PhD Student
Trupthi Joshi PhD Student	**Simone Brandenburg** Lab Technician	**Lotte Steeneken** Lab Technician	

GENOMIC INSTABILITY IN DEVELOPMENT AND DISEASE

Floris Foijer

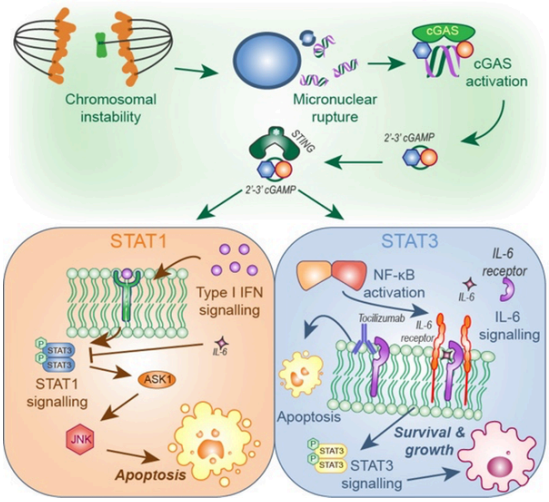
Introduction

Chromosomal instability (CIN) is a hallmark feature of cancer. CIN leads to cells with an abnormal DNA content, a state known as aneuploidy affecting >80% of all cancers. CIN and aneuploidy discriminate cancer cells from non-cancer cells and therefore provide an attractive therapeutic target. Paradoxically, in untransformed cells, CIN and aneuploidy decrease cellular fitness and lead to activation of stress pathways. This suggests that cancer cells have found ways to cope with the downsides of CIN. A better understanding of these coping strategies can lead to new therapies that target these mechanisms, and thus selectively kill the aneuploid cancer cells with fewer side effects on healthy cells. We study the how cells deal with chromosomal instability and aneuploidy, in vitro as well as in vivo. For this we 1) develop and exploit models and technology to faithfully measure chromosomal instability and aneuploidy in cultured cells as well as in living mice, 2) we develop mouse and advanced cell models to study CIN, which we 3) use to better understand the mechanisms that trigger the responses to CIN and 4) we exploit these mechanistic findings to design therapies that selectively kill cells with a CIN phenotype.

Research focus

Ongoing CIN leads to cells with variable karyotypes and thus to intratumour karyotype heterogeneity. CIN is therefore a strong driver of cancer cell evolution and associated with poor prognosis. Together with the research sequencing facility, we heavily invested in single cell DNA sequencing as a tool to quantify karyotype heterogeneity. We for instance used this tool to study how chromosomal instability drives the evolution of human cancers, for instance pediatric neuroblastoma or lymphoma (refs 1, 2). Furthermore, to better understand how chromosome missegregation affects the fitness of individual cells, we combine scWGS and scRNA-seq to better understand how individual karyotypes influence cellular fitness. For this, we take advantage of our earlier-published mouse models of CIN-induced T-ALL, from which we analyze primary tumor samples as well as T-ALL-derived cell lines, which is revealing that tumors with an ongoing CIN phenotype and semi-clonal karyotypes contain multiple smaller clones with unique karyotypes. We are currently investigating the biology of these smaller clones to better understand how chromosome missegregation drives cancer cell evolution, but also how CIN leads to cell populations that are less fit that ultimately will be selected against.

We recently found that CIN will trigger an inflammatory response in premalignant as well as cancer cells. Our work is indicating that this inflammatory response activates the immune system and thus leads to immune clearance of premalignant aneuploid cells. We find that cancer cells circumvent this inflammatory response by alleviating one of the main inflammatory routes in the cell: STAT1 signaling. This inflammatory response, triggered by CIN, critically relies on IL6 activity upstream of Stat1 and Stat3. In 2022, we showed that blocking IL6 signaling, e.g. by means of the clinically approved IL6R inhibitor tocilizumab is toxic to CIN tumor cells in vitro and in vivo, but well-tolerated by chromosomal stable cancers, revealing an unexpected Achilles heel of aneuploid cancers, which we are currently validating in models for T-ALL (funded by a Lymph&Co grant) and breast cancer (funded by a Vici grant). Furthermore, we are establishing mouse models in which we can knockout genes of choice using CRISPR in a tissue specific manner, also with a focus on breast cancer.



CIN leads to a STAT1 pro-death and STAT3 pro-survival inflammatory response that can be selectively targeted to kill cells with CIN.

As we found that cancer cells with CIN hide from the immune system, we set out to find factors that cells with CIN secrete to influence the tumor microenvironment. We found that cells with CIN secrete more extracellular vesicles (EVs) and that these EVs promote the migration and invasion of other cancer cells, suggesting that cancers with CIN can promote metastasis via EVs. We identified EFEMP1 as an EV-factor driving this phenotype and found that EFEMP1 expression is driven by the transcription factor STAT1, which we previously identified as a gene specifically downregulated in CIN-driven cancers. Together, this work identifies EFEMP1 as a potential factor promoting CIN-driven metastasis in cancer thus potentially revealing a new clinical target for CIN cancers (revision submitted).

Furthermore, in collaboration with the department of internal medicine, we found that pheochromocytoma, a cancer of the adrenal gland commonly shows chromosomal instability, and slightly more often in more aggressive subtypes. Pheochromocytoma infrequently recurs, years after initial diagnosis, and we tested whether preexisting CIN could predict this rare adverse outcome. While we found that CIN alone did not predict recurrence, we did identify transcriptome signatures present in the originating tumor that were also observed in recurring tumors. Future work should further investigate the predictive values of these signatures (ref 2).

The future

Now that we identified that lack of immunosurveillance is an essential feature of tumors displaying a CIN phenotype, we next want to understand which immune cells clear aneuploid cells and which interactions between immune cells and cancer cells trigger clearance. Further, we want to map the molecular mechanisms that cancers exploit to inactivate immune signaling and translate this knowledge into therapeutic interventions that selectively target aneuploid cells. For this, we are developing state-of-the art cellular reporters to read out inflammation and techniques such as CUT&Tag to map the transitional response to CIN. In addition to mapping how immune cells clear aneuploid cells, we are further investigating the molecular mechanisms that trigger the initial inflammation response, including CRISPR genome-wide screens.

Furthermore, we want to better understand how karyotype dynamics drive tumor evolution. For this, we will investigate how chromosome copy number changes change cellular fitness in cell models, but also in vivo, including intravital imageing models to visualize aneuploidy in vivo in zebrafish and, ultimately, in mice. For this, we will develop fitness reporters as well as new mouse models in which we can determine cellular fitness in cultured cells including genome-wide screens as well as in vivo. Finally, in close collaboration with the newly established company iPsomics, we plan to investigate the potential of single cell genomics-inferred karyotype heterogeneity as a biomarker for the outcome of human cancers and a tool to stratify cancer treatment.

Selected publication

Rendo V, Schubert M, Khuu N, Suarez Peredo Rodriguez MF, Whyte D, Ling X, van den Brink A, Huang K, Swift M, He Y, Zerbib J, Smith R, Raaijmakers J, Bandopadhayay P, Guenther LM, Hwang JH, Iniguez A, Moody S, Seo JH, Stover EH, Garraway L, Hahn WC, Stegmaier K, Medema RH, Chowdhury D, Colome-Tatche M, Ben-David U#, Beroukhim R#, Foijer F#. A compendium of Amplification-Related Gain Of Sensitivity genes in human cancer. Nat Commun. 2025 **Jan 27;16(1):1077.**

Abstract

While the effect of amplification-induced oncogene expression in cancer is known, the impact of copy-number gains on "bystander" genes is less understood. We create a comprehensive map of dosage compensation in cancer by integrating expression and copy number profiles from over 8000 tumors in The Cancer Genome Atlas and cell lines from the Cancer Cell Line Encyclopedia. Additionally, we analyze 17 cancer open reading frame screens to identify genes toxic to cancer cells when overexpressed. Combining these approaches, we propose a class of 'Amplification-Related Gain Of Sensitivity' (ARGOS) genes located in commonly amplified regions, yet expressed at lower levels than expected by their copy number, and toxic when overexpressed. We validate RBM14 as an ARGOS gene in lung and breast cancer cells, and suggest a toxicity mechanism involving altered DNA damage response and STING signaling. We additionally observe increased patient survival in a radiation-treated cancer cohort with RBM14 amplification.

Group members

Petra Bakker Lab manager	**Merlissa Goesten** Technician	**Anna Haider Rubio** PhD student	**Iris Harmsen** PhD student
Karina Kopke PhD student	**Xiao Ling** PhD student	**Ziqi Liu** PhD student	**Danielle Koot** PhD student
Alexis Maagenberg MD/PhD student	**Marsudi Siburian** PhD student	**Maria Suarez** Postdoc	**Ruifang Tian** PhD student
Anouk van den Brink PhD Student	**Alex van der Kaam** PhD student	**Declan Whyte** Postdoc	**Soraya Wobben** PhD student
Siqi Zheng PhD Student			

GENOME STRUCTURE AND AGEING

Victor Guryev

Introduction

Even though the completion of the human genome project was announced over 20 years ago, our knowledge of genome variants and their effects on the onset of ageing-related diseases is still far from being complete. Under-investigated large and complex alterations in our genomes affect many more DNA bases than small, single-nucleotide changes. Some of these structural genome changes can be predicted using a routine analysis procedure of DNA data, others, like large inversions or non-reference insertions, deserve further investigation.

Our research aims to identify a wide spectrum of DNA alterations, fine-map them to corresponding genomic locations, and characterize their effects on molecular function. Our group combines analysis of genome, transcriptome, and proteome profiling (functional genomics and proteogenomics approaches) to distinguish deleterious genomic variants from benign ones. These results should contribute to a better understanding of the content, function of variable segments in our genomes, their role in ageing-related diseases.

Research focus

Our research is focused on several approaches for investigating ageing-related molecular changes:

A. Investigation of genome alterations potentially associated with ageing-related diseases (Fig 1A). We are studying the distribution and role of large variants in our genomes. My team applies expertise developed in the Dutch genome project to characterize SVs in patients suffering from early-onset severe COPD, cancer, and other diseases.
B. Transcriptome regulation in ageing and onset of diseases (Fig 1B). Previous studies already identified several trends (e.g. more retained introns) in transcriptome processing that happen as we get older. Our group analyses transcriptomes of several patient cohorts to identify sources of these changes and their potential roles in disease etiology.
C. Combining differential expression and differential variability analysis (Fig 1C). Since many human diseases are very heterogeneous in their molecular and clinical manifestations, molecular subtyping and analysis of differential variability provide orthogonal approaches to classical disease association methods. We successfully employed methods for quantifying biological variability to get insight into cellular processes affected by ageing, lung diseases, sepsis, and COVID-19.

D. Multi-level data integration for personalized diagnostics and treatment (Fig 1D). Combining DNA variation data with other omics layers, such as gene expression, proteomics, metabolomics, and phenotypic data, is key for the discovery of function for DNA polymorphisms. Previously, we used a rat model of hypertension to demonstrate that such analysis of DNA, RNA, and proteins, where information 'flows' across omics-layers, is an efficient way to study disease (PMID:24290761). This observation supports the validity of our approach and suggests that it can be useful for studying relations between structural genome variants and molecular phenotypes that manifest themselves at RNA and protein levels and potentially play roles in human diseases.

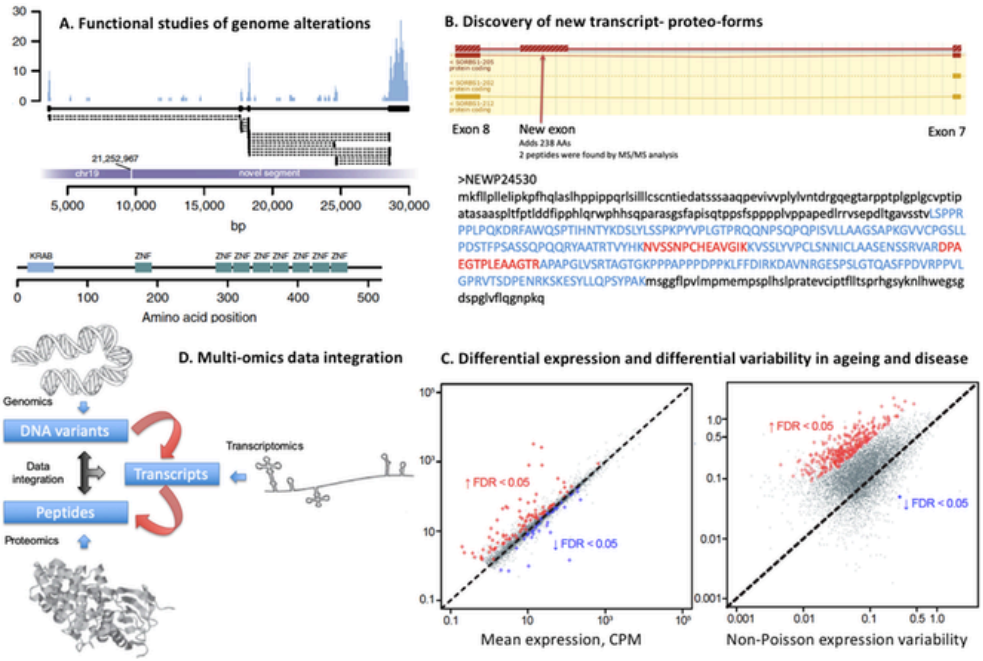


Figure 1. Major research directions. (A). Investigation and functional characterization of large genome alterations and their role in the onset of age-related diseases. An example of a long non-reference insert on chr19, that encodes for a new zinc finger gene. Transcript coverage by RNA-seq reads (top), reads supporting splicing events (middle), and domain structure of resulting protein product (bottom) are displayed. (B) Transcriptome analysis identifies new disease-associated protein-coding exons. An example of an exon in the SORBS1 gene that is differentially present in transcripts of COPD patients. The exon adds 238 amino acids to the protein product and was confirmed by 2 corresponding peptides (in red) with LC-MS/MS data. (C) Differential expression and differential variability analysis show age-specific changes in gene expression. Left panel: more genes show upregulation of expression level in old individuals (y-axis) compared to young (x-axis). Right panel: many more genes show an increase in inter-individual variability in old individuals (y-axis) than in young individuals (x-axis). (D) Our multi-omics data integration approach. A common analysis strategy is to perform separate analyses for each omics level using public reference (black arrows). In our studies, we perform sequential integration where each omics layer informs the analysis of the next levels by providing data on DNA variants (genomics), splice variants, and new transcript units (transcriptome) for better interpretation of ageing- and disease-related molecular changes.

The future

In the future, we aim to improve the prediction of functional consequences for large genome alterations in relation to human diseases. We plan to identify new transcriptional units and novel isoforms for known genes and link them to genome variation and dysregulated splicing factors (age- and disease-specific). Our short-term goal is to employ pathway and biochemical complex-centered analysis of gene expression variability. This will allow us to identify disruptions in particular gene ensembles on human diseases and better understand the underlying mechanism. Finally, we will continue to develop our computational framework for personalized multi-omics data integration and will utilize it for the analysis of omics data from other ageing-related diseases

Selected publications

Karabatic, A., van den Berge, M., Carroll, T. P., Guryev, V., & Faiz, A. (2025). Mendelian causes of early-onset emphysema: a review of the current literature. European respiratory review : an official journal of the European Respiratory Society, 34(178), Article 250125. https://doi.org/10.1183/16000617.0125-2025

Abstract

Currently, the only known clinically relevant hereditary risk factor for emphysema is limited to mutations within the SERPINA1 gene, encoding alpha-1 antitrypsin. Although several additional rare high-impact variants have been proposed, their role in emphysema pathophysiology is unclear. This review discusses recent cases investigating novel candidate genes that may be Mendelian causes for emphysema development. We also explore potential methods to confirm the causal relation to COPD. Identifying potential new rare high-impact genetic variants may lead to novel therapeutic targets, thus improving the personalised treatment of COPD. Several gene mutations have been implicated in emphysema development, including SERPINA1, SERPINA3, PTPN6, TERT, TR, NAF1, BICD1, ELN, FBLN, FLNA and SFTPC. Mutations of the SERPINA1 and PTPN6 genes are considered definitive causes of emphysema. Studies have ascertained rare variants in cutis laxa genes (ELN, FBLN and FLNA), which cause early-onset emphysema in infants and children via defective elastin synthesis. Telomerase pathway genes (TERT, TR, NAF1 and BICD1) have also been implicated in increased COPD risk along with another member of the serpin family (SERPINA3) and SFTPC. These probable mutations for emphysema tend to present later in life. Due to being unconfirmed, they may involve a more complex gene interaction that requires further interrogation with next-generation sequencing and molecular methods, including CRISPR (clustered regularly interspaced short palindromic repeats) screening libraries, whole-exome sequencing or whole-genome sequencing. Although multiple novel mutations have been reported to cause emphysema, further validation is needed. Next-generation sequencing offers a promising method to understand early-onset emphysema and COPD pathogenesis.

Group members

Fatemeh Ghorbani Postdoc	**Yanick Hagemeijer** PhD student	**Tatiana Karp** PhD student	**Yuan He** PhD student

CELLULAR BIOCHEMISTRY

Liesbeth Veenhoff

Introduction

The main research line in the group is to understand the role of the nuclear pore complex (NPC) in ageing. The NPCs are the sole gateways to the interior of the nucleus and their function is essential to all eukaryotic life. The NPC's function is intimately connected to the primary hallmarks of ageing of protein homeostasis and genome stability. We made contributions to the understanding of the structure and function of NPCs and in uncovering the vulnerabilities of NPCs in ageing cells. The surveillance of the intrinsically disordered proteins of the NPC is a main interest in the lab, as it appears that mechanisms that guard their structural state, also guard other intrinsically disordered proteins related to aggregation pathologies. This provides a new entry into the problem of protein aggregation pathologies and ageing. Complementing these studies aiming to uncover how the quality control of NPCs and intrinsically disordered proteins can be better safeguarded in ageing, we aim to contribute to a better understanding of the cellular ageing process in general.

Research focus

The NPC's function is intimately connected to the primary hallmarks of ageing of proteins homeostasis and genome stability, and several processes underlying these hallmarks are orchestrated at NPCs. The NPC's function is compromised in ageing and age-related aggregation pathologies, and we aim to uncover the mechanisms responsible for NPC quality control.

The NPC is a prime example of a molecular machine whose function relies on intrinsically disordered proteins, proteins that lack a persistent secondary or tertiary structure. The intrinsically disordered proteins of NPCs are named FG-nucleoporins (FG-Nups) and they form a selective barrier (Kozai et al., 2025; highlighted publication. below).

Away from the NPC, FG-Nups readily form condensates and aggregates, and we address how this behavior is surveilled in cells. In two manuscripts (Bergsma et al., 2024, Bergsma & Musskopf-Kolbe et al., 2025 BioRxiv, 2025) we report a method for imageing-based quantitative assessment of biomolecular condensates and studied the role of molecular chaperones in the surveillance of FG-Nups in the timeframe between their biogenesis in the cytosol and their incorporation in NPCs. We show that show that DNAJB6 and the closely related DNAJB2 and DNAJB8 prevent several FG-rich nucleoporins (FG-Nups) from undergoing aberrant phase-transitions. We demonstrate that this surveillance mechanism of DNAJB6 is encoded in an unusually highly conserved IDR that promotes the formation of stable, gel-like assemblies of the chaperone itself.

These assemblies likely provide a stable environment that can outcompete homotypic FG-Nup interactions and instead favors dynamic, multivalent heterotypic chaperone:FG-Nup interactions. The evolutionary conservation of the DNAJB6-IDR and mutant analyses suggest that the sequence space for encoding stable gel-like assemblies is narrow and optimized to avoid self-aggregation while providing remarkable anti-amyloidogenic capacity.

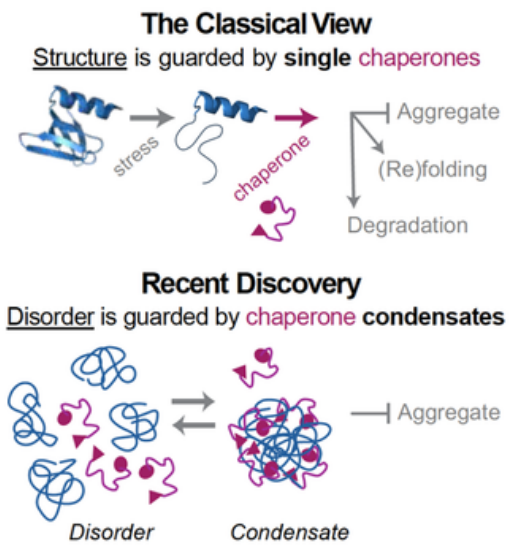


Figure 1. Top: Classical view how chaperones help proteins to fold or refold and prevent aggregation. Bottom: Proposed model showing that the chaperone DNAJB6 (pink) guards intrinsically disordered proteins (blue wiggled lines) by engageing with them in multivalent interactions within condensates. Image by Ilse Oosterlaken, www.thescicompanion.eu.

Our data contribute to a larger emerging theme of a tightly regulated interplay between FG-Nups, nuclear transport factors, and the molecular chaperones from the classical protein quality control system. Indeed, the well-established role of DNAJB6 is in interacting with and delaying the aggregation of disease-related IDPs (polyQ, FUS, FTD).

Aberrant phase state transitions of diverse intrinsically disordered proteins occurs in aged cells and in (models of) neurodegenerative diseases, and a better understanding of what regulates these transitions is much needed. This study identifies Nsp1 as a new player at these crossroads of NPC biology and protein quality control.

The future

We will continue to design our research from the viewpoint that studying “biology in time” is an unbiased way to reveal fundamental knowledge; knowledge that is needed to combat age-related diseases. Specifically, we aim to identify the proteins that detect damaged NPCs, to know the destiny of damaged NPCs, and to uncover the mechanisms that prevent damage to NPCs. Understanding how condensation of intrinsically disordered proteins is surveilled will also remain a main interest in the lab.Together, the planned research aims to uncover how the quality control of NPCs and intrinsically disordered proteins can be better safeguarded in ageing.

Selected publication

Kozai T, Fernandez-Martinez J, Kapinos LE, Gallardo P, van Eeuwen T, Saladin M, Eliasian R, Mazur A, Zhang W, Tempkin J, Panatala R, Delgado-Izquierdo M, Escribano-Marin R, Feng Q, Lin C, Sali A, Chait BT, Raveh B, Veenhoff LM, Rout MP, Lim RYH. Karyopherins remodel the dynamic organization of the nuclear pore complex transport barrier. Nat Cell Biol. **2025;27(12):2089-2101.**

Abstract

Nuclear pore complexes (NPCs) mediate selective exchange of macromolecules between the nucleus and cytoplasm, but the organization of their transport barrier has been a matter of debate. Here we used high-speed atomic force microscopy, complemented with orthogonal in vitro and in vivo approaches, to probe the dynamic behaviour of the NPC central channel at millisecond resolution. We found that nuclear transport factors dynamically remodel intrinsically disordered phenylalanine-glycine (FG) domains tethered within the NPC channel, partitioning the barrier into two zones: a rapidly fluctuating annular region and a highly mobile central plug. Increased FG-repeat density in mutant NPCs dampened barrier dynamics and impaired transport. Notably, NPC-like behaviour was recapitulated in DNA origami nanopores bearing transport factors and correctly tethered FG domains but not in in vitro FG hydrogels. Thus, the rotationally symmetric architecture of NPCs supports a nanoscopic barrier organization that contrasts with many of the bulk properties of in vitro FG-domain assemblies.

Group members

Anton Steen Research Associate	**Tegan Otto** PhD student	**Annemiek Veldsink** PhD student	**Tessa Bergsma** PhD student
Paola Gallardo Postdoc	**Amarins Blaauwbroek** Lab Technician	**Maiara Kolbe Musskopf** PhD student	**Sandra Ollivaud** PhD student

COENZYME A METABOLISM IN HEALTH AND DISEASE

Ody Sibon

Introduction

A deeper understanding of the pathological mechanisms underlying early-onset neurodegenerative diseases is essential not only for the development of effective therapies, but also for gaining insight into the biological processes that drive brain decline during normal ageing. Research in the Sibon lab focuses on childhood-onset neurodegenerative disorders related to coenzyme A metabolism. Coenzyme A is a central and indispensable metabolic cofactor required for all forms of life, participating in more than one hundred metabolic reactions. It is widely accepted that coenzyme A is synthesized exclusively from environmentally acquired vitamin B5. However, our laboratory has identified compelling evidence for alternative pathways through which cells and organisms can obtain coenzyme A. These pathways rely on precursors that are distinct from vitamin B5, although the mechanisms governing their cellular uptake remain largely unknown. Our research investigates these alternative pathways in detail, integrating fundamental mechanistic studies with translational approaches aimed at developing therapeutic strategies for inherited coenzyme A–related disorders. Our overarching goal is to elucidate how coenzyme A precursors cross biological membranes, are taken up and metabolized by cells, and contribute to coenzyme A homeostasis and organismal health.

Research focus

We have recently discovered that enzymatic activity within the Drosophila melanogaster gut microbiome can compensate for genetic defects in coenzyme A (CoA) metabolism of the host. The precursor pantethine is taken up by microbial species, converted into 4′-phosphopantetheine, excreted, and subsequently imported by host cells (yu yi et al., Mol. Cell 2022; Wedman et al., JBC 2025 (Figure 1). These findings indicate the existence of specific import and export mechanisms for CoA precursors and reveal a complex metabolic interplay between the microbiome and the host.

The aim of our research is to elucidate the molecular mechanisms governing the transport of CoA intermediates in model organisms and humans, and to explore how these insights can be translated into therapeutic strategies for childhood-onset neurodegenerative disorders caused by defects in specific enzymatic steps of the CoA biosynthetic pathway. To this end, we employ yeast, Drosophila, and mammalian model systems, integrating genetic, cell biological, biochemical, analytical, and structural approaches.

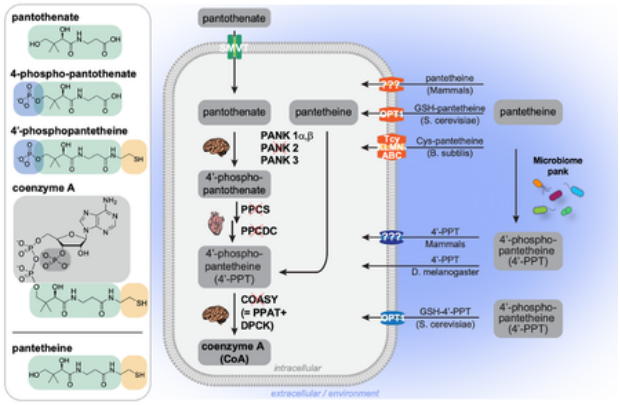


Figure 1. CoA precursors and biosynthesis. At the left are the chemical structures provided of CoA pathway intermediates and precursors that can be taken up from the environment. In the middle is a cell presented with the canonical CoA de novo biosynthesis; enzymes are in bold, intermediates are in grey boxes, red dotted crosses represent affected enzymes in 4 CoA-linked brain and heart diseases. At the right are alternative routes to CoA presented derived from our published work.

The future

Our future aims are to gain fundamental and structural insight how CoA precursors are taken up by cells (visualized by the question marks in Figure 1) and to translate this knowledge into therapeutical strategies for CoA-linked brain and cardiac diseases. In our research we also investigate the interplay of CoA-precursors exchange between microbiome species and their host.

Selected publication

Jouke Jan Wedman, Lotte de Vries, Bart van Lingen, Marianne van der Zwaag, Rubén Gómez-Sánchez, Ralph Hardenberg, Wim Huibers, Hjalmar Permentier, Erick Strauss, Michael Chang, Fulvio Reggiori, Anton I. de Kroon, Ody C. M. Sibon*, Hein Schepers*. Opt1 transports CoA precursors as glutathione mixed disulphides. *shared last. JBC 2025 301(9):110503. **DOI: 10.1016/j.molcel.2022.05.006**

Abstract

Pantothenate (vitamin B5) is essential for the synthesis of coenzyme A (CoA), a central metabolic cofactor. Cells typically produce CoA through a well-studied, five-step pathway that uses pantothenate, ATP, and cysteine. However, some organisms rely on alternative routes that start from pantetheine (PanSH) or 4′-phosphopantetheine (PPanSH), though how these molecules enter cells has remained unclear. Using in vivo experiments, yeast genetics, and traceable compounds, we identify a non-canonical CoA biosynthesis pathway. We show that extracellular PanSH and PPanSH form mixed disulfides with glutathione and are imported via the oligopeptide transporter Opt1, then converted into CoA. This pathway bypasses several canonical enzymes and provides a growth advantage under cysteine-limiting conditions. Our findings open new avenues for treating CoA-related diseases and for controlling the growth of organisms that depend on PanSH or PPanSH. See also Figure 1

Group members

Dr. Nicola Grzeschik
Senior researcher

Dr. Hein Schepers
Senior researcher

Dr. Anna Yudenko
Postdoc

Ellie Eggens
Technician

Marianne van der Zwaag
Technician

Erika Geubels
Technician

Jente Zeubring
PhD student

Ting Xu
PhD student

Sjoukje Polet
PhD student

Jouke Wedman
PhD student

4. Facts and Figures

Awards

1. **Marco Demaria** was listed as the top cited researcher on the **ScholarGPS** website.
2. **Wi Lienen**, under the supervision of Stijn Mouton, won the **KNCV Gouden Vlam 2025 award** during the Avond van de Chemie. Since 2018, the KNCV has awarded the Gouden Vlam annually to the best chemical graduation thesis in secondary vocational education. Submitted theses are evaluated by an expert jury, and the winner is announced during an official award ceremony. In addition to the recognition and honor, the award includes a cash prize of €1,000. More information: https://www.kncv.nl/nl/prijzen/gouden-vlam
3. **Ody Sibon** was awarded with the **FEBS Outstanding Women in Science award**. The 60th Anniversary of FEBS, nominated by the students of the NVBMB). As part of the FEBS 60th anniversary activities, FEBS constituent societies were invited to highlight outstanding women belonging to their Society for an eBook showing the diverse ways in which women navigate their careers in science alongside personal and family commitments. The resulting book presents 35 engageing accounts of paths in science across different countries, with the aim of inspiring future generations of female scientists.

Promotions

Date	Student	Title	Promoter(s)
6-1-2025	Josephine Hartung	The multifaceted roles of the tuberous sclerosis complex in cancer	Cor Calkhoven and Christine Müller
14-4-2025	Anne de Groot	Characterizing and targeting CBX7 activity in leukemia	Gerald de Haan and Cor Calkhoven
23-4-2025	Leticya Melo dos Santos	Exploring the Intersections of Immunosenescence and Cellular Senescence in Health and Disease	Marco Demaria and Florencia M. Barbé-Tuana
17-9-2025	Tegan Aileen Otto	Creating Order through Disorder: a Delicate Dance between the Nuclear Pore Complex and Protein Quality Control System	Liesbeth Veenhoff and Michael Chang
27-10-2025	Lale Güngördü	Modifying TDP-43 toxicity: the role of ion channels and neuronal networks	Ellen Nollen and Victor Guryev
29-10-2025	Sara Graves	Cyclin-dependent kinase inhibitors and neurodegenerative tauopathy	Marco Demaria and D. Baker
19-12-2025	Ruifang Tian	Chromosomal Instability as a Driver of Tumor Progression: From Intracellular Vulnerabilities to Extracellular Communication and Immune Modulation	Floris Foijer, Marco Demaria and Rudolf Fehrmann

Scientific publications

LAB OF GUT-LIVER AXIS IN HEALTHY AGEING

Folkert Kuipers

1. Zhang, T., Goya, M. E., Herron-Bedoya, A., van der Weerd, J. C., Tsagkari, D., Couzijn, S., Güngördü, L., Seinstra, R. I., Heiner Fokkema, M. R., Chang, M., Tavernarakis, N., Kuipers, F., & Nollen, E. A. A. (2025). Condensate-Driven Triglyceride Depletion Links α-Synuclein to Mitochondrial Dysfunction. (bioRxiv). BioRxiv. https://doi.org/10.1101/2025.10.22.682553 (Preprint)
2. Zhan, N., Martens, N., Li, Y., Voortman, G., Leijten, F., Friedrichs, S., Caspers, M. P. M., Verschuren, L., Vanmierlo, T., Smit, M., Kuipers, F., Jonker, J. W., Bloks, V. W., Palumbo, M., Zimetti, F., Adorni, M. P., Liu, H., Lütjohann, D., & Mulder, M. T. (2025). Divergent regulation of cellular cholesterol metabolism by seaweed-derived fucosterol and saringosterol. Frontiers in Marine Science, 12, Article 1728727. https://doi.org/10.3389/fmars.2025.1728727
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LAB OF GENOME STRUCTURE AND AGEING

Victor Guryev

1. van Smoorenburg, L. H., Karp, T., Ditz, B., van Geffen, W. H., Guryev, V., Almusa, A., Kistemaker, L., Gosens, R., van den Berge, M., & Kerstjens, H. A. M. (2025). Anti-inflammatory effects of tiotropium in COPD: a randomised double-blind trial. ERJ Open Research, 11(2), Article 00735-2024. https://doi.org/10.1183/23120541.00735-2024
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LAB OF MOLECULAR NEUROBIOLOGY OF AGEING

Ellen Nollen

1. Zhang, T., Goya, M. E., Herron-Bedoya, A., van der Weerd, J. C., Tsagkari, D., Couzijn, S., Güngördü, L., Seinstra, R. I., Heiner Fokkema, M. R., Chang, M., Tavernarakis, N., Kuipers, F., & Nollen, E. A. A. (2025). Condensate-Driven Triglyceride Depletion Links α-Synuclein to Mitochondrial Dysfunction. (bioRxiv). BioRxiv. https://doi.org/10.1101/2025.10.22.682553 (Preprint)
2. Fan, S., Zhang, Y., Ainslie, A. P., Seinstra, R., Zhang, T., Nollen, E., & Schirhagl, R. (2025). In Vivo Nanodiamond Quantum Sensing of Free Radicals in Caenorhabditis elegans Models. Advanced science, 12(14), Article 2412300. https://doi.org/10.1002/advs.202412300
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LAB OF STEM CELL REGULATION AND MECHANISMS OF REGENERATION

Eugene Berezikov

1. Müller, C., Muck, J. S., Ustyantsev, K., Kortman, G., Hartung, J., Berezikov, E., & Calkhoven, C. F. (2025). Enhanced C/EBPα Function Extends Healthspan and Lifespan in the African Turquoise Killifish. ageing Cell, 24(10), Article e70211. https://doi.org/10.1111/acel.70211
2. Ustyantsev, K., Stranges, M., Volpe, F. G., de Boer, J. F., Kuipers, F., Mouton, S., & Berezikov, E. (2025). One probe fits all: a highly customizable modular RNA in situ hybridization platform expanding the application of SABER DNA probes. DEVELOPMENT, 152(11), Article dev204775. https://doi.org/10.1242/dev.204775

TELOMERES AND GENOME INTEGRITY

Michael Chang

1. Swift, J., Cucchi, A., Chang, M., Faragher, R. G. A., Holland, C. A., Tueros, I., Dalby, M. J., & Canty-Laird, E. G. (2025). Considerations for creating effective academic–industrial partnerships. Nature ageing, 5, 2153–2157. https://doi.org/10.1038/s43587-025-00988-x
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LAB OF CELLULAR SENESCENCE AND AGE-RELATED PATHOLOGIES

Marco Demaria

1. Demaria, M. (2025). Cancer treatments accelerate ageing. Nature reviews cancer, 25, 751–752. https://doi.org/10.1038/s41568-025-00801-2
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LAB OF CELLULAR BIOCHEMISTRY

Liesbeth Veenhoff

1. Veldsink, A. C., Fischer, J. S., Hell, S., Weis, K., & Veenhoff, L. M. (2025). A tool to pulse-label yeast Nuclear Pore Complexes in imageing and biochemical experiments. eLife, Article RP108399. https://doi.org/10.7554/eLife.108399.1
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3. Veldsink, A. C., Fischer, J. S., Terpstra, H. M., Mannino, P., de Lange, E. MF., Hell, S., van Benthem, K. J., Saba, L. J., Steen, A., Vlijm, R., Heinemann, M., Weis, K., Lusk, C. P., & Veenhoff, L. M. (2025). Detecting Nuclear Pore Complex assembly in living cells. (bioRxiv). BioRxiv. https://doi.org/10.1101/2025.07.30.667432 (Preprint)
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6. de Vries, H. W., Barth, A., Fragasso, A., Otto, T. A., van der Graaf, A., van der Sluis, E. O., van der Giessen, E., Veenhoff, L. M., Dekker, C., & Onck, P. R. (2025). Spatial control of karyopherin binding avidity within NPC mimics revealed by designer FG- Nucleoporins. BioRxiv. https://doi.org/10.1101/2025.04.21.649908 (Preprint)

LAB OF GENE REGULATION IN AGEING AND AGE-RELATED DISEASES

Cor Calkhoven

1. Müller, C., Muck, J. S., Ustyantsev, K., Kortman, G., Hartung, J., Berezikov, E., & Calkhoven, C. F. (2025). Enhanced C/EBPα Function Extends Healthspan and Lifespan in the African Turquoise Killifish. ageing Cell, 24(10), Article e70211. https://doi.org/10.1111/acel.70211
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3. Zuidhof, H. R., Müller, C., Kortman, G., Wardenaar, R., Stepanova, E., Loayza-Puch, F., & Calkhoven, C. F. (2025). The m6A demethylase FTO promotes C/EBPβ-LIP translation to perform oncogenic functions in breast cancer cells. The FEBS Journal, 292(10), 2688-2709. https://doi.org/10.1111/febs.70033

LAB OF GENOMIC INSTABILITY IN DEVELOPMENT AND DISEASE

Floris Foijer

1. Rendo, V., Schubert, M., Khuu, N., Suarez Peredo Rodriguez, M. F., Whyte, D., Ling, X., van den Brink, A., Huang, K., Swift, M., He, Y., Zerbib, J., Smith, R., Raaijmakers, J., Bandopadhayay, P., Guenther, L. M., Hwang, J. H., Iniguez, A., Moody, S., Seo, J.-H., ... Foijer, F. (2025). A compendium of Amplification-Related Gain Of Sensitivity genes in human cancer. Nature Communications, 16(1), Article 1077. https://doi.org/10.1038/s41467-025-56301-2
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LAB OF COENZYME A METABOLISM IN HEALTH AND DISEASE

Ody Sibon

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Funding/Grants

Our scientists received a total of **€ 2,775,799.32** funding from various funding agencies and grants in 2025.

Researcher	Call/Funding agency	Title of the project	Amount
Daniëlle Koot (Floris Foijer's Group)	Stichting De Cock-Hadders	Establishing a model for inducible chromosomal instability in mice	€ 4,500.00
Ruifang Tian (Floris Foijer's group)	Stichting De Cock-Hadders	Elucidating the landscape and the functional dynamics of extracellular vesicles in CIN-induced p53-p21 dependent senescence	€ 4,500.00
Iris Harmsen (Floris Foijer's group)	Stichting De Cock-Hadders	Chromosomal Instability in Hodgkin Lymphoma	€ 4,500.00
Anton Stamm (Marco Demaria's group)	Stichting De Cock-Hadders	The role of cellular senescence in Idiopathic Pulmonary Fibrosis	€ 4,500.00
Cor Calkhoven	UMCG Kanker Researchfonds	Investigating the function and therapeutic potential of the C/EBPβ uORF peptide in Triple negative breast cancer	€ 4,771.42
Jamil Nehme (Marco Demaria's group)	UMCG Kanker Researchfonds 4901 HPC XA11	Evaluating the Role of the Retinoblastoma protein (pRB) in Response to a novel Sequential intervention of CDK4/6 inhibitors and Lysosomal Targeting drugs for Breast Cancer treatment	€ 5,000.00
Anouk van den Brink (Floris Foijer's group)	UMCG Kanker Researchfonds	Mitochondrial DNA escape: A hidden trigger of immune responses in Chromosomal unstable cancers?	€ 5,000.00
Stijn Mouton (Eugene Berezikov's group)	NWO ENW-XS	Improving healthy ageing by manipulating snoRNA expression	€ 50,000.00
Eugene Berezikov	NWO ENW-XS	Developing transient reprogramming approaches in an invertebrate model organism toward research on anti-ageing and ageing-related disease treatment strategies	€ 50,000.00

Daniele Novarina (Michael Chang's group)	NWO ENW-XS	Understanding the molecular trigger of repeat expansion diseases	€ 50,000.00
Jamil Nehme (Marco Demaria's group)	NWO ENW-XS	LIF6:A genetic key to cancer resistance and healthy ageing?	€ 50,000.00
Brecht Attema (Folkert Kuipers' group)	UMCG Kanker Researchfonds	Deciphering the role of the microbiome-derived bile acid deoxycholic acid as a driver of colorectal cancer	€ 65,000.00
Ody Sibon	St. Zeldzame Zekten Fonds	PKAN 4'PPT	€ 130,148.50
Marco Demaria	Boehringer Ingelheim	The exploration of the senescence pathways and signatures in key human iPSC-based liver cell models	€ 223,000.00
Ody Sibon	European Communities	Hub molecules of Metabolism and signalling- key regulators of life	€ 230,630.40
Anna Ainslie and Suzzane Couzijn (Ellen Nollen's group)	Parkinson Fonds-Research Grant Application – Cycle 2025	Protecting against alpha-synuclein toxicity at molecular and physiological levels	€ 303,400.00
Liesbeth Veenhoff	NWO-XL	Holey Trap- Disordered proteins guard the gap	€ 790,849.00
Eugene Berezikov	ZonMw	Genomic profiling and subsequent ex situ treatment of injured human donor livers.	€ 800,000.00
Total			**€ 2,775,799.32**

***NWO:** The Dutch Research Council
***ZonMW:** Netherlands Organisation for Health Research and Development

People

77	23	30	18
Employees	PhD Students	International employees	Nationalities

47	29	48
Dutch employees	Men	Women

Management team

Folkert Kuipers
Scientific Director

Marnix Labberte
Manager

Support Staff

Jesse Medema
Finance Project Controller

Megha Upadhyay
Research Coordinator

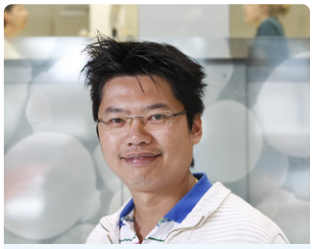
Ria Ubels
Staff Advisor

Wyste Hogewerf
Staff Advisor

Karin van Wageningen
Secretary

Sylvia Hoks
Secretary

Joke Eleveld
Secretary



Yin Fai Chan
Technician

5. Facilities

iPsomics - ERIBA facilities

Introduction: iPsomics was founded in 2024 as a UMCG spinout company to valorize iPSC, CRISPR and sequencing technology developed and implemented at ERIBA. iPsomics is the commercial continuation of two ERIBA research facilities, the Research Sequencing Facility (established in 2019 by Diana Spierings) and the Functional Genomics Centre (established in 2016 by Floris Foijer). In addition, iPsomics provides Organ-on-a-Chip services, for which expertise is provided by the Department of Genetics (Sebo Withoff, Iris Jonkers and Jing Fu). iPsomics is supported by a € 5.7 million National Growth Fund grant (PharmaNL) supplemented with a € 5.7 million in kind contribution by the UMCG (equipment & personnel). With the current budget, iPsomics will in addition need to earn in ~ € 2 million in revenue from projects to break even in 2029. The business model for iPsomics is to further develop existing technology and develop new related applications (50% of our time) while at the same time providing service to local, national and international customers (academic and commercial). Furthermore, we participate in collaborative projects and grant applications. During the project period (2024-2029), we will work towards becoming self-sustainable by investing in a service portfolio based on a combination of demand of the market and our expertise.

iPsomics services. In 2025, iPsomics earned ~€ 290,000 in revenue from various services described below.

High throughput generation of iPSCs. In 2020, the Functional Genomics Center acquired a high throughput liquid handler designed by us to automate the generation of iPSCs as the first (and still only) academic institute in the Netherlands. The setup is centered around a Beckman Coulter BioMek robot and allows us to generate 100-250 iPSC lines per year with 1 FTE of operator (compared to ~24 lines a year per full time technician in the past). So far, the robot (Selfie) has helped us generate ~100 iPSC lines, and thus our future business development will include selling the robot's capacity to increase usage.

Other unique selling points of our iPSC portfolio include RNA-sequencing based phenotyping of clones, single cell genomics to validate euploid karyotypes and a close like to LifeLines. For the latter, iPsomics and LifeLines are establishing a strategic partnership in 2026 that should allow for the generation of iPSCs of deeply phenotyped LifeLines donors.

CRISPR genome engineering. Over the past 10 years, the Functional Genomics Centre has assisted over many teams with CRISPR genome engineering in various cell types. Furthermore, powered by a KWF infrastructure consortium (ScreeninC), we have supported CRISPR screens in various cell types including iPSCs, organoids and in vivo. We are currently implementing and validating PRIME-editing as a tool for precise editing in iPSCs and will continue to provide CRISPR genome engineering services as iPsomics.

Bulk RNA sequencing. RNA-sequencing services are one of the key services we currently provide to customers. In 2025, our team has developed improved and lower cost protocols for SMART3-seq (3' end sequencing and SmartComplete (whole transcript sequencing. In 2026, we will continue to improve these protocols and automate them so that libraries can be prepared using low volume liquid handlers.

Single Cell RNA seq. iPsomics also continues to provide single cell RNA sequencing services using the 10X Genomics platform, the SeekGene platform and the new Illumina single cell RNA-seq platform. In 2025, we optimized cell preparation from human fat, intestine and liver and we will optimize other tissues as requests will come in.

Single cell whole genome sequencing (scWGS). iPsomics continues to offer single cell DNA sequencing services to quantify karyotype heterogeneity in primary (tissue) samples at resolutions down to 40 kb. A large part of 2025 was devoted to improve our current low volume protocols (CellenOne) and to provide scWGS services to our customers. We also tested alternative liquid handler protocols and purchased an Echo acoustic liquid handler to increase throughput and improve reproducibility between runs. The Echo will be installed in 2026. In 2026, we will furthermore develop new higher throughput protocols to karyotype thousands of single cells and protocols to identify point mutations in single cells.

Other services. Finally, iPsomics is commonly asked to provide custom services that relate to either of the above technologies. These services include overnight sequencing, circulating DNA sequencing, methylation sequencing, Nanopore-based sequencing etc.

Who

Peter Ketelaar - CEO
Henk Heidekamp – CFO
Floris Foijer – CSO and lead scWGS
Marilu Losito – Project manager and business developer iPSCs, CRISPR and sequencing
Joram Mooiweer - Project manager and business developer OoC services
Steyn Mos – Quality Assurance and resource manager
Eugene Berezikov – lead RNA sequencing
Sebo Withoff – Co-lead OoC
Iris Jonkers – Co-lead OoC
Jing Fu – Co-lead OoC
Stijn Mouton – Postdoc Sequencing services
Kirill Ustyantsev – Postdoc Sequencing services
Nancy Halsema – Technician Sequencing Services
Rianna Arjaans – Technician Sequencing Services
Sanne Witziers – Technician Sequencing Services
Laura Kempe – Technician Sequencing and iPSC Services
Mathilde Broekhuis – Technician iPSC & CRISPR Services
Lotte Bouthoorn – Technician OoC services
Rene Wardenaar – Bioinformatician

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6. Education

ERIBA scientists contribute extensively to education at multiple levels. In various programs—most notably the MMIT, BCN, BMS, and JSM programs of the RuG—we serve as mentors, track coordinators, and members of advisory and program committees. We lecture in numerous courses, and a selection of the courses coordinated by ERIBA scientists is listed below.

In addition, we provide students with opportunities to develop their research skills through individual literature assignments (essays and colloquia) and research internships. Dozens of students from various RuG-based master's programs, as well as from HBO and MBO institutions in the northern Netherlands, have been hosted for research internships, typically lasting 4–6 months for master's students and up to 10 months for HBO or MBO students. During this period, we teach and mentor students with dedication.

COURSE TITLE: **Age Research ERIBA Course 2025**

COORDINATOR(S):	10 ECTS	12 Number of students
Cor Calkhoven & Anna de Bruyn-Rybczynska		

Objective

Wet lab research course

COURSE TITLE: **REGENERATE-IT network Summer School 2**

COORDINATOR(S):	1 ECTS	12 Number of students
E. Berezikov		

Objective

This 6-day Summer School was dedicated to experimental models in regeneration research. It had a substantial practical component and provided an opportunity for Doctoral Candidates (DCs) to learn first-hand the variety of model organisms that we have in our Doctoral Network.

COURSE TITLE: **Molecular Biology of Ageing and Age-related Diseases**

COORDINATOR(S):

Liesbeth Veenhoff &
Michael Chang

5 ECTS

19 Number of students

Objective

Ageing can be defined as the gradual loss of the ability of the organism to maintain homeostasis. In this course, we focus on the molecular and cellular mechanisms by which tissue and organ function deteriorate and homeostasis fails, resulting in ageing and age related disease. We will evaluate to what extent the up-to date knowledge on the molecular biology provides opportunities for interventions, also when considering what we learn from evolutionary theories of ageing. We present the model systems and experimental strategies that are used in ageing research. This course will be supported by a team of specialists in different fields of ageing that will provide lectures and reading material. The course not only gives an overview of the research field of ageing but also teaches scientific writing, active listening and giving feedback to peers

COURSE TITLE: **Model organisms in Ageing Research**

COORDINATOR(S):

Floris Foijer

3 ECTS

9 Number of students

Objective

This course serves to expose MD students to basic biology. The students interact with various researchers who use various model organisms or systems to study ageing biology or ageing-associated disease. At the end, the students prepare a presentation in which they present a research proposal to study a disease of their choice using 2 or 3 models organisms highlighting the advantages and disadvantages of each.

7. Presentations at (inter)national meetings

Researcher	Institution and Name of the event	Title of the Presentation	Location
Cor Calkhoven	FLI, Jena, Groningen-Jena Ageing Meeting 2025	The C/EBP Regulatory Network: A Key Driver of Health and Lifespan determination	Jena, Germany
Cor Calkhoven	UvA, Amsterdam, DuSRA annual meeting	Enhanced C/EBPα function extends healthspan and lifespan in the African turquoise killifish	Amsterdam, The Netherlands
Marco Demaria	National Seoul University, Invited seminar Institute series	Heterogeneity in cellular senescence: from mechanisms to interventions	Seoul, Korea
Marco Demaria	University of Milan, Milan Longevity Summit	Senolytics and senomorphics: a new path to longevity	Milan, Italy
Marco Demaria	University of Padova, Breast in Translation 2.0	Cellular senescence and accelerated ageing in breast cancer patients	Padova, Italy
Marco Demaria	Osaka University, 25th conference of the Japanese Anti-ageing Medicine Society (JAMM)	Cellular senescence and the future of preventive medicine in an ageing society	Osaka, Japan
Marco Demaria	Kyotyango, 1st World Longevity Summit	From mechanisms to medicine: targeting senescence to promote healthy ageing	Kyotyango, Japan
Marco Demaria	University of Lugano, Senotherapeutics Revolution conference	Discriminating beneficial and detrimental senescence for refined therapeutic approaches	Lugano, Switzerland
Marco Demaria	University of Copenhagen, 12th ageing Research and Drug Discovery (ARDD) meeting	Purinergic signalling as a vulnerable node of detrimental senescence	Copenhagen, Denmark
Marco Demaria	National Research Center (CNR), 10th Annual meeting International Cell Senescence Association (ICSA)	TSPAN13 as a novel regulator of senescence	Rome, Italy
Marco Demaria	Research Center for Molecular Medicine (CeMM), Invited seminar Institute series	Heterogeneity in cellular senescence: from mechanisms to interventions	Vienna, Austria
Folkert Kuipers	Nordic Ageing Society (NAS)	Gut–Liver Axis in Healthy Ageing: Emerging Roles of Secondary Bile Acids	Reykjavik, Iceland
Folkert Kuipers	Nobel Conference	Role of Bile Acid Hydrophobicity in Cholangiopathies	Stockholm, Sweden

Marco Demaria	BioCity Turku, Invited seminar Frontiers of Science series	Heterogeneity in cellular senescence: from mechanisms to interventions	Turku, Finland
Marco Demaria	University of Foggia, Conference on Medicine and Gender	Cellular senescence and gender: a novel paradigm in ageing biology	Foggia, Italy
Eugene Berezikov	Janelia Research Campus, Genetic Tools for New Model Organisms	Proliferation-enriched single-cell atlas delineates germline from somatic neoblasts and identifies early neoblast-specific genes in the flatworm Macrostomum lignano	Ashburn, VA, United States
Michael Chang	32nd International Conference on Yeast Genetics and Molecular Biology	Genetic dissection of the mechanisms affecting the stability of short tandem DNA repeats	Paris, France
Floris Foijer	Hubrecht, Hubrecht Laboratory invited seminar	CIN-induced inflammation – a catch 22 for cancer cells	Utrecht, The Netherlands
Floris Foijer	ESMO congress 2025, Berlin	CIN-induced inflammation – a catch 22 for cancer cells	Berlin, Germany
Floris Foijer	Netherlands Cancer Institute, NKI Symposium farewell Hein te Riele	CIN-induced inflammation – a catch 22 for cancer cells	Amsterdam, The Netherlands
Floris Foijer	UMCG, MoHad Institute day	CIN-induced inflammation – a catch 22 for cancer cells	Groningen, The Netherlands
Floris Foijer	Leiden University, hDMT-infra kickoff event	iPsomics - a UMCG startup commercialising iPSC and sequencing technology	Leiden, The Netherlands
Floris Foijer	University of Groningen, Oratie Floris Foijer	Hoe slordigheid leidt tot stress, maar ook tot CINnige kankertherapie	Groningen, The Netherlands
Ody Sibon	Polish NBIA patient organisation, Scientists for the NBIA Community University of Gdańsk	Clinical trial with 4'-PPT for PKAN and our initiatives to bring this further	Gdańsk, Poland
Ody Sibon	International Network for Fatty Acid Oxidation Research & Management, (INFORM)	Coenzyme A metabolism	Kyoto, Japan

8. Public Outreach & Dissemination

ERIBAs public outreach and dissemination efforts in 2025 were characterized by deep community engagement and a commitment to making ageing research accessible to the general public.

deVerdieping Trouw

Interview for TROUW

article with title “Poetin en Xi dromen van een eeuwig leven, maar de wetenschap gaat ze niet redden”.

Go to article

Researcher Involved:
Cor Calkhoven

RTV NOORD
radio • televisie • online

Video interview RTV Noord

about ERIBA anniversary and killifish project (together with Ellen Nollen):

Go to video

Research involved:
Cor Calkhoven and Ellen Nollen

In 2025, Prof. Marco Demaria contributed to several high-profile public-facing activities aimed at disseminating advances in cellular senescence and senotherapeutics to a broad scientific, clinical, and innovation-focused audience.

He participated in interviews and round-table discussions at the Senotherapeutics Summit (Rome) and at the Senotherapeutic Revolution Conference (Lugano), engageing with academic leaders, clinicians, industry representatives, and policymakers. These sessions focused on the biological basis of ageing, the translational potential of senescence-targeting interventions, and the challenges associated with moving senotherapeutics toward clinical implementation

In addition, Prof. Demaria took part in a round-table discussion at the ARDD meeting in Copenhagen, focusing on publishing and evaluating ageing research. The discussion addressed standards for rigor and reproducibility, peer-review challenges in interdisciplinary ageing studies, and the role of journals and editors in shaping responsible and impactful ageing research.

Prof. Demaria also authored two News & Views / opinion articles in ageing (Albany NY) addressing the broader societal and clinical implications of ageing biology. In “Longevity clinics: between promises and perils” (2025), he critically examined the rapid rise of commercial longevity clinics, highlighting both their innovation potential and the risks associated with insufficient evidence, regulation, and transparency. In “Rethinking healthcare through ageing biology” (2025), he discussed how integrating fundamental ageing mechanisms into healthcare systems could shift medicine from disease-centered treatment toward prevention and health-span extension.

Researcher Involved:
Marco Demaria

SCIENCE IN A BOX

‘Science in a Box’ is an outreach project developed by Stijn Mouton. With the Science Boxes, we offer a hands-on experience to study regeneration. It is helpful to stimulate enthusiasm for biology and scientific research and can be used by secondary schools and Hogescholen.

Researcher Involved:
Stijn Mouton

Read more →

Connected by Coenzyme A workshop

Ody Sibon was the main organizer of the Lorentz Center workshop: Connected by CoA in Leiden; Coenzyme A is essential for life, but recent findings suggest that its importance reaches beyond its classic roles associated with energy and fatty acid metabolism. This interactive workshop gathered researchers from diverse fields with a shared interest in CoA to critically re-evaluate its roles through out-of-the-box thinking, to provide new insights into our understanding of CoA in biology.

Researcher Involved:
Ody Sibon

Read more →

Zpannend Zernike 2025: Little Researchers Explore the Secrets of Life!

On Saturday, October 4, 2025, ERIBA and the UMCG departments of Genetics and Pediatrics opened their doors for Zpannend Zernike, part of the national Weekend van de Wetenschap. We welcomed 1,123 curious visitors aged 7 to 14 for a day of hands-on science and healthcare activities.

Our team of scientists ran four engaging activities: extracting DNA from a banana, exploring model organisms under the microscope, practicing "taking blood" from a fake arm, and posing in lab coats at our scientist photobooth.

A huge thank you to all the volunteers from ERIBA, Genetics, and Pediatrics whose enthusiasm made it such a success. We hope to see our little researchers again next year!

Involved:
Anton Steen and outreach committee ERIBA

Read more →

9. Sponsors

The European Institute for the Biology of Ageing is made possible by:

- Ministry of Economic Affairs, Agriculture and Innovation
- The Province of Groningen
- Collaboration of the Northern Netherlands (SNN)
- The European Union
- The Noaber Foundation

ERIBA

European Research Institute for the Biology of Ageing

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