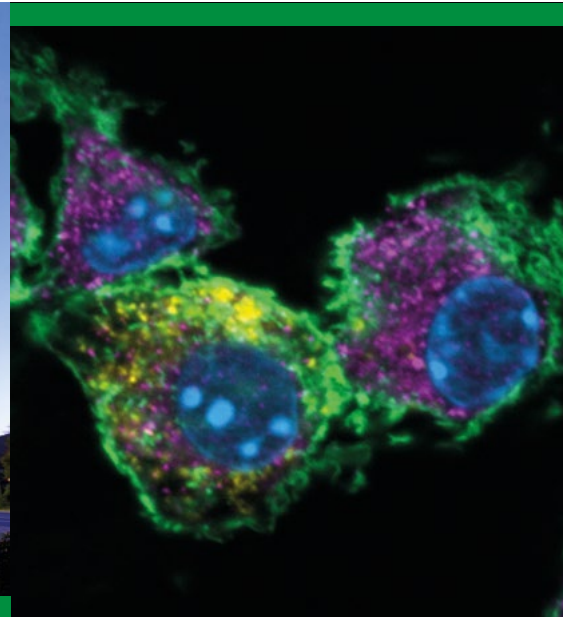
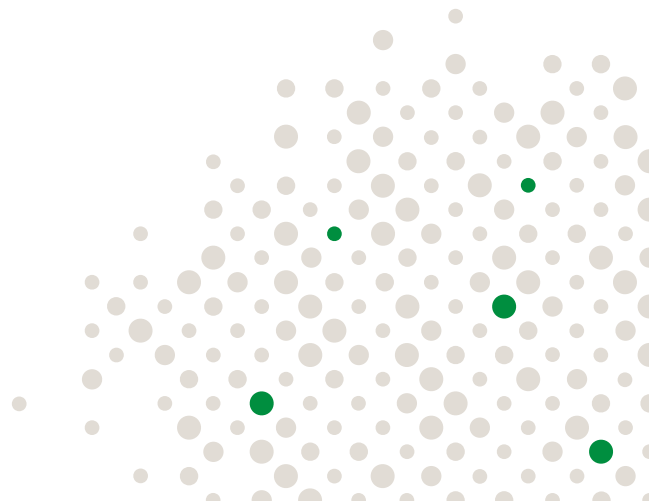


Leibniz Institute on Aging –  
Fritz Lipmann Institute



**2021–2022**

Annual Report





**2021–2022**

Annual Report

**Leibniz Institute on Aging –  
Fritz Lipmann Institute (FLI)**

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**The Board of Directors of the FLI.**  
Dr. Daniele Barthel and Prof. Dr. Alfred Nordheim.

# Welcome

*At the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) we investigate the biological processes that underlie aging. Our aim is to decipher the genetic, epigenetic and molecular processes involved, and to point the way toward new therapies that reduce the risk of developing debilitating conditions associated with aging, such as muscular atrophy and dementia.*

*To further improve the evaluation of the data obtained in our experiments and analyses, we have expanded systems biology into a cross-sectional area over the last ten years. Microbiome research in particular builds on this expertise and infrastructure, which we have recently strengthened by establishing new research groups. The goal is to clarify the role played by the trillions of microorganisms that colonize the human body in the development and prevention of age-related diseases and dysfunctions.*

*At the FLI, we initiated pioneering projects and collaborations during the reporting period. One of these is the Leibniz Research Alliance “Resilient Ageing,” in which researchers from 15 Leibniz institutes are looking at the individual biological aging process in connection with lifestyle, nutrition, education and other socioeconomic and sociopolitical factors. With such interdisciplinary research approaches, we want to ensure that biological research on aging achieves a sustainable social effect.*

*Our research into the genetic basis of aging using the turquoise killifish (*Nothobranchius furzeri*) is attracting a great deal of attention. The complete sequencing of the genome of this short-lived fish species by FLI researchers (simultaneously with researchers from Stanford University in the US) has opened up new perspectives in the study of aging processes for researchers throughout the world.*

*At the FLI, we are working diligently to expand the knowledge base on aging (processes) so that in the future it will be possible to extend the health span of the elderly, helping to make demographic change positive for all of us.*

*We wish an enjoyable read and exciting insights into our research at the FLI.*



**Prof. Dr. Alfred Nordheim**  
Scientific Director of FLI



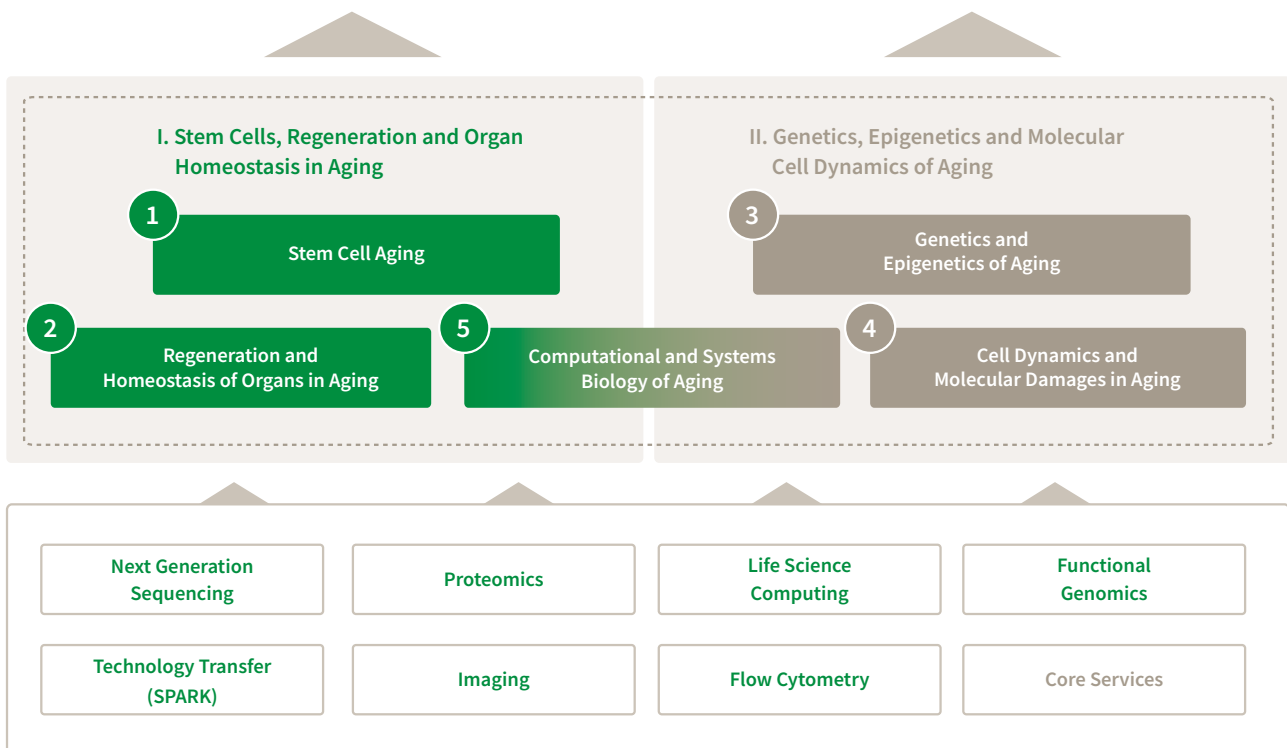
**Dr. Daniele Barthel**  
Administrative Director of FLI

# Mission & Objectives

Aging is a multifactorial process, determined by genetic factors and environmental influences. The Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) in Jena is dedicated to researching the underlying biological mechanisms.

At the FLI, 14 interdisciplinary and international research groups – supported by seven associated research groups – focus on questions of stem cell aging and regeneration, molecular damage and epigenetic aging processes. With this focus, the FLI has established a leading position in international research on aging.

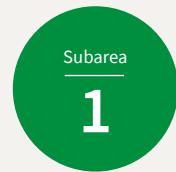
## Identification of causative mechanisms of aging to enable aging in good health



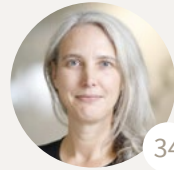
**Research focus at the FLI.** Research at the FLI is organized into five subareas that work closely together (top half of the diagram above). They are supported by scientific and technological Core Facilities and Services (bottom half).



## Research Area I: Stem Cells, Regeneration and Organ Homeostasis in Aging



Rudolph  
Senior Research Group



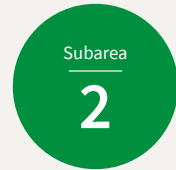
Waskow  
Senior Research Group



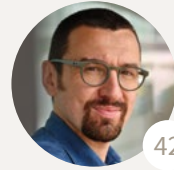
von Maltzahn  
Junior Research Group



Heidel  
Associated Research Group



Morrison  
Senior Research Group



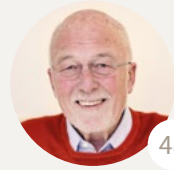
Valenzano  
Senior Research Group



von Eyss  
Junior Research Group



Winek  
Junior Research Group



Herrlich  
Associated Research Group



Ploubidou  
Associated Research Group

## Research Area II: Genetics, Epigenetics and Molecular Cell Dynamics of Aging



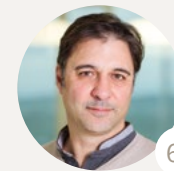
Englert  
Senior Research Group



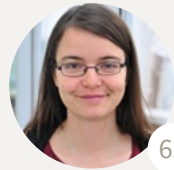
Neri  
Junior Research Group



Bierhoff  
Associated Research Group



Cellerino  
Associated Research Group



Marz  
Associated Research Group



Wang  
Senior Research Group

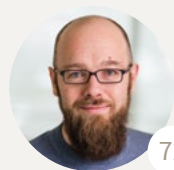
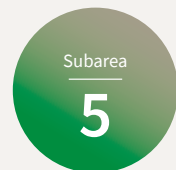


Kaether  
Senior Research Group

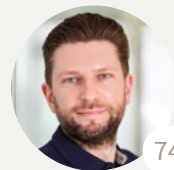


Ermolaeva  
Junior Research Group

## Cross-sectional Subarea 5 : Computational and Systems Biology of Aging



Hoffmann  
Senior Research Group



Ori  
Junior Research Group



Kestler  
Associated Research Group

# Biennial Review 2021 – 2022

With its scientific reorganization in 2012, the FLI established two main research areas:

**(I) Stem Cells, Regeneration, and Organ Homeostasis in Aging**

**(II) Genetics, Epigenetics, and Molecular Cell Dynamics of Aging**

The research groups collaborate in various projects that span different focal areas. To structure the content of these project-based collaborations, five subareas have been

institutionalized. Subarea 5, “Computational and Systems Biology of Aging,” functions as an area of cross-sectional overlap.

After the scientific evaluation of 2016, microbiome research was designated as a new research focus and was initiated in 2021 with the establishment of the Senior Research Group “Evolutionary Biology / Microbiome–Host Interactions in Aging” and the appointment of its research group leader Dario R. Valenzano at the Medical Faculty of Friedrich Schiller University Jena (FSU).

## Subarea 1: Stem Cell Aging

Age-related deterioration of stem cell function is one of the main reasons for declining organ maintenance, organ dysfunction, reduced regenerative capacity and disease development in old age. The following overarching topics currently form the focus of the research in Subarea 1:

- Age-dependent selection mechanisms of stem cell subpopulations and mutant stem cell clones in old age (Björn von Eyss, Claudia Waskow)
- Influence of growth signals and metabolic activity during development on epigenetic memory, the selection of stem cell subpopulations and aging (K. Lenhard Rudolph)
- Metabolic changes and epigenetic memory of aging stem cells (K. Lenhard Rudolph, Francesco Neri, Alessandro Ori).
- Influence of stem cell niche, intrinsic changes and systemic factors on aging of muscle stem cells (Julia von Maltzahn, Alessandro Ori)
- Regenerative pathways in the hematopoietic system and their impact on the aging immune system (Claudia Waskow)

- Interactions between hematopoietic stem cells and their niche during aging (Claudia Waskow, Florian Heidel)
- Age as a factor influencing the immune response in sepsis (Claudia Waskow)
- Age-dependent effects of dietary restriction on stem cell function (K. Lenhard Rudolph).

Overall, Subarea 1, “Stem Cell Aging,” aims to investigate the basic concepts and consequences of stem cell aging in the context of aging organisms. Subarea 1 is strongly interconnected with Subarea 2, “Regeneration and Homeostasis of Organs in Aging,” because stem cells play a central role in the maintenance and regeneration of organs. Conversely, changes in the cell composition and microenvironment of aging organs influence the self-renewal and differentiation capacity of stem cells. The interrelationships are bidirectional and therefore justify the strong collaboration between the two subareas. The strategic concept of Subarea 1 is to further intensify the cooperation between the groups by collaborating with researchers from the research focus “Microbiota and Aging,” established in 2021.

## Subarea 2: Regeneration and Homeostasis of Organs in Aging

The functionality of all organs and tissues declines during aging. This deterioration process contributes decisively to a decrease in the quality of life and to the development of diseases during aging. The mechanisms that lead to the failure of the aging organism to maintain homeostasis and functionality of organs during the post-reproductive lifespan remains poorly understood.

Research in Subarea 2 focuses primarily on mechanisms of tissue aging, involving non-stem cells, micro-milieu conditions, and systemic signaling pathways that together lead to impairments in organ maintenance. The subarea focuses on the following main topics:

- aging-related impairment of cell-to-cell communication in regeneration and disease (Helen Morrison)
- the Hippo pathway as a central regulator of tissue homeostasis, stem cell biology and carcinogenesis (Björn von Eyss)
- microbiome–host interactions in aging (e.g., in killifish) – influence of host immune aging on the microbiome and, in turn, how the microbiota impacts the immune function and health of the host (Dario Valenzano)
- protein CD44 and metastasis; TRIP6 protein and hydrocephalus (Peter Herrlich); cancer and the cytoskeleton (Aspasia Ploubidou).

## Subarea 3: Genetics and Epigenetics of Aging

A significant share of individual differences in aging is due to genetic and epigenetic factors. If we can identify the genes and epigenetic switches that account for these differences between individuals or different species, this will have a considerable impact on understanding the basic molecular processes of aging. This subarea focuses on:

- the investigation of the genetic basis of organ development as well as of regenerative processes, particularly in the zebrafish and turquoise killifish (Christoph Englert)
- the influence of the epigenome – chemical changes in DNA that control its activation or deactivation – on aging and cancer development (Francesco Neri)
- the investigation of epigenetic changes such as decreasing DNA methylation or altered histone modification (Alessandro Cellierino, Scuola Normale Superiore di Pisa, Italy and Holger Bierhoff, Friedrich Schiller University Jena, Germany)
- the role of long, non-coding RNAs and micro-RNAs in gene activity (Manja Marz, Friedrich Schiller University Jena, Germany).

Subarea 3 applies comparative genomic and functional genetic analyses to identify genetic and epigenetic factors and regulatory mechanisms that contribute to the accumulation of molecular damage and consequent reduction in stem cell function and organ maintenance during aging.

## Subarea 4: Cell Dynamics and Molecular Damages in Aging

Aging is a multifactorial process, characterized by the accumulation of damage to molecular structures and subcellular organelles. Why the prevention and repair of molecular damage become increasingly ineffective in an aging organism remains poorly understood.

The main aim of Subarea 4 is to study the causes and consequences of damage accumulation in DNA, proteins and subcellular organelles in aging cells and tissues:

- DNA damage response in brain development and the prevention of aging-related neuropathies (Zhao-Qi Wang)
- protein trafficking, proteostasis and organelle damage response during aging (Christoph Kaether)
- maintenance of stress response and metabolism in healthy aging (Maria Ermolaeva).

In order to understand cellular and organismal malfunctions during aging, it is of vital importance to investigate aging-associated molecular damage and responses to it, including repair mechanisms. Both the impaired removal of damaged or senescent cells and alterations in metabolism can cause molecular damage in stem cells and tissues. Given these functional and bidirectional interactions, Subarea 4 works closely with Subareas 1, 2, and 3. Its research is also central to the overall mission of the FLI.

## Subarea 5: Computational and Systems Biology of Agings

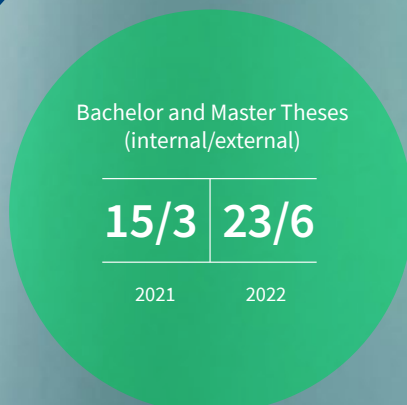
With its research focus on age-related deterioration of stem cell function and organ maintenance and the underlying molecular and genetic mechanisms, the FLI has developed a unique position in research on aging, both nationally and internationally. In order to elucidate the interrelationships at different levels of the organism as a whole, the research area “Computational and Systems Biology of Aging” was created.

Researchers in this area investigate connections among biological networks that influence aging: at the level of genes, proteins and molecular regulatory circuits as well as at the level of communication between cells and organs.

The subarea addresses the following topics:

- the development of proprietary methods for analyzing large, multidimensional biological datasets with the goal of better understanding how the epigenome controls processes of gene expression (Steve Hoffmann)
- the investigation of how age, mutations and environmental factors affect our organs and cells at the molecular level, using ultrasensitive methods for proteomic analysis (Alessandro Ori)
- the application of statistical procedures and database evaluations for data from high-throughput analyses (Hans A. Kestler, University of Ulm).

# Facts & Figures at a Glance



\* as of December 31, 2022, Employees with institutional and third-party funding, freelance staff, trainees

\*\* as of December 31, 2022

## Core Facilities and Services

The staff of the Core Facilities and Services (CF/CS) provides all research groups at the FLI the advanced technology and expertise they require for their work in the field of molecular biology and medical aging research, to ensure that they remain internationally visible and competitive.

### Increasing throughput, sensitivity and complexity

These technologies include state-of-the-art light, fluorescence and electron microscopy, proteome analysis using mass spectrometry, single cell analysis in flow cytometry, second- and third-generation DNA sequencing, the functional analysis of cellular processes using RNAi and CRISPR/Cas technology and the analysis of highly complex data sets with advanced bioinformatics methods and a powerful computing infrastructure. A focus spanning many CFs is the aim of increasing the throughput, sensitivity and complexity of individual methods in order to better understand physiological and pathological processes in their entirety and individuality.

All FLI research groups have equal access to the technology, and free capacity can also be made available to external cooperation partners. The CF/CS staff shares expert knowledge in seminars, offers workshops and conducts user surveys in order to adapt their offerings, if necessary. They also provide support for teaching and trainings.

### Contributing to third-party funding and scientific publications

The Core Facilities directly contribute to the increase in third-party funding. For example, CF projects have been funded within the framework of a DFG priority program as well as by the German Center for Cardiovascular Research and the Thüringer Aufbaubank (TAB). Moreover, the Core Facility Technology Transfer also contributes indirectly through Startup funding and mentoring for individual projects. This has enabled new funding lines to be opened up, for example with the TAB and the Federal Ministry of Education and Research (BMBF).

CF/CS staff is involved, on average, in half of all FLI scientific publications and also serves as co-author in one third. Gender parity at the management level is being promoted, and the share of women in management positions has reached to 43% (as of December 2022).

# Analytic Platform (CF/CS)

## Core Facilities:



Life Science Computing



Flow Cytometry



Functional Genomics



Next Generation Sequencing



Proteomics



Imaging



Technology Transfer (SPARK)

## Core Services (CS)



Histology, Pathology and Electron Microscopy



Protein Production



Isotope Laboratory



Irradiation Chamber



Small Animal CT

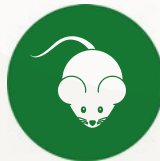


CS S2-Safety Level Laboratories



Media Preparation

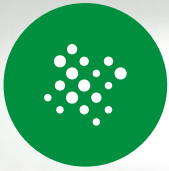
## Animal Facilities (AF):



Mice



Fish  
*D. rerio / N. furzeri*



Long Night of Sciences Jena 2022







## Research Collaborations 2021 – 2022

In a time of rapid technological progress, the pace of scientific research is also increasing. Networking both nationally and internationally is therefore of enormous importance for the FLI. As part of this networking, the FLI has also promoted interdisciplinary exchange within research on aging since its foundation.

The FLI cooperates with Friedrich Schiller University Jena (FSU) and the Jena University Hospital and is active in more than 300 national research collaborations and alliances beyond this regional networking. Researchers at the FLI maintain systematic exchanges with research institutions in numerous countries around the world. This ensures that their research is always at the cutting edge and that the FLI makes a significant international contribution in the field of research on aging.

### Leibniz Research Alliances (LRA)

As people age, organ dysfunction and aging-associated disease increase sharply. This can severely limit the quality of life of older adults as well as their participation in society. At the same time, the growing share of the elderly in the population can lead to social and economic burdens. To address this problem area from an interdisciplinary perspective, the Leibniz Research Alliance Healthy Ageing (LRA Healthy Ageing) unites the scientific expertise of 21 Leibniz institutions from the fields of biology, medicine, psychology, education, sociology, and economics. The researchers work on the fundamental questions of aging, design joint research projects and exchange resources and know-how. This is intended to provide the foundation for an improved quality of life for older individuals as well as a sustainable societal impact. The LRA Healthy Ageing is coordinated at the FLI.

Since 2022 the new LRA Resilient Ageing has been working under the joint leadership of the FLI and the Leibniz Institute for Resilience Research (LIR) in Mainz. Researchers from 15 research institutions are looking at the biological

aging process in individuals in connection with lifestyle, nutrition, education and other socio-economic and socio-political factors. The aim of the research is to develop strategies at all levels so that more people can grow old in good health.



Aging-associated pathologies also call for specialized agents – molecules that induce specific physiological changes in target organisms. Many agents are of natural origin and have been optimized by chemical and/or biotechnological processes to achieve the best possible effect when applied. In another Leibniz Research Alliance, the LRA Bioactive Compounds and Biotechnology, the FLI, as one of 16 Leibniz institutions, is making an important contribution to broad-based research on molecules with biological effects.

### BMBF Funding Line for Preclinical Studies: Nerve Tumors and Nerve Regeneration

At the FLI a protein has been identified that inhibits the growth of tumors of the peripheral nervous system and improves nerve function. Promising results from the mouse model are to be further developed in a preclinical study. Cooperation partners – including for study design and data analysis – are the University Hospitals of Leipzig and Jena. The aim of the BMBF funding line for preclinical studies is to rapidly translate findings from basic research into suitable therapies. This concept is also being pursued by the Core Facility Technology Transfer at the FLI, within the framework of which the project was initiated.



## IMPULS – Identification and Manipulation of the Physiological and Psychological Clocks of the Lifespan

Researchers at the FLI, together with colleagues from Friedrich Schiller University Jena, the Jena University Hospital and University of Leipzig, are investigating how biological age can be precisely determined and which factors influence the complex aging processes in humans. With this aim, since September 2020, the Carl Zeiss Foundation has been funding the interdisciplinary research project IMPULS, which attempts to bridge the gap between molecular biology and psychology, with around 4.5 million euros over five years.



## CanPathPro

From 2016 to 2022, the CanPathPro project received almost 11 million euros in funding from the EU under the Horizon 2020 program. Researchers from six countries have jointly developed a new systems biology platform for predictive modeling of cancer-associated signaling processes.



## ProExcellence Project RegenerAging

From 2015 to 2021 the research project Aging-Induced Inhibition of Regeneration and Tissue Homeostasis – RegenerAging was funded through the ProExcellence-Initiative 2 of the state of Thuringia. For this project, the FLI worked closely with Friedrich Schiller University Jena, the Jena University Hospital and Carl Zeiss Microscopy GmbH in Jena. The focus was on interdisciplinary research into age-related changes at the cellular level, with an emphasis on the epigenetics of aging, stem cell aging and the immunology of aging.

## Further New Collaborations at the FLI

- DFG graduate program ProMoAge – Protein Modifications: Key Mechanisms of Aging (second funding period)
- Project within the framework of the Chan Zuckerberg Initiative (CZI) – new approaches to research into neurodegenerative diseases
- BMBF project: Targeting TRPS1 in breast cancer – development of active agents for the treatment of an aggressive form of breast cancer
- European Research Training Group RESEAgeing – cardiovascular diseases
- PhD program of the Jena School for Molecular Medicine (JSMM) with Shenzhen University, China.

## Selected Publications

2022

Bagnoli S, Fronte B, Bibbiani C, Terzibasi Tozzini E, Cellerino A.  
Quantification of noradrenergic-, dopaminergic-, and tectal-neurons during aging in the short-lived killifish *Nothobranchius furzeri*.  
*Aging Cell* 2022, 21(9), e13689.

Mazzetto M, Caterino C, Groth M, Ferrari E, Reichard M, Baumgart M, Cellerino A.  
RNA-seq analysis of brain aging in wild specimens of short-lived turquoise killifish. Commonalities and differences with aging under laboratory conditions.  
*Mol Biol Evol* 2022, 39(11), msac219.

Reuter H, Perner B, Wahl F, Rohde L, Koch P, Groth M, Buder K, Englert C.  
Aging activates the immune system and alters the regenerative capacity in the zebrafish heart.  
*Cells* 2022, 11(3), 345.

Ermolaeva M, Boyman L.  
Career pathways, part 8.  
*Nat Metab* 2022, 4(4), 407-9.

Demircan MB, Mgbecheta PC, Kresinsky A, Schnoeder TM, Schröder K, Heidel FH, Böhmer FD.  
Combined activity of the redox-modulating compound Setanaxib (GKT137831) with cytotoxic agents in the killing of acute myeloid leukemia cells.  
*Antioxidants (Basel)* 2022, 11(3), 513.

Ernst P, Schnöder TM, Huber N, Perner F, Jayavelu AK, Eifert T, Hsu CJ, Tubio-Santamaria N, Crodel CC, Ungelenk M, Hübner CA, Clement JH, Hochhaus A, Heidel FH.  
Histone demethylase KDM4C is a functional dependency in JAK2-mutated neoplasms.  
*Leukemia* 2022, 36(7), 1843-9.

Perner F, Schnoeder TM, Xiong Y, Jayavelu AK, Mashamba N, Santamaria NT, Huber N, Todorova K, Hatton C, Perner B, Eifert T, Murphy C, Hartmann M, Hoell JI, Schröder N, Brandt S, Hochhaus A, Mertens PR, Mann M, Armstrong SA, Mandinova A, Heidel FH.  
YBX1 mediates translation of oncogenic transcripts to control cell competition in AML.  
*Leukemia* 2022, 36(2), 426-37.

Schnoeder TM, Schwarzer A, Jayavelu AK, Hsu CJ, Kirkpatrick J, Döhner K, Perner F, Eifert T, Huber N, Arreba-Tutusa P, Dolnik A, Assi SA, Nafria M, Jiang L, Dai YT, Chen Z, Chen SJ, Kellaway SG, Ptasinska A, Ng ES, Stanley EG, Elefanti AG, Buschbeck M, Bierhoff H, Brodt S, Matziolis G, Fischer KD, Hochhaus A, Chen CW, Heidenreich O, Mann M, Lane SW, Bullinger L, Ori A, von Eyss B, Bonifer C, Heidel F.  
PLCG1 is required for AML1-ETO leukemia stem cell self-renewal.  
*Blood* 2022, 139(7), 1080-97.

Coronel\* L, Häckes\* D, Schwab\* K, Riege K, Hoffmann\*\* S, Fischer\*\* M.  
p53-mediated AKT and mTOR inhibition requires RFX7 and DDIT4 and depends on nutrient abundance.  
*Oncogene* 2022, 41(7), 1063-9 (\* equal contribution, \*\* co-corresponding authors).

Fischer M, Hoffmann S.  
Synthesizing genome regulation data with vote-counting.  
*Trends Genet* 2022, 38(12), 1208-16.

Fischer M, Schade AE, Branigan TB, Müller GA, DeCaprio JA.  
Coordinating gene expression during the cell cycle.  
*Trends Biochem Sci* 2022, 47(12), 1009-22.

Schwarz R, Koch P, Wilbrandt\* J, Hoffmann\* S.  
Locus-specific expression analysis of transposable elements.  
*Brief Bioinform* 2022, 23(1), bbab417 (\* equal contribution).

Mock F, Kretschmer F, Kriese A, Böcker S, Marz M.  
Taxonomic classification of DNA sequences beyond sequence similarity using deep neural networks.  
*Proc Natl Acad Sci U S A* 2022, 119(35), e2122636119.

Morales-Prieto DM, Murrieta-Coxa JM, Stojiljkovic M, Diezel C, Streicher PE, Henao-Restrepo JA, Röstel F, Lindner J, Witte OW, Weis S, Schmeer C, Marz M.  
Small extracellular vesicles from peripheral blood of aged mice pass the blood-brain barrier and induce glial cell activation.  
*Cells* 2022, 11(4), 625.

Wollny D, Vernot B, Wang J, Hondele M, Safrastyan A, Aron F, Micheel J, He Z, Hyman A, Weis K, Camp JG, Tang TYD, Treutlein B.  
Characterization of RNA content in individual phase-separated coacervate microdroplets.  
*Nat Commun* 2022, 13(1), 2626.

Žarković\* M, Hufsky\* F, Markert\*\* UR, Marz\*\* M.  
The role of non-coding RNAs in the human placenta.  
*Cells* 2022, 11(9), 1588 (\* equal contribution, \*\* co-senior authors).

Schacke S, Kirkpatrick J, Stocksdales A, Bauer R, Hagel C, Riecken LB, Morrison H.  
Ezrin deficiency triggers glial fibrillary acidic protein upregulation and a distinct reactive astrocyte phenotype.  
*Glia* 2022, 70(12), 2309-29.

Lu J, Annunziata F, Sirvinskas D, Omrani O, Li H, Rasa SMM, Krepelova A, Adam L, Neri F.  
Establishment and evaluation of module-based immune-associated gene signature to predict overall survival in patients of colon adenocarcinoma.  
*J Biomed Sci* 2022, 29(1), 81.

Suo M, Rommelfanger MK, Chen Y, Amro EM, Han B, Chen Z, Szafranski K, Chakkarappan SR, Boehm BO, MacLean AL, Rudolph KL. Age-dependent effects of Igf2bp2 on gene regulation, function, and aging of hematopoietic stem cells in mice. *Blood* 2022, 139(17), 2653-65.

Bradshaw WJ, Poeschla M, Placzek A, Kean S, Valenzano DR. Extensive age-dependent loss of antibody diversity in naturally short-lived turquoise killifish. *eLife* 2022, 11, e65117 (published during change of institution).

Izgi H, Han D, Isildak U, Huang S, Kocabiyyik E, Khaitovich\*\* P, Somel\*\*\* M, Dönertas\*\* HM. Inter-tissue convergence of gene expression during ageing suggests age-related loss of tissue and cellular identity. *eLife* 2022, 11, e68048 (\*\* co-corresponding authors).

Kim\* KM, Mura-Meszaros\* A, Tollot\* M, Krishnan MS, Gründl M, Neubert L, Groth M, Rodriguez-Fraticelli A, Svendsen AF, Campaner S, Andreas N, Kamradt T, Hoffmann S, Camargo FD, Heidel FH, Bystrykh LV, de Haan G, von Eyss B. Taz protects hematopoietic stem cells from an aging-dependent decrease in PU.1 activity. *Nat Commun* 2022, 13(1), 5187 (\* equal contribution).

Gschwind\* A, Marx\* C, Just MD, Severin P, Behring H, Marx-Blümel L, Becker S, Rothenburger L, Förster M, Beck JF, Sonnemann J. Tight association of autophagy and cell cycle in leukemia cells. *Cell Mol Biol Lett* 2022, 27(1), 32 (\* equal contribution).

Kristofova M, Ori A, Wang ZQ. Multifaceted microcephaly-related gene MCPH1. *Cells* 2022, 11(2), 275.

Marx C, Sonnemann J, Maddocks ODK, Marx-Blümel L, Beyer M, Hoelzer D, Thierbach R, Maletzki C, Linnebacher M, Heinzl T, Krämer OH. Global metabolic alterations in colorectal cancer cells during irinotecan-induced DNA replication stress. *Cancer Metab* 2022, 10(1), 10.

Wang Y, Zong W, Sun W, Chen C, Wang\*\* ZQ, Li\*\* T. The central domain of MCPH1 controls development of the cerebral cortex and gonads in mice. *Cells* 2022, 11(17), 2715 (\*\* co-corresponding authors).

Wu\* X, Xu\* S, Wang P, Wang ZQ, Chen H, Xu X, Peng B. ASPM promotes ATR-CHK1 activation and stabilizes stalled replication forks in response to replication stress. *Proc Natl Acad Sci U S A* 2022, 119(40), e2203783119 (\* equal contribution).

Articles in Peer-Reviewed Journals

111 | 115

2021 | 2022

Cumulative Impact Factor

798 | 907

2021 | 2022

## Selected Publications

2021

Greifenstein\* AA, Jo\* S, Bierhoff H.  
RNA:DNA triple helices: from peculiar structures to pervasive chromatin regulators.  
*Essays Biochem* 2021, 65(4), 731-40 (\* equal contribution).

Marfil-Sánchez A, Zhang L, Alonso-Pernas P, Mirhakkak M, Mueller M, Seelbinder B, Ni Y, Santhanam R, Busch A, Beemelmanns C, Ermolaeva\*\* M, Bauer\*\* M, Panagiotou\*\* G.  
An integrative understanding of the large metabolic shifts induced by antibiotics in critical illness.  
*Gut Microbes* 2021, 13(1), 1993598 (\*\* co-corresponding authors).

Coronel L, Riege K, Schwab K, Förste S, Häckes D, Semerau L, Bernhart SH, Siebert R, Hoffmann\*\* S, Fischer\*\* M.  
Transcription factor RFX7 governs a tumor suppressor network in response to p53 and stress.  
*Nucleic Acids Res* 2021, 49(13), 7437-56 (\*\* co-corresponding authors).

Fischer M.  
Mice are not humans: The case of p53.  
*Trends Cancer* 2021, 7(1), 12-4.

Sahm\*\* A, Koch P, Horvath S, Hoffmann\*\* S.  
An analysis of methylome evolution in primates.  
*Mol Biol Evol* 2021, 38(11), 4700-14 (\*\* co-corresponding authors).

Sahm\* A, Platzer M, Koch P, Henning Y, Bens M, Groth M, Burda H, Begall S, Ting S, Goetz M, Van Daele P, Staniszewska M, Klose J, Costa PF, Hoffmann\*\* S, Szafranski\*\* K, Dammann\*\* P.  
Increased longevity due to sexual activity in mole-rats is associated with transcriptional changes in HPA stress axis.  
*eLife* 2021, 10, e57843 (\* corresponding author, \*\* co-senior authors).

Woodstock DL, Sammons MA, Fischer M.  
p63 and p53: Collaborative partners or dueling rivals?  
*Front Cell Dev Biol* 2021, 9, 701986.

Shomron O, Nevo-Yassaf I, Aviad T, Yaffe Y, Erez Zahavi E, Dukhovny A, Perlson E, Brodsky I, Yeheskel A, Pasmanik-Chor M, Mironov A, Beznoussenko GV, Mironov AA, Sklan EH, Patterson GH, Yonemura Y, Sannai M, Kaether\*\* C, Hirschberg\*\* K.  
COPII collar defines the boundary between ER and ER exit site and does not coat cargo containers.  
*J Cell Biol* 2021, 220(6), e201907224 (\*\* co-corresponding authors).

Völkel\* G, Laban\* S, Fürstberger\* A, Kühlwein SD, Ikonomi N, Hoffman TK, Brunner C, Neuberg DS, Gaidzik V, Döhner H, Kraus\*\* JM, Kestler\*\* HA.  
Analysis, identification and visualization of subgroups in genomics.  
*Brief Bioinform* 2021, 22(3), bbaa217 (\* equal contribution, \*\* co-senior authors).

Collatz M, Mock F, Barth E, Hölzer M, Sachse K, Marz M.  
EpiDope: A deep neural network for linear B-cell epitope prediction.  
*Bioinformatics* 2021, 37(4), 448-55.

Hölzer M, Marz M.  
PoSeiDon: a Nextflow pipeline for the detection of evolutionary recombination events and positive selection.  
*Bioinformatics* 2021, 37(7), 1018-20.

Mock F, Viehweger A, Barth E, Marz M.  
VIDHOP, viral host prediction with Deep Learning.  
*Bioinformatics* 2021, 37(3), 318-25.

Di Sanzo\* S, Spengler\* K, Leheis A, Kirkpatrick JM, Rändler TL, Baldensperger T, Dau T, Henning C, Parca L, Marx C, Wang ZQ, Glomb MA, Ori\*\* A, Heller\*\* R.  
Mapping protein carboxymethylation sites provides insights into their role in proteostasis and cell proliferation.  
*Nat Commun* 2021, 12(1), 6743 (\* equal contribution, \*\* co-senior authors).

Schüler SC, Kirkpatrick\* JM, Schmidt\* M, Santinha D, Koch P, Di Sanzo S, Cirri E, Hemberg M, Ori\*\* A, von Maltzahn\*\* J.  
Extensive remodeling of the extracellular matrix during aging contributes to age-dependent impairments of muscle stem cell functionality.  
*Cell Rep* 2021, 35(10), 109223 (\* equal contribution, \*\* co-senior authors).

Becker F, Rudolph KL.  
Targeting enzyme aging.  
*Science* 2021, 371(6528), 462-3.

Chen Y, Rudolph KL.  
Granulocyte colony-stimulating factor acts on lymphoid-biased, short-term hematopoietic stem cells.  
*Haematologica* 2021, 106(6), 1516-8.

Deb S, Felix DA, Koch P, Deb MK, Szafranski K, Buder K, Sannai M, Groth M, Kirkpatrick J, Pietsch S, Gollowitzer A, Groß A, Riemenschneider P, Koeberle A, González-Estévez\*\* C, Rudolph\*\* KL.  
Tnfrsf25/exoc3-driven lipid metabolism is essential for stem cell differentiation and organ homeostasis.  
*EMBO Rep* 2021, 22(1), e49328 (\*\* co-corresponding authors).

Yi\* W, Zhang\* Y, Liu B, Zhou Y, Liao D, Qiao X, Gao D, Xie T, Yao Q, Zhang Y, Qiu Y, Huang G, Chen Z, Chen C, Ju Z.  
Protein S-nitrosylation regulates proteostasis and viability of hematopoietic stem cell during regeneration.  
*Cell Rep* 2021, 34(13), 108922 (\* equal contribution).

Schmidt M, Weidemann A, Poser C, Bigot A, von Maltzahn J.  
Stimulation of non-canonical NF- $\kappa$ B through lymphotoxin- $\beta$ -receptor impairs myogenic differentiation and regeneration of skeletal muscle.  
*Front Cell Dev Biol* 2021, 9, 721543.

Schüler SC, Kirkpatrick\* JM, Schmidt\* M, Santinha D, Koch P, Di Sanzo S, Cirri E, Hemberg M, Ori\*\* A, von Maltzahn\*\* J.  
Extensive remodeling of the extracellular matrix during aging contributes to age-dependent impairments of muscle stem cell functionality.  
*Cell Rep* 2021, 35(10), 109223 (\* equal contribution, \*\* co-senior authors).

Kirtay M, Sell J, Marx C, Haselmann H, Ceanga M, Zhou ZW, Rahmati V, Kirkpatrick J, Buder K, Grigaravicius P, Ori A, Geis\*\* C, Wang\*\* ZQ.  
ATR regulates neuronal activity by modulating presynaptic firing.  
*Nat Commun* 2021, 12(1), 4067 (\*\* co-corresponding authors).

Liu\* X, Schneble-Löhnert\* N, Kristofova M, Qing X, Labisch J, Hofmann S, Ehrenberg S, Sannai M, Jörß T, Ori A, Godmann M, Wang ZQ.  
The N-terminal BRCT domain determines MCPH1 function in brain development and fertility.  
*Cell Death Dis* 2021, 12(2), 143 (\* equal contribution).

Marx C, Schaarschmidt MU, Kirkpatrick J, Marx-Blümel L, Halilovic M, Westermann M, Hoelzer D, Meyer FB, Geng Y, Buder K, Schadwinkel HM, Siniuk K, Becker S, Thierbach R, Beck JF, Sonnemann\* J, Wang\* ZQ.  
Cooperative treatment effectiveness of ATR and HSP90 inhibition in Ewing's sarcoma cells.  
*Cell Biosci* 2021, 11(1), 57 (\* equal contribution).

Marx C, Sonnemann J, Beyer M, Maddocks ODK, Lilla S, Hauzenberger I, Piéce-Staffa A, Siniuk K, Nunna S, Marx-Blümel L, Westermann M, Wagner T, Meyer FB, Thierbach R, Mullins CS, Kdimati S, Linnebacher M, Neri F, Heinzel T, Wang ZQ, Krämer OH.  
Mechanistic insights into p53-regulated cytotoxicity of combined entinostat and irinotecan against colorectal cancer cells.  
*Mol Oncol* 2021, 15(12), 3404-29.

Tapias\* A, Lázaro\* D, Yin\* BK, Rasa SMM, Krepelova A, Kelmer Sacramento E, Grigaravicius P, Koch P, Kirkpatrick J, Ori A, Neri F, Wang ZQ.  
HAT cofactor TRRAP modulates microtubule dynamics via SP1 signaling to prevent neurodegeneration.  
*eLife* 2021, 10, e61531 (\* equal contribution).

Coppin\* E, Sundarasetty\* BS, Rahmig S, Blume J, Verheyden NA, Bahlmann F, Ravens S, Schubert U, Schmid J, Ludwig S, Geissler K, Guntinas-Lichius O, von Kaisenberg C, Groten T, Platz A, Naumann R, Ludwig B, Prinz I, Waskow\*\* C, Krueger\*\* A.  
Enhanced differentiation of functional human T cells in NSGW41 mice with tissue-specific expression of human interleukin-7.  
*Leukemia* 2021, 35(12), 3561-7 (\* equal contribution, \*\* co-senior authors).

Fröbel J, Landspersky T, Percin G, Schreck C, Rahmig S, Ori A, Nowak D, Essers M, Waskow C, Oostendorp RAJ.  
The hematopoietic bone marrow niche ecosystem.  
*Front Cell Dev Biol* 2021, 9, 705410.

## Awards and Prizes

2022

In acknowledgement of the FLI's extraordinary commitment to the expansion of equal opportunities and diversity, the **TOTAL E-QUALITY** award, with the add-on “diversity,” was presented to Equal Opportunity Commissioner Kerstin Wagner in Erfurt on October 25, 2022. This is the fourth time that the FLI has received the award.

For the exhibition “**Micro Macro – Life Sciences in Jena**” (May 30 to June 11, 2022) scientific photos taken by Birgit Perner (Englert Research Group), Gülce Itir Percin Schulz (Waskow Research Group), and Asya Martirosyan (Ermolaeva Research Group) were selected.

On June 10, 2022, Maria Ermolaeva, head of the research group “Stress Tolerance and Homeostasis,” and her PhD student Asya Martirosyan were honored by the German Association for Aging Research (DGfA) with the **Dieter Platt Award for Experimental Gerontology**. They received the prize, which is endowed with 10,000 euros, for their studies on investigating metabolic stress responses to ultraviolet irradiation.



Once again the FLI will be awarded with the Total E-Quality award in 2022.

2021

Francesca Bruno (Kaether Research Group) was awarded a Scientific Exchange Grant from the European Molecular Biology Organization (EMBO) in November 2021.

At the **9th GSCN Conference of the German Stem Cell Network** in Dresden (October 6–8, 2021) Ellen Späth (Ori Research Group) won a prize for her **poster** with the title: “Proteome dynamics during myogenesis identify the cytoskeletal protein Leiomodin 1 as a promoter of muscle stem cell differentiation.”

Stephan Culemann (Waskow Research Group) received a **DMM Conference Travel Stipendium** from The Company of Biologists to participate in the 4th International Conference on Stem Cells in Kos, Greece (September 30 – October 5, 2021).

The **4th Nothobranchius Symposium**, a platform for researchers interested in biological, biomedical, and ecological issues involving the fish species *Nothobranchius furzeri*, was held online on June 3–4, 2021. **Three young scientists from the FLI** were honored during the event: Johannes Krug (Englert Research Group) received first place for best oral presentation and Asya Martirosyan (Ermolaeva Research Group) took third place. Chiara Giannuzzi (Cellerino Research Group) received the prize for best poster.



## Scientific Meetings and Workshops

09/19/2022 – 3rd German p53 Workshop, Jena  
 09/23/2022 Organization: Christine Blattner (Karlsruhe Institute of Technology) and Martin Fischer (FLI)

04/06/2022 – DGDR-Krupp 2022 Symposium, Jena  
 04/09/2022 Organization: Zhao-Qi Wang (FLI) and Julian Stingele (Ludwig-Maximilians-University Munich)

10/20/2021 – Groningen-Jena Aging Meeting (G-JAM), Jena  
 10/23/2021 Organization: Alessandro Ori, Helen Morrison, Lenhard Rudolph (FLI), and Cornelis Calkhoven, Gerald de Haan (European Research Institute for the Biology of Ageing - ERIBA) Groningen, Netherlands, in association with Aging Research Center (ARC) Jena, Jena Centre for Healthy Ageing, and the Leibniz Research Alliance Healthy Ageing

09/06/2021 – (online) EMBO|FEBS Lecture Course, Jena  
 09/09/2021 Organization: Christoph Englert (FLI), Frank Madeo (University of Graz, Austria), and Julia von Maltzahn (FLI)

**3rd German p53 Workshop**  
 SEPTEMBER 19-20, 2022

**SPEAKERS**  
 Volker Dötsch : Goethe University Frankfurt  
 Kurt Engeland : University of Leipzig  
 Martin Fischer : Leibniz Institute on Aging  
 Sabrina Gerber : University of Göttingen  
 Heiko Hermeking : Ludwig Maximilians University Munich  
 Carsten Herskind : Heidelberg University  
 Andreas Jörger : Goethe University Frankfurt  
 Alexander Löwer : Technical University of Darmstadt  
 Thomas Meyer : Christian Albrechts University of Kiel  
 Ramona Schulz-Heddergott : University of Göttingen  
 Thorsten Stiewe : Philipps University Marburg  
 Zhao-Qi Wang : Leibniz Institute on Aging  
 Lisa Wiesmüller : University of Ulm

**ORGANIZERS**  
 Christine Blattner : Karlsruhe Institute of Technology  
 Martin Fischer : Leibniz Institute on Aging

**VENUE**  
 Leibniz Institute on Aging - Fritz Lipmann Institute (FLI),  
 Beutenbergstr. 11, 07745 Jena, Seminar Room „Nucleus“

**CONTACT & REGISTRATION**  
 Martin.Fischer@leibniz-flf.de

leibniz institute on aging - Fritz Lipmann Institute

**DGDR-KRUPP 2022 SYMPOSIUM**  
**DNA REPAIR AND HUMAN DISEASE**  
 6 - 9 APRIL 2022  
 JENA, GERMANY

**REGISTRATION:**  
 Julian Stingele : LMU Munich, Germany  
 Zhao-Qi Wang : Leibniz Institute on Aging, Germany

**KEYNOTE SPEAKERS:**  
 Matthias Altmeppen : University of Bonn, Germany  
 Peter Bailly : University of Montreal, Canada  
 Alexander Borker : University of Göttingen, Germany  
 Keith W. Calvert : University of Texas, USA  
 David Caron : Imperial University, London, UK  
 Julian Drenth : University of Cambridge, UK  
 David E. Hargrett : University of Oxford, UK  
 Maria Esmailzadeh : Leibniz Institute on Aging, Germany  
 Maria Fomina : Max Institute of Experimental Medicine, St. Petersburg, Russia  
 Andrew Hayflick : University of California, Berkeley, USA  
 Karl Peter Hojner : Leibniz Institute on Aging, Germany  
 Caroline Keller : University of Göttingen, Germany  
 Paul Kapranos : Max Institute of Experimental Medicine, St. Petersburg, Russia  
 Markus Landrock : Leibniz Institute on Aging, Germany  
 Brian Lill : University of California, San Diego, USA  
 Yoshiki Mizushima : Max Planck, USA  
 Heiko Mühlbauer : University of Göttingen, Germany  
 André Nussenzweig : National Institute of Health, USA  
 Katalin Pentelecz : University Hospital Bonn, Germany  
 Stephanie Pinter : Max Planck Institute for Biology of Aging, Germany  
 Thomas Powell : University of Bonn, Germany  
 Boris Pospelov : Leibniz Institute on Aging, Germany  
 Yves Pommier : National Institute of Health, USA  
 Helmut Pospelov : Leibniz Institute on Aging, Germany  
 Kristijan Rahnulovic : University of Oxford, UK  
 Evgin Schumacher : University of Göttingen, Germany  
 Julian Stingele : LMU Munich, Germany  
 Françoise Stutz : University of Zurich, Switzerland  
 Heiko Storch : Leibniz Institute on Aging, Germany  
 Zhao-Qi Wang : Leibniz Institute on Aging, Germany  
 Lisa Wiesmüller : University of Ulm, Germany  
 Lutz Willer : Leibniz Institute on Aging, Germany

**REGISTRATION:**  
 Online Registration (https://www.dgdr.de)  
 Abstract Submission & Early Bird Registration (Deadline: 11 January 2022)  
 Registration Fee: 37 February 2022

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**ERIBA**  
**GRONINGEN-JENA AGING MEETING**

**# VIRTUAL #**  
**OCTOBER 20-23, 2021**  
 (IAS Meeting: Cancer Development, October 20)

**SPEAKERS**  
 Andrea Ablasser, Switzerland  
 Anne Bertolotti, UK  
 Dongsheng Cai, USA  
 Floris Fokker, The Netherlands  
 David J. Glass, USA  
 Florian Heidel, Germany  
 Heinrich Jasper, USA  
 Ranko Kapali, USA  
 Pekka Katajisto, Finland  
 James L. Kirkland, USA  
 William Lowry, USA  
 Emi Nishimura, Japan  
 Ellen Nolten, The Netherlands  
 Michael Rape, USA  
 Michael Ristow, Switzerland  
 Hans-Willem Snook, USA  
 Aleksandra Trifunovic, Germany  
 Björn von Eschberg, Germany  
 Julia von Maltzahn, Germany

**KEYNOTES**  
 Andrew Dillin, USA  
 Vera Gorbunova, USA  
 Manuel Serrano, Spain

**SESSIONS**  
 • Mitochondria and Protein Homeostasis  
 • Systemic and Niche Factors  
 • Epigenetics, DNA Damage, Genome Integrity  
 • Stem Cells and Regeneration  
 • Interventions

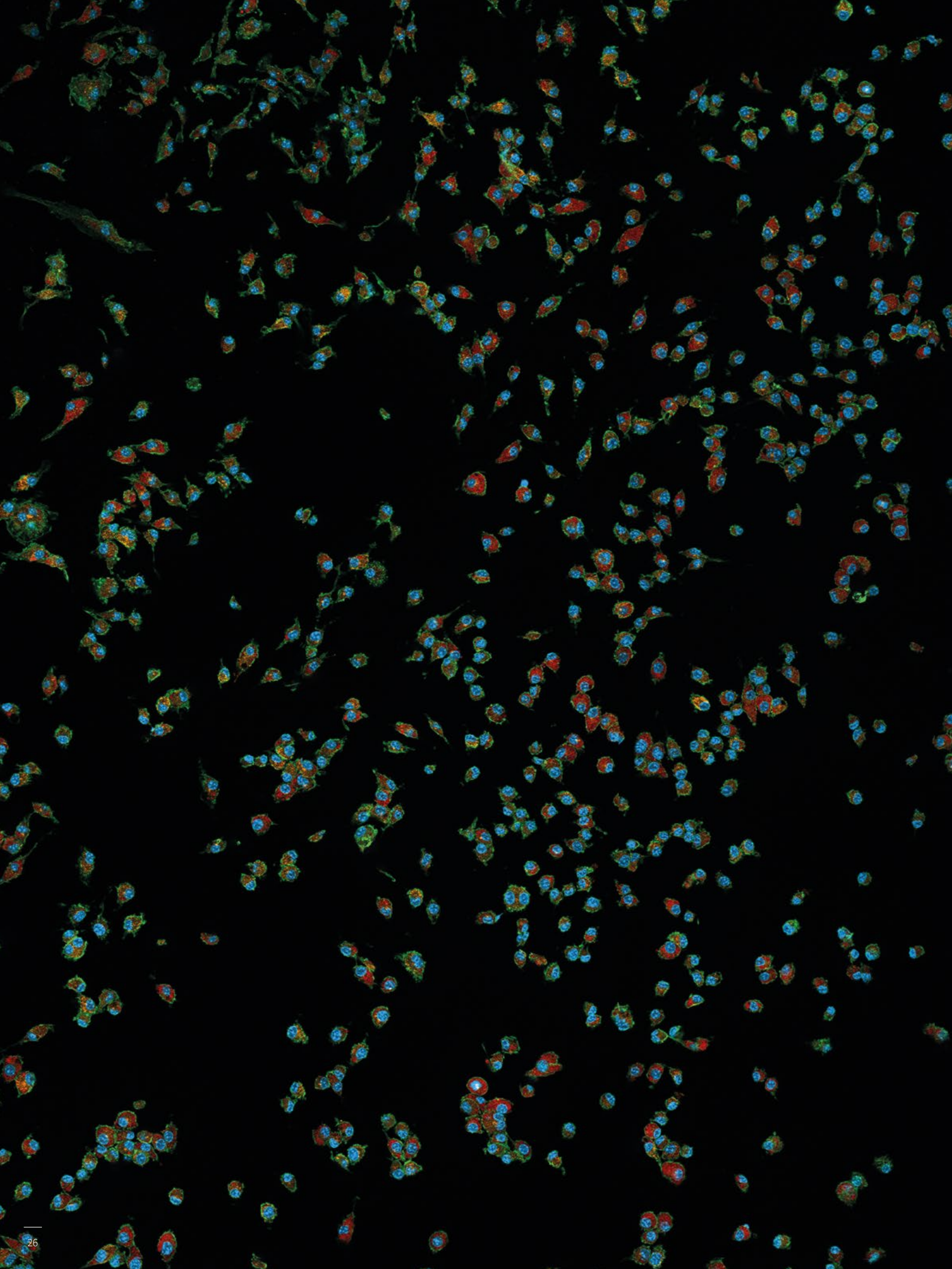
**CONTACT**  
 g-jam@leibniz-flf.de

Further information:  
 www.leibniz-flf.de/g-jam2021

**Organizers:**  
 Leibniz Institute on Aging - Fritz Lipmann Institute (FLI)  
 Alessandro Ori, Helen Morrison, Lenhard Rudolph  
 European Research Institute for the Biology of Ageing (ERIBA)  
 Cornelis Calkhoven, Gerald de Haan

In cooperation with:  
 Aging Research Center (ARC) Jena | Jena Centre for Healthy Ageing | LRA Healthy Ageing

leibniz institute on aging - Fritz Lipmann Institute (FLI) Beutenbergstr. 11 07745 Jena, Germany  
 g-jam@leibniz-flf.de www.leibniz-flf.de





# Research Balance

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# Research Balance

To provide a foundation for new therapies that improve health in old age, the FLI focuses on two research areas, supported by bioinformatics expertise:

## Program Area I

### Stem Cells, Regeneration, and Organ Homeostasis in Aging

With age, the ability to maintain body tissues decreases. This leads to impaired organ function and an increased risk of the development of aging-associated diseases. One reason for this is the diminished functionality of adult stem cells, which are responsible for the lifelong self-renewal and regeneration of organs and tissues. The molecular causes of this age-associated inhibition of stem cell function and its effects on the maintenance of various organ systems are being researched.

This should make it possible in the future to develop therapies to maintain the function of the body's own stem cells and thus reduce the risk of developing dysfunction and disease in old age. Program Area I includes Subareas 1 "Stem Cell Aging" and 2 "Regeneration and Homeostasis of Organs in Aging."

## Program Area II

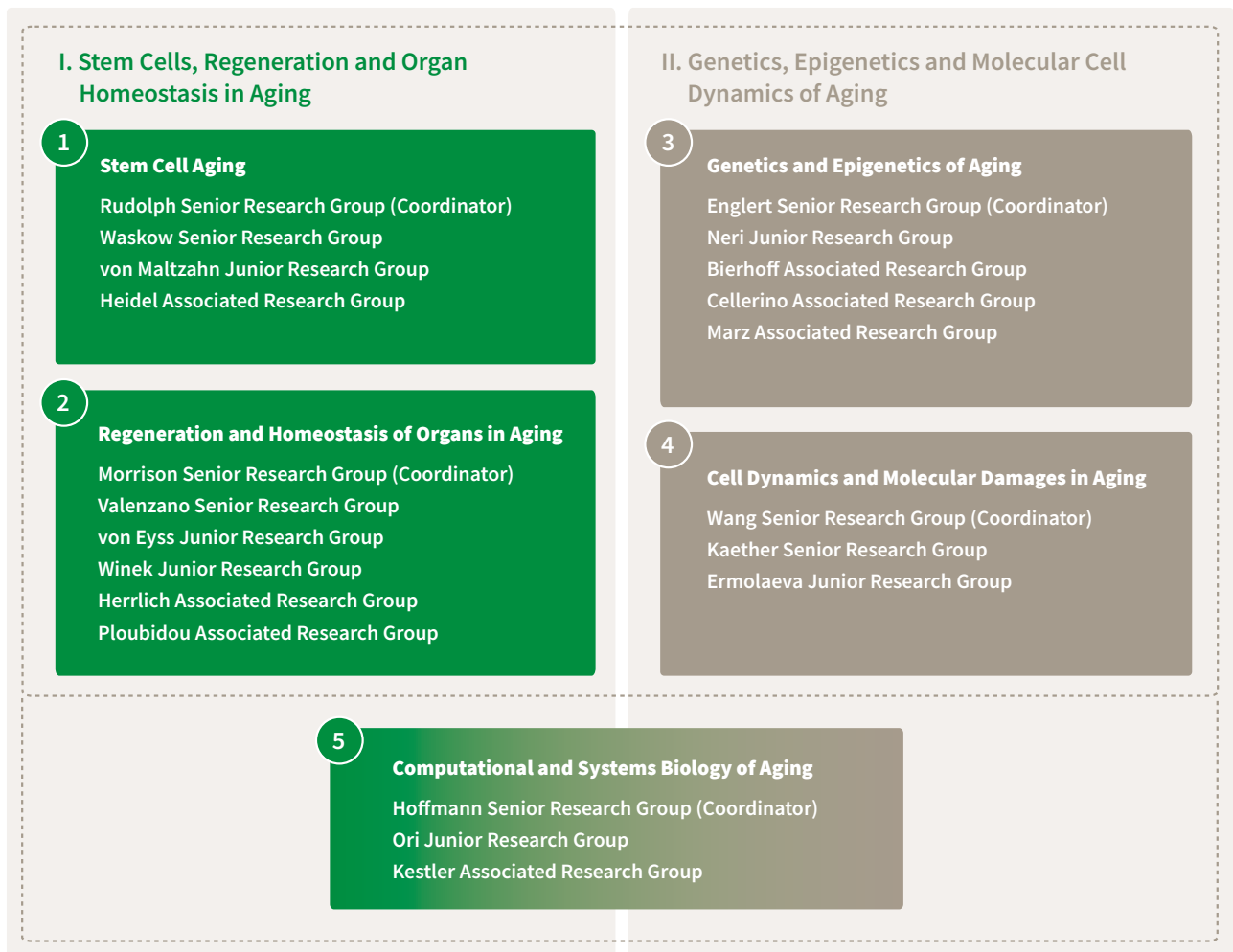
### Genetics, Epigenetics and Molecular Cell Dynamics of Aging

A central phenomenon observed in aging is the accumulation of damage in the molecular building blocks of cells. Among other things, this affects proteins and the genetic information, DNA. There is increasing evidence that damage to proteins and DNA contributes to stem cell dysfunction and disruption of tissue maintenance. The causes of the age-related accumulation of damage to DNA and proteins remain largely unknown. Additionally, the question arises as to which genetic factors influence the rate of the "aging" of these molecular building blocks. To answer these questions, comparative analyses and targeted modifications of genomes and transcriptomes of short- and long-lived model organisms are being performed. The goal is to find genetic and epigenetic variations that also determine the individual predisposition for healthy aging or for aging-related diseases in humans. Program Area II includes Subareas 3 "Genetics and Epigenetics of Aging" and 4 "Cell Dynamics and Molecular Damages in Aging."

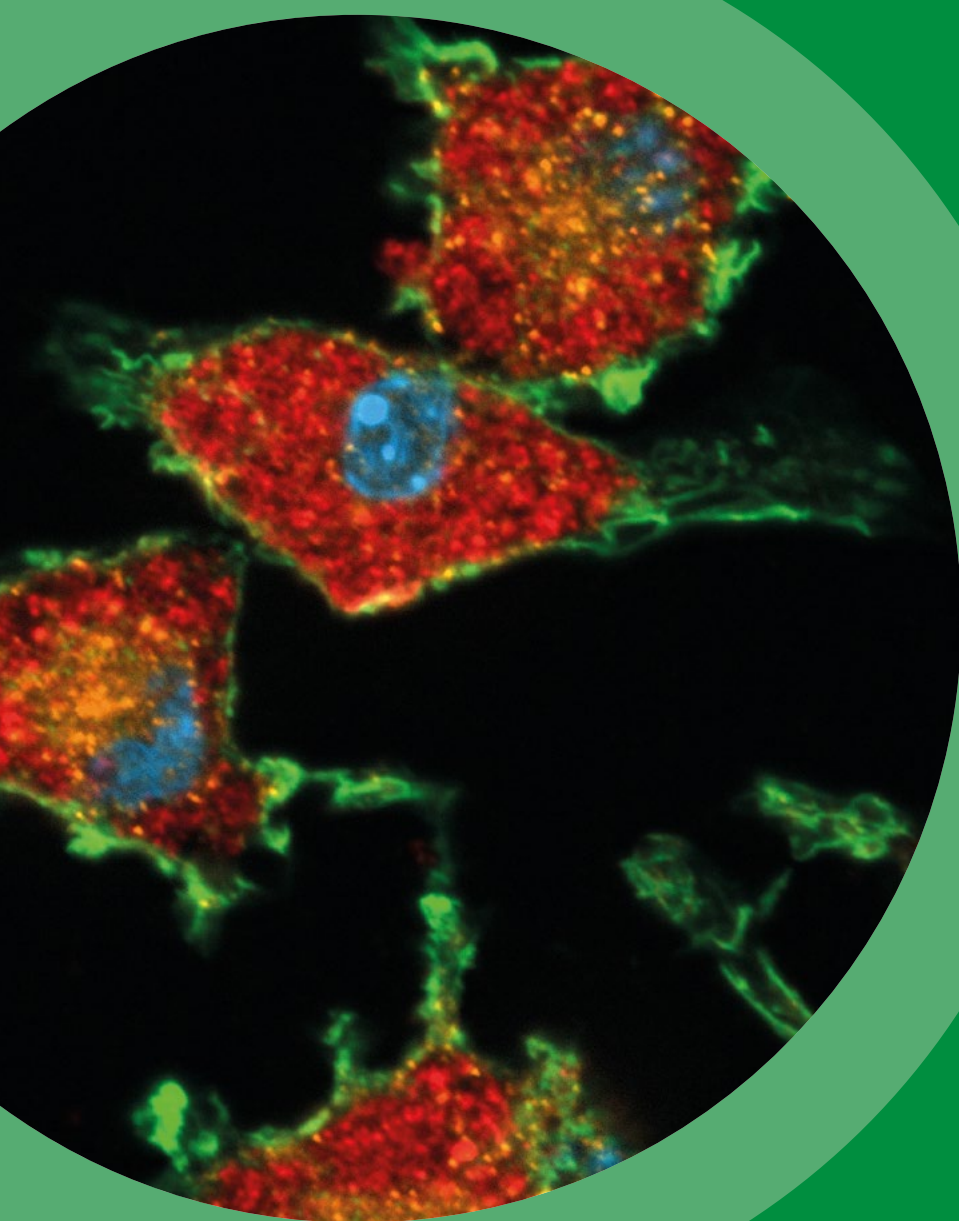
## Cross-sectional Subarea 5: Computational and Systems Biology of Aging

Using systems biology and bioinformatics analyses, research results obtained in model organisms and on human samples are compared in order to derive hypotheses and predictions about the molecular causes of aging in humans. These hypotheses are tested in collaboration with medical researchers to determine their role in the pathogenesis of disease in old age. Computational and Systems Biology of Aging (Subarea 5) is an area of overlap between Program Areas I and II.

## Identification of causative mechanisms of aging to enable aging in good health



Research groups that conducted research in subareas 1 to 5 at the FLI during the period 2021/2022.



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# Program Area I

## Stem Cells, Regeneration, and Organ Homeostasis in Aging

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### **Subarea 1: Stem Cell Aging** .....

1

- 30 *Rudolph Senior Research Group*
- 32 *Waskow Senior Research Group*
- 34 *von Maltzahn Junior Research Group*
- 36 *Heidel Associated Research Group*

### **Subarea 2: Regeneration and Homeostasis of Organs in Aging** .....

2

- 38 *Morrison Senior Research Group*
- 40 *Valenzano Senior Research Group*
- 42 *von Eyss Junior Research Group*
- 44 *Winek Junior Research Group*
- 46 *Herrlich Associated Research Group*
- 48 *Ploubidou Associated Research Group*



Prof. Dr. K. Lenhard Rudolph  
Group Leader

## Rudolph Senior Research Group: Stem Cell Aging

1

CENTRAL RESEARCH QUESTIONS:

**Which mechanisms contribute causally to aging and in which phase of the life cycle is their influence strongest?**

### Focus of Research

In the past five years we have obtained our most important findings in the field of aging-related changes in metabolism and stem cells. This work has led us to the discovery of dietary interventions that improve stem cell and organ function when applied in old age. Dietary restriction (DR) is known to be the most powerful intervention to delay aging across species. However, recent studies from our lab indicate that DR is less effective at improving the function of stem cells when begun later in life. We have initiated a new line of research aiming to identify genetic, epigenetic and dietary interventions to ensure that the full health benefits of DR are realized even when it is begun only at an advanced age.

Furthermore, we are investigating aging-associated changes in metabolism in stem cells and organs. Our work has identified an age-dependent decline in fat metabolism in the liver. We have discovered a dietary intervention that has the potential to reactivate fat metabolism in the livers of aged mice. Translational research and a human pilot trial are planned for 2023. We envision that this dietary intervention could be used to treat non-alcoholic fatty liver disease (NAFLD) – one of the most frequent metabolic diseases among older people.

From a translational point of view, these findings are of great importance, since dietary interventions are currently regarded

as one of the most realistic therapeutic approaches to combat aging. Our data provide new evidence that metabolism changes with aging and that it is possible to reprogram metabolism to a more youthful state through late life dietary interventions.

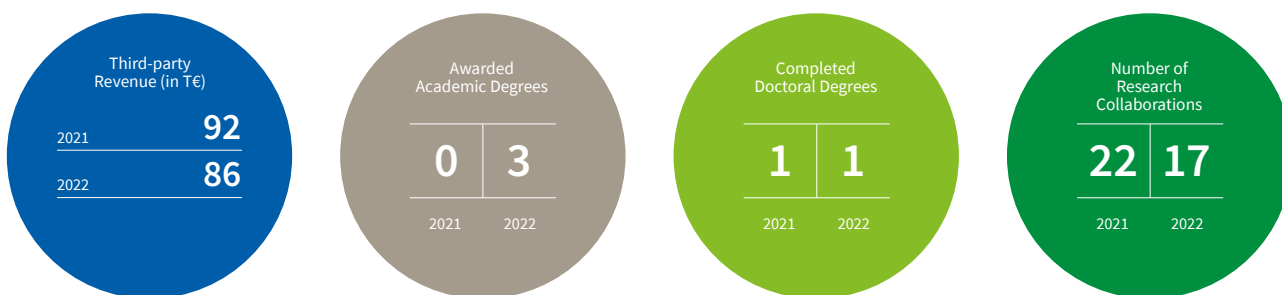
Another line of research in our lab focuses on the question of whether growth and metabolism at an early age influence the aging trajectories of stem cells and metabolic aging in later life. Our work provides experimental evidence that growth signaling and metabolic activity during development and early adulthood influence key aging phenotypes of hematopoietic stem cells (HSCs), such as the expansion of myeloid-biased HSCs.

We aim to understand the biological mechanisms through which early life stress (such as metabolic activity and growth factor signaling or inflammatory signaling) creates a memory in stem cells and tissues. We analyze how this in turn influences aging, and how genetics or dietary intervention can reverse such effects to ameliorate the aging process. Our current studies on

1. cohesin-mediated inflammatory signaling,
2. insulin-like growth factor (IGF) signaling and
3. tunneling-nanotube (TNT) mediated stress responses provide innovative entry points to address these questions.



## Key Figures

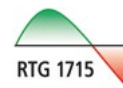


## Selected Publications

Suo M, Rommelfanger MK, Chen Y, Amro EM, Han B, Chen Z, Szafranski K, Chakkarappan SR, Boehm BO, MacLean AL, Rudolph KL. Age-dependent effects of Igf2bp2 on gene regulation, function, and aging of hematopoietic stem cells in mice. *Blood* 2022, 139(17), 2653-65.

Deb S, Felix DA, Koch P, Deb MK, Szafranski K, Buder K, Sannai M, Groth M, Kirkpatrick J, Pietsch S, Gollowitzer A, Groß A, Riemenschneider P, Koeberle A, González-Estévez\*\* C, Rudolph\*\* KL. Tnfrsf25/exoc3-driven lipid metabolism is essential for stem cell differentiation and organ homeostasis. *EMBO Rep* 2021, 22(1), e49328 (\*\* co-corresponding authors).

## Third-party Funding (selection)





Prof. Dr. Claudia Waskow  
Group Leader

## Waskow Senior Research Group: Immunology of Aging – Regeneration in Hematopoiesis

1

CENTRAL RESEARCH QUESTIONS:

**Cellular and molecular regulatory mechanisms of immune response and hematopoiesis – how and why do immunological responses change with age?**

### Focus of Research

The preservation of stem cell functionality is critically important for the continuous renewal of tissues, as the function of many organs depends on the lifelong production of new cells by stem cells. This is especially true for organs and tissues that have high cell turnover, such as the intestine, skin or blood. Only with an understanding of the cellular- and molecular-level mechanisms of the decision-making processes that differentiate tasks in stem cells – quiescence, cell division or hematopoiesis – can ways be found in the future to produce healthy tissues to replace damaged ones.

As we age, the efficiency of the immune system declines, a condition known as immune senescence. This leads to increased susceptibility to infection-related morbidity and mortality. Another important change in aging is the increased involvement of cellular clones in hematopoiesis. This so-called clonal hematopoiesis is strictly correlated with a significantly increased general mortality rate, the incidence of cardiovascular diseases and the development of (blood) tumors. These two phenomena put hematopoiesis at the center of interest in research on aging. Moreover, defects in hematopoiesis can lead to life-threatening blood diseases.

At the same time, the fact that all blood and immune cells are continuously formed from hematopoietic stem cells through the lifetime is exploited clinically. After a bone marrow transplant, donor stem cells develop their considerable regenerative potential in the recipient; over a long period of time, they repeatedly form new blood cells to replace the body's own defective blood cells. In this way, a new immune system establishes and regenerates itself from the donor cells. However, although blood stem cells have been used therapeutically in the clinic for decades, mechanisms such as the interaction among receptors or the signaling pathways that regulate decision-making processes are largely unknown. The research group is therefore investigating cell-intrinsic and cell-extrinsic signals that control decision-making in immune cells and blood stem cells.

### Current Projects

The research focuses on immune responses and immune cell formation in mice and in humans. State-of-the-art techniques are used to investigate how cell physiological processes in the context of the organism influence immune cell and stem and progenitor cell function. The research group continues to develop new tools to address this question *in vivo*.

Key questions include:

- How and why does immune cell function change with age?
- When does a stem cell remain a stem cell and what stimulates it to differentiate?
- Is it possible to promote blood cell formation and immune cell function in old age?

## Key Figures



## Selected Publications

Brings C, Fröbel J, Cadeddu RP, Germing U, Haas R, Gattermann N. Impaired formation of neutrophil extracellular traps (NETs) in patients with myelodysplastic syndrome. *Blood Adv* 2022, 6(1), 129-37.

Schwarz M, Rizzo S, Paz WE, Kresinsky A, Thévenin D, Müller JP. Disrupting PTPRJ transmembrane-mediated oligomerization counteracts oncogenic receptor tyrosine kinase FLT3 ITD. *Front Oncol* 2022, 12, 1017947.

Fröbel J, Landspersky T, Percin G, Schreck C, Rahmig S, Ori A, Nowak D, Essers M, Waskow C, Oostendorp RAJ. The hematopoietic bone marrow niche ecosystem. *Front Cell Dev Biol* 2021, 9, 705410.

Coppin\* E, Sundarasetty\* BS, Rahmig S, Blume J, Verheyden NA, Bahlmann F, Ravens S, Schubert U, Schmid J, Ludwig S, Geissler K, Guntinas-Lichius O, von Kaisenberg C, Groten T, Platz A, Naumann R, Ludwig B, Prinz I, Waskow\*\* C, Krueger\*\* A. Enhanced differentiation of functional human T cells in NSGW41 mice with tissue-specific expression of human interleukin-7. *Leukemia* 2021, 35(12), 3561-7 (\* equal contribution, \*\* co-senior authors).

Cossarizza A (...) Fröbel J (...) Percin GI (...) Waskow C. Guidelines for the use of flow cytometry and cell sorting in immunological studies (third edition). *Eur J Immunol* 2021, 51(12), 2708-3145.

Ai J, Wörmann SM, Görgülü K, Vallespinos M, Zagorac S, Alcalá S, Wu N, Kabacaoglu D, Berninger A, Navarro D, Kaya-Aksoy E, Ruess DA, Ciecieski KJ, Kowalska M, Demir EI, Ceyhan GO, Heid I, Braren R, Riemann M, Schreiner S, Hofmann S, Kutschke M, Jastroch M, Slotta-Huspenina J, Muckenhuber A, Schlitter AM, Schmid RM, Steiger K, Diakopoulos KN, Lesina M, Sainz B, Algül H. BCL3 couples cancer stem cell enrichment with pancreatic cancer molecular subtypes. *Gastroenterology* 2021, 161(1), 318-32.

## Third-party Funding (selection)

**DFG** Deutsche Forschungsgemeinschaft

**Leibniz**  
Leibniz  
Gemeinschaft

**E-Rare**

**C3S**  
Carl Zeiss  
Stiftung

**POLYTARGET**  
SFB 1278

**IMPULS**



Dr. Julia von Maltzahn  
Group Leader

# von Maltzahn Junior Research Group: Stem Cells in Skeletal Muscle

(until 04/2022)

1



CENTRAL RESEARCH QUESTION:

**Why does skeletal muscle regeneration worsen with age?**

## Focus of Research

Skeletal muscle performs multiple tasks in the organism, exhibiting an amazing capacity for adaptation and regeneration. Muscle stem cells – also known as satellite cells – are essential for the regeneration of skeletal muscle. With age, however, not only their number but also their functionality decreases sharply. This is due on the one hand to intrinsic changes in the muscle stem cells but also to changes in the muscle stem cell niche, as well as to systemic factors. The interplay of these different changes, which occur with increasing age, leads to the fact that the skeletal muscle is less and less able to regenerate as the organism ages.

The research group is addressing both the intrinsic differences between old and young muscle stem cells and those that result from changes in the stem cell niche. The researchers are studying signaling pathways that are altered in old muscle stem cells, and they are looking for ways to “rejuvenate” aged muscle by interfering with these signaling pathways. Here, they focus on how intrinsic differences in muscle stem cells interact with changes in the muscle stem cell niche. Furthermore, the group is investigating changes in muscle stem cells and their niche in diseases such as cachexia or in altered innervation, which are more likely to occur with increasing age.

## Methodology

To better understand muscle stem cell function, muscle stem cells will be isolated from adult, old and geriatric mice and

examined for changes in the transcriptome or proteome. Methods used for functional analysis of muscle stem cell function include:

- **Isolating and culturing muscle stem cells**  
In isolated and cultured muscle fibers, a cluster containing different muscle stem cell populations forms from a muscle stem cell within 72 hours. The signaling pathways involved in this process can be studied very well in the experimental system independent of other cells but associated with the muscle fiber.
- **Injuring the skeletal muscles.**  
Skeletal muscles of adult, old or geriatric mice are damaged by injection of the snake venom cardiotoxin. In this way, the entire regeneration process can be analyzed.

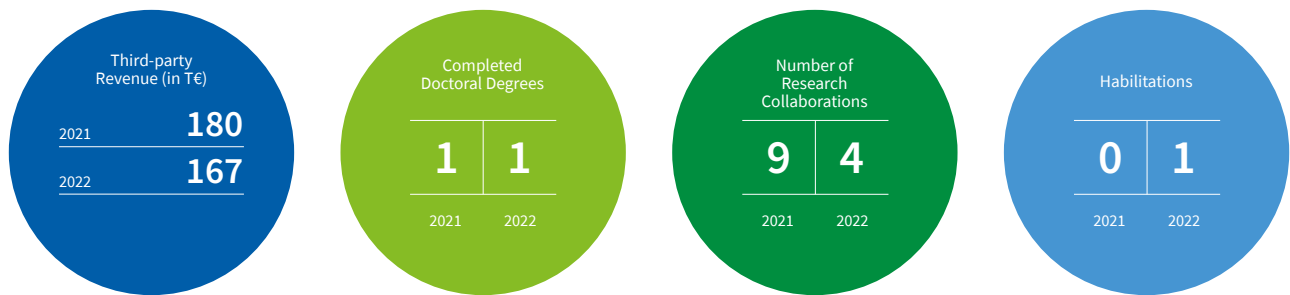
## Research Results

With our research, we were able to demonstrate, among other things, that the extracellular matrix in skeletal muscle changes significantly with age. This change leads to aberrant activation of the ERK signaling pathway in muscle stem cells and contributes to a deterioration of skeletal muscle regeneration. Furthermore, we were able to show that the hairpin region of the extracellular ligand Wnt7a alone is sufficient for the full function of this messenger in skeletal muscle and can, for example, counteract cancer-induced cachexia. We were also able

to demonstrate that stimulation of the non-canonical NF-κB-pathway impairs skeletal muscle cell differentiation, a phenomenon that also occurs with increasing age.

The long-term goal of our research is to improve the regenerative capacity of skeletal muscle after acute injury in old age or due to diseases that occur with aging.

## Key Figures



## Selected Publications

Schmidt M, Poser C, Janster C, von Maltzahn J. The hairpin region of WNT7A is sufficient for binding to the Frizzled7 receptor and to elicit signaling in myogenic cells. *Comput Struct Biotechnol J* 2022, 20, 6348-59.

Abdellatif M, Trummer-Herbst V, Koser F, Durand S, Adão R, Vasques-Nóvoa F, Freundt JK, Voglhuber J, Pricolo MR, Kasa M, Türk C, Arahamian F, Herrero-Galán E, Hofer SJ, Pendl T, Rech L, Kargl J, Anto-Michel N, Ljubojevic-Holzer S, Schipke J, Brandenberger C, Auer M, Schreiber R, Koyani CN, Heinemann A, Zirlik A, Schmidt A, von Lewinski D, Scherr D, Rainer PP, von Maltzahn J, Mühlfeld C, Krüger M, Frank S, Madeo F, Eisenberg T, Prokesch A, Leite-Moreira AF, Lourenço AP, Alegre-Cebollada J, Kiechl S, Linke WA, Kroemer G, Sedej S. Nicotinamide for the treatment of heart failure with preserved ejection fraction. *Sci Transl Med* 2021, 13(580), eabd7064.

Franzka P, Henze\* H, Jung\* MJ, Schüler SC, Mittag S, Biskup K, Liebmann L, Kentache T, Morales J, Martínez B, Katona I, Herrmann T, Huebner AK, Hennings JC, Groth S, Gresing LJ, Horstkorte R, Marquardt T, Weis J, Kaether C, Mutchinick OM, Ori A, Huber O, Blanchard V, von Maltzahn J, Hübner CA. GMPGA defects cause a neuromuscular disorder with α-dystroglycan hyperglycosylation. *J Clin Invest* 2021, 131(9), e139076 (\* equal contribution).

Hüttner SS, Hayn C, Ahrens HE, Schmidt M, Henze H, von Maltzahn J. Single myofiber culture assay for the assessment of adult muscle stem cell functionality ex vivo. *J Vis Exp* 2021, (168), e62257.

Schmidt M, Weidemann A, Poser C, Bigot A, von Maltzahn J. Stimulation of non-canonical NF-κB through lymphotoxin-β-receptor impairs myogenic differentiation and regeneration of skeletal muscle. *Front Cell Dev Biol* 2021, 9, 721543.

Schüler SC, Kirkpatrick\* JM, Schmidt\* M, Santinha D, Koch P, Di Sanzo S, Cirri E, Hemberg M, Ori\*\* A, von Maltzahn\*\* J. Extensive remodeling of the extracellular matrix during aging contributes to age-dependent impairments of muscle stem cell functionality. *Cell Rep* 2021, 35(10), 109223 (\* equal contribution, \*\* co-senior authors).

## Third-party Funding (selection)





Prof. Dr. Florian Heidel  
Collaboration with  
Greifswald University Medicine

## Heidel Associated Research Group: Stem Cell Aging / Myeloid Neoplasms

1

### CENTRAL RESEARCH QUESTIONS:

**Which signaling pathways and molecules are involved in self-renewal and differentiation during the aging process of hematopoietic stem cells, and which of these changes lead to malignant transformation?**

### Focus of Research

The Heidel research group is searching for molecules responsible for cell competition, cell fate decisions and self-renewal in hematopoietic stem cells during the aging process and during the development of age-associated neoplasms. To this end, global transcriptome and proteome analyses are used in combination with *in vitro* and *in vivo* CRISPR/Cas9 genome editing approaches. Researchers are developing genetically engineered mouse models to validate the functional significance of signaling molecules and epigenetic and metabolic targets that are critical for clonal changes in hematopoiesis in aging and play an important role in the development of myeloid neoplasms and their transformation into acute leukemias.

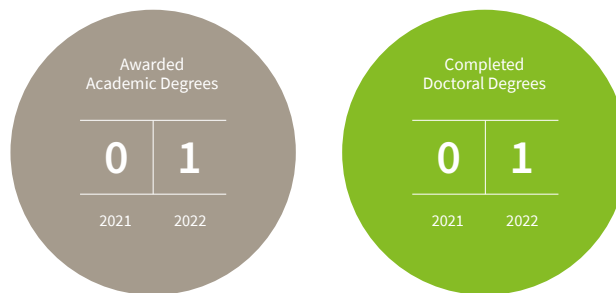
The goal of the research group is to bring basic research findings closer to clinical practice. For this reason, artificially reprogrammed stem cells, so-called induced pluripotent stem cells (iPSC technology), as well as cell models derived from patient samples (patient-derived xenograft models, PDX), are used in preclinical studies.

### Current Projects

Current work projects include:

- Characterization of signaling pathways in aging hematopoietic stem cells and in malignant transformation *in vitro* and *in vivo*.
- Development and characterization of genetically engineered mouse models and development of PDX models for clonal blood disorders and myeloid malignancies.
- Identification of genetic targets in myeloid pre-neoplasms and neoplasms.

## Key Figures



## Selected Publications

Ernst P, Schnöder TM, Huber N, Perner F, Jayavelu AK, Eifert T, Hsu CJ, Tubío-Santamaría N, Crodel CC, Ungelenk M, Hübner CA, Clement JH, Hochhaus A, Heidel FH.  
Histone demethylase KDM4C is a functional dependency in JAK2-mutated neoplasms.  
*Leukemia* 2022, 36(7), 1843-9.

Perner F, Schnoeder TM, Xiong Y, Jayavelu AK, Mashamba N, Santamaria NT, Huber N, Todorova K, Hatton C, Perner B, Eifert T, Murphy C, Hartmann M, Hoell JI, Schröder N, Brandt S, Hochhaus A, Mertens PR, Mann M, Armstrong SA, Mandinova A, Heidel FH.  
YBX1 mediates translation of oncogenic transcripts to control cell competition in AML.  
*Leukemia* 2022, 36(2), 426-37.

Schnoeder TM, Schwarzer A, Jayavelu AK, Hsu CJ, Kirkpatrick J, Döhner K, Perner F, Eifert T, Huber N, Arreba-Tutusa P, Dolnik A, Assi SA, Nafria M, Jiang L, Dai YT, Chen Z, Chen SJ, Kellaway SG, Ptasinska A, Ng ES, Stanley EG, Elefanty AG, Buschbeck M, Bierhoff H, Brodt S, Matziolis G, Fischer KD, Hochhaus A, Chen CW, Heidenreich O, Mann M, Lane SW, Bullinger L, Ori A, von Eyss B, Bonifer C, Heidel F.  
PLCG1 is required for AML1-ETO leukemia stem cell self-renewal.  
*Blood* 2022, 139(7), 1080-97.

## Third-party Funding (selection)





Prof. Dr. Helen Morrison  
Group Leader

## Morrison Senior Research Group: Nerve Regeneration

2

CENTRAL RESEARCH QUESTION:

**How do the signaling pathways that regulate the maintenance and regeneration of the nervous system become impaired during aging?**

### Focus of Research

The core interest of the “Nerve Regeneration” group lies in the age-related changes that cause functional impairments in the human nervous system. The nervous system is a complex organ system consisting of several different cell types that collectively make up sophisticated central and peripheral neural networks. These networks, which require careful life-long maintenance to ensure proper function, are progressively compromised by age-associated nerve pathologies. Such pathologies represent a great medical need, which calls for translational research to improve healthy human aging.

The research group addresses this need by exploring the regenerative potential of nerves and detailing the cellular and molecular strategies that safeguard nerve integrity, with a focus on whether and how different neuron-associated supporting glial cells contribute to aging and disease processes. In a holistic approach, the group also explores the interactions between different cell types and the surrounding nerve microenvironment. The group’s multidisciplinary approach combines *in vitro* model systems, cellular and mouse models and human tissue samples.

### Key Findings

Thus far, the work of the Morrison group has yielded insight into nerve regeneration, carcinogenesis, neuropathies and pain sensation, while also bridging the gap between basic research and clinical application.

The most important scientific achievements are: (1) the establishment of a multi-factorial model of tumor induction, including axonal factors, mechanical nerve irritation and chronic inflammation; (2) development of a protein replacement therapy for the treatment of nerve sheath tumors; (3) identification of impaired lipid metabolism as a disease mechanism in demyelinating neuropathies, highlighting the therapeutic potential of targeting myelin lipid metabolism; (4) identification of an age-dependent, chronically altered and overshooting immune response that affects peripheral nerve maintenance and regeneration, thus paving the way for the development of effective anti-inflammatory therapies to improve nerve maintenance and regeneration in the elderly; and (5) dissection of the cellular and molecular pathways of the central nerve involved in neuroprotection and repair processes, healthy brain aging and brain repair after injury.

### Current Projects

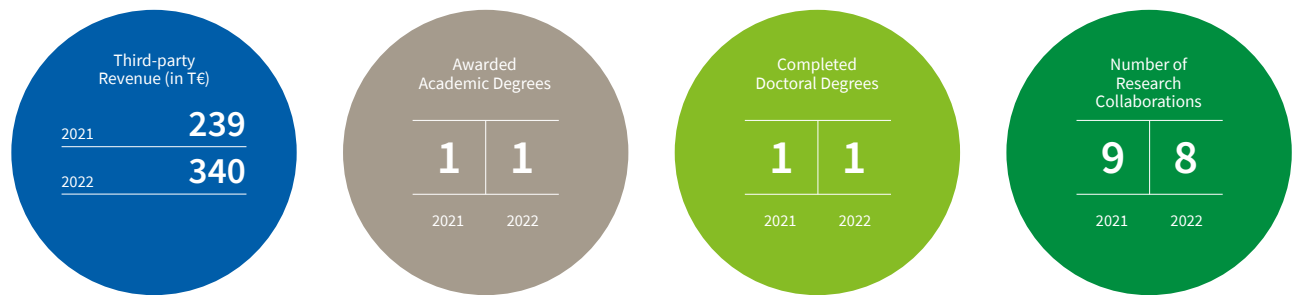
It is widely known and accepted that the aging process significantly impairs the ability of peripheral nerves to regenerate after injury – but the cellular and molecular pathways that impact long-term nerve maintenance and prevent efficient repair remain unknown.

In the laboratory, the research group is engaged in a number of projects related to the peripheral nervous system (PNS). These include:



- investigating the plasticity of the Schwann cell differentiation state
- researching Schwann cell and axonal interactions
- investigating macrophage-mediated nerve dysfunction in aging
- elucidating the role of the microenvironment, in both cell repair and cancer development
- exploring the interplay between lipid metabolism and peripheral nerve pathologies
- utilizing novel mouse models for the study of tumor development in neurofibromatosis type 2 disease (NF2)
- utilizing novel mouse models for the study of impaired energy homeostasis and pain development in schwannomatosis.

## Key Figures



## Selected Publications

Bischoff JP, Schulz A, Morrison H.  
The role of exosomes in inter-cellular and inter-organ communication of the peripheral nervous system.  
*FEBS Lett* 2022, 596(5), 655-64.

Cai WT, Kim WY, Kwak MJ, Rim H, Lee SE, Riecken LB, Morrison H, Kim JH.  
Disruption of amphetamine sensitization by alteration of dendritic thin spines in the nucleus accumbens core.  
*J Neurochem* 2022, 161(3), 266-80.

Drude NI (...) Jung MJ, Riecken LB (...) Toelch U.  
Planning preclinical confirmatory multicenter trials to strengthen translation from basic to clinical research – a multi-stakeholder workshop report.  
*Transl Med Commun* 2022, 7(24), <https://doi.org/10.1186/s41231-022-00130-8>.

Schacke S, Kirkpatrick J, Stocksdale A, Bauer R, Hagel C, Riecken LB, Morrison H.  
Ezrin deficiency triggers glial fibrillary acidic protein upregulation and a distinct reactive astrocyte phenotype.  
*Glia* 2022, 70(12), 2309-29.

Chang LS (...) Riecken LB (...) Morrison H (...) Synodos for NF2 Consortium.  
Brigatinib causes tumor shrinkage in both NF2-deficient meningioma and schwannoma through inhibition of multiple tyrosine kinases but not ALK.  
*PLoS One* 2021, 16(7), e0252048.

Cui\*\* Y, Ma L, Schacke S, Yin JC, Hsueh YP, Jin H, Morrison\*\* H.  
Merlin cooperates with neurofibromin and Spred1 to suppress the Ras-Erk pathway.  
*Hum Mol Genet* 2021, 29(23), 3793-806 (\*\* co-corresponding authors).

Third-party  
Funding (selection)



DFG Deutsche  
Forschungsgemeinschaft





Prof. Dr. Dario R. Valenzano  
Group Leader

## Valenzano Senior Research Group: Evolutionary Biology / Microbiome- Host Interactions in Aging

(since 07/2022)

2

CENTRAL RESEARCH QUESTION:

**What is the impact of evolution and ecology on species-specific aging phenotypes in nature?**

### Focus of Research

We study how aging is affected by evolution and ecology, with a focus on the turquoise killifish (*Nothobranchius furzeri*). We investigate the impact of population size on species evolution, aging-related phenotypes and crosstalk between host aging and commensal microbes. Our research combines evolutionary theory, molecular genetics and microbiome studies.

### Current Projects

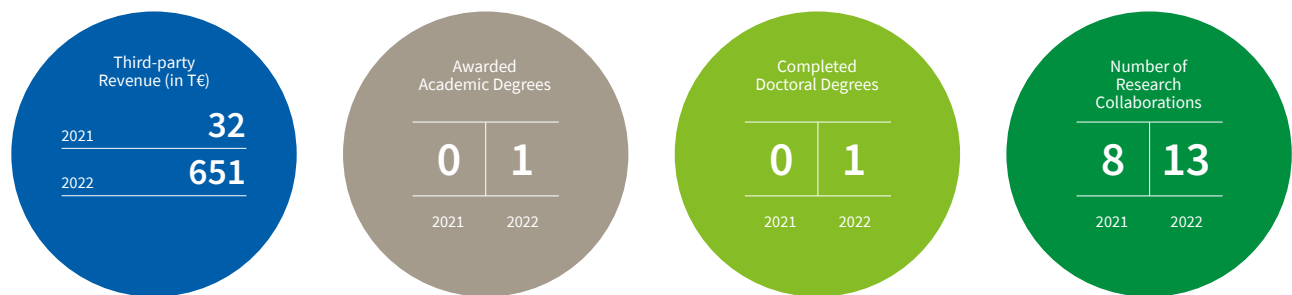
- **Evolution of life history traits under finite population size:** we have developed AEGIS, an in silico tool to test the impact of different ecological and demographic scenarios on the evolution of lifespan.
- **Population genetics in wild killifish:** we are studying genetics in natural habitats in Zimbabwe and have set up a formal collaboration with the Gonarezhou National Park, which contains the natural habitat of the turquoise and spotted killifish.
- **Aging of the immune system in turquoise killifish:** we are investigating the molecular and cellular basis of immune system aging.
- **Immune-microbiome crosstalk during host aging:** we are investigating perturbation of commensal microbes due to immune system aging.

- **Brain-gut axis in aging:** we are studying the crosstalk between brain aging and the gut microbiome by manipulating the gut microbiome and studying the impact on brain aging.
- **Comparative brain degeneration across killifish species:** we are examining the genetic and molecular basis of varying brain aging rates across killifish species.
- **Impact of parental age on offspring fitness (Lansing effect):** we are studying the effect of parental age on offspring fitness using simulations and laboratory experiments in killifish and budding yeast.
- **Bayesian causal inference in aging research:** we are developing a statistical framework to distinguish correlation from causation in quantitative aging studies.

### Methods

We use various methods, including simulations, analytical models, genetics, genomics and genome editing, with a focus on host-microbiome manipulations.

## Key Figures



## Selected Publications

Izgi H, Han D, Isildak U, Huang S, Kocabiyik E, Khaitovich\*\* P, Somel\*\* M, Dönertaş\*\* HM.  
Inter-tissue convergence of gene expression during ageing suggests age-related loss of tissue and cellular identity.  
*eLife* 2022, 11, e68048 (\*\* co-corresponding authors).

Promislow D, Anderson RM, Scheffer M, Crespi B, DeGregori J, Harris K, Natterson Horowitz B, Levine ME, Riolo MA, Schneider DS, Spencer SL, Valenzano DR, Hochberg ME.  
Resilience integrates concepts in aging research.  
*iScience* 2022, 25(5), 104199.

Bradshaw WJ, Poeschla M, Placzek A, Kean S, Valenzano DR.  
Extensive age-dependent loss of antibody diversity in naturally short-lived turquoise killifish.  
*eLife* 2022, 11, e65117 (published during change of institution).

Khallaf MA, Cui R, Weissflog J, Svatoš A, Dweck HKM, Valenzano DR, Hansson BS, Knaden M.  
Large-scale characterization of sex pheromone communication systems in *Drosophila*.  
*Nat Commun* 2021, 12(1), 4165.

Cui R, Tyers AM, Malubhoy ZJ, Wisotsky S, Valdesalici S, Henriette E, Kosakovsky Pond SL, Valenzano DR.  
Ancestral transoceanic colonization and recent population reduction in a non-annual killifish from the Seychelles archipelago.  
*Mol Ecol* 2021, 30(14), 3610-23.

## Third-party Funding (selection)

**DFG** Deutsche Forschungsgemeinschaft

**c3s** Carl Zeiss Stiftung

**EMBO**

**NWO**



Dr. Björn von Eyss  
Group Leader

## von Eyss Junior Research Group: Transcriptional Control of Tissue Homeostasis

2

CENTRAL RESEARCH QUESTION:

**What is the role of the transcriptional regulators YAP and TAZ in tissue maintenance, regeneration and carcinogenesis?**

### Focus of Research

The human body is composed of approximately 30 trillion cells and renews about four million cells per second. It is thus clear that in long-lived organisms, even the smallest imbalance in tissue homeostasis can sooner or later lead to serious consequences – such as premature aging or cancer. A key regulator of tissue regeneration is the so-called Hippo signaling pathway. This signaling pathway has two effector proteins: the transcriptional coactivators YAP and TAZ.

Because a deep understanding of the regulation of the Hippo signaling pathway will lead to new insights into aging, stem cell biology and tissue homeostasis, the research group focuses on different aspects of the biology of YAP/TAZ. The goal is to identify novel signaling pathways and thus target sites that control YAP/TAZ activity. In addition, the research aims to identify the YAP/TAZ target genes that are essential for the biological function of YAP/TAZ. Such target genes and the signaling pathways associated with them could be of great medical use, for example, because they could improve regeneration in old age.

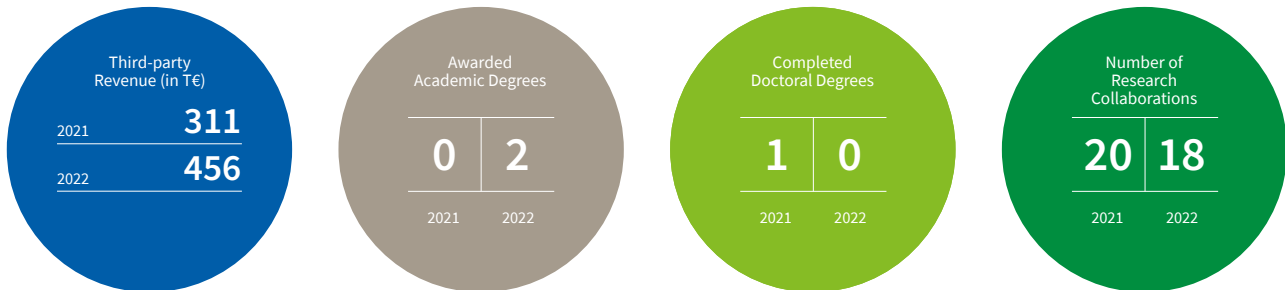
Furthermore, the researchers are investigating the exact role of the two transcriptional regulators in tissue homeostasis, regeneration, stem cell biology and carcinogenesis. These questions will be elucidated *in vivo* using novel mouse models.

### Methodology

To study YAP/TAZ-mediated transcription and its phenotypes *in vivo*, state-of-the-art methods are used:

- Single cell technologies: scRNA-Seq, CITE-Seq, scATAC-Seq
- Pooled *in vivo* CRISPR screens in combination with single cell transcriptomics: CROP-Seq, Perturb-Seq
- Genome-wide transcriptomics: CUT & RUN, CUT & TAG, ATAC-Seq, RNA-Seq, 4SU-Seq, SLAM-Seq
- Pooled genome-wide CRISPR screens and focused screens: CRISPR, shRNA, SAM and siRNA
- Inducible mouse models

## Key Figures



## Selected Publications

Kim\* KM, Mura-Meszaros\* A, Tollot\* M, Krishnan MS, Gründl M, Neubert L, Groth M, Rodriguez-Fraticelli A, Svendsen AF, Campaner S, Andreas N, Kamradt T, Hoffmann S, Camargo FD, Heidel FH, Bystrykh LV, de Haan G, von Eyss B.  
Taz protects hematopoietic stem cells from an aging-dependent decrease in PU.1 activity.  
*Nat Commun* 2022, 13(1), 5187 (\* equal contribution).

Heuberger J, Grinat J, Kosel F, Liu L, Kunz S, Vidal RO, Keil M, Haybaeck J, Robine S, Louvard D, Regenbrecht C, Sporbert A, Sauer S, von Eyss B, Sigal M, Birchmeier W.  
High Yap and Mll1 promote a persistent regenerative cell state induced by Notch signaling and loss of p53.  
*Proc Natl Acad Sci U S A* 2021, 118(22), e2019699118.

Schnoeder TM, Schwarzer A, Jayavelu AK, Hsu CJ, Kirkpatrick J, Döhner K, Perner F, Eifert T, Huber N, Arriba-Tutusaus P, Dolnik A, Assi SA, Nafria M, Jiang L, Dai YT, Chen Z, Chen SJ, Kellaway SG, Ptasinska A, Ng ES, Stanley EG, Elefanty AG, Buschbeck M, Bierhoff H, Brodt S, Matziolis G, Fischer KD, Hochhaus A, Chen CW, Heidenreich O, Mann M, Lane SW, Bullinger L, Ori A, von Eyss B, Bonifer C, Heidel F.  
PLCG1 is required for AML1-ETO leukemia stem cell self-renewal.  
*Blood* 2022, 139(7), 1080-97.

Svendsen AF, Yang D, Kim KM, Lazare SS, Skinder N, Zwart E, Mura-Meszaros A, Ausema A, von Eyss B, de Haan G, Bystrykh LV.  
A comprehensive transcriptome signature of murine hematopoietic stem cell aging.  
*Blood* 2021, 138(6), 439-51.

## Third-party Funding (selection)





Dr. Katarzyna Winek  
Group Leader

## Winek Junior Research Group: Microbiome in Stroke and Aging

(since 07/2022)

2

CENTRAL RESEARCH QUESTIONS:

**What is the impact of the gut microbiome on the outcome of an ischemic stroke?**

**What are the regulators of the immune response after a stroke?**

### Focus of Research

Ischemic stroke is one of the leading causes of death and disability worldwide and poses a significant clinical challenge. Although the impact of the immune system on stroke outcome has already been established, the underlying mechanisms regulating specific cell populations remain incompletely understood. A stroke induces an orchestrated immune response, including 1) infiltration of immune cells into the brain and 2) suppression of the immune response in the rest of the body. Peripheral (and local) immune cells in the central nervous system contribute to tissue damage but also aid in repair processes, depending on the cell type and time point after the stroke. Simultaneously, systemic immunosuppression leads to infectious complications. A detailed investigation of the fine-tuners of immune responses in both the brain and the periphery, as well as an integrative view of processes at both sites, is therefore of great importance for the identification of new therapeutic targets.

The research group specifically focuses on the gut microbiome but also on small noncoding RNAs as regulators of the immune system in ischemic stroke. The gut microbiome, the collective community of commensal microorganisms, plays a critical role in maintaining health and preventing disease and has been shown to be a regulator of immune responses. Small

noncoding RNAs, including microRNAs (miRNAs), are the perfect medium for rapid and effective communication between brain and body.

### Current Projects

Key questions addressed include:

- How exactly does the gut microbiome contribute to the regulation of immune responses after ischemic stroke?
- What are the most important communication pathways between the gut microbiome and brain after a stroke?
- Which small RNA molecules regulate specific immune cell populations that are important for stroke outcome?

### Methods

*In vitro* cell culture models, *in vivo* mouse models, RNA sequencing, FACS (fluorescence-activated cell sorting), MACS (magnetic-activated cell sorting), standard molecular biology techniques and bioinformatic approaches.

## Key Figures



## Selected Publications<sup>†</sup>

Winek K, Tzur Y, Soreq H.  
Biological underpinnings of sex differences in neurological disorders.  
*Int Rev Neurobiol* 2022, 164, 27-67.

Chovsepian A, Berchtold D, Winek K, Mamrak U, Ramírez Álvarez I, Dening Y, Golubczyk D, Weitbrecht L, Dames C, Aillery M, Fernandez-Sanz C, Gajewski Z, Dieterich M, Janowski M, Falkai P, Walczak P, Plesnila N, Meisel A, Pan-Montojo F.  
A primeval mechanism of tolerance to desiccation based on glycolic acid saves neurons in mammals from ischemia by reducing intracellular calcium-mediated excitotoxicity.  
*Adv Sci (Weinh)* 2022, 9(4), e2103265.

Winek K, Soreq H, Meisel A.  
Regulators of cholinergic signaling in disorders of the central nervous system.  
*J Neurochem* 2021, 158(6), 1425-38.

Messerschmidt C, Foddiss M, Blumenau S, Müller S, Bentele K, Holtgrewe M, Kun-Rodrigues C, Alonso I, do Carmo Macario M, Morgadinho AS, Velon AG, Santo G, Santana I, Mönkäre S, Kuuluvainen L, Schleutker J, Pöyhönen M, Myllykangas L, Senatore A, Berchtold D, Winek K, Meisel A, Pavlovic A, Kostic V, Dobricic V, Lohmann E, Hanagasi H, Guven G, Bilgic B, Bras J, Guerreiro R, Beule D, Dirnagl U, Sassi C.  
PHACTR1 genetic variability is not critical in small vessel ischemic disease patients and PcomA recruitment in C57BL/6J mice.  
*Sci Rep* 2021, 11(1), 6072.

Weitbrecht L, Berchtold D, Zhang T, Jagdmann S, Dames C, Winek K, Meisel C, Meisel A.  
CD4+ T cells promote delayed B cell responses in the ischemic brain after experimental stroke.  
*Brain Behav Immun* 2021, 91, 601-14.

Winek K, Cuervo Zanatta D, Zille M.  
Brain-body communication in stroke: Mens sana in corpore sano.  
*Neuroforum* 2021, 28(1), 31-9.

<sup>†</sup> Originated before the move to the FLI.



Prof. Dr. Peter Herrlich  
Scientific Director Emeritus  
Group Leader Emeritus

## Herrlich Associated Research Group: Cancer Cell Biology

2

### CENTRAL RESEARCH QUESTIONS:

**What is the molecular basis for the development of hydrocephalus resulting from the absence of the gene for TRIP6?**

**How does the multifunctional protein CD44 promote the metastasis of osteosarcoma?**

### Focus of Research

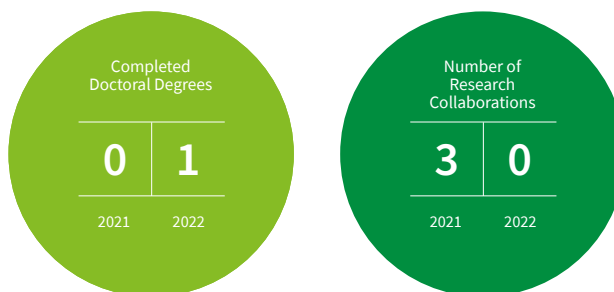
TRIP6 (thyroid hormone receptor interaction protein 6) is a protein that, unlike enzymes, has no catalytic function. However, it has multiple protein interaction sites and can therefore act as an assembly factor. For example, it can assemble activating components of the transcription-initiation complex – a function that led to the original discovery of TRIP6. In another context, it can attach transcription-inhibiting components to the complex.

Mice, in which the TRIP6 gene has been knocked out, develop hydrocephalus. In their search for the mechanism that leads to hydrocephalus, the researchers discovered a new assembly function: TRIP6 promotes the formation of cilia, which are responsible for the circulation of cerebrospinal fluid. If circulation is impeded by non-fully functional or absent cilia, the outflow stops even while new fluid formation remains constant.

Mice with a mutation in the tumor suppressor gene Nf2 develop more osteosarcomas, which metastasize. If these mice simultaneously lack the gene for CD44, metastasis is greatly reduced. This leads to the question of which step the CD44 gene catalyzes in the establishment of cancer cells in other tissues. The systematic search revealed that CD44 mediates the binding of cancer cells to endothelial cells and their migration through capillary walls.



## Key Figures



## Selected Publications

Gerardo-Ramírez M, Keggenhoff FL, Giam V, Becker D, Groth M, Hartmann N, Straub BK, Morrison H, Galle PR, Marquardt JU, Herrlich P, Hartmann M.  
CD44 contributes to the regulation of MDR1 protein and doxorubicin chemoresistance in osteosarcoma.  
*Int J Mol Sci* 2022, 23(15), 8616.

Norizadeh Abbariki T, Gonda Z, Kemler D, Urbaneck P, Wagner T, Litfin M, Wang ZQ, Herrlich P, Kassel O.  
The LIM domain protein nTRIP6 modulates the dynamics of myogenic differentiation.  
*Sci Rep* 2021, 11(1), 12904.

Shukla S, Haenold\* R, Urbánek\* P, Frappart L, Monajembashi S, Grigaravicius P, Nagel S, Min WK, Tapias A, Kassel O, Heuer H, Wang ZQ, Ploubidou\*\* A, Herrlich\*\* P.  
TRIP6 functions in brain ciliogenesis.  
*Nat Commun* 2021, 12(1), 5887 (\* equal contribution, \*\* co-senior authors).

Tuckermann J, Herrlich P, Caratti G.  
Transcriptional Regulation.  
In: Offermanns S, Rosenthal W (eds) *Encyclopedia of Molecular Pharmacology*. Springer, Cham. 2021, 1504-12.



Aspasia Ploubidou, PhD  
Associated Group Leader

## Ploubidou Associated Research Group: Virus-induced Oncogenesis

(until 02/2022)

2

CENTRAL RESEARCH QUESTION:

**Can mathematical modeling, applied to biological models of cancer, generate interpretable new hypotheses and accurate predictions on oncogenesis?**

### Focus of Research

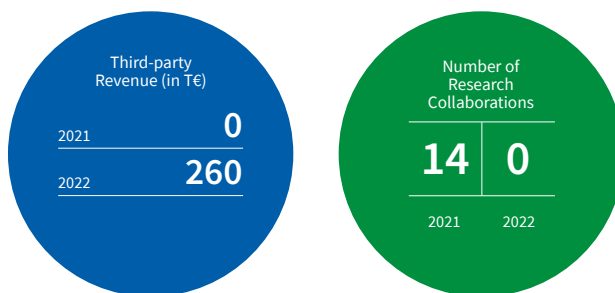
Our research topic is cancer, a major age-related pathology with two prominent features: altered molecular signaling circuits and disruption of tissue microarchitecture.

Cancer cells subvert the microarchitecture of the tissue in which they proliferate, creating the tumor. A major regulator of cellular and tissue architecture is the cytoskeleton, which fulfills its diverse functions by converting intra- and extra-cellular signals into processes of structure formation and remodeling. The aim is to understand how these signal pathways – in particular centrosome activity – contribute to cell renewal and cell differentiation and how this signaling is subverted in cancer. We have identified molecular mechanisms that induce misplacement of cells from stem cell compartments, with oncogenic consequences, suggesting that premature exit of progenitors from their niche can be oncogenic per se.

The numerous and highly complex genetic defects present in cancer cells can now be identified by extremely precise measurements (genomics, transcriptomics, proteomics, etc.). Nonetheless, understanding the underlying disease process

requires a shift from the focus on single molecular defects (previously deemed “necessary and sufficient”) to methodologies that compute the interdependencies of thousands of components. To this end, the group initiated an interdisciplinary approach to build and validate a computer-aided mechanistic model of cancer signaling, with a consortium of mathematicians, physicists and cancer researchers, funded by the European Union (CanPathPro.eu). The input for the mechanistic model is “omics” data on protein composition derived from preclinical models of virus-induced cancer, as well as breast and lung cancers. In an iterative process of in silico modeling and experimental validation, the consortium identified and verified (>80%) both expected but also unexpected signaling hypotheses for the individual components and signal pathways promoting these cancers.

## Key Figures



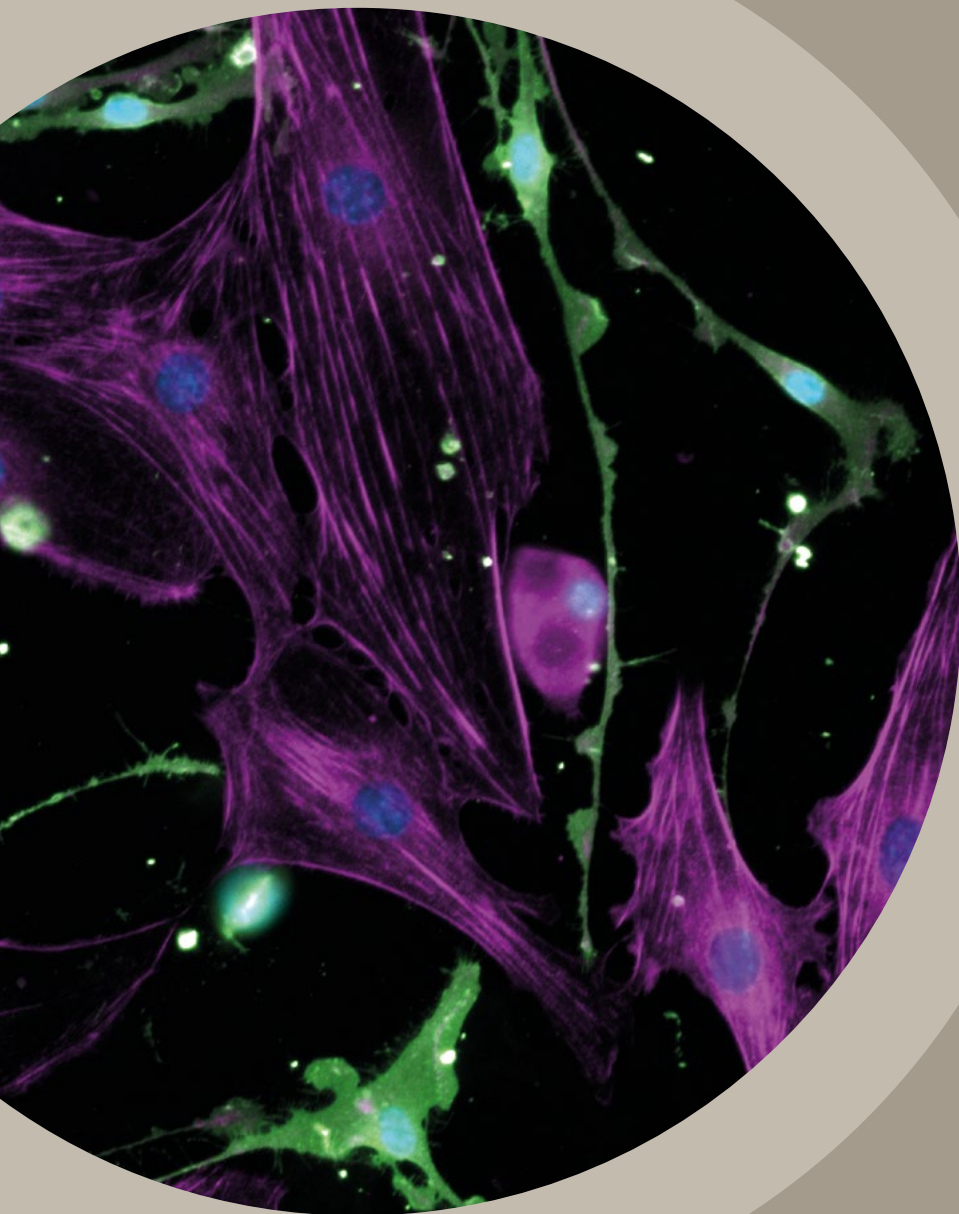
## Selected Publications

Ahmad M, Krüger BT, Kroll T, Vettorazzi S, Dorn AK, Mengele F, Lee S, Nandi S, Yilmaz D, Stolz M, Tangudu NK, Vázquez DC, Pachmayr J, Cirstea IC, Spasic MV, Ploubidou A, Ignatius A, Tuckermann J. Inhibition of Cdk5 increases osteoblast differentiation and bone mass and improves fracture healing. *Bone Res* 2022, 10(1), 33.

Shukla S, Haenold\* R, Urbánek\* P, Frappart L, Monajembashi S, Grigaravicius P, Nagel S, Min WK, Tapias A, Kassel O, Heuer H, Wang ZQ, Ploubidou\*\* A, Herrlich\*\* P. TRIP6 functions in brain ciliogenesis. *Nat Commun* 2021, 12(1), 5887 (\* equal contribution, \*\* co-senior authors).

## Third-party Funding (selection)





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# Program Area II

## Genetics, Epigenetics and Molecular Cell Dynamics of Aging

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### **Subarea 3: Genetics and Epigenetics of Aging .....**

3

- 52 *Englert Senior Research Group*
- 54 *Neri Junior Research Group*
- 56 *Bierhoff Associated Research Group*
- 58 *Cellerino Associated Research Group*
- 60 *Marz Associated Research Group*

### **Subarea 4: Cell Dynamics and Molecular Damages in Aging .....**

4

- 62 *Wang Senior Research Group*
- 64 *Kaether Senior Research Group*
- 66 *Ermolaeva Junior Research Group*



Prof. Dr. Christoph Englert  
Group Leader

## Englert Senior Research Group: Molecular Genetics

3



CENTRAL RESEARCH QUESTION:

**How do genes control aging, as well as the development and regeneration of organs?**

### Focus of Research

**Molecular basis of urogenital development** | Many human “disease genes” also play a crucial role in the development of specific organs. One example is the Wilms tumor suppressor gene *Wt1*. It is indispensable for the development of the gonads and kidneys in both humans and mice, but in its mutated form causes kidney cancer in childhood. The goal of the research group is to understand how mutations of the gene cause these abnormalities in humans. To this end, the researchers are studying the *Wt1* protein and the molecular mechanisms underlying its function with the help of biochemical and cell biological methods as well as using different animal models.

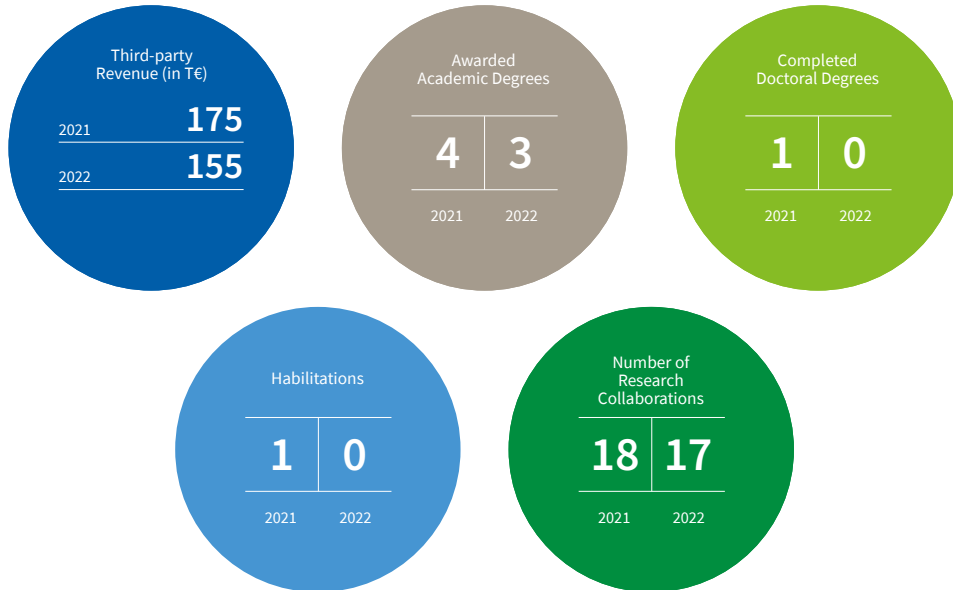
**Signaling pathways regulating aging and lifespan in short-lived vertebrates** | The identification of vertebrate genes that control the aging process is complicated by the relatively long lifespan of the animal models available until recently. In 2004, an annual fish species with an exceptionally short lifespan was described as an animal model for the first time: the turquoise killifish (*Nothobranchius furzeri*). In captivity, it has a maximum life expectancy of only a few months. Genes can be selectively switched off and on in *N. furzeri* using the CRISPR/Cas9 method. The group is using this technology to identify and characterize genetic programs and biochemical signaling pathways that regulate vertebrate aging.

**Organ regeneration** | The regenerative capacity of individual organs varies widely in humans. Blood and skin cells have a high regenerative potential, whereas brain or kidney cells, for example, can barely regenerate at all. In amphibians and fish, in contrast, almost all organs have a very high regenerative potential. For its animal models, the research group mainly uses the zebrafish as well as the turquoise killifish to analyze the regeneration of various organs such as the caudal fin, heart and kidney. The researchers are particularly interested in clarifying whether this regenerative capacity is age-dependent and why the regeneration potential differs so much between species. The ultimate goal of the research is to improve the regenerative capacity of organs in humans, such as the kidney.

### Current Projects

- Characterization of the role of the Wilms tumor protein *Wt1* in organ development and homeostasis
- Analysis of the age dependence of regeneration using the kidney and heart as examples
- Analysis of the biochemical signaling pathways that regulate the aging process in the short-lived vertebrate *N. furzeri*
- Generation of *N. furzeri* and zebrafish mutants with respect to aging-associated genes using CRISPR/Cas9
- Analysis of the importance of senescent cells for aging and regeneration

## Key Figures



## Selected Publications

Hopfenmüller\* VL, Perner\* B, Reuter H, Bates TJD, Große A, Englert C. The Wilms tumor gene *wt1a* contributes to blood-cerebrospinal fluid barrier function in zebrafish. *Front Cell Dev Biol* 2022, 9, 809962 (\* equal contribution).

Marques IJ, Ernst A, Arora P, Vianin A, Hetke T, Sanz-Morejón A, Naumann U, Odriozola A, Langa X, Andrés-Delgado L, Zuber B, Torroja C, Osterwalder M, Simões F, Englert C, Mercader N. WT1 transcription factor impairs cardiomyocyte specification and drives a phenotypic switch from myocardium to epicardium. *Development* 2022, 149(6), dev200375.

Reuter H, Perner B, Wahl F, Rohde L, Koch P, Groth M, Buder K, Englert C. Aging activates the immune system and alters the regenerative capacity in the zebrafish heart. *Cells* 2022, 11(3), 345.

Richter A, Krug J, Englert C. Molecular sexing of *Nothobranchius furzeri* embryos and larvae. *Cold Spring Harb Protoc* 2022, 2022(12), 630-40.

Štundlová J, Hospodářská M, Lukšíková K, Voleníková A, Pavlica T, Altmanová M, Richter A, Reichard M, Dalíková M, Pelikánová Š, Marta A, Simanovsky SA, Hříman M, Jankásek M, Dvořák T, Bohlen J, Ráb P, Englert C, Nguyen P, Sember A. Sex chromosome differentiation via changes in the Y chromosome repeat landscape in african annual killifishes *Nothobranchius furzeri* and *N. kadleci*. *Chromosome Res* 2022, 30(4), 309-33.

Lam S, Hartmann N, Benfeitas R, Zhang C, Arif M, Turkez H, Uhlén M, Englert C, Knight R, Mardinoglu A. Systems analysis reveals ageing-related perturbations in retinoids and sex hormones in Alzheimer's and Parkinson's diseases. *Biomedicines* 2021, 9(10), 1310.

## Third-party Funding (selection)





Francesco Neri, PhD  
Group Leader

## Neri Junior Research Group: Epigenetics of Aging – DNA Damage Accumulation

(until 02/2022)

3

CENTRAL RESEARCH QUESTION:

**How can epigenome alterations that occur during stem cell aging be functionally characterized?**

### Focus of Research

Aging is associated with defective organ maintenance and increased tissue dysfunction as well as with a higher risk for the development of pathological conditions, including cancer. Colorectal cancer is one of the most frequent and lethal neoplasms and its incidence exponentially increases with age. Numerous studies have demonstrated that intestinal stem cells represent the cells-of-origin of cancer and that clonal dominance of mutant stem cells becomes particularly pronounced in old age.

There is increasing evidence that genetic and epigenetic factors impact on the functionality and homeostasis of adult stem cells during aging, thereby favoring the selective advantage of dominant clones and the onset of cancer. One factor in particular, DNA methylation (a stable and heritable epigenetic modification) has been associated with aging-induced diseases and cancer development. Only recently has it been discovered that DNA methylation can be actively reversed by TET (ten-eleven-translocation) proteins. The decisive role of this epigenetic modification has been demonstrated in several biological models.

### Research Objectives

The focus of the research group “Epigenetics of Aging/ DNA Damage Accumulation” is the functional characterization of

transcriptome and epigenome alterations that occur during adult stem cell aging in the intestinal system. The main aims are:

1. to describe the transcriptional and epigenetic alterations of stem cells during aging (focusing on altered DNA methylation patterns together with histone modifications)
2. to characterize the mechanistic basis for the development of these changes
3. to understand the functional consequences of aging-induced epigenetic alterations on stem cell function in organ maintenance and delineate their role in the emergence of clonal dominance and neoplastic transformation.

### Methods

The group employs genome-wide and single-cell techniques to analyze alterations of the transcriptional and epigenetic landscape of the stem cells of the small intestine and colon in mice. Functional experiments are carried out by utilizing *in vitro* systems (intestinal organoids) and *in vivo* mouse models. In addition, the group has developed novel tools to identify dormant stem cells in the intestine *in vivo*, to characterize *in vitro* organoid systems and to analyze DNA methylation in rare cells.



## Key Figures



## Selected Publications

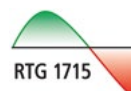
Lu J, Annunziata F, Sirvinskas D, Omrani O, Li H, Rasa SMM, Krepelova A, Adam L, Neri F.  
Establishment and evaluation of module-based immune-associated gene signature to predict overall survival in patients of colon adenocarcinoma.  
*J Biomed Sci* 2022, 29(1), 81.

Nunna S, Huang YP, Rasa M, Krepelova A, Annunziata F, Adam L, Käppel S, Hsu MH, Neri F.  
Characterization of novel  $\alpha$ -Mangostin and paeonol derivatives with cancer-selective cytotoxicity.  
*Mol Cancer Ther* 2022, 21(2), 257-70.

Rasa\* SMM, Annunziata\* F, Krepelova A, Nunna S, Omrani O, Gebert N, Adam L, Käppel S, Höhn S, Donati G, Jurkowski TP, Rudolph KL, Ori A, Neri F.  
Inflammaging is driven by upregulation of innate immune receptors and systemic interferon signaling and is ameliorated by dietary restriction.  
*Cell Rep* 2022, 39(13), 111017 (\* equal contribution).

Freter R, Falletta P, Omrani O, Rasa M, Herbert K, Annunziata F, Minetti A, Krepelova A, Adam L, Käppel S, Rüdiger T, Wang ZQ, Goding\*\* CR, Neri\*\* F.  
Establishment of a fluorescent reporter of RNA-polymerase II activity to identify dormant cells  
*Nat Commun* 2021, 12(1), 3318 (\*\* co-corresponding authors).

## Third-party Funding (selection)





Dr. Holger Bierhoff  
Collaboration with the  
Friedrich Schiller University Jena

## Bierhoff Associated Research Group: Epigenetics of Aging / Chromatin Landscape

3

CENTRAL RESEARCH QUESTION:

**How do aging-related epigenetic changes, mediated in particular by noncoding RNAs, contribute to genome misexpression and destabilization?**

### Focus of Research

Genetic material is present in the cell nucleus as chromatin, a macromolecular structure in which DNA is associated with proteins and regulatory non-coding RNAs (ncRNAs). The chromatin structure enables stable packaging of the genetic material as well as the regulation of gene expression.

The associated research group is investigating these epigenetic regulatory mechanisms in a class of genes (rRNA genes) that are characterized by a high copy number and by strong activity, and is also focusing on the functions of ncRNAs. In particular, the group will explore how certain ncRNAs can interact directly with the genome through the formation of RNA:DNA triple helices (triplexes).

The group hopes its work will contribute to a broader understanding of chromatin-related aging processes, as well as clarifying the mechanisms that lead to epigenetic deregulation of rRNA genes and to dysfunction of ncRNAs in old age.

### Current Projects

- Influence of rRNA synthesis on the lifespan and health span
- Correlation between the aging and stability of rRNA genes
- Regulation of rRNA genes by non-coding RNA PAPAS
- Control of the KRAS proto-oncogene through the interaction of G-quadruplex and RNA:DNA triplex structures
- Genome-wide identification of RNA:DNA triplexes

## Key Figures



## Selected Publications

Schnoeder TM, Schwarzer A, Jayavelu AK, Hsu CJ, Kirkpatrick J, Döhner K, Perner F, Eifert T, Huber N, Arreba-Tutusaus P, Dolnik A, Assi SA, Nafria M, Jiang L, Dai YT, Chen Z, Chen SJ, Kellaway SG, Ptasinska A, Ng ES, Stanley EG, Elefanty AG, Buschbeck M, Bierhoff H, Brodt S, Matziolis G, Fischer KD, Hochhaus A, Chen CW, Heidenreich O, Mann M, Lane SW, Bullinger L, Ori A, von Eyss B, Bonifer C, Heidel FH.  
 PLCG1 is required for AML1-ETO leukemia stem cell self-renewal.  
*Blood* 2022, 139(7), 1080-97.

Greifenstein\* AA, Jo\* S, Bierhoff H.  
 RNA:DNA triple helices: from peculiar structures to pervasive chromatin regulators.  
*Essays Biochem* 2021, 65(4), 731-40 (\* equal contribution).

## Third-party Funding (selection)





Prof. Alessandro Cellerino, PhD  
Leibniz-Chair, Collaboration with the  
Scuola Normale Superiore di Pisa, Italy

## Cellerino Associated Research Group: Biology of Aging

3



CENTRAL RESEARCH QUESTION:

**How do molecular mechanisms control  
lifespan and brain aging?**

### Focus of Research

The main interest of the associated research group “Biology of Aging” is to use the turquoise killifish (*Nothobranchius furzeri*), the vertebrate with the shortest lifespan, as a model organism to identify novel biological mechanisms of aging.

### Current Projects

#### **Proteome Regulation, Protein Aggregation and Neurodegeneration during Brain Aging**

Investigation of post-transcriptional and post-translational mechanisms that are responsible for proteome changes during aging, with particular emphasis on protein aggregation.

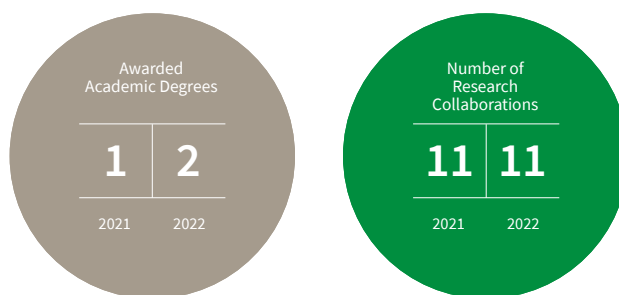
#### **Aging of Neuronal Stem Cells**

Functional investigation of newly identified conserved genes expressed in neuronal stem cells.

#### **Longitudinal Studies of Aging**

Identification and functional validation of early molecular markers that are predictors of longevity.

## Key Figures



## Selected Publications

Bagnoli S, Fronte B, Bibbiani C, Terzibasi Tozzini E, Cellerino A. Quantification of noradrenergic-, dopaminergic-, and tectal-neurons during aging in the short-lived killifish *Nothobranchius furzeri*. *Aging Cell* 2022, 21(9), e13689.

Mazzetto M, Caterino C, Groth M, Ferrari E, Reichard M, Baumgart M, Cellerino A. RNA-seq analysis of brain aging in wild specimens of short-lived turquoise killifish. Commonalities and differences with aging under laboratory conditions. *Mol Biol Evol* 2022, 39(11), msac219.

Holtze S, Gorshkova E, Braude S, Cellerino A, Dammann P, Hildebrandt TB, Hoeflich A, Hoffmann S, Koch P, Terzibasi Tozzini E, Skulachev M, Skulachev VP, Sahm A. Alternative animal models of aging research. *Front Mol Biosci* 2021, 8, 660959.

## Third-party Funding (selection)





Prof. Dr. Manja Marz  
Collaboration with the  
Friedrich Schiller University Jena

## Marz Associated Research Group: Non-coding RNAs in Aging

3

CENTRAL RESEARCH QUESTION:

**What is the impact of non-coding RNAs  
on the aging process?**

### Focus of Research

A large proportion of known vertebrate genes are transcribed as non-coding RNAs (ncRNAs): small molecules that play an important role in controlling biological signaling pathways. Micro-RNAs (miRNAs) are an example of these small genetic regulators. Currently, about 4,200 ncRNA families are known, but their function is poorly understood: Which ncRNAs play a role in the aging process? What are their functions, and how great is their influence at different stages of aging? How are ncRNAs related to aging-associated diseases such as neurodegeneration?

The associated research group “Non-coding RNAs in Aging” approaches these questions in an interdisciplinary manner by combining state-of-the-art high-throughput bioinformatics with laboratory approaches. It leverages its expertise in RNA sequencing data analysis, in silico identification and characterization of ncRNA, and virus bioinformatics. The group is also working on RNA:DNA triplex and G4 quadruplex structures, which represent a new level of genomic regulation through the control of chromatin organization.

### Current Projects

- Tissue-specific aging in mice
- Micro-RNA regulation of aging processes
- Aging-related RNA:DNA triplex structures
- Alteration of alternative splicing machinery in aging
- Changes in the expression of inflammatory and immune genes during aging
- Alteration of hematopoiesis in aging
- Genetic regulation of longevity

## Key Figures



## Selected Publications

Mock F, Kretschmer F, Kriese A, Böcker S, Marz M.  
Taxonomic classification of DNA sequences beyond sequence similarity using deep neural networks.  
*Proc Natl Acad Sci U S A* 2022, 119(35), e2122636119.

Morales-Prieto DM, Murrieta-Coxca JM, Stojiljkovic M, Diezel C, Streicher PE, Henao-Restrepo JA, Röstel F, Lindner J, Witte OW, Weis S, Schmeer C, Marz M.  
Small extracellular vesicles from peripheral blood of aged mice pass the blood-brain barrier and induce glial cell activation.  
*Cells* 2022, 11(4), 625.

Wolny D, Vernot B, Wang J, Hondele M, Safrastyan A, Aron F, Micheel J, He Z, Hyman A, Weis K, Camp JG, Tang TYD, Treutlein B.  
Characterization of RNA content in individual phase-separated coacervate microdroplets.  
*Nat Commun* 2022, 13(1), 2626.

Žarković\* M, Hufsky\* F, Markert\*\* UR, Marz\*\* M.  
The role of non-coding RNAs in the human placenta.  
*Cells* 2022, 11(9), 1588 (\* equal contribution, \*\* co-senior authors).

Barth E, Srivastava A, Wengerodt D, Stojiljkovic M, Axer H, Witte OW, Kretz\*\* A, Marz\*\* M.  
Age-dependent expression changes of circadian system-related genes reveal a potentially conserved link to aging.  
*Aging (Albany NY)* 2021, 13(24), 25694-716.

Collatz M, Mock F, Barth E, Hölzer M, Sachse K, Marz M.  
EpiDope: a deep neural network for linear B-cell epitope prediction.  
*Bioinformatics* 2021, 37(4), 448-55.

## Third-party Funding (selection)





Prof. Dr. Zhao-Qi Wang  
Group Leader

## Wang Senior Research Group: Genomic Stability

4

CENTRAL RESEARCH QUESTION:

**How does the malfunction of DNA damage response affect tissue impairment in humans?**

### Focus of Research

When DNA is damaged by intrinsic or extrinsic factors, there is a prompt cellular response. This DNA damage response (DDR) includes damage signaling, DNA repair, cell cycle control, apoptosis and transcription. Studying the mechanisms of DDR advances our understanding of the fundamental cellular processes that govern the maintenance of stem cell competence and ensure proper tissue homeostasis. The Research Group “Genomic Stability” uses cellular and molecular tools as well as animal models to decipher the DDR signaling pathways, providing insights into premature aging and age-related pathogenesis (such as neurodegenerative diseases) in humans.

### Current Projects

#### **The Cellular Response to DNA Damage**

Two protein kinases – ATM and ATR – are key regulators of the cellular response to DNA damage. ATM is primarily activated in the event of DNA double-strand breaks (DSBs), ATR in the event of DNA single-strand breaks (SSBs) or stalled replication forks. As a damage-sensor and modulator, the protein complex MRN (MRE11/RAD50/NBS1) activates ATM and also ATR to initiate DNA repair and, hence, to maintain genome stability. The research group aims at understanding the function of the molecules involved in DDR in pathological development and aging processes.

#### **The Function of Poly(ADP-ribosylation)**

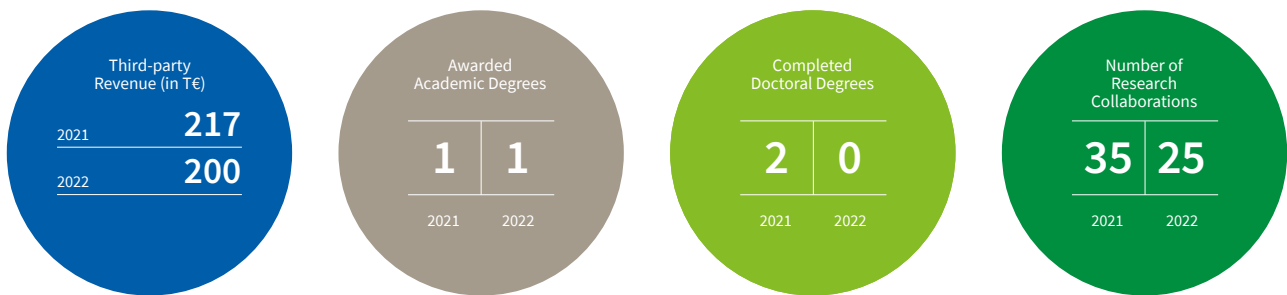
Poly(ADP-ribosylation) – also called PARylation – is the fastest response to DNA damage, especially in the case of SSBs and replication stress. Polymerase 1 (PARP1) detects the DNA damage, binds to the site, and induces the building of long polymer chains of ADP-ribose (PAR). PARylation and PARP1 activity play an important role in many cellular processes as well, e.g., in DNA repair, transcription, chromatin remodeling, proliferation, apoptosis, inflammatory response and aging processes. The group is interested in elucidating how PARP1 sends signals to other proteins and triggers a cellular response.

#### **Neurogenesis and neurodegeneration**

For brain development, neural stem cells have to be strictly controlled. The genetic and epigenetic mechanisms are crucial for neural stem cell proliferation and differentiation (neurogenesis) as well as for the maintenance of neurons (to prevent neurodegeneration). The research objective of the group is to understand the genetic and epigenetic modification of histones and the regulation of cell cycle progression in brain development and homeostasis during aging, thus laying the foundation for the development of novel therapeutic strategies to improve cognitive capabilities in the elderly.



## Key Figures



## Selected Publications

Wang Y, Zong W, Sun W, Chen C, Wang\*\* ZQ, Li\*\* T.  
The central domain of MCPH1 controls development of the cerebral cortex and gonads in mice.  
*Cells* 2022, 11(17), 2715 (\*\* co-corresponding authors).

Zong W, Gong Y, Sun W, Li T, Wang ZQ.  
PARP1: Liaison of chromatin remodeling and transcription.  
*Cancers (Basel)* 2022, 14(17), 4162.

Guerra GM, May D, Kroll T, Koch P, Groth M, Wang\*\* ZQ, Li TL, Grigaravicius\*\* P.  
Cell type-specific role of RNA nuclease SMG6 in neurogenesis.  
*Cells* 2021, 10(12), 3365 (\*\* co-corresponding authors).

Kirtay M, Sell J, Marx C, Haselmann H, Ceanga M, Zhou ZW, Rahmati V, Kirkpatrick J, Buder K, Grigaravicius P, Ori A, Geis\* C, Wang\*\* ZQ.  
ATR regulates neuronal activity by modulating presynaptic firing.  
*Nat Commun* 2021, 12(1), 4067 (\*\* co-corresponding authors).

Liu\* X, Schneble-Löhnert\* N, Kristofova M, Qing X, Labisch J, Hofmann S, Ehrenberg S, Sannai M, Jörß T, Ori A, Godmann M, Wang ZQ.  
The N-terminal BRCT domain determines MCPH1 function in brain development and fertility.  
*Cell Death Dis* 2021, 12(2), 143 (\* equal contribution).

Tapias\* A, Lázaro\* D, Yin\* BK, Rasa SMM, Krepelova A, Kelmer Sacramento E, Grigaravicius P, Koch P, Kirkpatrick J, Ori A, Neri F, Wang ZQ.  
HAT cofactor TRRAP modulates microtubule dynamics via SP1 signaling to prevent neurodegeneration.  
*eLife* 2021, 10, e61531 (\* equal contribution).

## Third-party Funding (selection)





Dr. Christoph Kaether  
Group Leader

## Kaether Senior Research Group: Membrane Trafficking in Aging

4



CENTRAL RESEARCH QUESTION:

**How are membrane proteins transported inside cells and delivered to their destinations?**

### Focus of Research

The research group focuses on the transport as well as the localization of membrane proteins inside cells. These membrane proteins include, on the one hand, receptors that are responsible for the correct transport of proteins and thus for the specific signal transduction into the interior of cells, but also proteins that are involved in aging processes. The aim is to elucidate fundamental cell biological processes and to derive approaches for the therapy of aging-associated diseases.

### Current projects

#### **“Anti-aging” hormone Klotho**

The membrane protein Klotho is located on the surface of cells and also circulates in the bloodstream as an “anti-aging hormone.” Mice, lacking this protein, age extremely quickly. They show symptoms and diseases similar to those of human aging after only a brief lifespan. Mice with an excess of Klotho, on the other hand, live longer than usual. In humans, too, certain variants of this protein have been linked to longer lifespan and better cognitive performance. Klotho is produced in the kidney and brain, where it is responsible for different hormonal regulatory processes. The research group is studying the role of Klotho in the brain.

#### **Rer1, a new type of retrieval receptor**

A very important function of the endoplasmic reticulum (ER) is to ensure the transport of correctly folded protein complexes. The research group is studying the retrieval receptor Rer1, which transports proteins from the cis-Golgi apparatus back to the ER. Rer1 is thus an important part of ER quality control. The aim of the research is to understand the function of this receptor and to investigate which proteins are transported by Rer1.

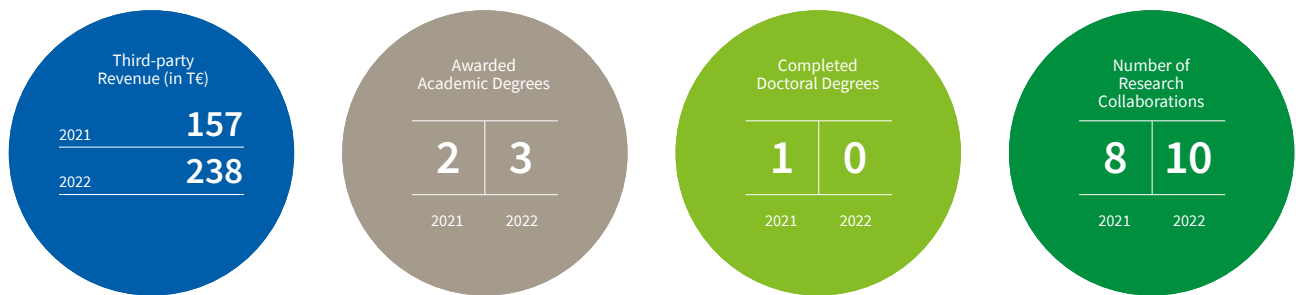
#### **Export from the endoplasmic reticulum**

The ER is the largest membrane organelle in the cell and is significantly involved in the production and sorting of one third of all proteins. How these proteins are sorted and exported from the ER as well as the quality control of these processes, is the subject of our research.

#### **Axonopathies and the endoplasmic reticulum**

There are a number of sensory and motor neuropathies in which the membrane proteins of the ER are mutated. These membrane proteins are responsible for the structure of the ER, but it is unclear why mutations in these proteins can lead to degeneration of the longest axons in our bodies. The research group aims to find out how these axonopathy-associated mutations function at the molecular level.

## Key Figures



## Selected Publications

Malis Y, Hirschberg K, Kaether C.  
Hanging the coat on a collar: same function but different localization and mechanism for COPII.  
*Bioessays* 2022, 44(10), e2200064.

Behrendt L, Hoischen C, Kaether C.  
Disease-causing mutated ATLASTIN 3 is excluded from distal axons and reduces axonal autophagy.  
*Neurobiol Dis* 2021, 155, 105400.

Shomron O, Nevo-Yassaf I, Aviad T, Yaffe Y, Erez Zahavi E, Dukhovny A, Perlson E, Brodsky I, Yeheskel A, Pasmanik-Chor M, Mironov A, Beznousenko GV, Mironov AA, Sklan EH, Patterson GH, Yonemura Y, Sannai M, Kaether\*\* C, Hirschberg\*\* K.  
COPII collar defines the boundary between ER and ER exit site and does not coat cargo containers  
*J Cell Biol* 2021, 220(6), e201907224 (\*\* co-corresponding authors).

## Third-party Funding (selection)



**DFG** Deutsche  
Forschungsgemeinschaft

**c3s**  
Carl Zeiss  
Stiftung

**ProMoAge**

**SAND**



Dr. Maria Ermolaeva  
Group Leader

## Ermolaeva Junior Research Group: Stress Tolerance and Homeostasis

4

### CENTRAL RESEARCH QUESTIONS:

**How do metabolic resilience and adaptive stress responses change with age and how can these changes be reversed to enable healthy longevity?**

### Focus of Research

The research group “Stress Tolerance and Homeostasis” uses the nematode *C. elegans*, mammalian cells, mice and short-lived killifish to identify changes in metabolism and stress responses that occur during aging, with an outlook toward restoring youthful stress responses in later life.

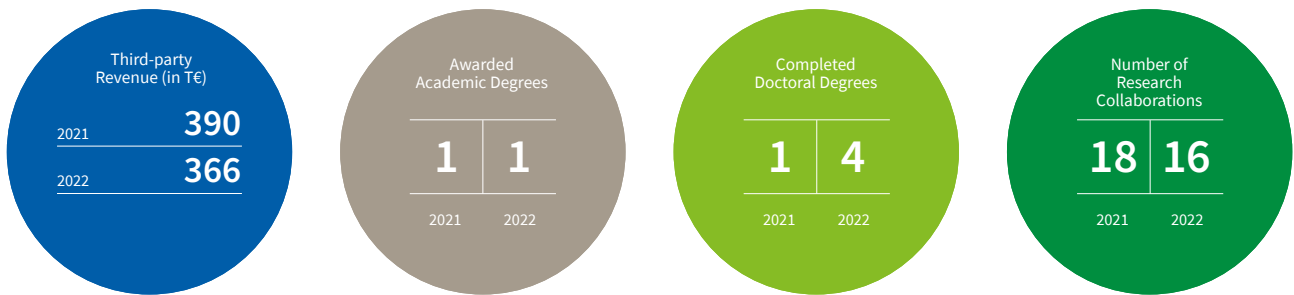
Our current focus is on the loss of mitochondrial homeostasis during aging, and we were able to prove in a recent study that aging-associated mitochondrial dysfunction abrogates the longevity benefits of the dietary restriction mimetic metformin. To follow up on this finding, we are using whole-animal single-cell sequencing in *C. elegans* and protein analyses (omics) in killifish to probe tissue-specific and sex-specific responses to dietary restriction mimetic compounds in young and old organisms. In addition, we are testing the effect of elevated or decreased energy expenditure on mitochondrial integrity and metabolic fitness during aging.

Our other key focus is the role of external stressors, such as environmental toxins (arsenic) and circadian clock disruption, in the development of systemic proteostasis failures, such as those triggered by the expression of aggregation-prone proteins. We are using the *C. elegans* models of Alzheimer’s disease and Huntington’s disease in order to investigate these important interactions.

Another important topic is the use of *C. elegans* as a non-vertebrate model for studying host–microbiome interactions in aging. In collaboration with colleagues at the Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute (HKI), we are performing screens for microbial isolates that extend host longevity. In addition, we have established a novel method of anaerobic microbial transfer into germ-free *C. elegans* hosts. This can be used to probe effects on the host of anaerobic microbial strains that are differentially enriched during human diseases such as sepsis.

Finally, we have used omics tests in long- and short-lived *C. elegans* strains to discover conserved biomarkers of metabolic health, which are detectable in human cells and blood samples with antibody- and qPCR-based methods. Currently, we are establishing cooperation with several clinics to test these biomarkers for their ability to predict human metabolic disorders at the single-cell level earlier than is possible using conventional diagnostics methods, such as BMI and blood serum markers (cholesterol, insulin, glucose).

## Key Figures



## Selected Publications

Ermolaeva M, Boyman L.  
Career pathways, part 8.  
*Nat Metab* 2022, 4(4), 407-9.

Meron E (...) Ermolaeva M (...) Rudolph KL (...) Valenzano DR (...) Scheibye-Knudsen M.  
Meeting Report: Aging research and drug discovery  
*Aging (Albany NY)* 2022, 14(2), 530-43.

Li H, Li Y, Zhang Y, Tan B, Huang T, Xiong J, Tan X, Ermolaeva\*\* MA, Fu\*\* L.  
MAPK10 expression as a prognostic marker of the immunosuppressive tumor microenvironment in human hepatocellular carcinoma.  
*Front Oncol* 2021, 11, 687371 (\*\* co-corresponding authors).

Marfil-Sánchez A, Zhang L, Alonso-Pernas P, Mirhakkak M, Mueller M, Seelbinder B, Ni Y, Santhanam R, Busch A, Beemelmans C, Ermolaeva\*\* M, Bauer\*\* M, Panagiotou\*\* G.  
An integrative understanding of the large metabolic shifts induced by antibiotics in critical illness.  
*Gut Microbes* 2021, 13(1), 1993598 (\*\* co-corresponding authors).

## Third-party Funding (selection)





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# Cross-sectional Subarea 5: Computational and Systems Biology of Aging

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	<b>Subarea 5: Computational and Systems Biology of Aging .....</b>	<b>5</b>
70	<i>Hoffmann Senior Research Group</i>	
72	<i>Ori Junior Research Group</i>	
74	<i>Kestler Associated Research Group</i>	





Prof. Dr. Dr. Steve Hoffmann  
Group Leader

## Hoffmann Senior Research Group: Computational Biology of Aging

5

CENTRAL RESEARCH QUESTION:

**How does the epigenome control processes of gene expression and maturation?**

### Focus of Research

Since late 2017, the group has focused on disentangling networks that control genome activity during aging and disease, investigating mechanisms relevant to epigenomic (dys)regulation. The group's expertise in developing computational methods for epigenomics and transcriptomics is complemented by wet-lab work to study genome regulation. One focus is on the role of epigenomic modifications such as cytosine methylation (5mC) and hydroxymethylation (5hmC). The group collaborates with numerous research groups worldwide and is involved in several high-profile international consortia.

#### **Methods for the Analysis of Differential Hydroxymethylation**

DNA hydroxymethylation, which is highly age-dependent, plays a critical role in embryonic development, cellular reprogramming and cancer. Despite this recognized role, there are no robust approaches for computational analysis of key measurement methods such as oxidative bisulfite sequencing. The research group is intensifying its efforts to develop such methods.

#### **Activation and Role of Jumping Genes**

The expression of transposable elements (TEs), so-called jumping genes, is associated with aging processes. The group is thus interested in the epigenomic mechanisms that lead to the activation of these elements. However, due to their repetitive DNA sequences, it is difficult to accurately measure the

expression of TEs and link these data to specific epigenomic mechanisms. The group is therefore dedicated to improving the quantification of TEs. This should lead to the identification of causative epigenomic perturbations and transcription factors that will provide new insights into the regulation of jumping genes.

#### **The Network of the Tumor Suppressor p53**

The tumor suppressor p53 plays a central role in research on both, aging and cancer. Despite decades of research, it is not clearly understood how p53 exerts its effects and which direct and indirect target genes it acts upon. To better understand these interactions and to identify novel target genes, networks and epigenomic consequences, researchers are combining computational methods with various wet-lab protocols.

#### **Evolution of the Epigenome**

The evolutionary conservation of a biological trait can be an indication of an important function. For this reason, the group is increasingly interested in the question of whether it is possible to find epigenomic traits that have been conserved across multiple species and thus over millions of years. As a first step toward developing a model of epigenomic evolution, the researchers have applied classical sequence-based phylogenetic methods to the level of the epigenome. This initial bioinformatics work is complemented by activities in the wet lab.



## Key Figures



## Selected Publications

Fischer M, Hoffmann S.  
Synthesizing genome regulation data with vote-counting.  
*Trends Genet* 2022, 38(12), 1208-16.

Fischer\* M, Schwarz R, Riege K, DeCaprio JA, Hoffmann S.  
TargetGeneReg 2.0: a comprehensive web-atlas for p53, p63, and cell cycle-dependent gene regulation.  
*NAR Cancer* 2022, 4(1), zcac009 (\* corresponding author).

Schwarz R, Koch P, Wilbrandt\* J, Hoffmann\* S.  
Locus-specific expression analysis of transposable elements.  
*Brief Bioinform* 2022, 23(1), bbab417 (\* equal contribution).

Coronel L, Riege K, Schwab K, Förste S, Häckes D, Semerau L, Bernhart SH, Siebert R, Hoffmann\*\* S, Fischer\*\* M.  
Transcription factor RFX7 governs a tumor suppressor network in response to p53 and stress.  
*Nucleic Acids Res* 2021, 49(13), 7437-56 (\*\* co-corresponding authors).

Sahm\*\* A, Koch P, Horvath S, Hoffmann\*\* S. (2021).  
An analysis of methylome evolution in primates.  
*Mol Biol Evol* 2021, 38(11), 4700-14 (\*\* co-corresponding authors).

Sahm\* A, Platzer M, Koch P, Henning Y, Bens M, Groth M, Burda H, Begall S, Ting S, Goetz M, Van Daele P, Staniszewska M, Klose J, Costa PF, Hoffmann\*\* S, Szafranski\*\* K, Dammann\*\* P.  
Increased longevity due to sexual activity in mole-rats is associated with transcriptional changes in HPA stress axis.  
*eLife* 2021, 10, e57843 (\* corresponding author, \*\* co-senior authors).

## Third-party Funding (selection)





Alessandro Ori, PhD  
Group Leader

## Ori Junior Research Group: Aging of Protein Complexes

5

CENTRAL RESEARCH QUESTION:

**What is the chain of molecular events that leads to the decline of organ function, impaired regenerative capacity and increased risk of disease in the elderly?**

### Focus of Research

The research group “Aging of Protein Complexes” examines how age, mutations and diet affect our organs at the molecular level. The goal is to identify functionally relevant changes in the proteome to reveal mechanisms of organ deterioration that impact on healthy lifespan and render the elderly more susceptible to disease.

### Current Projects

#### **Stem Cell Aging**

Adult (somatic) stem cells play a crucial role in organ maintenance and regeneration. However, their function and number decrease during aging. A particular focus of the group is to understand the molecular mechanisms that lead to the loss of these cells’ regenerative capacity. Focusing on the intestinal epithelium and skeletal muscle, the group examines proteome profiles of stem cells and surrounding tissue across age groups and following injury and evaluates the consequences of anti-aging interventions such as dietary restriction.

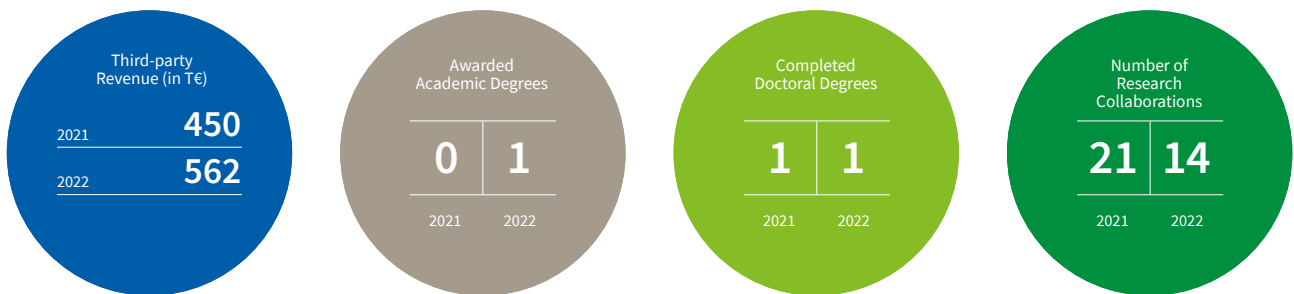
#### **Mechanisms of Convergence between Aging and Neurodegeneration**

The impairment of proteostasis and resulting aggregation of misfolded proteins are associated with age-related diseases such as neurodegenerative disorders. The group’s research focuses on (i) how aging perturbs major protein complexes involved in protein synthesis (ribosomes) and degradation (proteasomes), (ii) how protein localization and post-translational modifications influence protein function in aging and (iii) how mutations linked to increase risk of neurodegeneration interact with the aging process.

#### **Organelle Maintenance During Aging and Age-Related Diseases**

Lysosomes play a central role in autophagy and therefore in protein quality control and aggregate clearance. In addition, lysosomes are involved in intracellular signaling and in regulating cellular physiology in response to changes in nutrient availability, via the mTORC1 complex, a key modulator of aging. The research group, together with collaborators from Stanford University, is investigating the composition of lysosomes in different cell types of the brain and in a model of Batten disease.

## Key Figures



## Selected Publications

Di Fraia D, Anitei M, Mackmull MT, Parca L, Behrendt L, Andres-Pons A, Gilmour D, Helmer Citterich M, Kaether C, Beck M, Ori A. Conserved exchange of paralog proteins during neuronal differentiation. *Life Sci Alliance* 2022, 5(6), e202201397.

Döhla J, Kuuluvainen E, Gebert N, Amaral A, Englund JI, Gopalakrishnan S, Konovalova S, Nieminen AI, Salminen ES, Torregrosa Muñumer R, Ahlqvist K, Yang Y, Bui H, Otonkoski T, Käkälä R, Hietakangas V, Tyynismaa H, Ori A, Katajisto P. Metabolic determination of cell fate through selective inheritance of mitochondria. *Nat Cell Biol* 2022, 24(2), 148-54.

Laqtom NN, Dong W, Medoh UN, Cangelosi AL, Dharamdasani V, Chan SH, Kunchok T, Lewis CA, Heinze I, Tang R, Grimm C, Dang Do AN, Porter FD, Ori A, Sabatini DM, Abu-Remaileh M. CLN3 is required for the clearance of glycerophosphodiester from lysosomes. *Nature* 2022, 609(7929), 1005-11.

Di Sanzo\* S, Spengler\* K, Leheis A, Kirkpatrick JM, Rändler TL, Baldensperger T, Dau T, Henning C, Parca L, Marx C, Wang ZQ, Glomb MA, Ori\*\* A, Heller\*\* R. Mapping protein carboxymethylation sites provides insights into their role in proteostasis and cell proliferation. *Nat Commun* 2021, 12(1), 6743 (\* equal contribution, \*\* co-senior authors).

Schüler SC, Kirkpatrick\* JM, Schmidt\* M, Santinha D, Koch P, Di Sanzo S, Cirri E, Hemberg M, Ori\*\* A, von Maltzahn\*\* J. Extensive remodeling of the extracellular matrix during aging contributes to age-dependent impairments of muscle stem cell functionality. *Cell Rep* 2021, 35(10), 109223 (\* equal contribution, \*\* co-senior authors).

## Third-party Funding (selection)





Prof. Dr. Hans Kestler  
Collaboration with the University of Ulm

## Kestler Associated Research Group: Bioinformatics and Systems Biology of Aging

5

CENTRAL RESEARCH QUESTION:

**How can statistical and mathematical methods contribute to the analysis and understanding of molecular biology data?**

### Focus of Research

The increasing importance of molecular biology also requires the expansion of statistical and mathematical methods for analyzing research results. Bioinformatics in particular plays a major role in extracting and integrating the central findings of high-throughput experiments. Furthermore, systems biology provides approaches for modeling and simulating the processes in biological systems.

The research focus of the associated research group “Bioinformatics and Systems Biology of Aging” is located at the interface between computer science, statistics and life sciences and is focused on three areas:

- Statistical methods and database evaluations for data from high-throughput analyses, especially function selection, classification and cluster analysis
- Modeling, simulation and analysis of regulatory networks, especially differential equations, Boolean and rule-based approaches
- Visualization and functional annotation.

## Key Figures



## Selected Publications

Mayer\* G, Müller\* W, Schork K, Uszkoreit J, Weidemann A, Wittig U, Rey M, Quast C, Felden J, Glöckner FO, Lange M, Arend D, Beier S, Junker A, Scholz U, Schüler D, Kestler HA, Wibberg D, Pühler A, Twardziok S, Eils J, Eils R, Hoffmann S, Eisenacher M, Turewicz M.  
Implementing FAIR data management within the German Network for Bioinformatics Infrastructure (de.NBI) exemplified by selected use cases.  
*Brief Bioinform* 2021, 22(5), bbab010 (\* equal contribution).

Müller\* A, Lausser\* L, Wilhelm A, Ropinski T, Platzer M, Neumann\*\* H, Kestler\*\* HA.  
A perceptually optimised bivariate visualisation scheme for high-dimensional fold-change data.  
*Adv Data Anal Classif* 2021, 15, 463-80  
(\* equal contribution, \*\* co-corresponding authors).

Völkel\* G, Laban\* S, Fürstberger\* A, Kühlwein SD, Ikonomi N, Hoffman TK, Brunner C, Neuberg DS, Gaidzik V, Döhner H, Kraus\*\* JM, Kestler\*\* HA.  
Analysis, identification and visualization of subgroups in genomics.  
*Brief Bioinform* 2021, 22(3), bbaa217  
(\* equal contribution, \*\* co-senior authors).

## Third-party Funding (selection)







# Organization

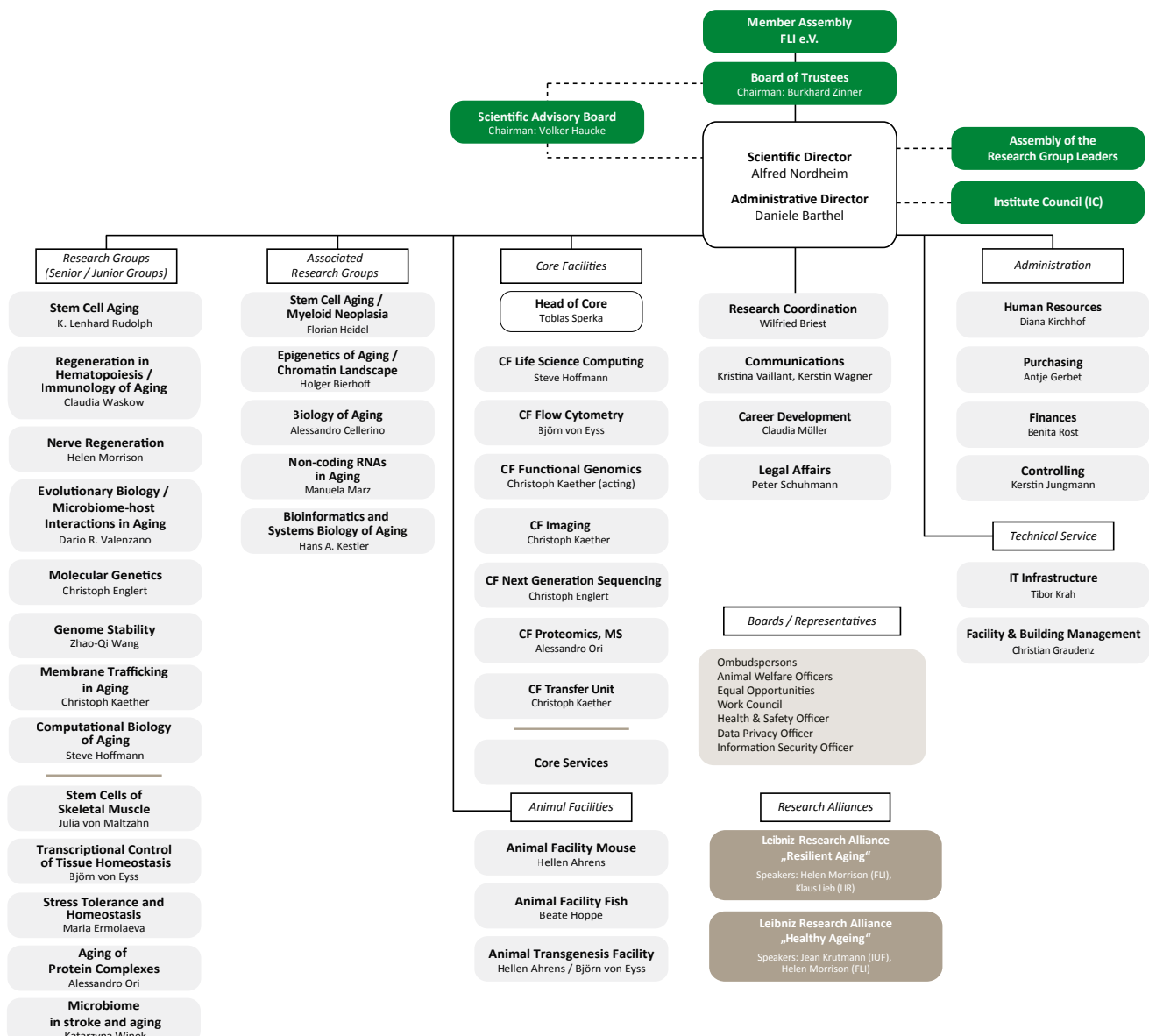
# Organization

The Leibniz Institute on Aging (FLI) is one of 97 research institutions of the Leibniz Association. These are funded by the Federal Ministry of Education and Research (BMBF) and the respective state governments. The FLI has been a registered association since 1992 and since 2004 has pursued the goal of promoting research, science, education and training in the academic field of research on aging.

The FLI is an institute with flat hierarchies. It is headed by the Scientific Director and the Administrative Director. The highest governing body is the Members Assembly of the organization. The basic organizational structure is comprised of the leaders

of the research groups; there are no subordinate departments below them. The organization also includes staff units, the administration, Core Facilities and Service and scientific coordinators.

The Institute Council (IC) advises the management on strategic decisions. The external supervisory body of the FLI is the Board of Trustees. It determines the general research objectives and decides on the medium-term financial and investment planning of the association. The Scientific Advisory Board (SAB) has an advisory function.



Organizational Chart of FLI. (As of July 2022)



## Executive Bodies

### Members Assembly

Members	represented by
Ernst-Abbe-Hochschule Jena, University of Applied Sciences, Jena, Germany	Prof. Dr. Steffen Teichert, Rector
Thuringian Ministry for Economic Affairs, Science and Digital Society (TMWWDG), Erfurt, Germany	Carolin Greiner Mai, Dep. 54 Institutional Research
Friedrich Schiller University Jena (FSU), Jena, Germany	Prof. Dr. Georg Pohnert, Vice President for Research
City of Jena, Germany	Dr. Thomas Nitzsche, Mayor

### Board of Trustees

Members	
Burkhard Zinner (Chair)	Thuringian Ministry for Economic Affairs, Science and Digital Society (TMWWDG), Dep. 51, Erfurt, Germany
Dr. Joachim Klein	Federal Ministry of Education and Research (BMBF), Dep. 615, Berlin, Germany
Prof. Dr. Georg Pohnert	Friedrich Schiller University Jena (FSU), Jena, Germany
Prof. Dr. med. Andreas Hochhaus	University Hospital Jena, Department of Hematology / Internal Oncology, Jena, Germany
Prof. Dr. med. Nisar P. Malek	University Hospital Tübingen, Department of Internal Medicine I, Tübingen, Germany
Prof. Dr. Dr. h.c. mult. Ernst Th. Rietschel	Hamburg, Germany
Prof. Dr. Volker Haucke (Head of Scientific Advisory Board)	Leibniz-Institut für Molekular Pharmakologie im Forschungsverbund Berlin e. V. (FMP), Berlin, Germany
Prof. Dr. Sara Wickström (Deputy Head of Scientific Advisory Board)	Max Planck Institute for Molecular Medicine, Münster, Germany

### Scientific Advisory Board, SAB

Members	
Prof. Dr. Volker Haucke (Head)	Leibniz-Institut für Molekular Pharmakologie im Forschungsverbund Berlin e. V. (FMP), Berlin, Germany
Prof. Dr. Sara Wickström (Deputy Head)	Max Planck Institute for Molecular Medicine, Münster, Germany
PhD Anne Ephrussi	EMBL Heidelberg, Heidelberg, Germany
Prof. Dr. Marco Foiani	IFOM-IEO Campus, Mailand, Italy
Prof. Dr. med. Christian Hübner	University Hospital Jena, Jena, Germany
Prof. Dr. Stephan Sigrist	Free University of Berlin, Berlin, Germany
Sir Richard Treisman, PhD	The Francis Crick Institute, London, United Kingdom

(As of December 2022)

## Personnel Development

Over the past ten years, the FLI has steadily expanded in terms of personnel. As of December 31, 2022, the institute employed 286 people (employees with institutional and third-party funding, freelancers, trainees). At this time, there were also 42 guests working at the FLI, around half of whom were students, as well as visiting researchers, interns, scholarship holders and employees with contracts from external partners.

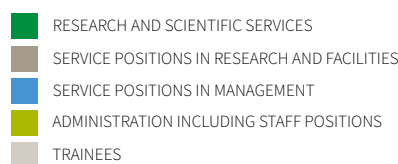
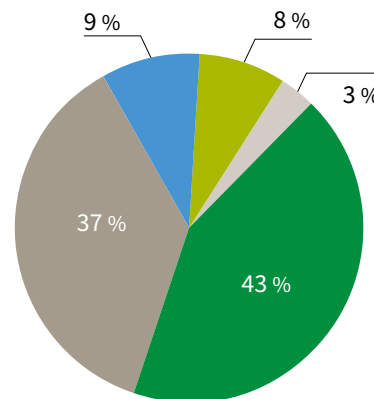
## Gender Equality & Family Friendliness

For the FLI, equal opportunities and family friendliness are part of a contemporary human resources policy. Thus, the FLI follows the equal opportunity standards of the DFG and the Leibniz Association for recruiting and staff development, and is also a member of the Jena Alliance for Families and various regional and national dual-career networks. The FLI also supports its employees with numerous measures to help them better combine work and family/caregiving, which include: a parent-child office, cooperation agreements with nearby day-care centers in Jena, (caregiving) workshops and mentoring programs as well as measures for the reintegration of female scientists (Welcome-Back Fellowship) and doctoral degree funding for female doctoral candidates.

The FLI managed to increase its share of women employees even further, particularly among scientific personnel: as of December 31, 2022, the share of women employees was 61 % (2012: 55 %); among scientific personnel, including students and visiting scientists, a share of 50 % was achieved (2012: 44 %).

## Variety and Diversity

With employees from around 40 countries around the world, we at the FLI have a wealth of cultural backgrounds and values that make it very diverse and multi-faceted. In 2013 the FLI signed the “Diversity Charter,” an initiative to promote diversity in companies and institutions in Germany. The Diversity Charter serves the FLI as a model for an organizational culture that embodies diversity, fairness, tolerance and appreciation, and in which everyone at the institute is valued. Regardless of age, ethnic origin or nationality, gender or



Employees by area of work  
(as of December 31, 2022)

gender identity, physical or mental abilities, religion or ideology, sexual orientation or social background – everyone at the institute should have the same professional opportunities in a prejudice-free working environment. This understanding is an important and central component of our equality- and family-oriented and thus progressive research.

Furthermore, flexible target quotas for increasing the proportion of women in science and research are anchored in the FLI Gender Equality Plan, which is similar to the cascade model of the DFG’s “Research-Oriented Gender Equality Standards” and are stipulated in the program budget.

In recognition of its successful equal opportunity work, the FLI was awarded the “Total-E-Quality” (TEQ) rating in 2022 for the fourth time – for the third time also with the add-on “Diversity.”



## Internationalization of Research

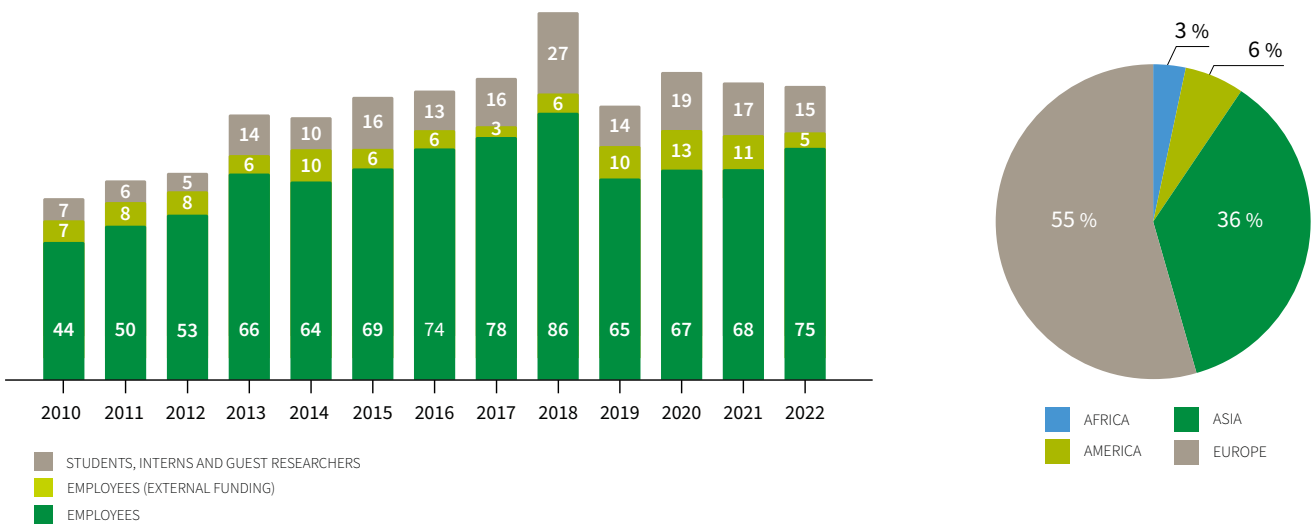
At the FLI, people from around 40 different nations come together to research, work and study. About 30% of all personnel have come to Jena from abroad.

Over the last ten years, the proportion of foreign employees in the total FLI workforce has increased and currently stands at 30% (as of December 31, 2022). Half of the scientists at the FLI now come from abroad – compared to a third ten years ago. Among doctoral students, the share of foreign personnel has almost doubled, from 39% in 2012 to 74% in 2022.

The welcoming culture at the FLI is highly valued by new employees. The Institute’s internal relocation service supports new employees from abroad in dealing with the authorities, informs them about childcare options and the local school system and helps them find accommodation.

## Number of Employees from Abroad (number and origin)

As of December 31, 2022



## Third-Party Funded Projects (selection)

### DFG Research Group

The FLI is part of the DFG-funded research group “Hematopoietic Niches” (2013–2021) with the research project “Cellular and Molecular Components of a Functional Niche for Murine and Human Hematopoietic Stem Cells” (Prof. Dr. Claudia Waskow).



### DFG Collaborative Research Center 1278 PolyTarget

The project “Multicomponent nanoparticles for efficient manipulation of inflammatory signaling and memory in hematopoietic stem and myeloid cells” (Prof. Dr. K. Lenhard Rudolph) is part of the Collaborative Research Center PolyTarget at FSU Jena. There, polymer-based, nanoparticulate carrier materials are developed for the targeted application of pharmaceutical agents (since 2019).



### DFG Collaborative Research Centre 1310 Predictability in Evolution

With their research on “Co-evolution of gut microbiota and immune cells during aging in killifish,” Dr. H. Melike Dönertaş and Prof. Dr. Dario R. Valenzano are part of the Collaborative Research Center (CRC) Predictability in Evolution at Cologne University (2022–2025). The CRC aims at predicting signaling pathways and outcomes of future evolutionary processes using rapidly evolving systems.



### DFG Research Training Group Molecular Signatures of Adaptive Stress Responses

The FLI is involved in several projects in the Research Training Group “Molecular Signatures of Adaptive Stress Responses” (RTG 1715) (2012–2021).



### Leibniz Research Alliance Resilient Ageing

How can people remain healthy into old age and continue to take part in the life of society? This is a highly relevant question for both health science and socioeconomics. To deliver some answers to this complex topic, the Leibniz Association funds the Leibniz Research Alliance “Resilient Ageing,” which enables multidisciplinary research (2022–2026).



### Chan Zuckerberg Initiative

The Chan Zuckerberg Initiative funds a collaboration between Dr. Alessandro Ori (FLI) and Dr. Michael Ward (NIH, USA), to support research on TDP-43 mislocalization in aging, a central but poorly understood hallmark of multiple neurodegenerative diseases (2022–2026).



## IMPULS Research Consortium

The goal of the IMPULS Research Consortium (identification and manipulation of the physiological and psychological clocks of lifespan) is to extend the already established epigenetic and brain organic clocks with further aging indicators and to elucidate their mutual interactions. The identification and characterization of such cellular and organ-based physiological processes (lifespan clocks) in combination with psychosocial aspects should contribute to a holistic and multidimensional understanding of biological aging and to the development of new strategies for healthy aging. IMPULS is funded as part of the Carl Zeiss Foundation's "Breakthrough" program (2020–2025). Prof. Dr. Christoph Englert is the spokesperson for IMPULS.



## Other funding organizations

Numerous research projects at the FLI are additionally funded by various organizations. These include, among others:



Prof. Dr. Dieter Platt-Stiftung



Third-party Revenue  
(in m€, including outside managed funding)

3,53 | 4,79

2021

2022

# Outlook

The research focus of the FLI has been further sharpened in recent years through intensive restructuring and the establishment of new research groups. Its thematic orientation is groundbreaking in the national and international research environment.

## Intensifying research on “Microbiome and Aging”

With the approval of additional funding via the special fund of the Leibniz Association, the new research area “Microbiome and Aging” will be further expanded in the coming years. This area will investigate the aging of the microbiome and its effects on the aging process of the entire organism. There is increasing evidence that the composition of symbiotic bacteria on our body surfaces, such as the intestine or the skin, changes with age, which in turn influences the aging process.

## Focus on systems biology

The research field of the systems biology of aging will also continue to grow in the future at the FLI. The systems biology approach provides new insights into the aging process from targeted comparisons between short- and long-lived organisms and humans, and improves the evaluation of large-scale data sets. This knowledge will help with the development of new therapeutic approaches to improve the health of people as they age.

## Further development of the building infrastructure

The infrastructure of the buildings is adapting step by step to the dynamic development of the institute. For example, the modernization of building complexes that date from the 1950s began in 2018. In 2020, one building was reoccupied after extensive renovation. Another building has been under complete renovation since 2022.



## Long-term perspectives

The appointment of a new Scientific Director will further develop and advance the long-term perspective of the FLI in terms of scientific strategy. In this way, the FLI can continue to expand its excellent international position in research on aging, establish new research groups and topics and continue to attract internationally acclaimed scientists.

Overall, the FLI is on a very promising path towards a better understanding of the basic processes of stem cell aging and declining organ maintenance in old age. It is thus making an important contribution to the development of future therapeutic approaches to improving health in old age.



#### PHOTO CREDITS:

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