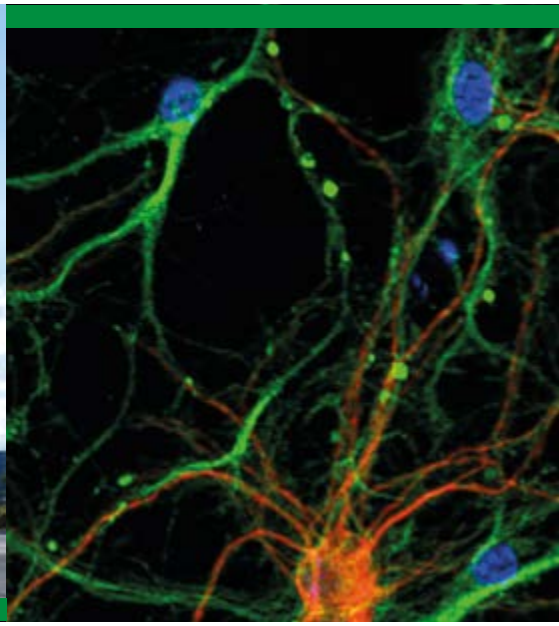
Leibniz Institute on Aging –
Fritz Lipmann Institute



2019 – 2020

Annual Report


Forschung
für ein gutes Alter

2019–2020

Annual Report

Leibniz Institute on Aging – Fritz Lipmann Institute (FLI)

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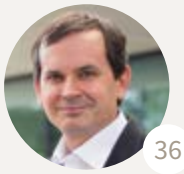
Table of Contents

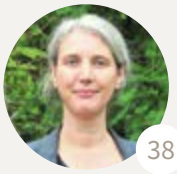
Research Groups

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

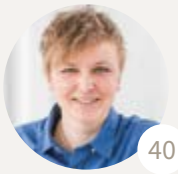
Subarea 1



Rudolph
Research Group



Waskow
Research Group



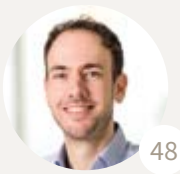
von Maltzahn
Research Group

González-Estévez
Fellow Group

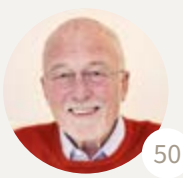
Heidel
Associated Research Group

Subarea 2

Morrison
Research Group



von Eyss
Research Group



Herrlich
Associated Research Group

Ploubidou
Associated Research Group

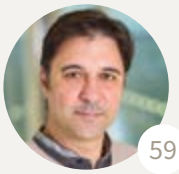
Research Area II: Genetics, Epigenetics and Molecular Cell Dynamics of Aging

Subarea 3

Englert
Research Group

Neri
Research Group

Bierhoff
Associated Research Group

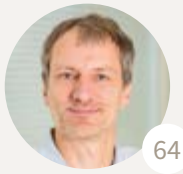


Cellerino
Associated Research Group

Marz
Associated Research Group

Subarea 4

Wang
Research Group

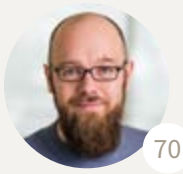


Kaether
Research Group

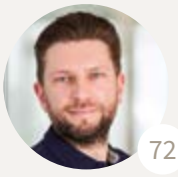
Ermolaeva
Research Group

Interconnecting Subarea: Computational and Systems Biology of Aging

Subarea 5



Hoffmann
Research Group



Ori
Research Group

Kestler
Associated Research Group

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

Welcome

Aging affects each and every one of us as individuals – but also society as a whole. The goal of research at the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) is to decipher the genetic, epigenetic as well as molecular and cellular processes underlying the biological aging process. This research focus is groundbreaking – in Germany and beyond.

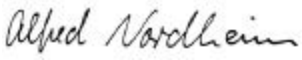
With age, stem cells lose their functionality and accumulate more damage, steadily decreasing the body's ability to regenerate and preventing organs from renewing themselves. This makes older people more susceptible to disease and can affect their quality of life. We have therefore refined and further developed the content of our research focus "Stem cell aging and organ preservation."
To enable an even better evaluation of the data obtained in our experiments and analyses, we have expanded Systems Biology as a cross-sectional area over the past ten years. Microbiome research, which will be established as a new research focus in the coming years, builds on this expertise and infrastructure. The aim 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 dysfunction.

In addition, we have initiated numerous pioneering projects in recent years. These include the Leibniz Research Alliance "Healthy Ageing," coordinated by the FLI, which bundles aging research in 21 Leibniz institutions across various disciplines. In the newly established research consortium IMPULS, the molecular biological perspective on aging is combined with approaches from psychology in particular. With such interdisciplinary research approaches, we want to ensure that biological aging research achieves a sustainable social impact on an aging society.

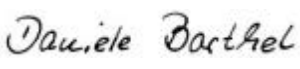
Our research into the genetic basis of aging using the turquoise killifish is attracting a great deal of attention. The recent sequencing of the complete genome of this short-lived fish species by FLI researchers has opened up new perspectives in the study of aging processes for researchers worldwide.

At the FLI, we are deeply committed to expanding the knowledge base so that in the future it will be possible to extend the human health span in old age and thus to shape demographic change positively for all of us.

We wish our readers an enjoyable reading experience and many 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 physiologically complex process, determined by genetic factors and environmental influences. At the FLI, the mechanisms that lead to a deterioration in stem cell function and organ maintenance during the aging process – and thus foster organ dysfunction and the development of diseases – are deciphered. The goal is to provide a knowledge base for the development of novel therapeutic approaches that will help extend the health span – the time during which human beings age in good health. This is important not only for individuals, but for society as a whole. Such contributions are vital to managing demographic change and the associated aging of society.

Groundbreaking Research at the FLI

The reduction of stem cell function and organ maintenance is the main cause of the decline in organ function in old age, with organs becoming more susceptible to damage and disease. This is often associated with a diminished quality of life. By studying stem cell aging and organ maintenance and focusing on their molecular, genetic and epigenetic causes, the FLI has established a leading position in international aging research.

In recent years, several institutes in Germany and Europe have followed the FLI's example and focused on aging research. They focus on the identification of genes that influence lifespan, cellular stress responses, neurodegenerative aging, changes in metabolism, cardiovascular diseases and external environmental influences. On a European level, there are also numerous approaches to the study of aging – whether in cancer research, the study of cellular aging, specific aging-associated diseases or particular animal models. The FLI's focus on epigenetic and genetic factors as causes of stem cell aging and organ maintenance has been groundbreaking in this research landscape.

The FLI maintains close research collaborations with many of these research institutions to benefit from their expertise and diverse perspectives and to take mutual advantage of the synergy that results. In addition, the FLI promotes interdisciplinary research approaches that incorporate psychological, political and socioeconomic perspectives. Only in this way can biological aging research achieve a sustainable social effect.

Overall, the FLI has become an internationally recognized force in the expansion of new research emphases for the generation of high-quality scientific knowledge. With their research results, networking activities and promotion of young talent, FLI scientists are helping to further strengthen the research field of aging research regionally, nationally and internationally.

Biennial Review 2019 – 2020

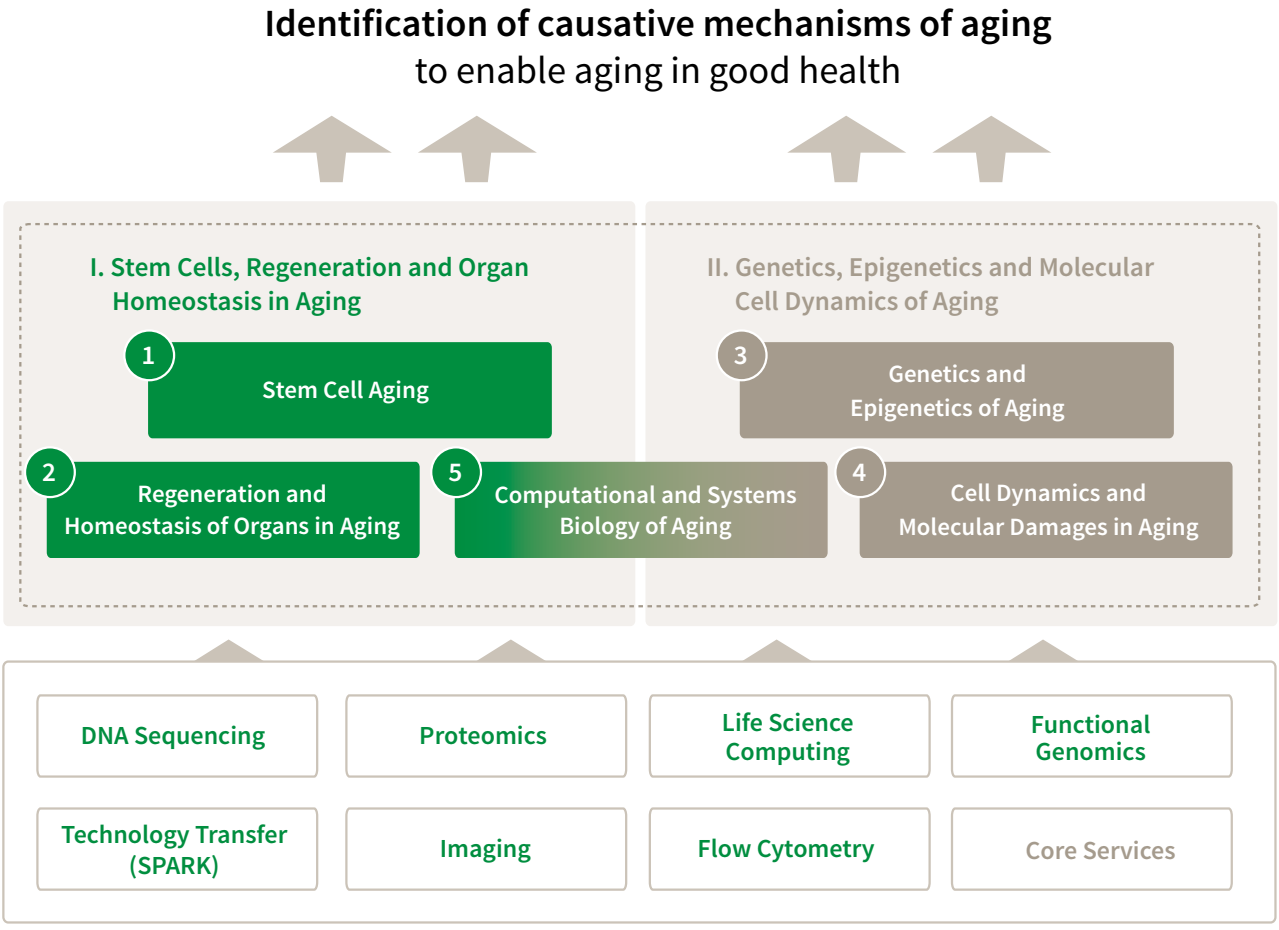
In 2012, the FLI began to reorganize its scientific focus. For this purpose, two main research areas were defined:

(I) Stem Cells, Regeneration and Organ Homeostasis in Aging
(II) Genetics, Epigenetics and Molecular Cell Dynamics of Aging

The research groups at the FLI collaborate in various research projects that span different focal areas. In order to be able to map these project-related collaborations organizationally, five subareas have been institutionalized. The subarea Systems Biology and Bioinformatics of Aging, with its expertise in data analysis, functions as an area of cross-sectional overlap (see below).

Since the scientific evaluation of 2016, microbiome research has been successively expanded as a new research focus, and in 2018 a corresponding position for a senior research group leader was advertised, combined with a professorship at the University of Jena. In the future, the microbiome research group will be part of the subarea "Regeneration and Homeostasis of Organs in Aging."

Furthermore, the FLI has established a Compliance Management System (CMS) with the aim of ensuring compliance with legal and operational guidelines. The focus of the work of the CMS staff and the compliance experts coming from eight working areas –such as research, animal husbandry and occupational safety, data protection, health management and equal opportunities – is the review of science-related processes.



Research focus at the FLI. Research at the FLI is organized into five subareas that cooperate closely. They are supported by a wide range of technical core facilities and core services.

Subarea 1:
Aging of Stem Cells

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 subarea "Aging of Stem Cells" was created at FLI in 2013 with the establishment of the research groups led by K. Lenhard Rudolph (blood and intestinal stem cells), Julia von Maltzahn (muscle stem cells) and Cristina González-Estévez (stem cells in planaria). With the group of Claudia Waskow, the research area was expanded to include the topic of human hematopoietic stem cells in the mouse model (immunology of aging: regeneration in hematopoiesis). Research groups from Subareas 2 and 5 are also working on stem-cell relevant issues (Björn von Eyss: Identification of functionally relevant subpopulations in aging hematopoietic stem cells; Alessandro Ori: Proteome aging of stem cells). In addition, the research group of Francesco Neri (research topic: epigenetic aging of stem cells) and the associated research group of Florian Heidel, Director of the Clinic of Internal Medicine C, University Medical Center Greifswald, Germany (research topic: blood stem cell diseases) belong to Subarea 1.

The following overarching questions currently form the focus of the research area's work:

- 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, Christoph Kaether)
- Selection of subpopulations of stem cells and mutant stem cell clones in aging (Florian Heidel, K. Lenhard Rudolph, Björn von Eyss, Claudia Waskow).
- Regenerative pathways in the hematopoietic system and their impact on the aging immune system (Claudia Waskow)

Overall, the subarea "Aging of Stem Cells" aims to investigate the basic concepts and consequences of stem cell aging in the context of aging organisms. The subarea 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 Research Area 1 is to further intensify the collaborations between the groups by collaborating with researchers of the soon to be established research focus "Microbiota and Aging" (Dario R. Valenzano).

Detail from a printed fleece on the phases of human life - designed by children and young people from Thuringian youth art schools. Commissioned in 2015, it is part of the art-in-architecture at the FLI (see also pp. 11, 13), curated by sculptor and graphic artist Walter Sachs.

Subarea 2: Regeneration and Homeostasis of Organs in Aging

The functionality of all organs and tissues declines during aging. As such, this deteriorative process represents a major factor contributing to a decrease in the quality of life and to disease development during aging. Mechanistically, the failure of the aging organism to maintain homeostasis and functionality of organs during the post-replicative lifespan remains poorly understood; this has been a focus of research on aging at FLI since its inception in 2004. As outlined above (see p. 8), stem cells play a pivotal role in this process, but aging-associated alteration in the non-stem cell compartment of organs and tissues is equally important to it. Research in Subarea 2 focuses primarily on mechanisms of tissue aging, involving non-stem cells, micro-milieu conditions and systemically acting signaling pathways that together lead to impairments in organ maintenance.

Subarea 2 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 cancer (Björn von Eyss)
- Protein CD44 and metastasis; trip6 protein and hydrocephalus (Peter Herrlich)
- immune aging and inflammation in organ maintenance and regeneration (Ronny Hänold, until 2017)

Together, Subarea 2 on “Regeneration and Homeostasis of Organs in Aging” studies cell-intrinsic and inter-cellular signals and networks that regulate organ maintenance and regeneration. This work is closely related to Subarea 1 on “Stem Cell Aging” and both subareas combine to form Research Area I: “Stem Cells, Regeneration, and Organ Homeostasis in Aging.” This research area strongly benefits from research in Subarea 5 on “Computational and Systems Biology of Aging,” which fosters the interconnection between Research Areas I and II at multiple scales.

The "Rollatornest", created by the artist Liz Bachhuber, stands for the mobility and restlessness of people who nevertheless try to create a home for themselves. The "nest", constructed from a walker and wickerwork, is thus also a memento of the past that people always and everywhere carry with them.

Subarea 3:
Genetics and Epigenetics of Aging

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

Building on its long-standing expertise in the study of genomes, the FLI formed the research area "Genomics of Aging" in 2004. This research area was subsequently further developed as the subarea "Genetics and Epigenetics of Aging."

- Christoph Englert and his group are investigating the genetic basis of developmental trajectories and regenerative processes, including those relating to the kidney.
- The "Genome Analysis" group led by Matthias Platzer (until 2018), together with Christoph Englert's group and the former junior group led by Alessandro Cellerino (in cooperation with the Scuola Normale Superiore di Pisa, Italy), has significantly advanced the genomic and functional analysis of the short-lived fish *N. furzeri* as a new model in aging research.
- The influence of the epigenome – chemical changes in DNA that control its activation or deactivation – on aging and cancer development has been studied by Francesco Neri since 2016.
- Epigenetic changes such as decreasing DNA methylation or altered histone modification are being investigated by the FLI in cooperation with Alessandro Cellerino (Scuola Normale Superiore di Pisa, Italy) and Holger Bierhoff (Friedrich Schiller University Jena, Germany). The associated research group of Manja Marz (Friedrich Schiller University Jena, Germany) is also investigating the role of long, non-coding RNAs and micro-RNAs in gene activity.
- The (until 2018) associated research group of Heinrich Jasper (Buck Institute for Research on Aging, Novato, CA, USA) combines Subareas 1, 2 and 3 with his research on genes and signaling pathways that affect stem cell and organ maintenance in *Drosophila melanogaster*.

In summary, 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. The research is closely linked to the work of the research groups in other subareas and benefits greatly from collaboration with the systems biology-oriented Subarea 5.

Photographer and author Harald Wenzel-Orf shows the beauty of old faces in his book "Mit hundert war ich noch jung" (2000). Six hand prints of his photos are hanging in the stairwell of the FLI main building.

Subarea 4:
Cell Dynamics and Molecular Damage in Aging

Aging is regarded as a multifactorial process, characterized by the accumulation of damages to molecular structures and subcellular organelles. Why the prevention and repair of molecular damage fails during the aging of organisms is poorly understood.

Research at FLI has focused since 2004 on the analysis of mechanisms that contribute to the accumulation of molecular damage in aging cells and tissues. The main aim of the sub-area "Cell Dynamics and Molecular Damage in Aging" is to investigate the causes and consequences of damage accumulation in DNA, protein and subcellular organelles in aging cells and tissues:

- DNA damage response in the development and maintenance of neuronal tissues (Zhao-Qi Wang)
- mechanisms of DNA replication in aging (Frank Große, until 2018)
- protein trafficking, proteostasis and organelle damage response in aging (Christoph Kaether)
- maintenance of stress response and metabolism in healthy aging (Maria Ermolaeva)

In order to understand the basic cellular and organismal malfunctions during aging, it is of vital importance to analyze the aging-associated induction of molecular damage and responses to it – including damage repair. Conversely, aging-associated impairments in stem cells and tissues can lead to the accumulation of molecular damage. Examples include an impaired removal of damaged and senescent cells, and alterations in metabolism that can induce molecular damages. Given these functional and bidirectional interactions, the sub-area 4 on "Cell Dynamics and Molecular Damages in Aging" is tightly linked to sub-areas 1, 2 and 3 and is a central theme of the overall research mission at the FLI.

In addition, the functional analysis of molecular damage at FLI has successfully fostered collaborations with the Friedrich Schiller University Jena (FSU) and contributed to the establishment of two DFG-funded research training groups on stress response (RTG 1715) and protein modifications in aging (RTG 2155).

The FLI is committed to entering into a dialog with the public. At the Jena Science Night 2019 (Lange Nacht der Wissenschaften), visitors engaged in hands-on activities about aging research and aging (see also p. 17).

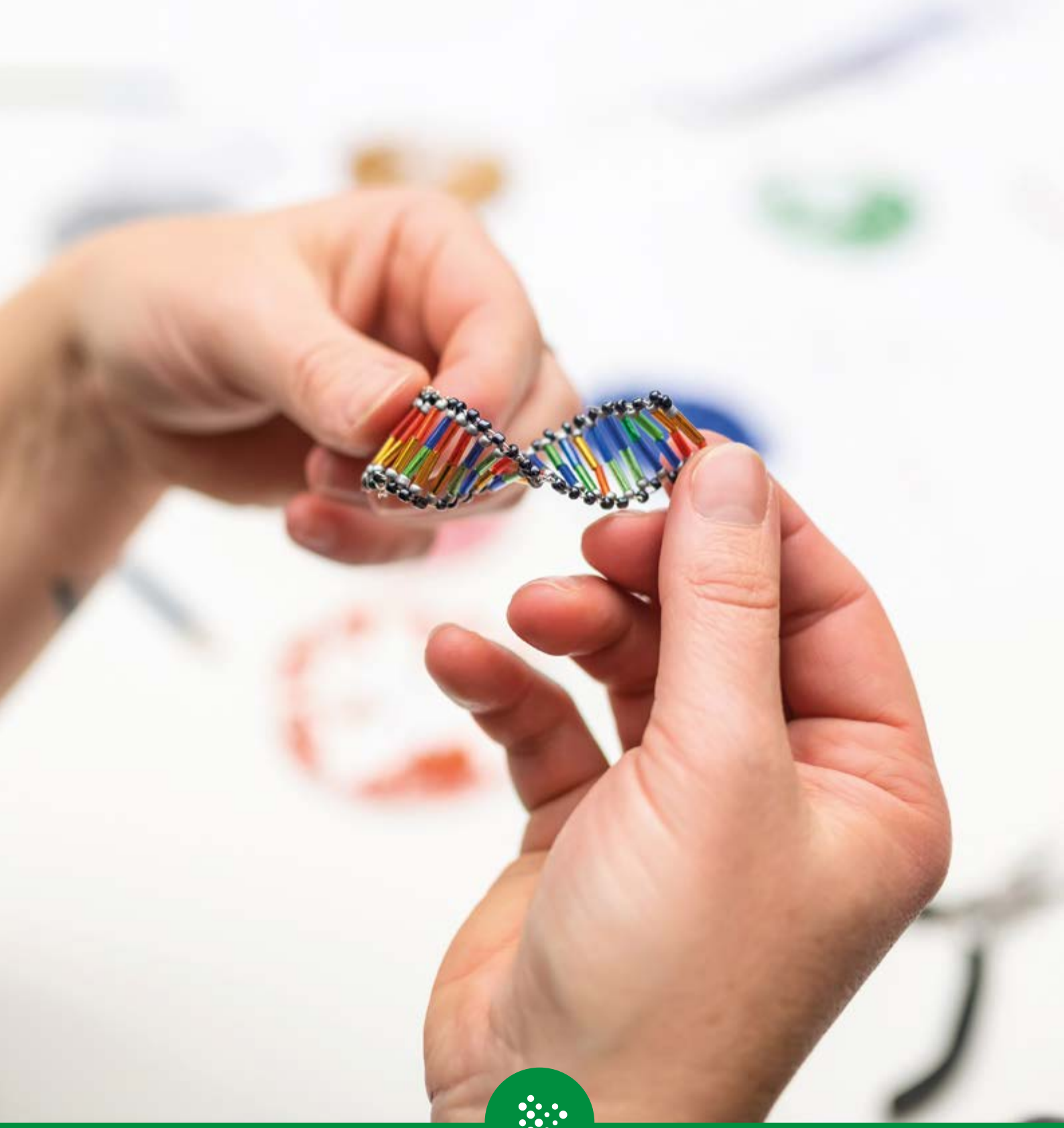
Subarea 5:
Systems Biology and Bioinformatics of Aging

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 aging research, both nationally and internationally. In order to elucidate the interrelationships at different levels of the organism as a whole, the research area "Systems Biology and Bioinformatics of Aging" was created at the FLI.
Researchers in this area investigate connections among biological networks that influence aging: at the level of genes and molecular regulatory circuits, and at the level of communication between cells and organs. The formation of this subfield was initiated by the GerontoSys program of the German Federal Ministry of Education and Research (BMBF) and supported by a collaborative project on bioinformatics analyses in Jena. The project used functional genomic analyses at FLI to compare the genes and signaling pathways of different species in order to identify genetic factors and molecular mechanisms involved in the aging process of cells and organs. The FLI has developed this research approach into a new subfield at the institute.

The subfield addresses the following questions:

- Since late 2017, Steve Hoffmann's research group has been developing proprietary methods for analyzing large, multidimensional biological datasets with the goal of better understanding how the epigenome controls processes of gene expression and maturation.
- Using ultrasensitive methods such as proteomic analysis, Alessandro Ori's group explores how age, mutations and environmental factors affect our organs at the molecular level.
- The research focus of the associated research group of Hans A. Kestler (University of Ulm) is located at the intersection of the fields of computer science, statistics and life sciences and concentrates, among other things, on statistical procedures and database evaluations for data from high-throughput analyses.

Overall, the establishment of Subarea 5 "Systems Biology and Bioinformatics of Aging" is an elementary foundation on the path to developing a comprehensive understanding of the complexity of aging on different organismal levels and to support and advance the research approaches of subareas 1 to 4 at FLI.



A simple model of the DNA double helix consisting of beads and wire - handmade by visitors at the Jena Science Night 2019 (Lange Nacht der Wissenschaften).

Core Facilities

The Core Facilities and Services (CF and CS) were reorganized as central facilities at the Leibniz Institute on Aging in 2016 and have been continuously developed since that time. Here, the Institute provides scientists with the high technology and expertise necessary to make their work in the field of molecular biology and medical aging research internationally visible and competitive. The technological methods provided include state-of-the-art light and fluorescence microscopy, proteome elucidation by mass spectrometry, single cell analysis in flow cytometry (FACS), characterization of the genome and epigenome with second and third generation DNA sequencing, functional analysis of cellular processes with RNAi and CRISPR/Cas technology, and analysis of highly complex datasets of diverse origins using advanced bioinformatics methods and a powerful computing infrastructure.

A prominent goal that we pursue with this strategy at the FLI is to consolidate and develop expertise in relevant key technologies. To achieve this, the staff of the Core Facilities is integrated on the one hand into the daily scientific routine of the FLI, offering seminars, lectures and user meetings, and on the other hand into national and international networks, through participation in conferences and workshops. All research groups at the FLI have equal access to the technology and receive individual advice, thus enabling them to achieve their respective research goals. This modus operandi also ensures that the large-scale research equipment is fully utilized both internally as well as by cooperation partners.

The past years have shown that the Core Facilities and Services contribute significantly to the achievement of the institute's own aims as well as the overarching goals of the Leibniz Association. Half of all FLI scientific publications published in 2019/2020 included contributions from at least one CF/CS, and 30% of the publications feature co-authors from the CF/CS. The FLI's third-party funding has been increased by the Core Facilities through participation in a DFG priority program (€ 225,000), a collaboration with the German Center for Cardiovascular Research (€ 34,000) and an infrastructure measure of the Thuringian Aufbaubank (TAB) (€ 356,000). A special role is played here by the Core Facility Technology Transfer, which supports selected research projects with transfer potential through start-up financing and mentoring in order to render them fit for further third-party financing. Funding for three research projects was successfully obtained from the BMBF and TAB (BMBF: € 1.272 million, TAB: € 700,000). Finally, the Core Facilities also contribute to gender equality at the FLI: 40% of the management staff are women.

Dr. Tobias Sperka
Head of Core Facilities

Life Science Computing

Flow Cytometry

Functional Genomics

DNA 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

Research Collaborations 2019 – 2020

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

The FLI cooperates with the Friedrich Schiller University of Jena and the Jena University Hospital and is active in more than 329 national research collaborations and alliances beyond this regional networking. Scientists at the FLI maintain a systematic exchange with research institutions in 27 countries around the world. In this way, we guarantee that our research is always up to date and makes a significant international contribution in the field of aging research.

Leibniz Research Alliances (LFV)

As people age, organic dysfunction and aging-associated disease increase sharply. This can severely limit the quality of life of older adults as well as their participation in social life. Due to the growing share of the elderly in the population, more and more people will be affected, which, together with a low birth rate, may lead to social and economic problems. To address this problem area from an interdisciplinary perspective, the Leibniz Research Alliance Healthy Ageing (LFV Healthy Ageing) unites the scientific expertise of 19 Leibniz institutions from the fields of biology, medicine, psychology, education, sociology and economics. The scientists work on the fundamental questions of aging, design joint research projects and promote the interdisciplinary exchange of resources and know-how. This is intended to provide the basis for an improved quality of life for older individuals as well as a sustainable societal impact. The LFV Healthy Ageing is coordinated at the FLI.

Aging-associated pathologies also call for specialized agents – molecules that induce specific physiological changes in target organisms. Many agents are of natural origin and are optimized by chemical and/or biotechnological processes to achieve the best possible effect when applied. In another Leibniz research alliance, the LFV Wirkstoffe und Biotechnologie (LFV Bioactive Compounds and Biotechnology), the FLI, as one of 16 Leibniz institutions, makes 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 idea is also 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, are investigating how biological age can be precisely determined and what factors influence the complex aging processes in humans. 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

In March 2016, the CanPathPro project was launched with 11 million euros in funding from the EU under the Horizon 2020 program. For six years, researchers from six countries will collaborate to develop a new systems biology platform for predictive modeling of cancer-associated signaling processes.

ProExcellence Project RegenerAging

The Center for Aging Research Jena (ZAJ) has developed the research project Aging-Induced Inhibition of Regeneration and Tissue Homeostasis – RegenerAging. For this, the FLI is working closely with Friedrich Schiller University Jena, the University Hospital of Jena and Carl Zeiss Microscopy GmbH in Jena. The project is funded with 4.1 million euros from 2015 to 2021 as part of the ProExcellence Initiative 2 of the state of Thuringia. The focus is on interdisciplinary research into age-related changes at the cellular level: the decline in function of cellular and extracellular signals that regulate both the ability of differentiated cells to divide and the self-renewal and functionality of stem cells, leads to a decrease in the regenerative capacity of tissues in old age. The focus is on the epigenetics of aging, stem cell aging and the immunology of aging.

Leibniz ScienceCampus Jena – Regenerative Aging

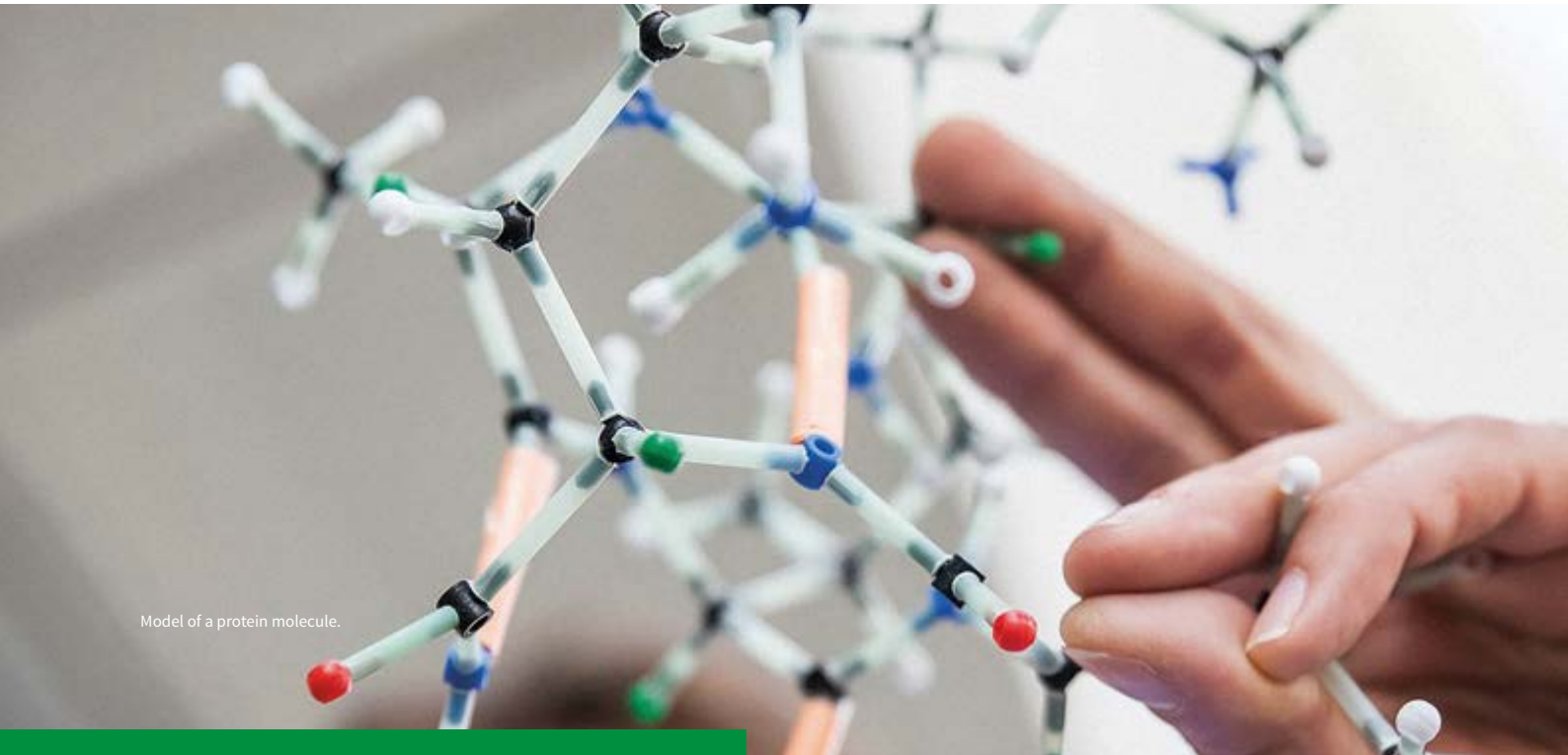
With the aim of strengthening and further networking research on aging at the Jena site, the Leibniz Association funded the establishment of the Leibniz ScienceCampus "Regenerative Aging" from 2015 to 2020. The ScienceCampus was co-financed by the ProExcellence Initiative 2 of the state of Thuringia.

Further New Collaborations at the FLI

- DFG Research Training Group 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 RESETageing – cardiovascular diseases
- PhD program of the Jena School for Molecular Medicine (JSMM) with Shenzhen University, China

International Presentations

To continuously strengthen the Institute's international visibility and scientific exchange, the FLI supports its researchers in presenting their research results at internationally renowned conferences and congresses. In 2019 and 2020, they gave a total of 125 presentations at scientific conferences.



Model of a protein molecule.

Facts and Figures at a Glance

Employees*

2019	2020
285	287

Associated Research Groups

7

2019 – 2020

Scientific Presentations

2019	2020
96	29

Awards for FLI Researchers

2019	2020
5	1

Number of Collaborations

2019	2020
367	331

Articles in Peer Reviewed Journals per Year

2019	2020
91	93

Collected Third-party Funding (in € million)****

2019	3.57
2020	4.53

Junior and Senior Research Groups

12

2019 – 2020

Cumulative Impact Factor of Scientific Papers

2019	2020
731	675

University Courses

2019	2020
79	71

* FLI-funded employees as of the reporting date December 31
** including externally managed third-party funds

Development of Publications

In 2019 and 2020, researchers at the FLI published a total of 218 scientific articles in peer-reviewed and other scientific journals. They were lead authors on more than half of these publications (119), and made a significant contribution as co-authors on another 99 publications. To increase the visibility of research at the FLI and to make research results publicly available, the FLI funds open access fees for publications in journals with a high impact factor (IF ≥ 7). This has helped to increase the share of publications that are open access to 68% (2020), nearly doubling it since 2013.

In 2020, the FLI also joined the open access transformation agreement DEAL with the publishers Wiley and Springer Nature. This is intended to shift the cost of open access to scientific publications from subscribers to authors. The contracts now allow all FLI members to read every article in journals published by Wiley and most articles in Springer Nature journals.

Selected Publications

2020

Gebert N, Cheng CW, Kirkpatrick JM, Di Fraia D, Yun J, Schädel P, Pace S, Garside GB, Werz O, Rudolph KL, Jasper H, Yilmaz ÖH, Ori A.
Region-Specific Proteome Changes of the Intestinal Epithelium during Aging and Dietary Restriction.
Cell Rep 2020, 31(4), 107565.

Jayavelu AK, Schnöder TM, Perner F, Herzog C, Meiler A, Krishnamoorthy G, Huber N, Mohr J, Edelmann-Stephan B, Austin R, Brandt S, Palandri F, Schröder N, Isermann B, Edlich F, Sinha AU, Ungelenk M, Hübner CA, Zeiser R, Rahmig S, Waskow C, Coldham I, Ernst T, Hochhaus A, Jilg S, Jost PJ, Mullally A, Bullinger L, Mertens PR, Lane SW, Mann M, Heidel FH.
Splicing factor YBX1 mediates persistence of JAK2-mutated neoplasms.
Nature 2020, *588(7836)*, 157-63.

Kelmer Sacramento* E, Kirkpatrick* JM, Mazzetto* M, Baumgart M, Bartolome A, Di Sanzo S, Caterino C, Sanguanini M, Papaevgeniou N, Lefaki M, Childs D, Bagnoli S, Terzibasi Tozzini E, Di Fraia D, Romanov N, Sudmant PH, Huber W, Chondrogianni N, Vendruscolo M, Cellerino** A, Ori** A.
Reduced proteasome activity in the aging brain results in ribosome stoichiometry loss and aggregation.
Mol Syst Biol 2020, *16(6)*, e9596
(* equal contribution, ** co-corresponding authors).

Khaminets A, Ronnen-Oron T, Baldauf M, Meier E, Jasper H.
Cohesin controls intestinal stem cell identity by maintaining association of Escargot with target promoters.
Elife 2020, 9, e48160.

Köhnlein* K, Urban* N, Guerrero-Gómez D, Steinbrenner H, Urbánek P, Priebs J, Koch P, Kaether C, Miranda-Vizuete A, Klotz LO.
A Caenorhabditis elegans ortholog of human selenium-binding protein 1 is a pro-aging factor protecting against selenite toxicity.
Redox Biol 2020, 28, 101323 (* equal contribution).

Napoli D, Lupori L, Mazziotti R, Sagona G, Bagnoli S, Samad M, Sacramento EK, Kirkpartick J, Putignano E, Chen S, Terzibasi Tozzini E, Tognini P, Baldi P, Kwok JC, Cellerino* A, Pizzorusso* T.
MiR-29 coordinates age-dependent plasticity brakes in the adult visual cortex.
EMBO Rep 2020, 21(11), e50431 (* equal contribution).

Njeru* SN, Kraus* J, Meena* JK, Lechel A, Katz SF, Kumar M, Knippschild U, Azoitei A, Wezel F, Bolenz C, Leithäuser F, Gollowitzer A, Omrani O, Hoischen C, Koeberle A, Kestler** HA, Günes** C, Rudolph** KL.
Aneuploidy-inducing gene knockdowns overlap with cancer mutations and identify Orp3 as a B-cell lymphoma suppressor.
Oncogene 2020, 39(7), 1445-65
(* equal contribution, ** co-corresponding authors).

Riege K, Kretzmer H, Sahm A, McDade SS, Hoffmann S, Fischer M.
Dissecting the DNA binding landscape and gene regulatory network of p63 and p53.
Elife 2020, 9, e63266.

Schulz A, Sekine Y, Oyeyemi MJ, Abrams AJ, Basavaraju M, Han SM, Groth M, Morrison H, Strittmatter SM, Hammarlund M.
The stress-responsive gene GDPGP1/mcp-1 regulates neuronal glycogen metabolism and survival.
J Cell Biol 2020, 219(2), e201807127.

Winkler I, Bitter C, Winkler S, Weichenhan D, Thavamani A, Hengstler JG, Borkham-Kamphorst E, Kohlbacher O, Plass C, Geffers R, Weiskirchen R, Nordheim A.
Identification of Ppar **γ** -modulated miRNA hubs that target the fibrotic tumor microenvironment.
Proc Natl Acad Sci U S A 2020, 117(1), 454-63.

Zhou ZW, Kirtay M, Schneble N, Yakoub G, Ding M, Rüdiger T, Siniuk K, Lu R, Jiang YN, Li TL, Kaether C, Barzilai A, Wang ZQ.
NBS1 interacts with Notch signaling in neuronal homeostasis.
Nucleic Acids Res 2020, 48(19), 10924-39.

2019

Behrendt L, Kurth I, Kaether C.
A disease causing ATLASTIN 3 mutation affects multiple endoplasmic reticulum-related pathways.
Cell Mol Life Sci 2019, 76(7), 1433-45.

Chen Z, Amro EM, Becker F, Hölzer M, Rasa SMM, Njeru SN, Han B, Di Sanzo S, Chen Y, Tang D, Tao S, Haenold R, Groth M, Romanov VS, Kirkpatrick JM, Kraus JM, Kestler HA, Marz M, Ori A, Neri F, Morita** Y, Rudolph** KL.
Cohesin-mediated NF-**γ** B signaling limits hematopoietic stem cell self-renewal in aging and inflammation.
J Exp Med 2019, 216(1), 152-75 (** co-corresponding authors).

Fricke M, Gerst R, Ibrahim B, Niepmann M, Marz M.
Global importance of RNA secondary structures in protein coding sequences.
Bioinformatics 2019, 35(4), 579-83.

Hölzer M, Marz M.
De novo transcriptome assembly: A comprehensive cross-species comparison of short-read RNA-Seq assemblers.
Gigascience 2019, 8(5).

Jacome-Galarza* CE, Percin* GI, Muller* JT, Mass* E, Lazarov T, Eitler J, Rauner M, Yadav VK, Crozet L, Bohm M, Loyher PL, Karsenty G, Waskow** C, Geissmann** F.
Developmental origin, functional maintenance and genetic rescue of osteoclasts.
Nature 2019, 568(7753), 541-5.
(* equal contribution, ** co-corresponding authors).

Korzelius** J, Azami S, Ronnen-Oron T, Koch P, Baldauf M, Meier E, Rodriguez-Fernandez IA, Groth M, Sousa-Victor P, Jasper** H.
The WT1-like transcription factor Klumpfuss maintains lineage commitment of enterocyte progenitors in the Drosophila intestine.
Nat Commun 2019, 10(1), 4123 (** co-corresponding authors).

Mende* N, Jolly* A, Percin* GI, Günther M, Rostovskaya M, Krishnan SM, Oostendorp RAJ, Dahl A, Anastassiadis K, Höfer** T, Waskow** C.
Prospective isolation of non-hematopoietic cells of the niche and their differential molecular interactions with HSCs.
Blood 2019, 134(15), 1214-26
(** co-senior authors, * equal contribution).

Rodriguez-Fernandez IA, Qi Y, Jasper H.
Loss of a proteostatic checkpoint in intestinal stem cells contributes to age-related epithelial dysfunction.
Nat Commun 2019, 10(1), 1050.

Tracy Cai X, Li H, Safyan A, Gawlik J, Pyrowolakis G, Jasper H.
AWD regulates timed activation of BMP signaling in intestinal stem cells to maintain tissue homeostasis.
Nat Commun 2019, 10(1), 2988.

Viehweger* A, Krautwurst* S, Lamkiewicz K, Madhugiri R, Ziebuhr J, Hölzer M, Marz M.
Direct RNA nanopore sequencing of full-length coronavirus genomes provides novel insights into structural variants and enables modification analysis.
Genome Res 2019, 29(9), 1545-54 (* equal contribution).

Awards and Prizes 2019 – 2020

2020

Dr. Michael Reuter's representation of the repair process of injured peripheral nerves is recognized as one of the top 30 submissions for its special creativity in BioRender's **Scientific Graphical Abstract competition**. Dr. Reuter is a research associate in the Morrison Research Group "Regeneration and Aging of Peripheral Nerves."

2019

Dr. Alessandro Cellerino, professor at the Scuola Normale Superiore di Pisa, Italy, is appointed to the position of **Leibniz Chair** of the Leibniz Association, honoring him for his successful and long-standing collaboration with the FLI. The neuroscientist pioneered the use of the short-lived turquoise killifish as a model in aging research and has been researching this fish with an FLI team since 2005. Dr. Cellerino heads the associated research group "Biology of Aging" at the FLI.

Dr. Alessandro Ori has been awarded the **Beutenberg Campus Award "Life Science and Physics" of the Jena e. V.** as the best junior scientist. Dr. Ori leads the research group "Aging of Protein Complexes" at the FLI.

At the **Leibniz-Kolleg for Young Researchers** of the Leibniz Association in Erfurt **Prerana Shrikant Chaudhari** wins the Science Slam with her presentation. The doctoral student in the Ermolaeva Research Group "Stress Tolerance and Homeostasis" is also honored with the **Fritz Boege Prize** for the best short talk at the Annual Meeting of the German Foundation for Aging Research (DGfA).

The prize for the best poster in the Evolutionary Biology division was won by **Dr. Jeanne Wilbrandt at the 112th Annual Conference of the German Zoological Society (DZG)** in Jena. Dr. Wilbrandt is a postdoc in the Core Facility Life Science Computing at the FLI and supports researchers with sustainable research data management as a data steward.

At the meeting of the **Society for Muscle Biology** of the US Society for Developmental Biology in San Jose (Costa Rica), **Dr. Svenja Schüler** receives an award for the best poster (Trainee Poster Presentation). Svenja Schüler was a PhD student in the Ori Research Group "Aging of Protein Complexes."

Dr. Alessandro Ori, recipient of the science award of the Beutenberg-Campus Jena e. V. 2019.

Leibniz Chair for the Italian Aging Researcher Alessandro Cellerino

Aging researcher Alessandro Cellerino

The internationally renowned aging researcher Prof. Dr. Alessandro Cellerino, from the Scuola Normale Superiore di Pisa, Italy, was honored in July 2019 with the Leibniz Chair by the Leibniz Association for his longstanding cooperation with the FLI. This title is granted for five years to outstanding researchers and honors their close cooperation with a Leibniz Research Institute.

Killifish as a Model for Aging Research

Dr. Cellerino was the first to propose, in 2003, the use of the short-lived turquoise killifish (*Nothobranchius furzeri*), with its lifespan of only four to twelve months, as a new model organism in aging research. This little fish from southeastern Africa ages in a similar fashion to human beings – only much more rapidly. Since Dr. Cellerino's pioneering work, *N. furzeri* has come to be regarded as the vertebrate with the shortest lifespan that can be kept under laboratory conditions. Because the fish ages as if in fast motion, it is particularly well suited as an animal model for the analysis of aging processes.

Growing Community of Killifish Researchers

Together with a research team at the FLI, Dr. Cellerino has been working since 2005 on the scientific introduction and use of the short-lived fish as an animal model. For this work, he and his colleagues at the FLI, research group leaders Prof. Dr. Christoph Englert and PD Dr. Matthias Platzer, were awarded the Max Bürger Prize of the German Society for Gerontology and Geriatrics (DGGG) in 2010. At the end of 2015, the team achieved another breakthrough: they sequenced the genome of the fish and identified genes associated with the rapid aging process. This laid the foundation for future genetic studies of the aging process in vertebrates. Since then, researchers worldwide have been able to investigate aging-related diseases on the basis of the genome, which is freely available as a data set.

The decisive contribution of the neurobiologist Cellerino is recognized by the constantly growing international community of killifish researchers from various disciplines. One indication of this is the large number of publications on the topic in renowned journals. In 2018 the entire FLI research team around Cellerino, Englert and Platzer was awarded the "Thuringian Research Award" in the category of basic research for this outstanding achievement.

Alessandro Cellerino heads the associated research group "Biology of Aging," a collaboration between the Scuola Normale Superiore di Pisa (Pisa, Italy) and the FLI – located in Pisa with guest status at the FLI.

Invited Speeches and Talks 2019 – 2020

International Guest Speakers at FLI (coming from Germany and other countries)

2020 (total: 18)			
Germany	Europe	Asia	America
9	1	1	7
2019 (total: 47)			
Germany	Europe	Asia	America
35	8	2	2

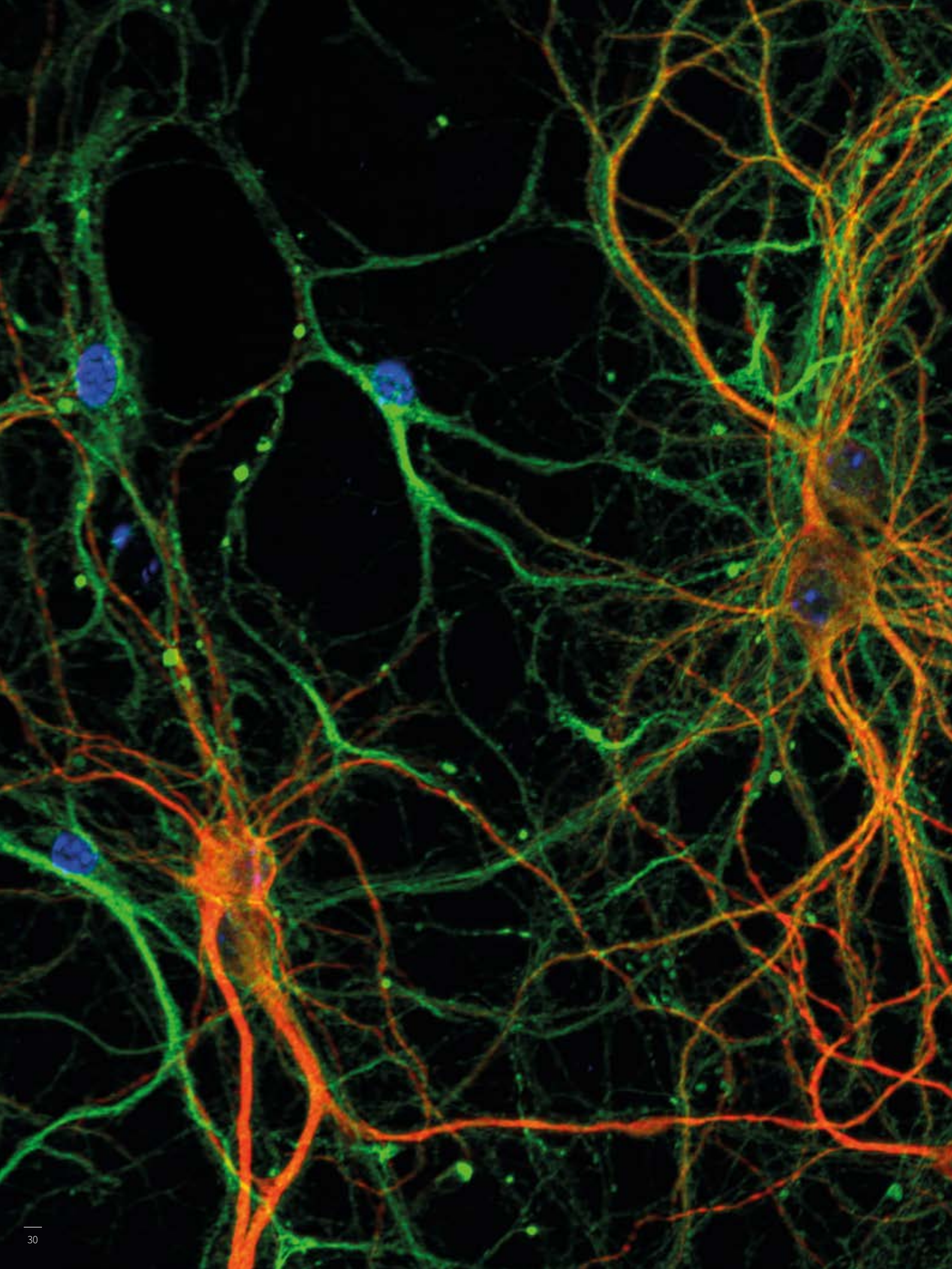
Talks by FLI-Scientists

2020 (total: 29)		
Presentations at scientific conferences and meetings	Guest lectures in other scientific institutions	Lectures in non-scientific institutions
15	14	0
2019 (total: 96)		
Presentations at scientific conferences and meetings	Guest lectures in other scientific institutions	Lectures in non-scientific institutions
74	21	1

Scientific Meetings and Workshops

09/23/2020 – 09/25/2020	(online) The 8th Annual German Stem Cell Network (GSCN) Conference. Organizers: Claudia Waskow (FLI) and German Stem Cell Network (Berlin, Germany)
10/03/2019 – 10/08/2019	3rd International Conference on Stem Cells, Chania, Crete, Greece. Organized by Claudia Waskow (FLI) and Laurie Boyer (MIT, US), Kursad Turksen (Springer Nature, CA), Jefferey Dillworth, Marjorie Brand (Ottawa Hospital Research Institute, CA), Jacob (Yaqub) Hanna (Weizmann Institute of Science, Israel), Magdalena Zernicka-Goetz (University of Cambridge, UK)
09/03/2019 – 10/03/2019	9th International Meeting Jena – Beijing: Molecular Signatures of Adaptive Stress Responses, Leipzig and Jena. Organized by: Zhao-Qi Wang (FLI), Thorsten Heinzel (FSU) and Xingzhi Xu (Shenzhen University)
05/22/2019 – 05/23/2019	Workshop: Embryotransfer, Jena, Germany. Organized by Antonina Klippert (FLI) and Tina Rüdiger (FLI)
03/06/2019 – 03/08/2019	de.NBI Meeting: Galaxy for linking Bisulfite sequencing with RNA sequencing, Rostock, Germany. Organized by: Steve Hoffmann (FLI) and Konstantin Riege (FLI)

Everyday laboratory work at FLI.



Research Balance

Research Balance

Research focus

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

I.

Stem Cells, Regeneration and Organ Homeostasis in Aging

Stem Cells, Regeneration and Organ Homeostasis in Aging

With age, the maintenance of 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 reduced activity 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 and 2.

II.

Genetics, Epigenetics and Molecular Cell Dynamics of Aging

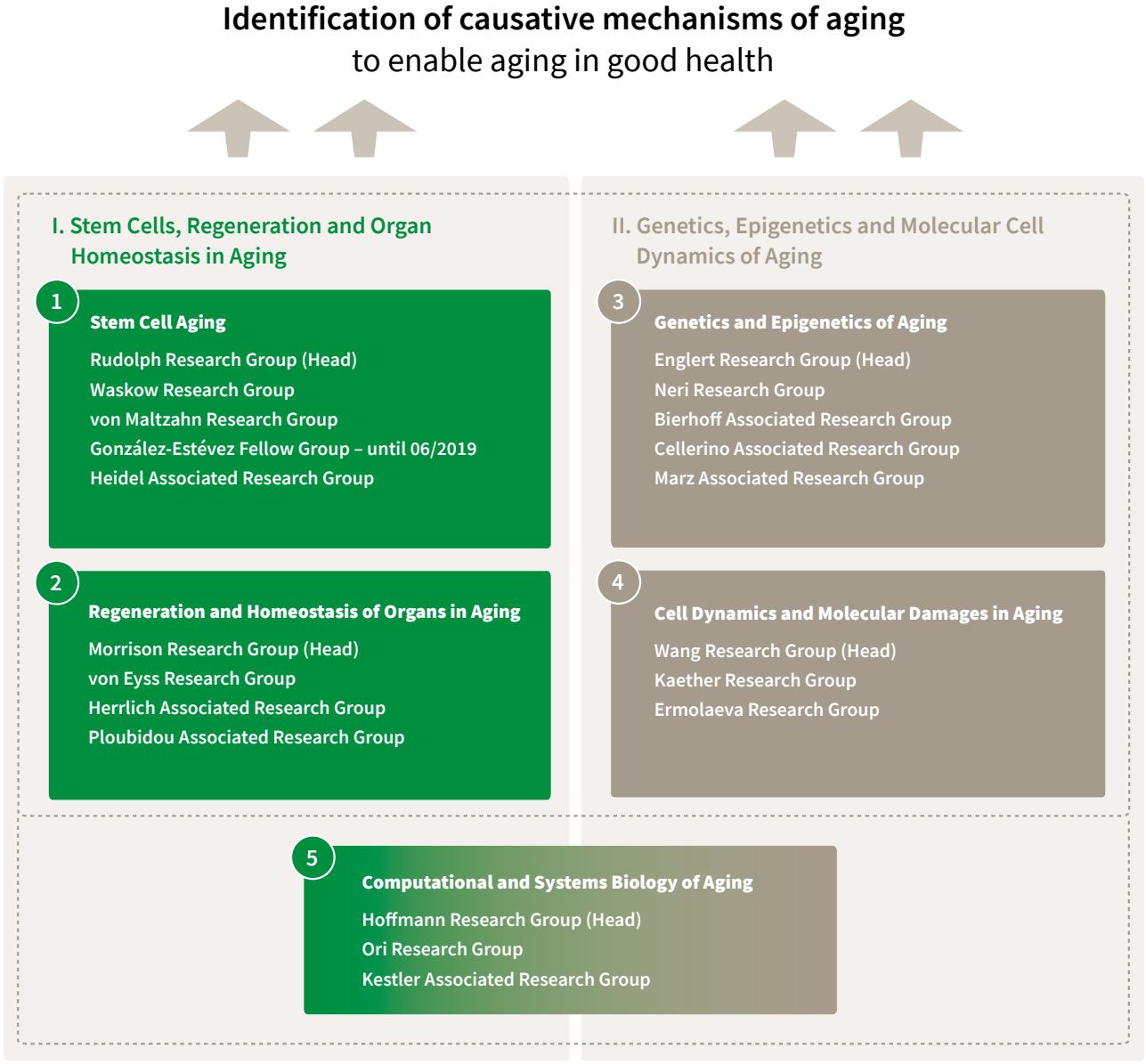
Genetics, Epigenetics and Molecular Cell Dynamics of Aging

A central phenomenon of 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 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 and 4.

Systems Biology and Bioinformatics of Aging

Systems Biology and Bioinformatics of Aging

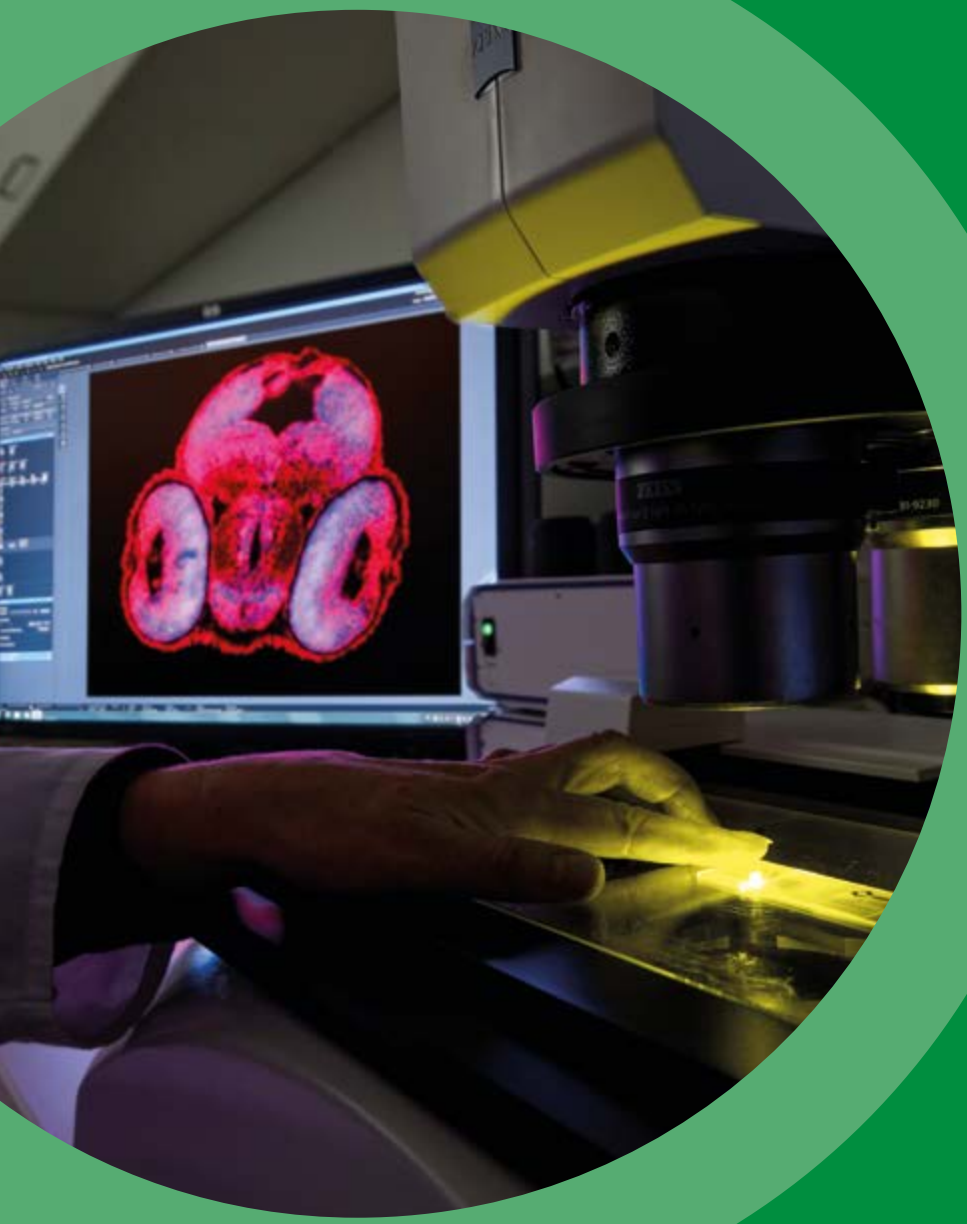
Systems biology and bioinformatics analyses compare the research results obtained in model organisms and on human samples in order to derive hypotheses and predictions about the molecular causes of aging in humans. These hypotheses are tested in collaboration with medical scientists to determine their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



Research Groups that conducted research at FLI in 2019/2020.

Research Area I

Stem Cells, Regeneration and Organ Homeostasis in Aging



Stem Cells, Regeneration and Organ Homeostasis in Aging

Rudolph Research Group:
Stem Cell Aging

Prof. Dr. K. Lenhard Rudolph
Group Leader

1

CENTRAL RESEARCH FOCUS:

What are the causes and consequences of age-related metabolic changes on stem cell function and can they be therapeutically influenced?

Focus of Research

The focus of this research is the fundamental loss of metabolic plasticity (adaptability) of the aging organism. The organism responds to a reduction in nutrient intake or to exercise by activating molecular stress signals in cells and tissues, which causes an increase in metabolic efficiency and counteracts the aging process. This basic principle of activation of health-promoting signals in response to mild stress (diet or exercise) is called hormesis (from the Greek: stimulation, adaptive response). Hormesis leads, for example, to damaged components of cells digesting themselves (autophagy), to age-related chemical changes in genetic information being erased (epigenetic aging) or to an improvement in the metabolic and functional performance of stem cells and tissues.

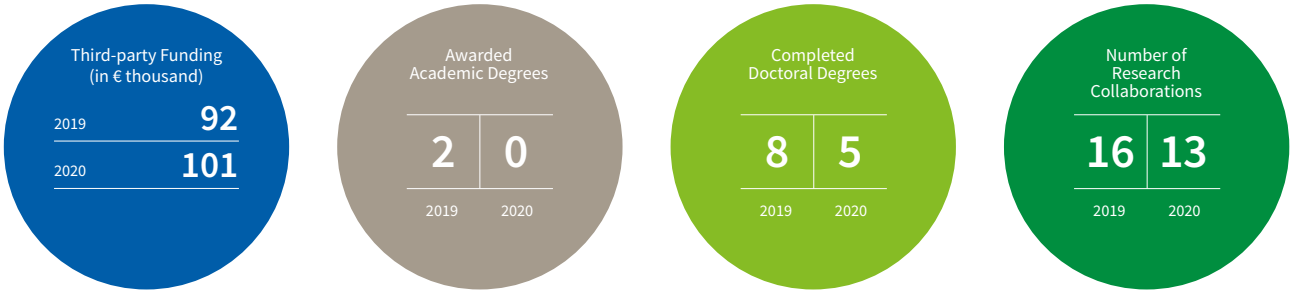
In various animal species, a significant increase in lifespan can be observed as a result of dietary restriction (DR), and improvement in health parameters also occurs in humans. However, recent studies show that DR is not as effective when treatment begins at an advanced age. The research group postulates that underlying this age-dependent failure of DR is a loss of metabolic adaptability and decreased activation of hormesis mechanisms.

Current Projects

1. Mechanisms of age-dependent loss of efficacy of dietary restriction.
2. Age-dependent changes in the metabolism of vitamins and their effects on stem cell and bodily functions.
3. Mechanisms of epigenetic memory in aging stem cells and tissues with respect to inflammatory signaling and metabolic stress.

Based on our mechanistic studies, we are developing and testing dietary, metabolic and epigenetic interventions to improve stem cell function, tissue maintenance and health in aging.

Key Figures



Selected Publications

Njeru* SN, Kraus* J, Meena* JK, Lechel A, Katz SF, Kumar M, Knippschild U, Azoitei A, Wezel F, Bolenz C, Leithäuser F, Gollowitzer A, Omrani O, Hoischen C, Koeberle A, Kestler** HA, Günes** C, Rudolph** KL.
Aneuploidy-inducing gene knockdowns overlap with cancer mutations and identify Orp3 as a B-cell lymphoma suppressor.
Oncogene 2020, 39(7), 1445-65
(* equal contribution, ** co-corresponding authors).

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.
Tnfaip2/exoc3-driven lipid metabolism is essential for stem cell differentiation and organ homeostasis.
EMBO Rep 2021, 22(1), e49328 (** co-corresponding authors).

Chen Z, Amro EM, Becker F, Hölzer M, Rasa SMM, Njeru SN, Han B, Di Sanzo S, Chen Y, Tang D, Tao S, Haenold R, Groth M, Romanov VS, Kirkpatrick JM, Kraus JM, Kestler HA, Marz M, Ori A, Neri F, Morita** Y, Rudolph** KL.
Cohesin-mediated NF-γB signaling limits hematopoietic stem cell self-renewal in aging and inflammation.
J Exp Med 2019, 216(1), 152-75 (** co-corresponding authors).

Tümpel S, Rudolph KL.
Quiescence: Good and Bad of Stem Cell Aging.
Trends Cell Biol 2019, 29(8), 672-85.

Third-party Funding (selection)

DFG Deutsche Forschungsgemeinschaft

Università degli Studi della Campania Luigi Vanvitelli

Leibniz Gemeinschaft

CSC SCHOLARSHIP A WAY TO YOUR DREAMS

NSFC

Prof. Dr. Claudia Waskow
Group Leader

Waskow Research Group: Immunology of Aging – Regeneration in Hematopoiesis

1

CENTRAL RESEARCH QUESTION:

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 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. 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 aging research. Moreover, defects in hematopoiesis can lead to life-threatening blood diseases.

On the other hand, the fact that all blood and immune cells are continuously formed from hematopoietic stem cells through the lifetime is being 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.

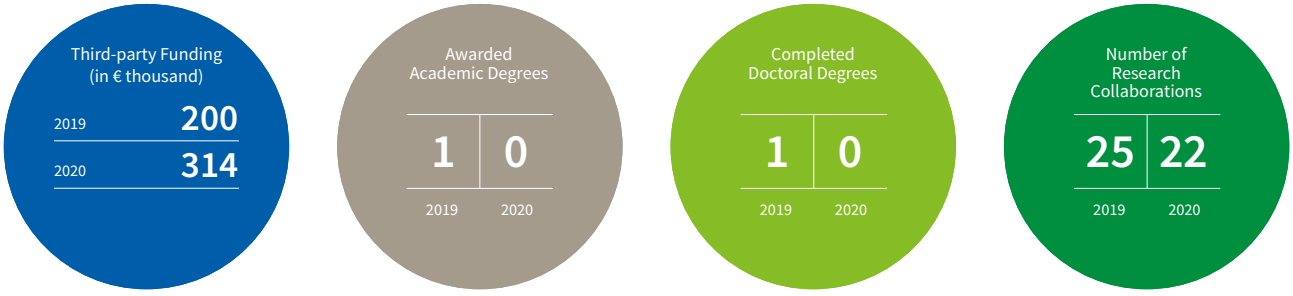
Current Projects

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.

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

Jayavelu AK, Schnöder TM, Perner F, Herzog C, Meiler A, Krishnamoorthy G, Huber N, Mohr J, Edelmann-Stephan B, Austin R, Brandt S, Palandri F, Schröder N, Isermann B, Edlich F, Sinha AU, Ungelenk M, Hübner CA, Zeiser R, Rahmig S, Waskow C, Coldham I, Ernst T, Hochhaus A, Jilg S, Jost PJ, Mullally A, Bullinger L, Mertens PR, Lane SW, Mann M, Heidel FH.
Splicing factor YBX1 mediates persistence of JAK2-mutated neoplasms.
Nature 2020, 588(7836), 157-63.

Weinberger T, Esfandyari D, Messerer D, Percin G, Schleifer C, Thaler R, Liu L, Stremmel C, Schneider V, Vagnozzi RJ, Schwanenkamp J, Fischer M, Busch K, Klapproth K, Ishikawa-Ankerhold H, Klösges L, Titova A, Molkentin JD, Kobayashi Y, Engelhardt S, Massberg S, Waskow C, Perdiguero EG, Schulz C.
Ontogeny of arterial macrophages defines their functions in homeostasis and inflammation.
Nat Commun 2020, 11(1), 4549.

Jacome-Galarza* CE, Percin* GI, Muller* JT, Mass* E, Lazarov T, Eitler J, Rauner M, Yadav VK, Crozet L, Bohm M, Loyher PL, Karsenty G, Waskow** C, Geissmann** F.
Developmental origin, functional maintenance and genetic rescue of osteoclasts.
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Mende* N, Jolly* A, Percin* GI, Günther M, Rostovskaya M, Krishnan SM, Oostendorp RAJ, Dahl A, Anastassiadis K, Höfer** T, Waskow** C.
Prospective isolation of non-hematopoietic cells of the niche and their differential molecular interactions with HSCs.
Blood 2019, 134(15), 1214-26.
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Garg S, Reyes-Palomares A, He L, Bergeron A, Lavallée VP, Lemieux S, Gendron P, Rohde C, Xia J, Jagdhane P, Müller-Tidow C, Lipka DB, Imren S, Humphries RK, Waskow C, Vick B, Jeremias I, Richard-Carpentier G, Hébert J, Sauvageau G, Zaugg J, Barabé F, Pabst C.
Hepatic leukemia factor is a novel leukemic stem cell regulator in DNMT3A, NPM1, and FLT3-ITD triple-mutated AML.
Blood 2019, 134(3), 263-76.

Third-party Funding (selection)

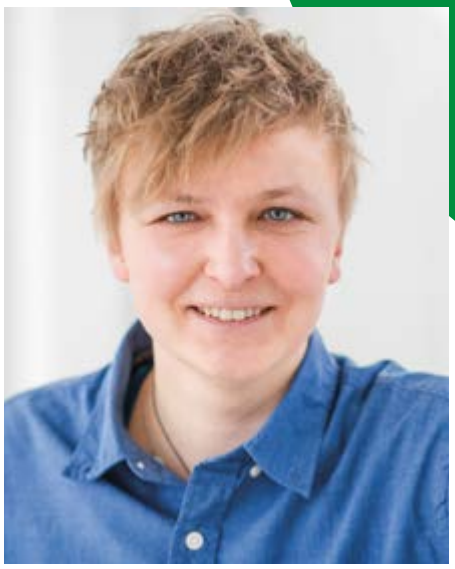
DFG Deutsche Forschungsgemeinschaft

Leibniz Gemeinschaft

E-Rare

Freistaat Thüringen
Ministerium für Wirtschaft, Wissenschaft und Digitale Gesellschaft

von Maltzahn Research Group: Stem Cells in Skeletal Muscle



Dr. Julia von Maltzahn
Group Leader

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 altered innervation, which are more likely to occur with increasing age.

Methodology

First, to better understand muscle stem cell function, muscle stem cells will be isolated from adult, old and geriatric mice and examined for changes. Methods used for functional analysis of muscle stem cell function include:

1. 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.
2. Injuring the skeletal muscles. Skeletal muscles of adult, old or geriatric mice are damaged by injection of the snake venom cardiotoxin. Thus, the entire regeneration process can be analyzed.

Research Results

With our research, we were able to show, among other things, that the JAK/STAT signaling pathway and the transcription factor Hoxa9 are more strongly expressed in old muscle stem cells than in muscle stem cells of adult mice, significantly worsening the regenerative capacity. Furthermore, we demonstrated that the muscle stem cell niche changes significantly with age, leading to activation of the ERK signaling pathway in muscle stem cells, which in turn impairs muscle stem cell functionality. 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

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Stange K, Ahrens HE, von Maltzahn J, Röntgen M.
Isolation and ex vivo cultivation of single myofibers from porcine muscle.
In Vitro Cell Dev Biol Anim 2020, 56(8), 585-92.

Weigel C, Hüttner SS, Ludwig K, Krieg N, Hofmann S, Schröder NH, Robbe L, Kluge S, Nierhaus A, Winkler MS, Rubio I, von Maltzahn J, Spiegel S, Gräler MH.
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J Vis Exp 2019 (* equal contribution).

Third-party Funding (selection)

González-Estévez Fellow Group: Stem Cells / Regeneration of Planarian (until 06/2019)

1

Cristina González-Estévez, PhD
Fellow Group Leader

CENTRAL RESEARCH QUESTION:

How does starvation regulate planarian stem cells?

Focus of Research

The fellow group "Stem Cells / Regeneration of Planarians" is interested in understanding how stem cells are regulated during fasting. It has been suggested that the beneficial effects of caloric restriction and fasting in delaying aging are due, at least in part, to an enhancement in stem cell function. The overall objective is the identification of mechanisms involved in stem cell regulation during fasting. To address this, the lab uses the freshwater planarian *Schmidtea mediterranea*.

All planarian organs are embedded in a mesodermal tissue known as parenchyma, which consists of several non-proliferating cell types and only one mitotically active cell type, the neoblast. Neoblasts are adult stem cells, which account for approximately 15–25 % of all parenchymal cells and include pluripotent stem cells. The proliferative capacity and pluripotency of these stem cells underlies the extreme and renowned tissue plasticity and regeneration capabilities of planarians. Planarians represent an excellent model with which to study stem cells – and specifically how fasting regulates them – since they are able to withstand long periods of starvation.

Research findings

1. It was found that the chaperonin TRiC, a component of the proteostasis network, is up-regulated in starved planarian stem cells and that its down-regulation abrogates the regeneration capacity of planarians during starvation, but is dispensable for regeneration in fed planarians. Under starvation, TRiC is required to maintain genome stability and mitotic fidelity through activation of the unfolded protein response (UPR), as well as to maintain ATP levels in starved planarians. The work also involved the mouse model and validated this novel regulatory axis in a mammalian regenerative system, that of mouse hematopoietic stem and progenitor cells (HSPCs) under glucose deprivation.
2. It was found that starvation increases the proportion of stem cells with long telomeres and also telomere length. The data showed that starvation is able to rejuvenate a stem cell pool in terms of telomere length through down-regulation of mTOR signalling.
3. The group has collaborated in a project from K. L. Rudolph demonstrating that the planarian model can be employed to identify the in vivo function of genes identified in a screen for pluripotency induction in culture.

Key Figures

Selected Publications

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Downregulation of mTOR Signaling Increases Stem Cell Population Telomere Length during Starvation of Immortal Planarians.
Stem Cell Reports 2019, 13(2), 405-18 (** co-corresponding authors).

Felix DA, Gutiérrez-Gutiérrez Ó, Espada L, Thems A, González-Estévez C.
It is not all about regeneration: planarians striking power to stand starvation.
Semin Cell Dev Biol 2019, 87, 169-81.

Heidel Associated Research Group:
Stem Cell Aging / Myeloid Neoplasms

1

Prof. Dr. Florian Heidel
Cooperation with Jena University Hospital, Jena, Germany

CENTRAL RESEARCH QUESTION:

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

Focus of Research

The Heidel group is searching for molecules responsible for cell competition, cell fate decisions and cell self-renewal in the development and maintenance 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. Therefore, artificially reprogrammed stem cells, so-called induced pluripotent stem cells, as well as cell models derived from patient samples (patient-derived xenograft models, PDX) are used in preclinical studies.

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J Am Soc Nephrol 2020, 31(11), 2589-608.

Key Figures

Third-party Funding (selection)

DFG Deutsche Forschungsgemeinschaft

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Wilhelm Sander-Stiftung
fördert medizinische Forschung

Laboratory work at FLI.

Morrison Research Group:
Nerve Regeneration

Prof. Dr. Helen Morrison
Group Leader

2

CENTRAL RESEARCH QUESTION:

How does the signaling that underlies maintenance and regeneration of the nervous system become impaired during aging?

Focus of Research

The research group "Nerve Regeneration" is interested in the processes of nerve regeneration, the nature of cell communication, and the mis-wiring of signaling pathways in disease and in the aging process. The lab focuses on age-dependent signaling impairments underlying nervous system maintenance and regeneration, and in disease mechanisms for disorders of myelinating cells and nervous system tumors. These disease areas represent a great medical need, and the lab's work aims to perform translational work in each area. Methodologically, a multidisciplinary approach is used that includes structural, cellular and mouse models.

Key Findings

The research group studies the tight control of the activation state of small GTPases; these proteins are central to many key biological processes. This interest in small GTPases was prompted by an observation that members of a family of actin-binding proteins – the tumor suppressor protein neurofibromin 2 (merlin) and the putative tumor promoters ezrin, radixin and moesin (ERM) – act as counterplayers in Ras activation. Merlin is inhibitory, while the ERM proteins appear to enhance Ras activity. These regulatory structures present a novel aspect in the type of signal transduction relevant in cancer and in all physiological processes involving Ras.

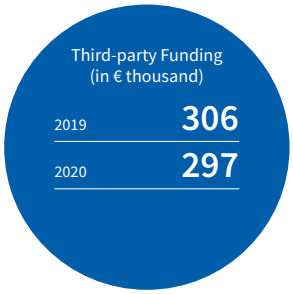
Current Projects

Peripheral Nerve Regeneration and Aging | It is accepted that the aging process significantly impairs the ability of peripheral nerves to regenerate after injury – but the molecular pathways that 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,
- elucidating the role of the microenvironment, both during cell repair and cancer development, and
- utilizing novel mouse models for the study of tumor development in Neurofibromatosis type 2 disease (NF2). The lab has extensive experience in NF2 research, including dissecting NF2 signaling pathways, and is part of the international clinical consortium "Synodos."

Brain Plasticity and the Regenerating Brain | The Morrison Lab research prioritizes Ras and Ras-like protein activity control in synaptic and structural neuroplasticity – the cellular basis for memory formation. Another goal of the lab is to dissect key signaling events and study the cellular components to learn about the molecular pathways involved in neuroprotection and repair, and to progress towards healthy brain aging as well as brain repair after injury.

Key Figures



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Third-party Funding (selection)

Bundesministerium für Bildung und Forschung

DFG Deutsche Forschungsgemeinschaft

Leibniz Gemeinschaft

Else Kröner Fresenius Stiftung

Dr. Björn von Eyss
Group Leader

Von Eyss 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 cancer development?

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.

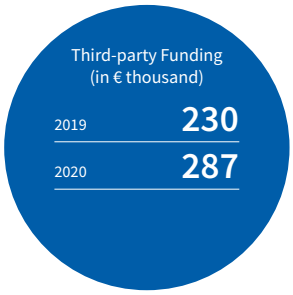
Because a deep understanding of the regulation of the Hippo signaling pathway will lead to new insights into aging, stem cell biology and tissue homeostasis, the research group focuses on different aspects of the biology of YAP/TAZ. The goal is to identify novel signaling pathways, and thus target sites, 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 cancer development. 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, ATAC-Seq, RNA-Seq, 4SU-Seq, SLAM-Seq, capture Hi-C
- Pooled genome-wide CRISPR screens and focused screens: CRISPR, shRNA, SAM and siRNA.
- Inducible mouse models

Key Figures



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Third-party Funding (selection)

DFG Deutsche Forschungsgemeinschaft

Bundesministerium für Bildung und Forschung

Else Kröner Fresenius Stiftung

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Alexander von Humboldt
Stiftung/Foundation

Herrlich Associated Research Group: Cancer Cell Biology

2

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

CENTRAL RESEARCH QUESTION:

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 osteosarcoma metastasis?

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.

In their search for the mechanism that leads to hydrocephalus, researchers discovered a new assembly function in mice in which the TRIP6 gene had been knocked out: 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 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.

Selected Publications

Ma* J, Klemm* J, Gerardo-Ramírez M, Frappart L, Castven D, Becker D, Zoch A, Parent R, Bartosch B, Minnich K, Giovannini M, Danckwardt S, Hartmann N, Morrison H, Herrlich** P, Marquardt** JU, Hartmann** M.
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Int J Cancer 2020, 147(9), 2564-77.
(** co-senior authors, * equal contribution).

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(* equal contribution, ** co-corresponding authors).

Key Figures

Third-party Funding (selection)

JUNG-Stiftung für Wissenschaft und Forschung

Ploubidou Associated Research Group: Virus-induced Oncogene

2

Aspasia Ploubidou, PhD
Associated Group Leader

CENTRAL RESEARCH QUESTION:

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

Focus of Research

Cancer is a major age-related pathology with etiology in genetic defects and 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 converts intra- and extra-cellular signaling into structures and structure remodeling. We investigate how cytoskeletal signaling contributes to cell renewal or commitment to differentiation and how this signaling is subverted in cancer. We have identified 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.

Cancer cells encode very complex and numerous defects, which can now be documented by very precise measurements (genomics, transcriptomics, proteomics, etc.). Nonetheless, understanding the underlying disease process requires a shift from the focus on single components to methodologies that compute the interdependencies of thousands of components. To this end, the group initiated an interdisciplinary approach to build and validate a computational mechanistic model of cancer signaling (CanPathPro.eu). The input for the mechanistic model is “omics” data 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, we have identified and verified both expected but also counterintuitive signaling hypotheses for the individual components and pathways promoting these cancers.

Selected Publications

Li* H, Shukla* S, Frappart L, Herrlich** P, Ploubidou** A.
CD44 deletion suppresses atypia in the precancerous mouse testis.
Mol Carcinog 2019, 58(5), 621-6.
(* equal contribution, ** co-corresponding authors).

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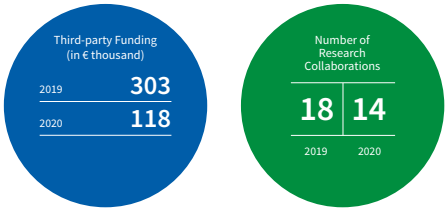
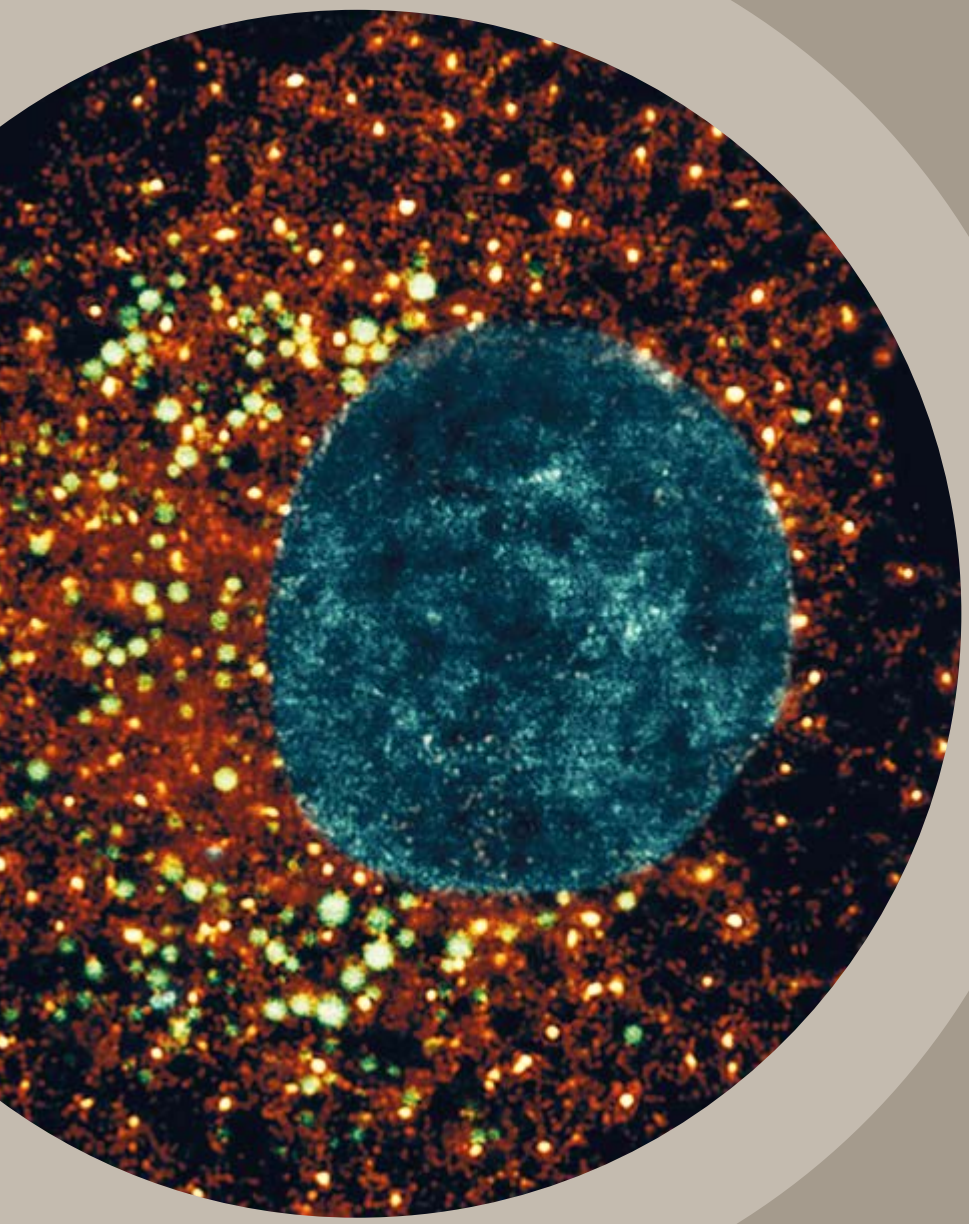
Key Figures



Third-party Funding (selection)

Research Area II

Genetics, Epigenetics and Molecular Cell Dynamics of Aging



Genetics, Epigenetics and Molecular Cell Dynamics of Aging

Englert Research Group:
Molecular Genetics

3

Prof. Dr. Christoph Englert
Group Leader

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. This is done with the help of biochemical and cell biological methods as well as using different animal models.

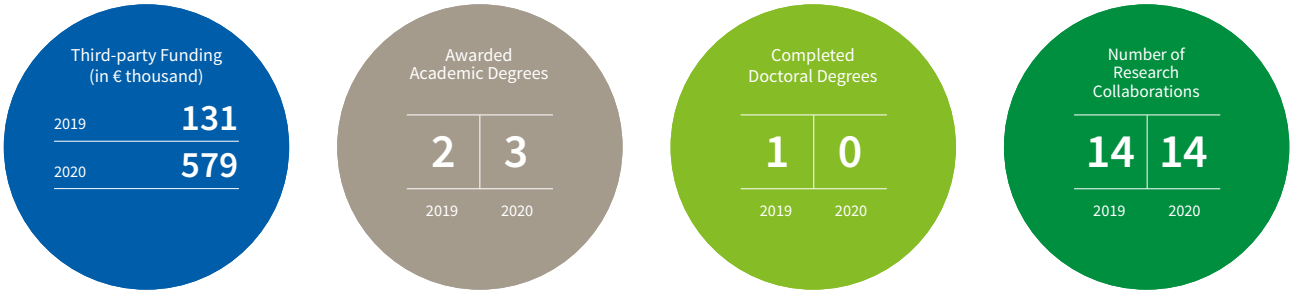
Signaling pathways that regulate aging and lifespan in short-lived vertebrates | The identification of vertebrate genes that control the aging process is complicated by the relatively long lifespan of animal models available until recently. In 2004, an annual fish species with an exceptionally short 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 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, on the other hand, 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 gourami 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



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Third-party Funding (selection)

Bundesministerium für Bildung und Forschung
DFG Deutsche Forschungsgemeinschaft
Leibniz Gemeinschaft
Else Kröner Fresenius Stiftung
FRIEDRICH-SCHILLER-UNIVERSITÄT JENA
Thüringer Aufbaubank Die Förderbank.
VELUX STIFTUNG
SHENZHEN UNIVERSITY 1983

Francesco Neri, PhD
Group Leader

Neri Research Group:
Epigenetics of Aging / Damage Accumulation

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. Several studies have demonstrated that intestinal stem cells represent the cells-of-origin of cancers and that clonal dominance of mutant stem cells appears frequently during aging.

Emerging evidence indicates 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. Among these factors, DNA methylation (a stable and heritable epigenetic modification) has been associated with aging-induced diseases and cancer development. Recent discovery that DNA methylation can be actively removed by TET proteins (ten-eleven-translocation) has revealed the importance of this epigenetic modification in several biological models.

Research Objectives

The focus of the Neri lab is the functional characterization of transcriptome and epigenome alterations that occur during adult stem cell aging in the intestinal system.

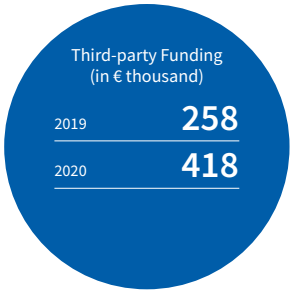
The main aims are:

1. to define transcriptional and epigenetic alterations of stem cells during aging (focusing on DNA methylation changes together with principal histone modifications)
2. to characterize the mechanistic basis of the evolution of these changes
3. to understand the functional consequences of aging-induced epigenetic alterations on stem cell function in organ homeostasis and delineate their role in promoting clonal dominance and neoplastic transformation.

Methods

The group employs genome-wide and single-cell technology to dissect alterations of the transcriptional and epigenetic landscape of the stem cells of the mouse small intestine and colon. 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 intestine in vivo, to characterize in vitro organoid systems and to analyze DNA methylation in rare cells.

Numbers



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Intestinal stem cells heterogeneity and clonal dominance during aging: two faces of the same coin?
Mech Ageing Dev 2020, 189, 111247 (* equal contribution).

Cencioni* C, Heid* J, Krepelova A, Rasa SMM, Kuenne C, Guenther S, Baumgart M, Cellerino A, Neri F, Spallotta** F, Gaetano** C.
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Cohesin-mediated NF-γB signaling limits hematopoietic stem cell self-renewal in aging and inflammation.
J Exp Med 2019, 216(1), 152-75 (** co-corresponding authors).

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EMBO J 2019, 38(3), e98250.

Third-party Funding (selection)

DFG Deutsche Forschungsgemeinschaft

Leibniz Gemeinschaft

Else Kröner Fresenius Stiftung

DZHK
DEUTSCHES ZENTRUM FÜR HERZ-KREISLAUF-FORSCHUNG E.V.

Chan Zuckerberg Initiative

Bierhoff Associated Research Group: Epigenetics of Aging / Chromatin Landscape

3

Dr. Holger Bierhoff
Cooperation with Friedrich Schiller University Jena (FSU), Germany

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 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 group is investigating these epigenetic regulatory mechanisms (rRNA genes), which are characterized by a high copy number and by strong activity. The functions of ncRNAs are also in focus. In particular, we 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. To this end they would like to clarify 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 healthspan
- Relationship between stability of rRNA genes and aging
- Regulation of rRNA genes by non-coding RNA PAPAS
- Control of the Kras proto-oncogene by the interplay of G-quadruplex and RNA:DNA triplex structures
- Genome-wide identification of RNA:DNA triplexes

Selected Publications

Joshi* G, Eberhardt* AO, Lange L, Winkler R, Hoffmann S, Kosan C, Bierhoff H.
Dichotomous Impact of Myc on rRNA Gene Activation and Silencing in B Cell Lymphomagenesis.
Cancers (Basel) 2020, 12(10), 3009. (* equal contribution).

Sharifi'* S, Costa* HFRd, Bierhoff H.
The circuitry between ribosome biogenesis and translation in stem cell function and ageing.
Mech Ageing Dev 2020, 189, 111282 (* equal contribution).

Kofuji S, Hirayama A, Eberhardt AO, Kawaguchi R, Sugiura Y, (...) Soga T, Grummt I, Bierhoff H, Sasaki AT.
IMP dehydrogenase-2 drives aberrant nucleolar activity and promotes tumorigenesis in glioblastoma.
Nat Cell Biol 2019, 21(8), 1003-14.

Key Figures

Third-party Funding (selection)

Thüringer Aufbaubank
Die Förderbank.

Cellerino Associated Research Group: Biology of Aging

3

Alessandro Cellerino, PhD
Cooperation with Scuola Normale Superiore di Pisa, Italy

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 Neuro-degeneration 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.

Selected Publications

Kelmer Sacramento* E, Kirkpatrick* JM, Mazzetto* M, (...) Cellerino** A, Ori** A.
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Mol Syst Biol 2020, 16(6), e9596.
(* equal contribution, ** co-corresponding authors).

Napoli D, Lupori L, (...) Cellerino* A, Pizzorusso* T.
MiR-29 coordinates age-dependent plasticity brakes in the adult visual cortex.
EMBO Rep 2020, 21(11), e50431 (* equal contribution).

Dolfi L, Ripa R, Antebi A, Valenzano DR, Cellerino A.
Cell cycle dynamics during diapause entry and exit in an annual killifish revealed by FUCCI technology.
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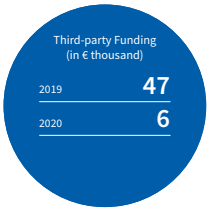
Analysis of the coding sequences of clownfish reveals molecular convergence in the evolution of lifespan.
BMC Evol Biol 2019, 19(1), 89.

Third-party Funding (selection)

DFG Deutsche Forschungsgemeinschaft

SCUOLA NORMALE SUPERIORE

Key Figures



Marz Associated Research Group:
Non-coding RNAs in Aging

3

Prof. Dr. Manja Marz
Cooperation with Friedrich Schiller University Jena (FSU), Germany

CENTRAL RESEARCH QUESTION:

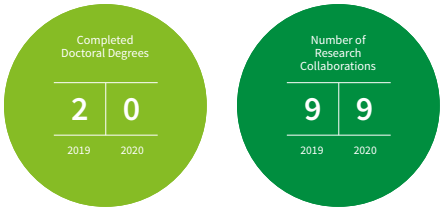
What is the impact of noncoding RNAs on the aging process?

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 2,400 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.

Key Figures



Current Projects

- Tissue-specific aging in mice
- Micro-RNA regulation of aging processes
- Aging-related RNA:DNA triplex structures
- ncRNAs as a cause of X-linked dystonia-parkinsonism
- Alteration of alternative splicing machinery in aging
- Expression changes of inflammatory and immune genes during aging
- Influence of age on circadian rhythms
- Alteration of hematopoiesis in aging

Selected Publications

Barth* E, Srivastava* A, Stojiljkovic* M, Frahm C, Axer H, Witte** OW, Marz** M.
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Aging (Albany NY) 2019, 11(19), 8556-72.
(** co-senior authors, * equal contribution).

Fricke M, Gerst R, Ibrahim B, Niepmann M, Marz M.
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Bioinformatics 2019, 35(4), 579-83.

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Placenta 2019, 88, 20-7 (* equal contribution).

Chen Z, Amro EM, (…) Marz M, Ori A, Neri F, Morita** Y, Rudolph** KL.
Cohesin-mediated NF-γB signaling limits hematopoietic stem cell self-renewal in aging and inflammation.
J Exp Med 2019, 216(1), 152-75 (** co-corresponding authors).

Fish husbandry at FLI: The zebrafish is an important model organism for studying the development of diseases.

Wang Research Group:
Genomic Stability

4

Prof. Dr. Zhao-Qi Wang
Group Leader

CENTRAL RESEARCH QUESTION:

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

Focus of Research

When DNA is damaged by intrinsic or extrinsic factors, there's 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 proper tissue homeostasis. The Research Group "Genomic Stability" uses cellular and molecular tools as well as animal models to determine the malfunction of DDR pathways and their work provides insights into premature aging and age-related pathogenesis (such as neurodegeneration) in humans.

Current Projects

The Cellular Response to DNA Damage

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

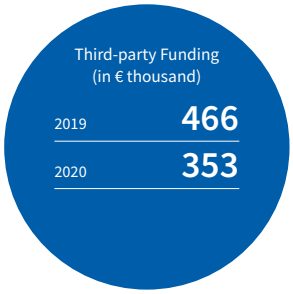
The Function of Poly(ADP-Ribosyl)ation

Poly(ADP-Ribosyl)ation – also called PARylation – is the fastest reaction to DNA damage, especially that incurred by SSBs and replication stress. Polymerase 1 (PARP1) detects the DNA damage, binds to it and provokes the building of long polymer chains (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 or inflammation and aging processes. The group is interested in elucidating how PAR signals to other proteins and executes 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 stem cell proliferation and differentiation (neurogenesis) as well as the maintenance of neurons (to prevent neurodegeneration). The research objective of the Wang laboratory is to understand the epigenetic modification of histones and the regulation of cell cycle progression in brain development and homeostasis during aging, thus laying the fundamentals for the development of new therapeutic strategies to improve cognitive capabilities in the elderly.

Key Figures



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Journiac N, Gilabert-Juan J, Cipriani S, Benit P, Liu X, Jacquier S, Faivre V, Delahaye-Duriez A, Csaba Z, Hourcade T, Melinte E, Lebon S, Violle-Poirsier C, Oury JF, Adle-Biassette H, Wang ZQ, Mani S, Rustin P, Gressens P, Nardelli J.
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Cell Rep 2020, 31(2), 107506.

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Am J Hum Genet 2020, 107(2), 364-73.

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ATR is essential for preservation of cell mechanics and nuclear integrity during interstitial migration.
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NBS1 interacts with Notch signaling in neuronal homeostasis.
Nucleic Acids Res 2020, 48(19), 10924-39.

Kamaletdinova* T, Fanaei-Kahrani* Z, Wang ZQ.
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Cells 2019, 8(12).

Third-party Funding (selection)

DFG Deutsche Forschungsgemeinschaft

German Israeli Foundation for Scientific Research & Development

Leibniz Gemeinschaft

Kaether Research Group:
Membrane Trafficking in Aging

4

Dr. Christoph Kaether
Group Leader

CENTRAL RESEARCH QUESTION:

How are membrane proteins transported and localized inside cells?

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

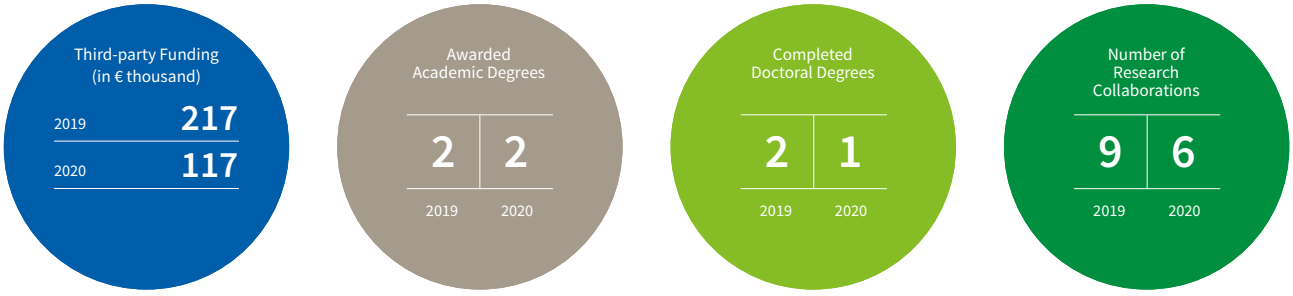
"Anti-aging" hormone Klotho | The membrane protein Klotho is located on the surface of cells and also circulates in the bloodstream as an "anti-aging hormone." Mice lacking this protein age extremely quickly. They show symptoms and diseases similar to those of human aging after only a brief lifespan. 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 reverse transporter 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 reverse transport 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



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A Caenorhabditis elegans ortholog of human selenium-binding protein 1 is a pro-aging factor protecting against selenite toxicity.
Redox Biol 2020, 28, 101323 (* equal contribution).

Zhou ZW, Kirtay M, Schneble N, Yakoub G, Ding M, Rüdiger T, Siniuk K, Lu R, Jiang YN, Li TL, Kaether C, Barzilai A, Wang ZQ.
NBS1 interacts with Notch signaling in neuronal homeostasis.
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Behrendt L, Kurth I, Kaether C.
A disease causing ATLASTIN 3 mutation affects multiple endoplasmic reticulum-related pathways.
Cell Mol Life Sci 2019, 76(7), 1433-45.

Kindermann B, Valkova C, Krämer A, Perner B, Engelmann C, Behrendt L, Kritsch D, Jungnickel B, Kehlenbach RH, Oswald F, Englert C, Kaether C.
The nuclear pore proteins Nup88/214 and T-ALL-associated NUP214 fusion proteins regulate Notch signaling.
J Biol Chem 2019, 294(31), 11741-50.

Kerp H, Engels K, Kramer F, Doycheva D, Sebastian Hönes G, Zwanziger D, Christian Moeller L, Heuer H, Führer D.
Age effect on thyroid hormone brain response in male mice.
Endocrine 2019, 66(3), 596-606.

Third-party Funding (selection)

DFG Deutsche Forschungsgemeinschaft

Carl Zeiss Stiftung

Ermolaeva Research Group:
Stress Tolerance and Homeostasis

4

Dr. Maria Ermolaeva
Group Leader

CENTRAL RESEARCH QUESTION:

How do metabolism and proteostasis change with age and how can these detrimental changes be attenuated?

Focus of Research

The research group "Stress Tolerance and Homeostasis" uses the nematode *C. elegans*, mammalian cells and short-lived killifish to identify changes in metabolism and stress responses that occur during aging, with an outlook toward restoring youthful responses to stress in later life. Our current focus is on the loss of mitochondrial homeostasis during aging, and our recent study discovered that aging-associated mitochondrial dysfunction abrogates the longevity benefits of the dietary restriction mimetic metformin. To follow up on this finding, we use whole animal single-cell sequencing in *C. elegans* and omics tests in killifish to probe tissue-specific and sex-specific responses to dietary restriction mimetic compounds in young and old organisms.

Role of External Stressors

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

Host Microbiome Interactions

Another topic of interest is the use of *C. elegans* as a non-vertebrate model for studying host microbiome interactions in aging. In collaboration with colleagues at the Hans Knöll Institute (HKI), we perform 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, and we are using this new technique in cooperation with colleagues at the University Hospital Jena and HKI to probe host effects of the microbial strains that are differentially enriched during human diseases such as sepsis.

Biomarkers of Metabolic Health

Finally, we 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 clinics to test these biomarkers for their ability to predict human metabolic disorders at the single-cell level, earlier than feasible using conventional diagnostics methods such as BMI and blood serum markers (cholesterol, insulin, glucose).

Key Figures

Selected Publications

Espada* L, Dakhovnik* A, Chaudhari* P, Martirosyan A, Miek L, Poliezhaieva T, Schaub Y, Nair A, Döring N, Rahnis N, Werz O, Koeberle A, Kirkpatrick J, Ori A, Ermolaeva MA.
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Nat Metab 2020, 2(11), 1316-31 (* equal contribution).

Chin-Chan M, Cobos-Puc L, Alvarado-Cruz I, Bayar M, Ermolaeva M.
Early-life Pb exposure as a potential risk factor for Alzheimer's disease: are there hazards for the Mexican population?
J Biol Inorg Chem 2019, 24(8), 1285-303.

Felix DA, Gutiérrez-Gutiérrez Ó, Espada L, Thems A, González-Estévez C.
It is not all about regeneration: planarians striking power to stand starvation.
Semin Cell Dev Biol 2019, 87, 169-81.

Third-party Funding (selection)

DFG Deutsche Forschungsgemeinschaft

DAAD Deutscher Akademischer Austauschdienst German Academic Exchange Service

Thüringer Aufbaubank Die Förderbank.

Interconnecting Subarea

Computational and Systems Biology of Aging

Computational and Systems Biology of Aging

Hoffmann Research Group:
Computational Biology of Aging

Prof. Dr. Dr. Steve Hoffmann
Group Leader

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

Highly age-dependent DNA hydroxymethylation 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.

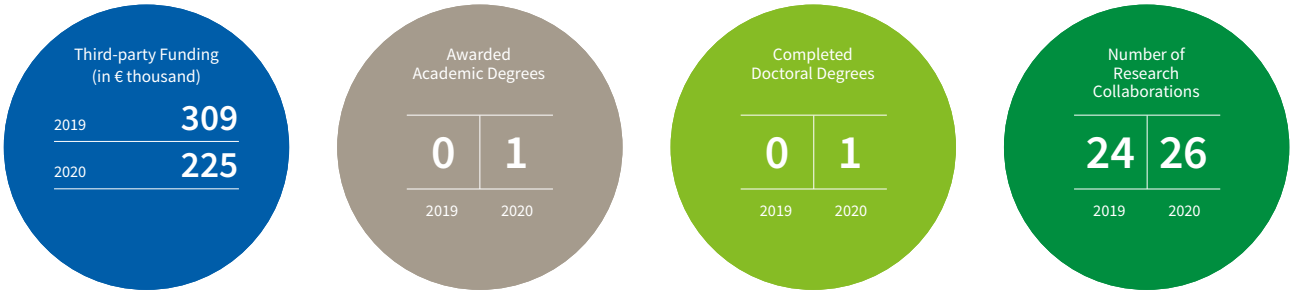
The Network of the Tumor Suppressor p53

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

Campbell PJ, Getz G, Korbel Jea, ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium.
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Third-party Funding (selection)

DFG Deutsche Forschungsgemeinschaft

Bundesministerium für Bildung und Forschung

JOACHIM HERZ STIFTUNG

Klaus Tschira Stiftung gemeinnützige GmbH

KTS

Ori Research Group:
Aging of Protein Complexes

Alessandro Ori, PhD
Group Leader

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 alterations of the proteome to reveal mechanisms of organ deterioration that impact on healthy lifespan and render the elderly more susceptible to disease.

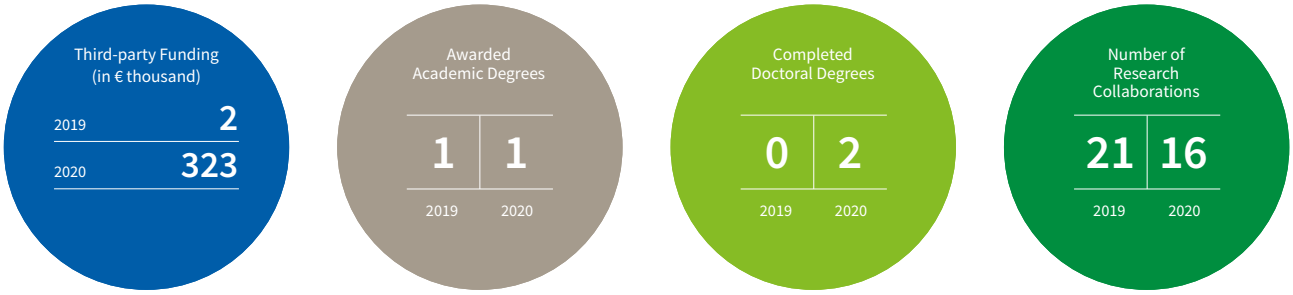
Current Projects

Stem Cell Aging | Adult (somatic) stem cells play a crucial role in maintaining and regenerating organs. However, their function and number decrease during aging. A particular focus of the group is to understand 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 Proteostasis Impairment in Aging and Neurodegeneration | The impairment of proteostasis and resulting aggregation of misfolded proteins are associated with age-related diseases such as neurodegenerative disorders and type II diabetes. 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) the interplay between mutations linked to increase risk of neurodegeneration and 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 Ori group, together with collaborators from Stanford University and Massachusetts Institute of Technology (MIT), pursues two major lines of research: (i) charting the composition of lysosomes in different brain cell types and in a model of Batten disease; (ii) studying the impact of aging and anti-aging interventions on the composition of lysosomes across multiple tissues.

Key Figures



Selected Publications

Gebert N, Cheng CW, Kirkpatrick JM, Di Fraia D, Yun J, Schädel P, Pace S, Garside GB, Werz O, Rudolph KL, Jasper H, Yilmaz ÖH, Ori A.
Region-Specific Proteome Changes of the Intestinal Epithelium during Aging and Dietary Restriction.
Cell Rep 2020, 31(4), 107565.

Kelmer Sacramento* E, Kirkpatrick* JM, Mazzetto* M, Baumgart M, Bartolome A, Di Sanzo S, Caterino C, Sanguanini M, Papaevgeniou N, Lefaki M, Childs D, Bagnoli S, Terzibasi Tozzini E, Di Fraia D, Romanov N, Sudmant PH, Huber W, Chondrogianni N, Vendruscolo M, Cellerino** A, Ori** A.
Reduced proteasome activity in the aging brain results in ribosome stoichiometry loss and aggregation.
Mol Syst Biol 2020, 16(6), e9596
(* equal contribution, ** co-corresponding authors).

Buczak K, Kirkpatrick JM, Truckenmueller F, Santinha D, Ferreira L, Roessler S, Singer S, Beck** M, Ori** A.
Spatially resolved analysis of FFPE tissue proteomes by quantitative mass spectrometry.
Nat Protoc 2020, 15(9), 2956-79 (** co-corresponding authors).

Muntel* J, Kirkpatrick* J, Bruderer R, Huang T, Vitek O, Ori** A, Reiter** L.
Comparison of protein quantification in a complex background by DIA and TMT workflows with fixed instrument time.
J Proteome Res 2019, 18(3), 1340-51
(** co-senior authors, * equal contribution).

Romanov N, Kuhn M, Aebersold R, Ori A, Beck M, Bork P.
Disentangling Genetic and Environmental Effects on the Proteotypes of Individuals.
Cell 2019, 177(5), 1308-18.

Third-party Funding (selection)

DZHK
DEUTSCHES ZENTRUM FÜR HERZ-KREISLAUF-FORSCHUNG E.V.

DFG Deutsche Forschungsgemeinschaft

Leibniz Gemeinschaft

Chan Zuckerberg Initiative

Else Kröner Fresenius Stiftung

Kestler Associated Research Group: Bioinformatics and Systems Biology of Aging

5

Prof. Dr. Hans Kestler
Cooperation with Ulm University, Germany

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 investigation results 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

Selected Publications

Lausser* L, Schäfer* LM, Kühlwein SD, Kestler AMR, Kestler HA.
Detecting Ordinal Subcascades
Neural Process Lett 2020, 52, 2583–2605 (* equal contribution).

Lausser* L, Szekely* R, Kestler HA.
Chained correlations for feature selection
Adv Data Anal Classif 2020, 14, 871–884 (* equal contribution).

Lausser L, Szekely R, Klimmek A, Schmid F, Kestler HA.
Constraining classifiers in molecular analysis: invariance and robustness.
J R Soc Interface 2020, *17(163)*, 20190612.

Dammann* P, Scherag* A, Zak N, Szafranski K, Holtze S, Begall S, Burda H, Kestler HA, Hildebrandt T, Platzer M.
Comment on 'Naked mole-rat mortality rates defy Gompertzian laws by not increasing with age'.
Elife 2019, 8 (* corresponding author).

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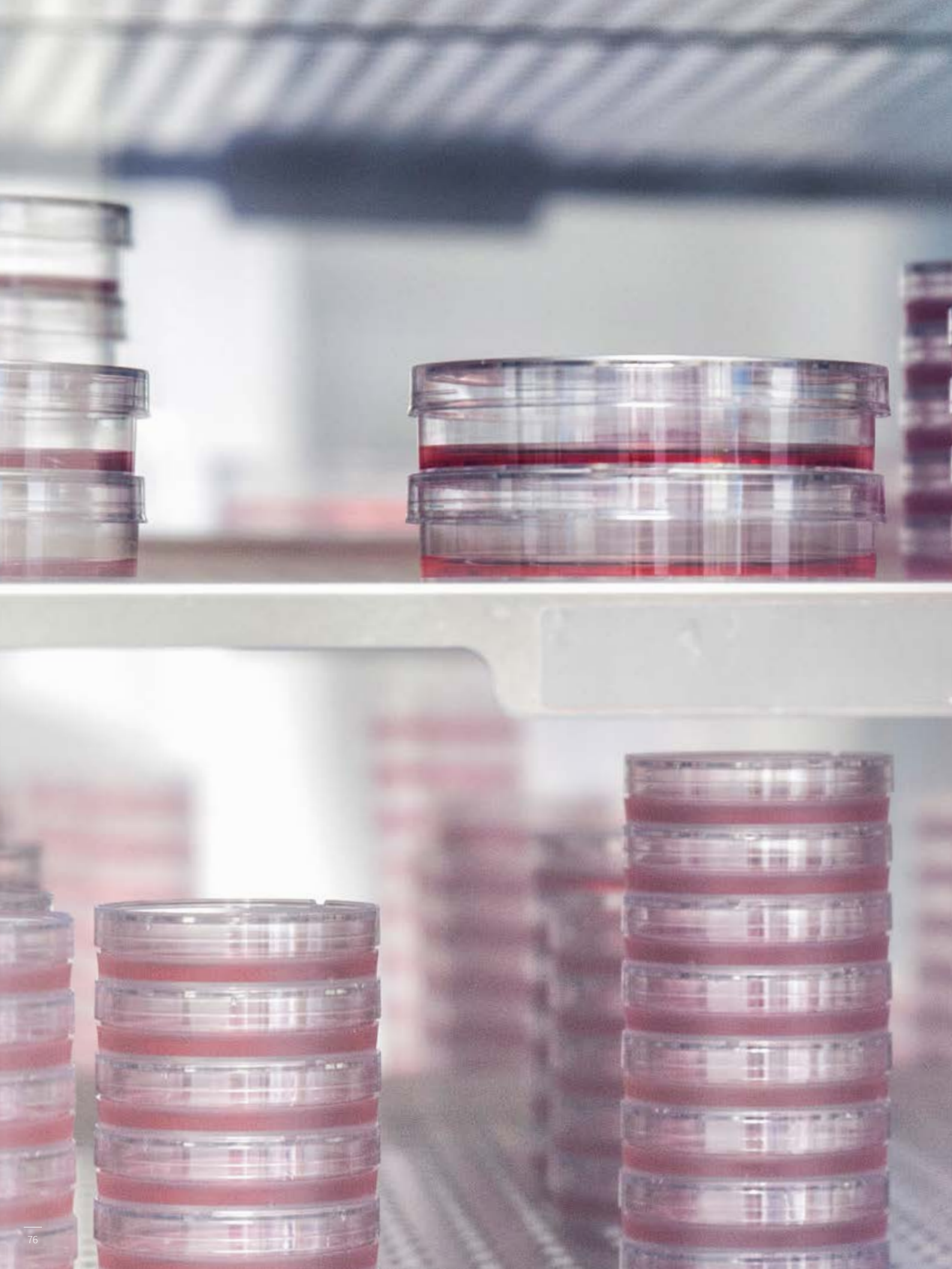
Author Correction: Epigenetic stress responses induce muscle stem-cell ageing by Hoxa9 developmental signals.
Nature 2019, *572(7769)*, E11-5 (** co-corresponding authors).

Key Figures

Server views.



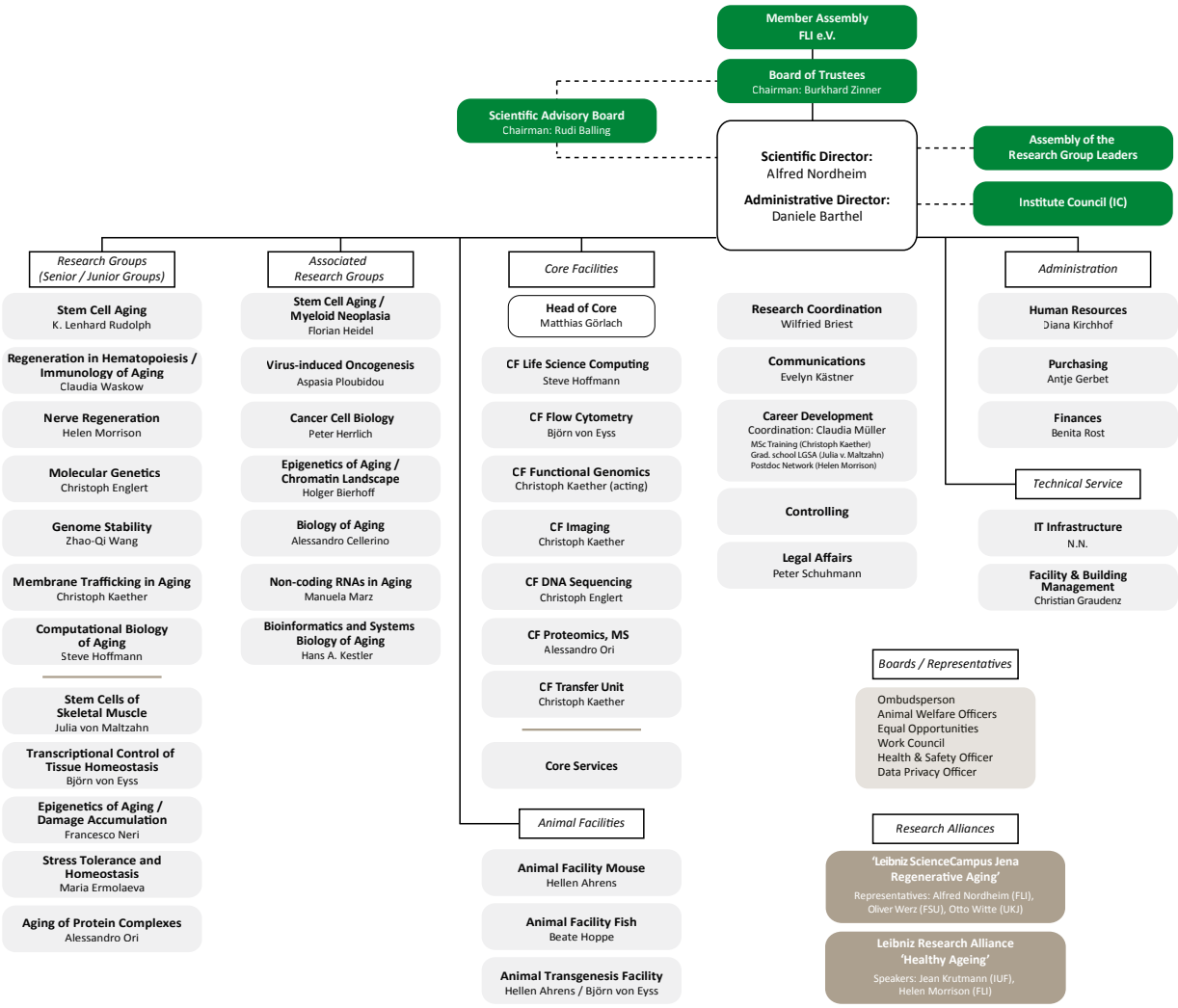
Organization

Organization and Structure

The Leibniz Institute for Aging Research (FLI) is one of 96 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 aging research.

The FLI is an institute with flat hierarchies. The Institute is headed by the Scientific Director and the Administrative Director. The basic organizational structure is comprised of the leaders of the research groups; there are no further hierarchical levels, such as departmental structures, below them. In addition, an Institute Council (IC) advises the Institute's management on strategic decisions, in particular on evaluations, cooperation projects, strategic partnerships, the phasing out of research groups, budget changes in the research groups and matters concerning the general scientific development of the FLI. The IC consists of up to four senior group leaders, who are appointed by the Scientific Director for two years, as well as an elected representative of the junior groups and the head of Core Facilities & Services.

The external control body of the Institute is the Board of Trustees. It determines the general research objectives and decides on the medium-term financial and investment planning of the association. In addition, an international Scientific Advisory Board (SAB) provides an advisory function. The organization also includes staff units, a core administration and a services department, which includes technical services, scientific service facilities and scientific coordinators.



Organizational Chart of FLI. (As of July 2019)

Executive Bodies

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Members	
Burkhard Zinner (Chair)	Thuringian Ministry for Economic Affairs, Science and Digital Society (TMWWDG), Ref. 51 Grundsatzangelegenheiten der Forschungspolitik, Erfurt, Germany
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Prof. Dr. med. Nisar P. Malek	University Hospital Tübingen, Department of Internal Medicine I, Germany
Prof. Dr. Dr. h.c. mult. Ernst Th. Rietschel	Hamburg, Germany
Prof. Dr. Rudi Balling (Head of Scientific Advisory Board)	University of Luxembourg, Luxembourg Centre for Systems Biomedicine
Prof. Dr. Magdalena Götz (Deputy Head of Scientific Advisory Board)	Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Stem Cell Research, Neuherberg, Germany

Scientific Advisory Board (SAB)

Members	
Prof. Dr. Rudi Balling (Head)	University of Luxembourg, Luxembourg Centre for Systems Biomedicine
Prof. Dr. Magdalena Götz (Deputy Head)	Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Stem Cell Research, Neuherberg, Germany
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Prof. Dr. Didier Stainier	Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany
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Members	Represented by
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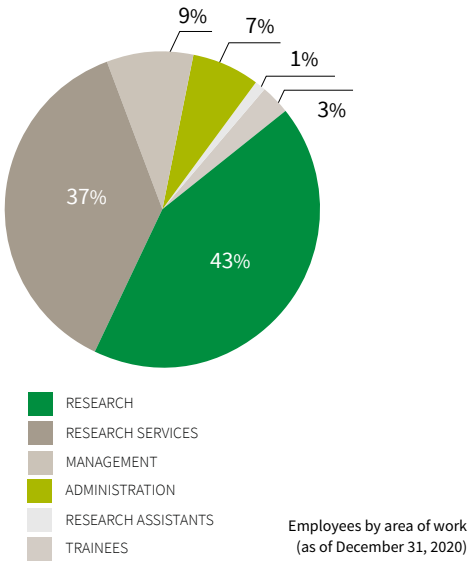
Friedrich Schiller University Jena (FSU), Germany	Prof. Dr. Georg Pohnert, Vice President for Research
City of Jena, Germany	Dr. Thomas Nitzsche, Mayor

(As of December 2020)

Personnel Development

Over the past ten years, the Leibniz Institute on Aging (FLI) has steadily evolved in terms of premises and personnel. The number of employees funded by the FLI increased from 272 (2010) to 290 (2020), and in 2020 there were also 53 scientists working as guests at the FLI.

With the commissioning of the new laboratory building in 2013, the usable area of the institute increased from 4,500 to about 10,000 square meters. In 2017, extensive renovation work began on the institute's existing facilities.



Employees by area of work (as of December 31, 2020)

Gender Equality & Family Friendliness

For the FLI, equal opportunities and family friendliness are a matter of course in its modern human resources policy. The proportion of women has been further increased, especially among the scientific staff: in 2020, the proportion of women employees was 58.6% (2010: 56.2%) and among the scientific staff, parity was almost achieved at 45.5% (2010: 37.2%).

In recruiting employees and in personnel development, the FLI follows the equal opportunity standards of the DFG and the Leibniz Association. The FLI supports its employees with numerous measures to help them balance work and family life as well as career and caregiving. These include, among other things, a modern parent-child office, cooperation agreements with nearby daycare centers in the form of funding for childcare places, health days/weeks and (caregiving) workshops, mentoring programs and company agreements that, for example, define the necessary framework for flexible working hours and work locations. The "Company Agreement on the Reintegration of Female Scientists (Welcome-Back Fellowship)" and doctoral degree funding for female doctoral students support reintegration after a period of family leave.

The FLI is a member of the Jena Alliance for Families and is involved in the working groups "Compatibility of Family and Career," "Managers in the Family" and "Diversity in Education," which meet to exchange information on a regular basis. Since it is becoming increasingly important to support newly hired personnel in finding suitable jobs for their life partners at their place of work or in the region, the FLI has been a member of the dual-career network of the Jena Alliance for Families as well as other (supra)regional dual-career networks for several years now.

The Diversity Charter serves the FLI as a guiding principle for an organizational culture that embodies diversity, fairness, tolerance and appreciation. The FLI is openly and transparently committed to this on its homepage and regularly participates in diversity days. 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 have been bindingly included in the program budget since 2015. These target quotas are reviewed annually.

One of the most recent successes is that the FLI was able to fill a newly established W3 "Neurobiology of Aging" professorship at the Faculty of Biosciences of the FSU Jena with the FLI group leader Dr. Helen Morrison. Furthermore, we succeeded in keeping another female

group leader at the institute with deliberate retention negotiations. Within the framework of the appointment procedure, this involved the conversion of a W2 to a W3 professorship.

In recognition of its successful equal opportunity work, the FLI was awarded the "Total-E-Quality" (TEQ) rating in 2019 for the third time and for the second time also with the add-on "Diversity." After re-certification, the FLI again received the regional "Jena Family Seal" (Jenaer Familiensiegel) in 2018. Both certificates honor the diverse equality measures at the institute.

Internationalization of Research

At the FLI, people from 40 different nations research, work and study together. Nearly one in four has come to Jena from abroad. Because of the international workforce and because the language of science is English, communication at the FLI is predominantly in English.

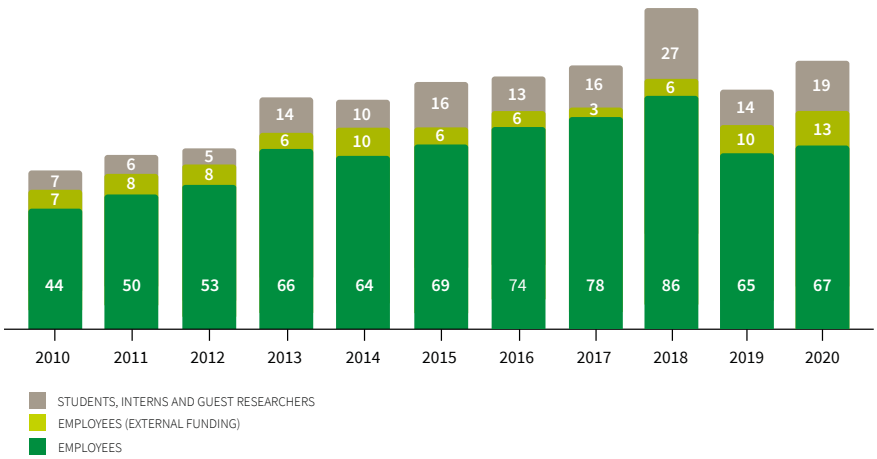
Within the last ten years, the share of international employees at the FLI has steadily increased: from 16.2% in 2010 to 23.1% in 2020. Among PhD students, the share has even more than doubled since 2010, to 63.2%. The trend among scientists has been similar: almost half now come from abroad – compared to a good quarter ten years ago.

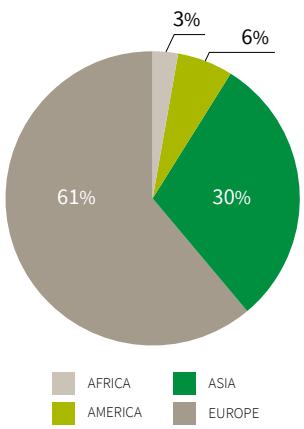
In order to better support researchers from abroad who come to Germany, the FLI has been a local service point in the EURAXESS Germany network since 2010. In 2015, the Institute also became a member of the European EURAXESS Services Network. Here, researchers receive individual advice and practical help on all aspects of international researcher mobility.

The FLI seeks to provide a distinctively welcoming culture. This is highly appreciated by new employees, especially those coming from abroad, because it makes the start at the FLI and in Jena so much easier. With the institute's internal relocation service, the FLI supports new employees in such matters as dealing with the authorities, learning about childcare options and the local school system, and finding a place to live.

Number of Employees from Abroad (number and origin)

As of December 31, 2020





Third-party Funded Projects (a selection)

Sofja Kovalevskaja Award of the Alexander von Humboldt Foundation

The Alexander von Humboldt Foundation presents the Sofja Kovalevskaja Award to Dr. Francesco Neri, thus supporting his research on the molecular causes of cancer development in old age (2016–2021).

Framework Program of the European Union (Horizon 2020)

At the initiative of Dr. Aspasia Ploubidou, the EU is funding the CanPathPro consortium with almost 11 million euros. The aim is to develop and validate a computer-based mechanistic model of cancer signaling. Among the eight participating institutions, the FLI will receive the largest share of the funding (2016–2021).

Emmy Noether Program of the DFG

Funded by the DFG program for outstanding early career researchers, Dr. Julia von Maltzahn has headed the research group on skeletal muscle regeneration since 2013 (2013–2020).

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 Research Training Groups

The FLI is involved in several research projects in the Research Training Groups “Molecular Signatures of Adaptive Stress Responses” (RTG 1715) and “Protein Modifications: Key Mechanisms of Aging – ProMoAge” (RTG 2155) (2016–2020).

Federal Ministry of Education and Research (BMBF)

Subproject A in the collaborative project Radiometabolom: Outside in: How is radiation resistance in the S-phase modulated by metabolism? (Englert Research Group, 2020–2022)
Preclinical study in cooperation with the University Hospitals of Leipzig and Jena for a protein replacement therapy for the treatment of nerve sheath tumors (Morrison Research Group, 2020–2023)

RegenerAging / State of Thuringia

The project "Aging-induced inhibition of regeneration and tissue homeostasis" (RegenerAging) at FSU Jena, the University Hospital of Jena (UKJ) and the FLI is funded by the ProExcellence Initiative 2 of the State of Thuringia (2015–2020). One of the three newly established research groups is located at the FLI.

Leibniz ScienceCampus / Leibniz Association

In order to further promote networking on aging research at the Jena site, the Leibniz Association is funding the establishment of a Leibniz ScienceCampus "Regenerative Aging." The research groups of the RegenerAging project are integrated into the Leibniz ScienceCampus (2015–2020).

Chan Zuckerberg Initiative

The Neurodegeneration Challenge program is funding a collaborative project between Dr. Alessandro Ori (FLI) and Dr. Michael E. Ward of the National Institutes of Health (NIH), USA, to develop new approaches for better insight into neurodegenerative diseases such as Alzheimer's, Parkinson's and ALS (2020–2022).

PostDoc Network / Leibniz Association

To improve postdoc training, the first Leibniz PostDoc Network on "Aging-induced impairments of regeneration and stem cell functionality (RegenerAging)" is founded at the FLI (2015–2019).

Other Foundations and Associations

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

VELUX STIFTUNG

Outlook

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

New Research Area Microbiome and Aging

With the approval of additional funding via the special fund of the Leibniz Association, for which the FLI applied in the 2016 evaluation, it will be possible to establish a new research area – "Microbiome and Aging" – in the coming years. 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. The interaction between host and microbiome is controlled by bacterial metabolic signals and epigenetic responses in target tissues. The new research area "Microbiome and Aging" will aim to investigate the aging of the microbiome and its impact on the aging process of the organism as a whole.

Research in Systems Biology Expanding

The continuously expanding research field of Systems Biology of Aging 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 improving the health of aging humans.

New Scientific Director to be Appointed

The appointment of a new Scientific Director will further develop and advance the long-term perspective of the Institute 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 attract internationally acclaimed scientists to the institute.

The infrastructure of the institute is also undergoing significant changes. In the coming years, necessary modernization measures will be carried out in the building complexes that date from the 1950s.

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.

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