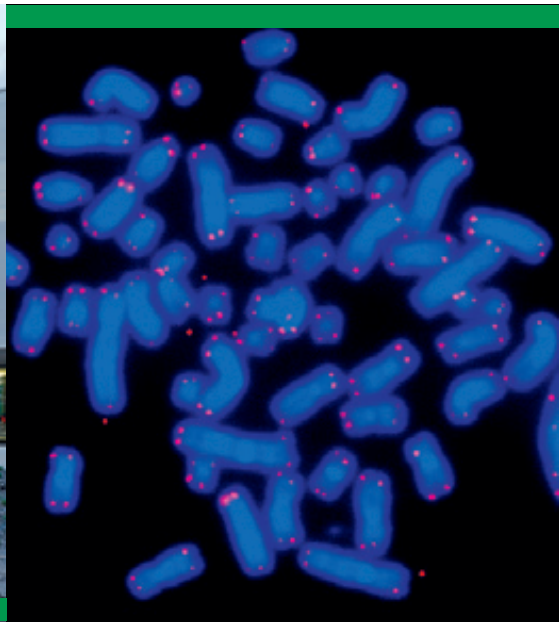
Leibniz Institute on Aging –
Fritz Lipmann Institute



2016 – 2018

Annual Report

2016 – 2018

Annual Report

Leibniz Institute on Aging – Fritz Lipmann Institute (FLI)

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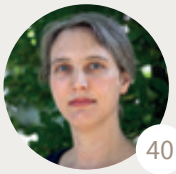
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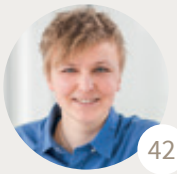
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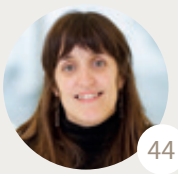
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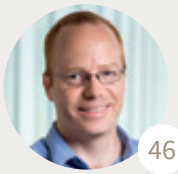
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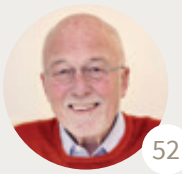
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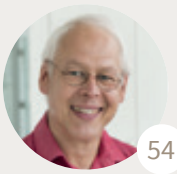
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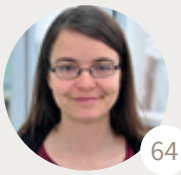
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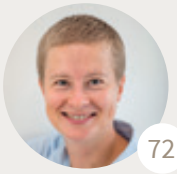
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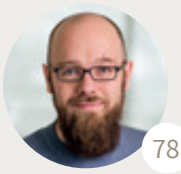
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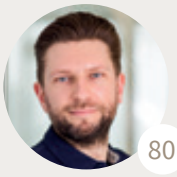
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Board of Directors at FLI.
Dr. Daniele Barthel and Prof. Dr. Alfred Nordheim.

Welcome

The Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) has refined and expanded its research focus on "Stem Cell Aging and Organ Maintenance". During aging, stem cells lose functionality and acquire mutation; the ability of the organism to maintain stem cell function and to regenerate declines. Thus, older people become more susceptible to diseases and leads to a deterioration in their quality of life. The aim of the biomedical aging research at FLI is to delineate the genetic, epigenetic and molecular processes that underlie these aging-induced impairments.

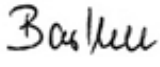
Our research focus is unique on the landscape of other research initiatives on aging in Germany and beyond. On a national level, many milestone projects were initiated during the last years to further strengthen our expertise: The State of Thuringia and the Leibniz Association fund the building of a Leibniz ScienceCampus on "Regenerative Aging", which will bridge research on aging between the FLI and our University partners. This collaboration will not only strengthen basic research on aging, but also translational projects aimed at developing future therapies for healthy aging. In pursuing similar goals, the FLI coordinates the Leibniz Research Alliance "Healthy Ageing" involving 21 Leibniz Institutes from different research disciplines.

Another, worldwide visible topic of the FLI is the investigation of the genetic basis of aging, especially using the short-lived killifish Nothobranchius furzeri as a model organism. The complete sequencing of its genome by FLI researchers at the end of 2015 has opened up new perspectives for the investigation of aging processes. Thanks to the freely available genome data, researchers worldwide are able to investigate, e.g. the influence of individual genes on aging or age-related diseases by switching genes on and off. This lays the basis for future genetic research of the aging process in vertebrates. For this outstanding achievement, the FLI research team was awarded the "Thüringer Forschungspreis 2018" in the category basic research.

Aging affects all of us. Our research on aging makes an important contribution to improving individual health in old age and to shaping demographic change in a positive way for all of us.

We wish you an enjoyable read and revealing insights into the research work pursued at the FLI.

Prof. Dr. Alfred Nordheim
Scientific Director of FLI



Dr. Daniele Barthel
Administrative Director of FLI

Mission & Vision

The Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) was – at the time of its conception in 2004 – the first national research institute in Germany focusing on biomedical research on human aging, a multifactorial process controlled by environmental and genetic factors.

The mission of the FLI is to disclose basic mechanisms that lead to impairments in stem cell function and organ maintenance during aging, thus increasing organismal dysfunction and the risk of disease development. Our research aims to provide a knowledge basis for the development of future therapies which extend the health span – the proportion of life that can be spent in preferably optimal health. This is of highest priority for individuals and also helps society to shape demographic change in a positive way.

What makes the FLI unique

Declines in stem cell function and organ maintenance are major factors limiting organismal functionalities and the quality of life during aging; both processes represent major causes for increases in organismal vulnerability and disease initiation during aging. Focusing on impairments in stem cell function and organ maintenance during aging and concentrating on their molecular, genetic, and epigenetic causes, the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) has developed a research focus, which is unique at national and international level.

During the last years, several institutes in Germany have followed the lead of FLI, laying their research focus on aging as well. These institutes concentrate on the identification of genes that influence lifespan, on cellular stress responses, demographic aspects of population research, neurodegenerative or metabolic age pathologies, cardiovascular diseases, or on environmental factors. However, research work in Jena with its focus on epigenetic and genetic factors impairing the maintenance of stem cells and tissues in the context of aging remains unique. In addition, at the European level, there are additional approaches to tackle aging research, be it cancer research, research on cell senescence or the focus on particular animal models or aging associated diseases.

FLI has initiated collaborations with many of these national and international research institutions to take advantage from differing research perspectives and to use synergies. Overall, the FLI has positioned itself in the international research arena on aging and has had significant influence on forming new interdisciplinary scientific foci. Scientists from the FLI contribute to fundamental discoveries, advances, networking and education in this field of research, at local, national and international level.

Three-Year Review 2016 – 2018

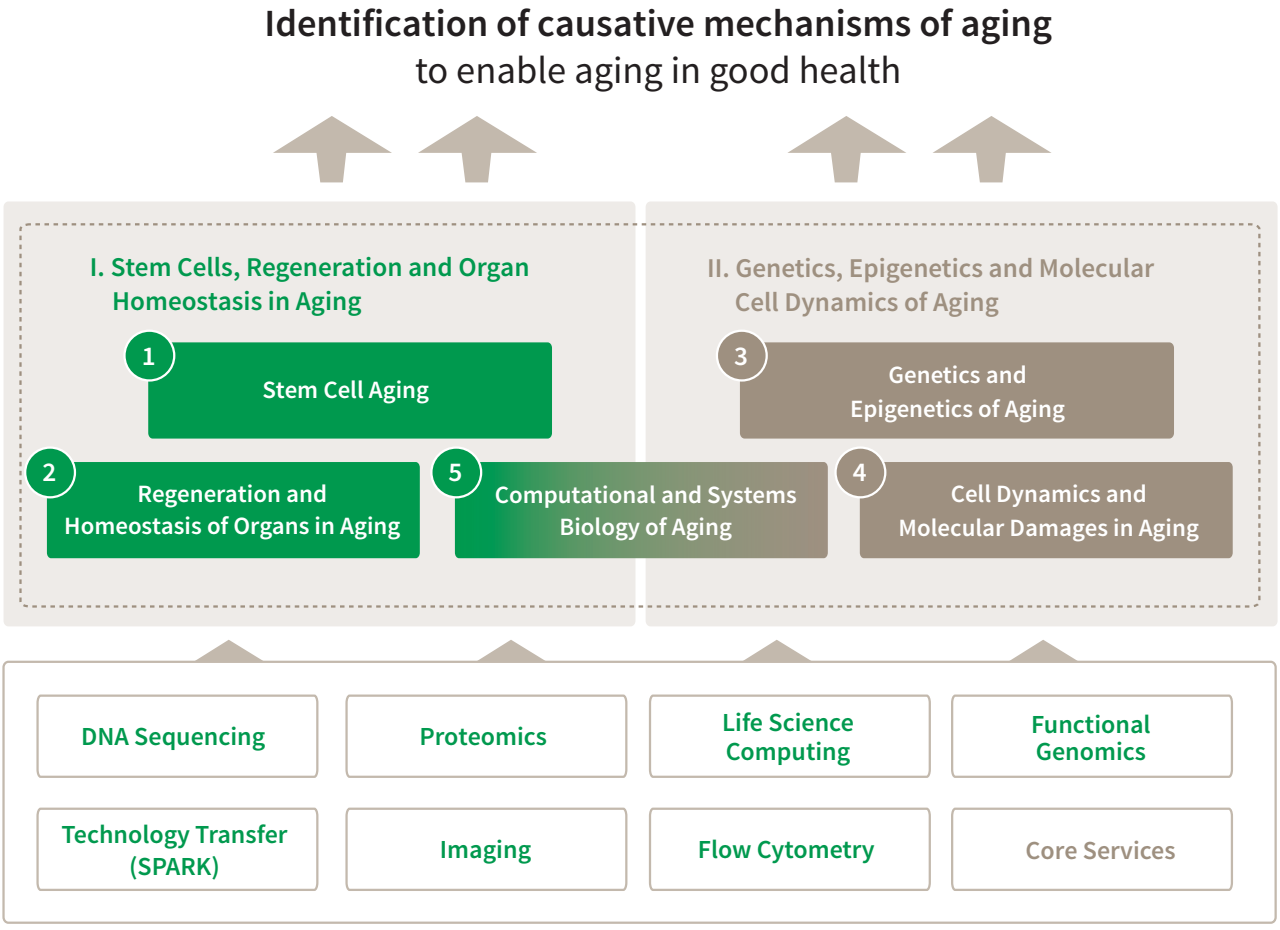
Successful Restructuring at FLI

Since 2012, the FLI has successfully entered a phase of scientific refocusing. The FLI makes an essential contribution to these challenges by implementing a basic research program focusing on

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

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

Research groups at the FLI work together collaboratively in several research projects. Therefore, five main project Subareas were installed in order to institutionalize the cooperative cross-group research.



Research focus at FLI. FLI research is structured in five Subareas that cooperate closely. They are supported by a wide range of technical Core Facilities and Core Services.

Subarea 1:
Stem Cell Aging

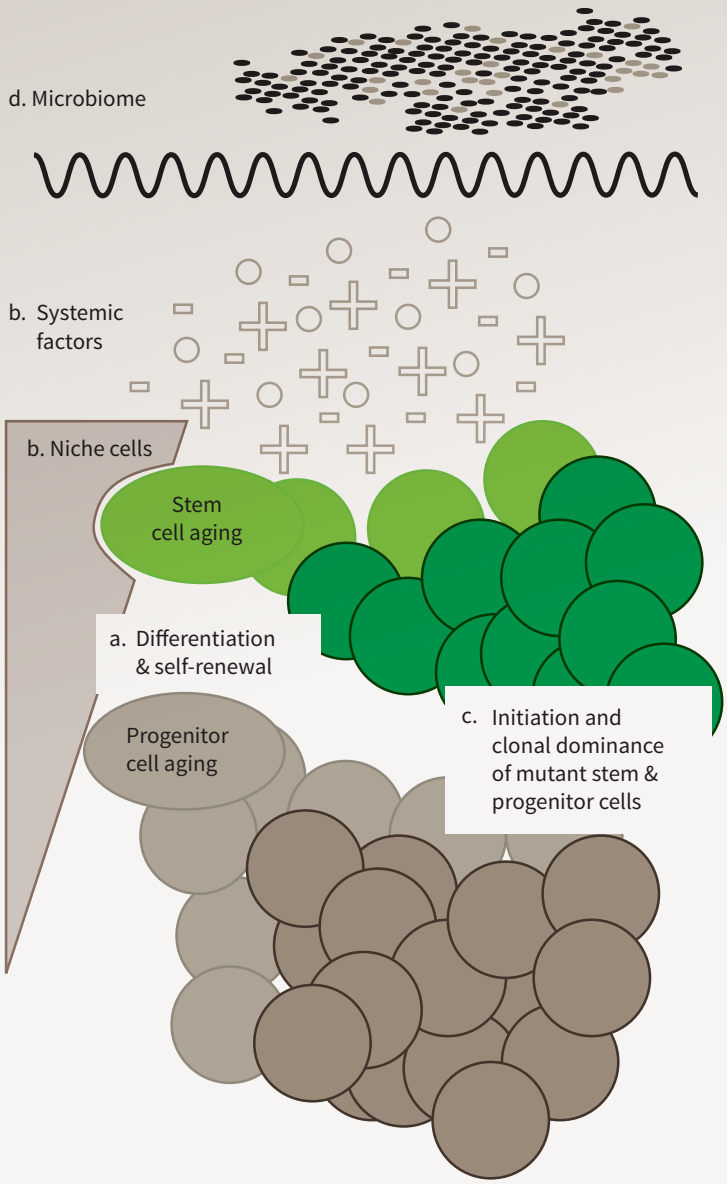
Aging-associated impairments in stem cell function represent a major contributing factor leading to impairments in organ maintenance, organismal dysfunction, and disease development during aging. The Subarea "Stem Cell Aging" began its work at FLI in 2013 with the establishment of the research groups of K. Lenhard Rudolph (hematopoietic and intestinal stem cell aging), Julia von Maltzahn (muscle stem cell aging) and Cristina González-Estévez (Planarian neoblast stem cells). With the research group of Claudia Waskow, focusing on human hematopoietic stem cells in mouse models, the Subarea was further expanded. In addition, Heinrich Jasper from the Buck Institute for Research on Aging in Novato, USA (*Drosophila* intestinal stem cells) and Florian Heidel from the Jena University Hospital (hematopoietic stem cells) established associated research groups at the FLI. This strategic ensemble of groups working on stem cell aging, across species from lower model organisms up to humanized mouse models, provides a unique discovery pipeline for genetic and functional studies on stem cell aging.

The Subarea investigates stem cell-intrinsic and extrinsic mechanisms that limit the function of stem cells and focuses on following topics:

- cell-intrinsic and extrinsic alterations that limit stem cell function in aging in response to DNA damage and metabolic changes (K. Lenhard Rudolph)
- the influence of developmental pathways, hormonal regulators and metabolic factors that alter the function of muscle stem cells (Julia von Maltzahn)
- clonal dominance of mutant hematopoietic stem cells in aging (Florian Heidel, K. Lenhard Rudolph)
- regeneration pathways of the hematopoietic system and their impact on immune aging (Claudia Waskow)
- mechanisms of immortal maintenance of pluripotent stem cells in planarian (Cristina González-Estévez)
- signaling pathways that disturb stem cell maintenance and function in the context of inflammation and aging (Heinrich Jasper)

Taken together, the "Stem Cell Aging" Subarea aims to study basic concepts and consequences of stem cell aging in the context of an aging organism. The Subarea is strongly connected to the Subarea 2 on "Regeneration and Homeostasis of Organs in Aging". Stem cells have a pivotal role in organ maintenance and regeneration. *Vice versa*, changes in the cellular composition and the micro-milieu of aging organs impinge on the stem cell's self-renewal and differentiation capacity. These interactions are bidirectional and therefore a strong basis for intense collaboration between the two Subareas.

1



Research focus of Subarea 1. a. It is currently not well understood what mechanisms impair cellular functions in aging. **b.** The relative contribution of niche cells and systemic acting factors on stem cell aging have yet to be determined in different tissues. **c.** Clonal expansion of mutant cells associates with disease development in aging humans. Mechanistically, the process remains poorly understood. Changes in color intensity depict clonal dominance originating from stem (green) or progenitor cells (gray). **d.** Emerging evidences indicate that aging associated alterations in microbiota influence stem cell function and *vice versa*.

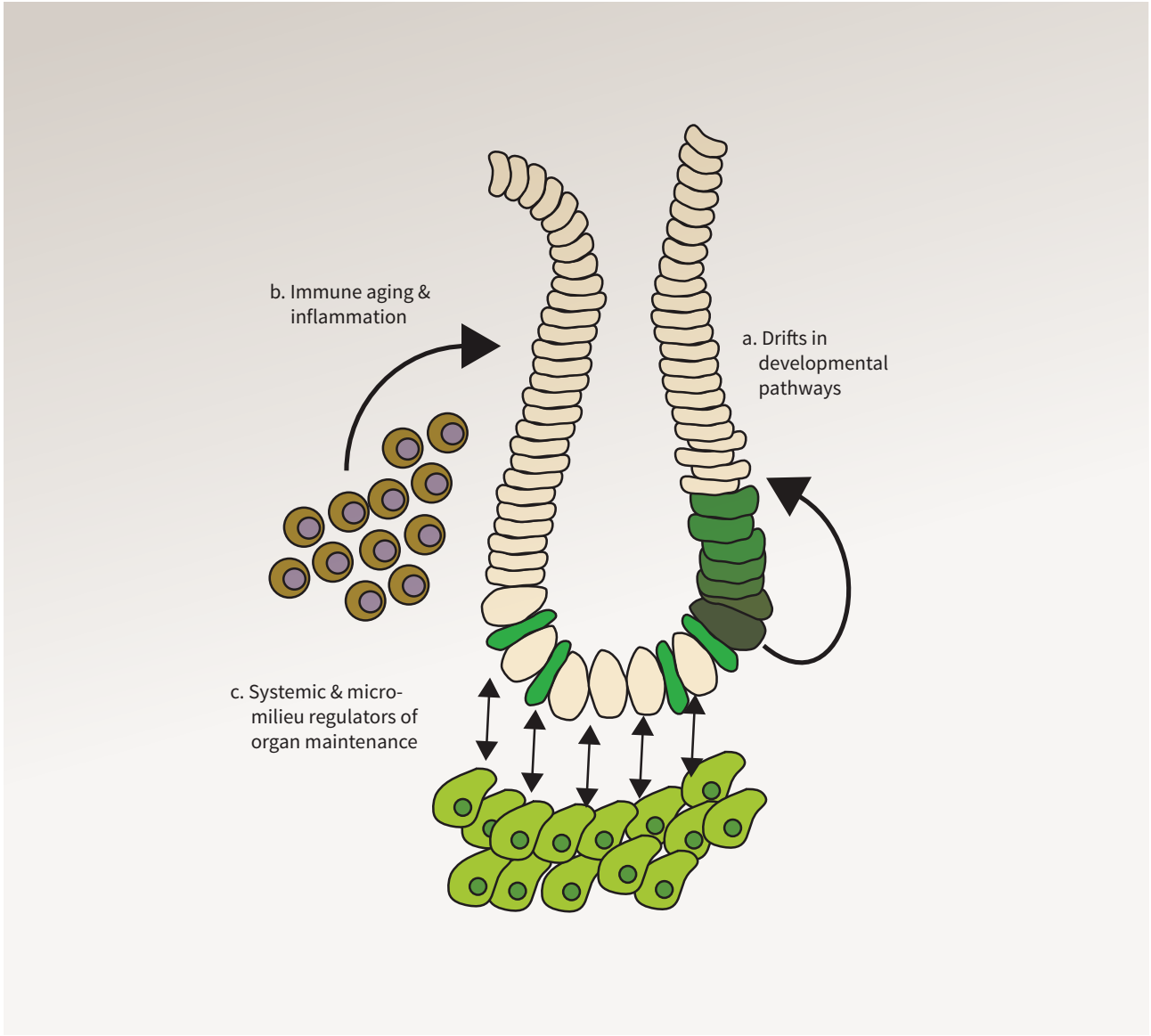
Subarea 2:
Regeneration and Homeostasis of Organs in Aging

The functionality of all organs and tissues declines during aging. As such, this deteriorative process represents a major factor contributing to decreases 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 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, stem cells play a pivotal role in this process, but aging-associated alteration in the non-stem cell compartment of organs and tissues are 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. The Subarea focuses on the following main topics:

- aging-related impairments of cell-to-cell communication in regeneration and disease (Helen Morrison)
- Hippo-pathway as a central regulator of tissue homeostasis, stem cell biology and cancer (Björn von Eyss)
- signaling pathways that control stem cell division (Peter Herrlich)
- immune aging and inflammation in organ maintenance and regeneration (Ronny Hänold)

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 Cell Aging and Organ Maintenance”. 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.

2



Research focus of Subarea 2. Organ maintenance is regulated by local and systemic factors, which are subject to aging-associated changes. Research of Subarea 2 focuses on the following research areas: **a.** Genetic and epigenetic modulation of developmental pathways has been shown to contribute to progressive aging and disease. It is critical to delineate mechanisms and consequences of aging-associated drifts to better understand organ maintenance during aging. **b.** Immunoaging and chronic inflammation elicits negative effects through reduced immune surveillance and aberrant organ repair and maintenance; all of which contributes to the evolution of organ pathologies and diseases during organismal aging. **c.** Furthermore, aging-associated alterations in systemic and extracellular factors derived from metabolic changes, microbiota alterations, chronic inflammation, senescent, or damaged cells might impinge on disease development and tumor initiation.

Subarea 3:
Genetics and Epigenetics of Aging

Twin studies indicate that 30% of inter-individual differences in human aging are related to genetic factors. It is expected that knowledge of genetic factors that determine differences in lifespan within a species or in cross-species comparisons, will improve our understanding of basic molecular processes driving cellular and organismal aging.

Building on its long-standing track record on genomic research, the newly focused research at FLI implemented a research program on "Genomics of Aging" back in 2004.

- The group of Christoph Englert investigates developmental pathways and immune function in kidney maintenance and regeneration during aging.
- The "Genome Analysis" group of Matthias Platzer and the "Molecular Genetics" group of Christoph Englert spearheaded, with the former junior group of Alessandro Cellerino (today in cooperation with Scuola Normale Superiore di Pisa, Italy), the genomic and functional analysis of the short-lived fish *N. furzeri* as a new model for research on aging.
- Since 2016, Francesco Neri has been elucidating the impact of the epigenome – chemical modifications of the DNA, which regulate its activation or deactivation – on aging and the emergence of cancer.
- The significant influence of epigenetic alteration, such as global decreases in DNA methylation and changes in histone modification on cellular and organismal aging is analyzed in collaboration with Alessandro Cellerino (Scuola Normale Superiore di Pisa, Italy) and Holger Bierhoff (Friedrich Schiller University Jena). Furthermore, the associated research group of Manja Marz (Friedrich Schiller University Jena) concentrates on the role of long non-coding RNAs and micro RNAs in influencing gene regulation in aging.
- The co-opting of Heinrich Jasper's group (Buck institute in Novato, USA) from Subarea 1, which employs *Drosophila melanogaster* genetics to identify genes and pathways that influence stem cell and organ maintenance, has further strengthened connections between Subareas 1, 2 and 3.

Together, Subarea 3 employs comparative genomics and functional genetics to identify genetic and epigenetic factors and higher order, gene regulatory mechanisms that influence the accumulation of molecular damages, stem cell function and organ maintenance during aging. This research is tightly connected to research of all other Subareas and strongly benefits from the implementation of the new Subarea on "Computational and Systems Biology of Aging".

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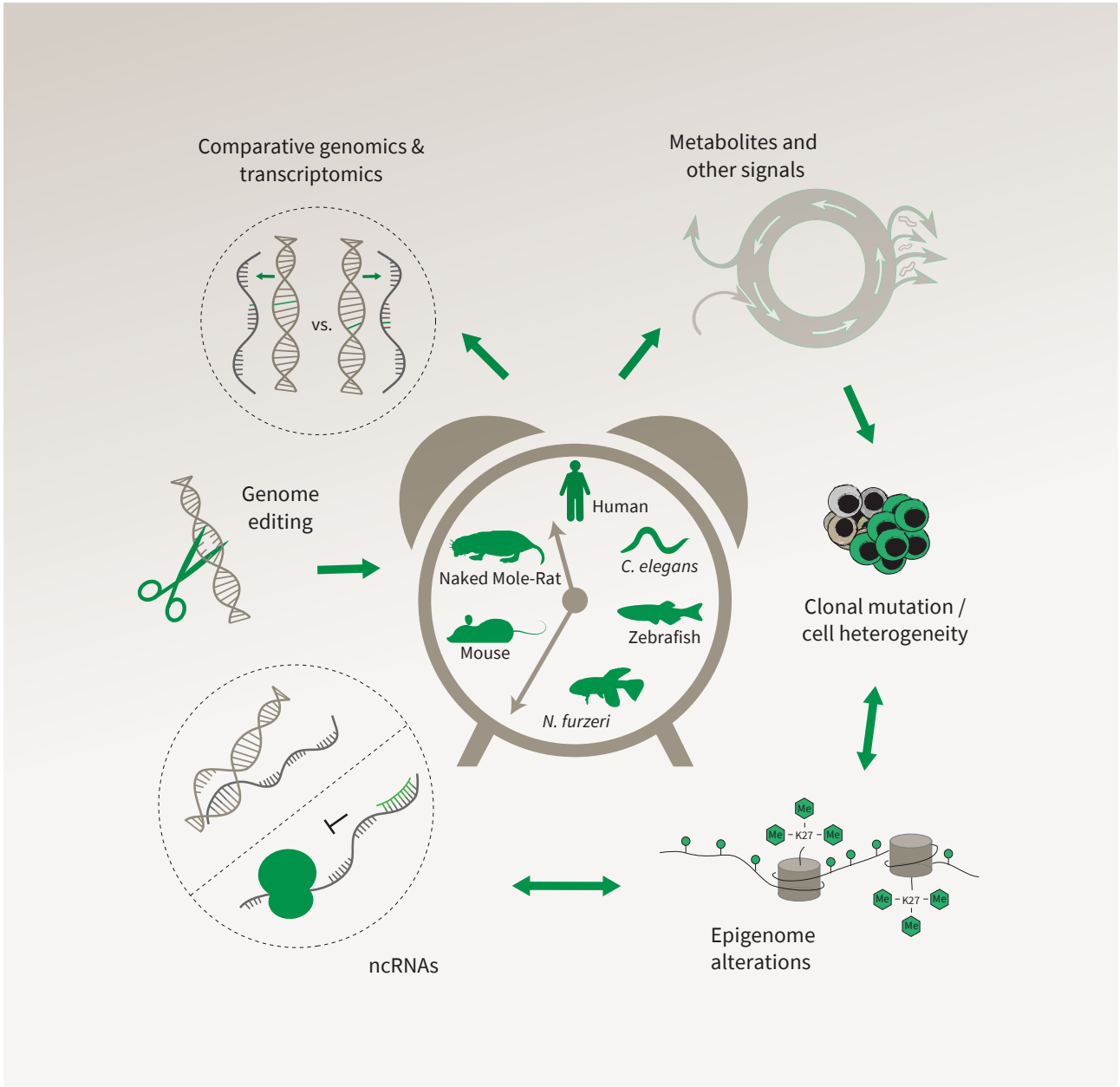

Research focus of Subarea 3. To uncover causative factors for aging, comparative genomics in short- and long-lived model systems are applied. Functional genomics is used to identify novel pathways contribute to aging of an organism and to validate the functional relevance of genetic and epigenetic changes that occur during aging. Furthermore, genetic risk factors for aging-related diseases are identified and functionally tested. The future development of the Subarea aims to integrate changes in host-microbiota interactions during aging, and how these influence clonal mutation and epigenetic alterations through metabolites and other signals.

Subarea 4:
Cell Dynamics and Molecular Damages in Aging

Aging is regarded as a multifactorial process, characterized by the accumulation of damages to molecular structures and subcellular organelles. It is not well understood as to why the prevention and repair of molecular damages fails during aging of organisms.

Research at FLI has focused since 2004 on the analysis of mechanisms that contribute to the accumulation of molecular damages in aging cells and tissues. The main aim of the Subarea "Cell Dynamics and Molecular Damages in Aging" concentrates on causes and consequences of DNA and protein damages in aging cells and tissues:

- DNA damage responses in the development and maintenance of neurons (Zhao-Qi Wang)
- protein trafficking, proteostasis and protein segregation in aging (Christoph Kaether)
- functional genetics analysis of aging, further strengthened by the recruitment of Maria Ermolaeva – using *C. elegans* to identify genetic factors that influence proteostasis, stress responses, and organ maintenance
- mechanisms of DNA repair in aging (Frank Große)

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 damages and responses to it – including damage repair.

Vice versa, aging-associated impairments in stem cell and tissues can impinge on the accumulation of molecular damages. Examples include aging-associated decreases in the reduced removal of damaged and senescent cells, or alterations in metabolism that lead to induction of molecular damages. Given these functional and bidirectional interactions, the Subarea 4 on "Cell Dynamics and Molecular Damages in Aging" is tightly linked to Subareas 1 and 2 and a central theme to the overall research mission at the FLI.

In addition, the functional analysis of molecular damages 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).

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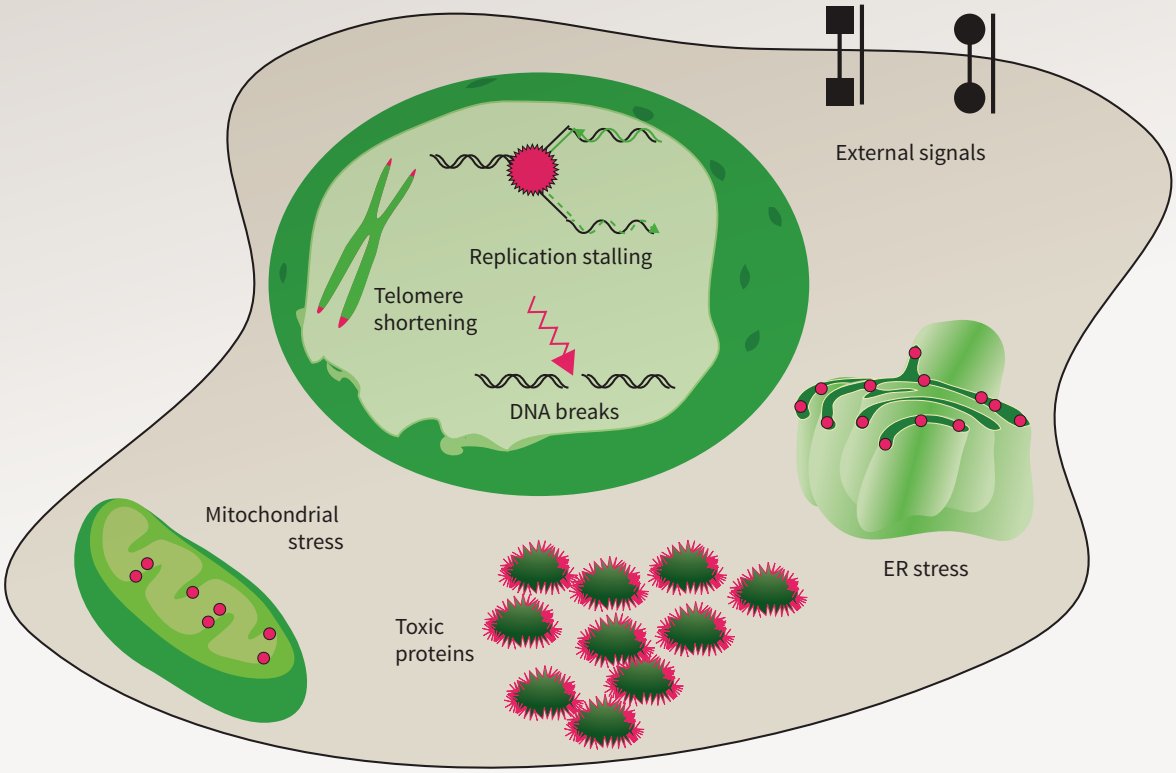

Research focus of Subarea 4. The accumulation of damaged macromolecules or subcellular organelles is associated with dysfunction of a cell, which contributes to tissue & organ failure. DNA damage, genomic instability, protein misfolding or defects in toxic protein degradation can compromise cell functionality. Alterations of mitochondrial DNA and protein complexes affect cellular metabolism, which will have a general impact on cell integrity.

Subarea 5:
Computational and Systems Biology of Aging

With the focus on aging-associated impairments in stem cell function and organ maintenance, as well as on the underlying molecular and genetic causes of these alterations, the FLI developed a stand-alone feature among research institutes on aging, both in Germany and at international level. In order to fully explore the interconnections that control these processes on different scales of organism aging (genetics and molecular networks, cellular networks, organ networks), the FLI developed the Subarea on "Computational and Systems Biology of Aging".

Building of this Subarea was initiated by the GerontoSys program of the Federal Ministry of Science and Education (BMBF) funding a collaborative project on computational analysis of aging from 2010 to 2015. The program successfully employed interspecies comparisons of genes and pathways in aging with functional genomics to identify genetic factors and molecular mechanisms that contribute to cellular and organismal aging. The FLI decided to fully develop this area to a new Subarea at the institute.

The following research questions are addressed in Subarea 5:

- Since the end of 2017, the research group of Steve Hoffmann has been developing methods for the analysis of big and multidimensional biological data sets in order to contribute to a better understanding of the epigenetic control of transcription.
- By means of ultra-sensitive proteomic approaches, Alessandro Ori's Lab is interested in studying how age, mutations and environmental factors affect organs at the molecular level.
- Research of Hans A. Kestler's associated group (Ulm University) is at the interface of computer science, statistics and life sciences and among other topics covers statistical and data mining approaches for high-throughput data.

Together, the development of Subarea 5 on "Computational and Systems Biology of Aging" is instrumental in understanding the complexity of aging at multi-scale level of the organism and will boost the interconnection between Subareas 1–4 of the FLI's research program.

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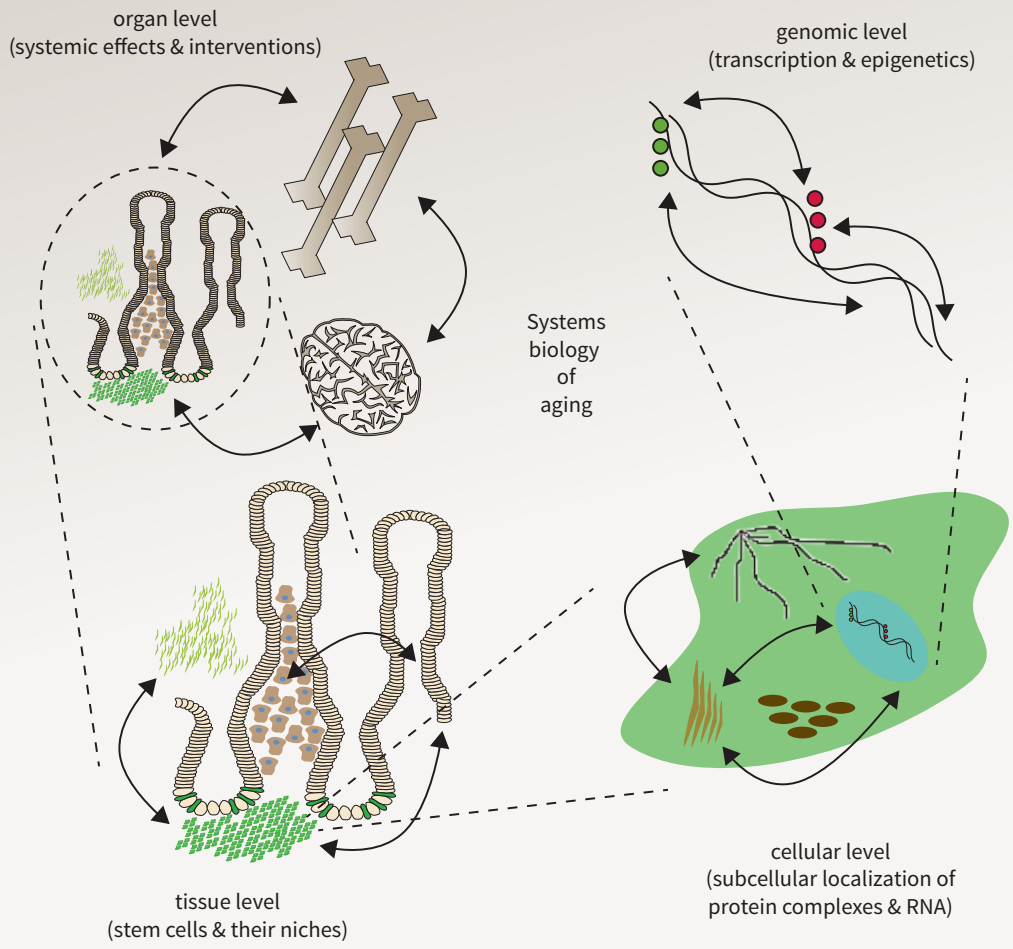
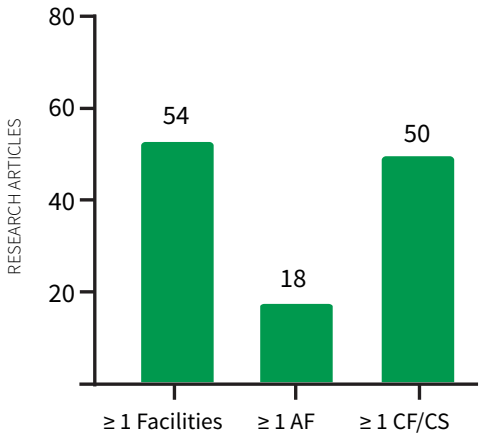


Research focus of Subarea 5. The biology of aging can be viewed as a multilayered array of networks at the level of organs, cells, molecules, and genes. The FLI wants to meet this complexity by establishing the new Subarea on "Computational and Systems Biology of Aging". The overall goal is to interconnect research at different scales, taking place in Subareas 1–4 of the Institute's research program. The new group on Systems Biology will integrate data from networks at multiple scales and will thus point to mechanisms and interactions that would not be seen in unilayer approaches.

Core Facilities and Services

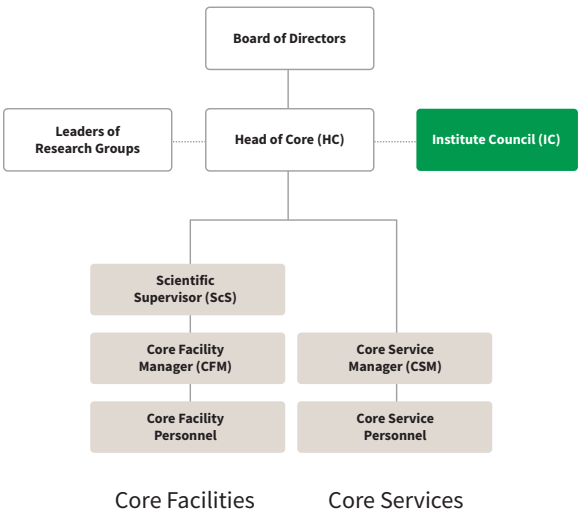
At the beginning of 2016, a “core” structure was put into effect that organized facility and service units as independent organizational entities from FLI’s research groups. A number of technology platforms (e.g. sequencing, mass spectrometry) grew out of individual methodological requirements for single research groups in the preceding years but developed into semiautonomous substructures. As consequence of re-focused research activities and the concomitant advent of new research groups at FLI, those units increasingly had to serve many FLI groups and collaborative research efforts in the Jena research area. To accommodate this development and to increase efficiency as well as transparency for users, facility personnel and for administrative processes, it came natural to re-organize such activities into independent units as “FLI Core Facilities and Services” and to phase out infrastructures considered non-essential for FLI’s research focus (X-ray crystallography and NMR spectroscopy).

FLI’s Core Facilities (CF) are managed by a CF Manager and are each scientifically guided in their activities and development by an FLI Group Leader, as Scientific Supervisor. The animal facility (AF) comprising fish and mouse facilities is run separately, as it involves a more complex organizational structure. Basic Core Services (CS) are directly led by the Head of Core (HC), who in turn is supported by individual CS Managers. Furthermore, the HC is responsible for coordinating the activities of all Core units, harmonizing the Core budget, procurement of large items, personnel and administrative issues, developing and ascertaining implementation of user guidelines and for managing service requests from external users. All facilities and services, including animal facilities, have a valuable contribution to FLI’s research articles; e.g. from 2016–2018, to 54% of all peer reviewed research publications.



Contribution of CFs, AF and CSs to research publications in 2016-2018.
Proportion of research publications prepared with the support of at least one of the facilities and/or services (Core Facilities, CF; Animal Facilities, AF; Core Services, CS).

Dr. Matthias Görlach
Head of Core



Core Facilities (CF):

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

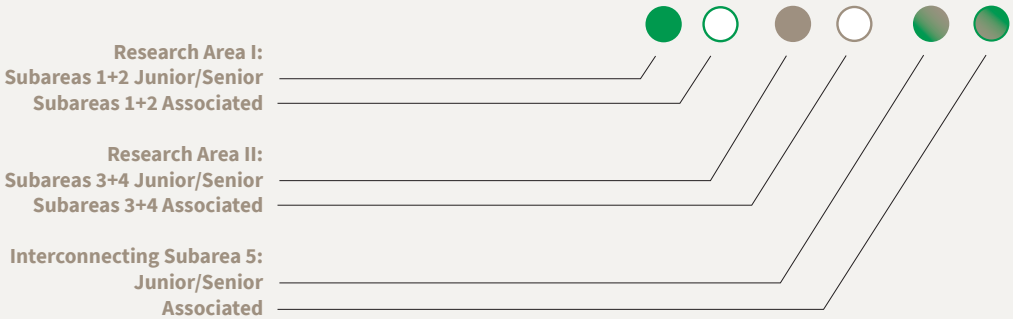
Fish
D. rerio / N. furzeri

Laboratory work at the FLI.

Group Fluctuation

At the end of 2018, the FLI accomodated 7 Senior Group Leaders, and 5 Junior Group Leaders. In addition, 1 Fellow Group and 8 Associated Research Groups were affiliated to the institute. From the total of 21 Group Leaders, only 7 (33%) were Group Leaders at the FLI before the year 2012. This significant turnover of Group Leaders within the last years evidences the dynamic nature of research at the FLI. The set-up of a new research building of the FLI in May 2013 doubled the space available for research. The attraction of a new team of Group Leaders has generated a momentum of innovation and collaborations at the FLI.

Dynamic Developments at FLI



Development of FLI research groups in 2016–2018.

Research Cooperations 2016 – 2018

To counter the accelerating development of technology and research, it is of high importance for the Leibniz Institute on Aging (FLI) to engage in scientific networks and cooperations. That's why, since its very beginnings, the FLI has been supporting the interdisciplinary interchange on issues with regard to aging and cancer research.

Apart from regional cooperations with Friedrich Schiller University Jena (FSU) and the Jena University Hospital, we are engaged in 297 national research cooperations as well as in collaborations with institutes from 31 nations worldwide. Thus, we provide ourselves with a state-of-the-art international knowledge and are able to significantly contribute to international aging research.

Leibniz Research Alliances (LRA)

Old age comes with an increased incidence of severe health problems that limit quality of life. At the same time, the growing percentage of elderly people in a society combined with a declining birth rate raises social and economic issues. These pressing issues, that will stamp the future, are the subject of the **Leibniz Research Alliance Healthy Ageing** (LRA Healthy Ageing), which is coordinated at FLI. Since 2012, LRA Healthy Ageing has successfully bundled 21 Leibniz Institutes in the fields of Biology, Medicine, Psychology, Education, Sociology and Economy. The collaboration between these diverse scientific disciplines includes research on the biological and social foundations of aging as well as the application for common projects and the exchange of resources and knowhow.

Our rapidly growing and aging modern society demands continuous responses to new challenges – also for the development of new bioactive compounds. Many active agents (molecules that cause a defined physiological change in target organisms) are derived from nature and are optimized for application using biotechnological or chemical processes. Together with 16 other Leibniz institutions, the Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) is collaborating on this issue within the **LRA Bioactive Compounds and Biotechnology**.

Aging Research Center (ARC) Jena

The Aging Research Center (ARC) Jena was founded in 2013 as interfaculty profile center of the Friedrich Schiller University Jena (FSU) Jena in close cooperation with the Leibniz Institute on Aging. It is part of FSU's research profile "Life". The center serves to pool the whole spectrum of aging related sciences in Jena to foster interdisciplinary projects.

ProExzellenz Project "RegenerAging"

The research project "RegenerAging" was developed by the members of the Aging Research Center (ARC) Jena. It is a close cooperation between FLI, the Jena University Hospital and the Friedrich Schiller University Jena as well as Carl Zeiss Microscopy GmbH in Jena. The project is funded within the "ProExzellenz Initiative 2" of the State of Thuringia from 2015-20 with 3.9 million euros. The functional analysis of the underlying molecular mechanisms of aging-associated impairments is the main focus within the "RegenerAging" project. This comprises imbalances in signaling pathways that control the functionality of stem cells and differentiated cells in regenerative processes and, hence, impair regeneration and organ homeostasis during aging. Research focuses on the "Epigenetics of Aging", "Stem Cell Aging" and "Immunology of Aging". To our knowledge, there is currently no other initiative in Germany focusing on aging induced impairments in the functionality of stem cells and differentiated cells in regeneration and organ homeostasis.

Leibniz ScienceCampus Jena – Regenerative Aging

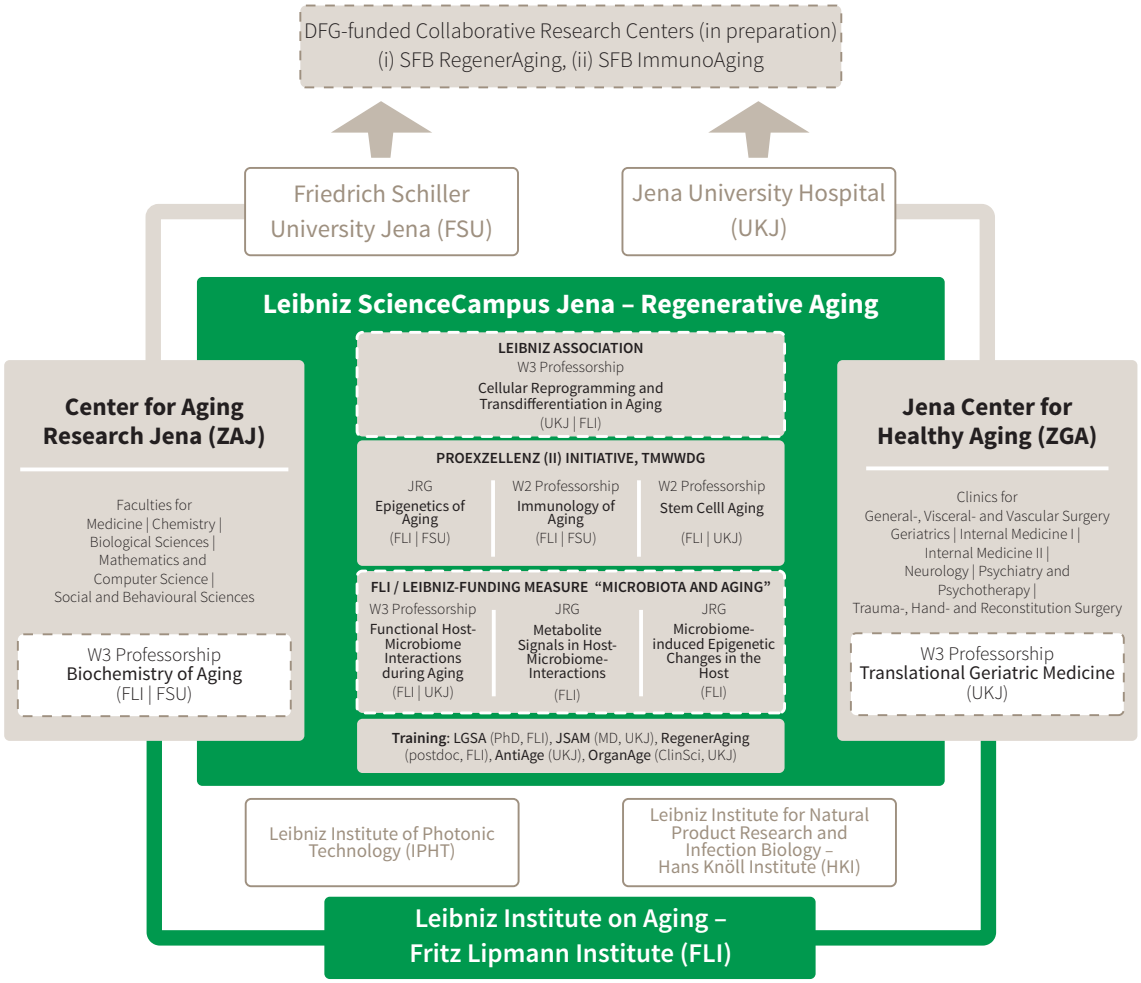
To further enhance the expertise and networking of aging research in Jena, the FLI receives funding from the Leibniz Association for the Leibniz ScienceCampus "Regenerative Aging". It will be funded until 2020 and is co-financed by the ProExzellenz Initiative of the State of Thuringia.

Further new Cooperations

In March 2016, the project **"CanPathPro",** supported by the EU as part of the Horizon 2020 program, was launched. It is funded for 5 years with a budget of almost 11 million euro (www.canpathpro.eu). An international group of scientists from 6 countries is pooling their resources and expertise to develop a new systems biology platform for the predictive modeling of cancer-associated signaling processes. The FLI is part of the DFG-funded research network **"Heme and heme degradation products" (hhdp)** as well as of BMBF-funded project **"Model-based optimisation and individualisation of treatment strategies in haematology" (HaematoOpt)** and the Research Training Group **"Protein Modification: A Key Mechanism for Aging – ProMoAge"** (RTG 2155) with two projects.

International Talks and Presentations

In order to foster international visibility and scientific exchange of the FLI, our researchers are promoted to visit internationally recognized meetings and present their data. A total of 206 oral presentations were given by our scientists on scientific meetings in 2016 – 2018.



Scientific embedding of FLI within the region of Jena (as of July 2019).

Numbers & Facts
2016 – 2018 at a Glance

Number of employees*:

2016	2017	2018
307	316	309

Number of Associated Research Groups:

2016 – 2018
9

Scientific Talks:

2016	2017	2018
78	125	106

Research Awards for FLI Scientists:

2016	2017	2018
7	8	12

Number of Cooperating Institutions:

2016	2017	2018
398	365	390

Articles in Peer-Reviewed Journals

2016	2017	2018
111	100	93

Third-Party Funding (absolute in k€):**

2016	3.633
2017	3.115
2018	4.177

Number of Research Groups:

2016	2017	2018
13	15	12

Cumulative Impact Factor of FLI Publications:

2016	2017	2018
849	766	657

Number of Lectures/ Courses held by FLI Scientists at local Universities:

2016	2017	2018
63	63	69

* as of December, 31 - financed employees
** including externally administrated funds

Development of Publications

Due to the intermediate stop of animal experiments in 2016 and the obligation to re-apply for many experiments, the number of publications in 2016–2018 has slightly decreased compared to the years before. However, the quality of published papers has further increased – corresponding with FLI's general strategy to increase the quality of research publications, rather than quantity. The cumulative impact factor (IF) of all publications has doubled since 2009 and further increased in the last years. Setting a cut-off for the impact factor (IF≥7) in 2016 – 2018 37% are considered to be high impact publications. Undeniably, these publication measures point to an increase in scientific excellence, as well as in the standing of the FLI as a highly performing institute at national and international level.

Selected Publications 2016 – 2018

2018

Arndt K, Kranz A, Fohgrub J, Jolly A, Bledau AS, Di Virgilio M, Lesche M, Dahl A, Höfer T, Stewart AF, Waskow C.
SETD1A protects HSCs from activation-induced functional decline *in vivo*.
Blood 2018, *131(12)*, 1311-24.

Bens* M, Szafranski* K, Holtze S, Sahm A, Groth M, Kestler HA, Hildebrandt** TB, Platzer** M.
Naked mole-rat transcriptome signatures of socially suppressed sexual maturation and links of reproduction to aging.
BMC Biol 2018, *16(1)*, 77 (** co-senior authors, * equal contribution).

Büttner R, Schulz A, Reuter M, Akula AK, Mindos T, Carlstedt A, Riecken LB, Baader SL, Bauer R, Morrison H.
Inflammaging impairs peripheral nerve maintenance and regeneration.
Aging Cell 2018, *17(6)*, e12833.

Doose G, Bernhart SH, Wagener R, Hoffmann S.
DIEGO: detection of differential alternative splicing using Aitchison's geometry.
Bioinformatics 2018, *34(6)*, 1066-8.

Elster* D, Tollot* M, Schlegelmilch K, Ori A, Rosenwald A, Sahai E, von Eyss B.
TRPS1 shapes YAP/TEAD-dependent transcription in breast cancer cells.
Nat Commun 2018, *9(1)*, 3115 (* equal contribution).

Heinze* I, Bens* M, Calzia* E, Holtze S, Dakhovnik O, Sahm A, Kirkpatrick JM, Szafranski K, Romanov N, Sama SN, Holzer K, Singer S, Ermolaeva M, Platzer** M, Hildebrandt** T, Ori** A.
Species comparison of liver proteomes reveals links to naked mole-rat longevity and human aging.
BMC Biol 2018, *16(1)*, 82 (** co-senior authors, * equal contribution).

Mayerl S, Schmidt M, Doycheva D, Darras VM, Hüttner SS, Boelen A, Visser TJ, Kaether C, Heuer** H, von Maltzahn** J.
Thyroid hormone transporters MCT8 and OATP1C1 control skeletal muscle regeneration.
Stem Cell Reports 2018, *10(6)*, 1959-74 (** co-corresponding authors).

Parca L, Beck M, Bork P, Ori A.
Quantifying compartment-associated variations of protein abundance in proteomics data.
Mol Syst Biol 2018, *14(7)*, e8131.

Percin GI, Eitler J, Kranz A, Fu J, Pollard JW, Naumann R, Waskow C.
CSF1R regulates the dendritic cell pool size in adult mice via embryo-derived tissue-resident macrophages.
Nat Commun 2018, *9(1)*, 5279.

Wyant* GA, Abu-Remaileh* M, Frenkel EM, Laqtom NN, Dharamdasani V, Lewis CA, Chan SH, Heinze I, Ori** A, Sabatini** DM.
NUFIP1 is a ribosome receptor for starvation-induced ribophagy.
Science 2018, *360(6390)*, 751-8 (* equal contribution, ** co-corresponding authors).

2017

Li H, Kroll T, Moll J, Frappart L, Herrlich P, Heuer H, Ploubidou A.
Spindle misorientation of cerebral and cerebellar progenitors is a mechanistic cause of megalencephaly.
Stem Cell Reports 2017, *9(4)*, 1071-80.

Liu P, Lee S, Knoll J, Rauch A, Ostermay S, Luther J, Malkusch N, Lerner UH, Zaiss MM, Neven M, Wittig R, Rauner M, David JP, Bertolino P, Zhang CX, Tuckermann JP.
Loss of menin in osteoblast lineage affects osteocyte-osteoclast crosstalk causing osteoporosis.
Cell Death Differ 2017, *24(4)*, 672-82.

Liu X, Zong W, Li T, Wang Y, Xu X, Zhou** ZW, Wang** ZQ.
The E3 ubiquitin ligase APC/C(C)(dh1) degrades MCPH1 after MCPH1-βTrCP2-Cdc25A-mediated mitotic entry to ensure neurogenesis.
EMBO J 2017, *36(24)*, 3666-81. ** co-corresponding authors

Mackmull MT, Klaus B, Heinze I, Chokkalingam M, Beyer A, Russell RB, Ori** A, Beck** M.
Landscape of nuclear transport receptor cargo specificity.
Mol Syst Biol 2017, *13(12)*, 962. ** co-corresponding authors, highlighted in the "Principle of Systems Biology" - *Cell Systems* 6 - 2018

Mascher M, Gundlach H, Himmelbach A, Beier S, Twardziok SO, Wicker T, Radchuk V, Dockter C, Hedley PE, Russell J, Bayer M, Ramsay L, Liu H, Haberer G, Zhang XQ, Zhang Q, Barrero RA, Li L, Taudien S, Groth M, Felder M, Hastie A, Šimková H, Staňková H, Vrána J, Chan S, Muñoz-Amatriaín M, Ounit R, Wanamaker S, Bolser D, Colmsee C, Schmutzer T, Aliyeva-Schnorr L, Grasso S, Tanskanen J, Chailyan A, Sampath D, Heavens D, Clissold L, Cao S, Chapman B, Dai F, Han Y, Li H, Li X, Lin C, McCooke JK, Tan C, Wang P, Wang S, Yin S, Zhou G, Poland JA, Bellgard MI, Borisjuk L, Houben A, Doležel J, Ayling S, Lonardi S, Kersey P, Langridge P, Muehlbauer GJ, Clark MD, Caccamo M, Schulman AH, Mayer KFX, Platzer M, Close TJ, Scholz U, Hansson M, Zhang G, Braumann I, Spannagl M, Li C, Waugh R, Stein N.
A chromosome conformation capture ordered sequence of the barley genome.
Nature 2017, *544(7651)*, 427-33.

Neri F, Rapelli S, Krepelova A, Incarnato D, Parlato C, Basile G, Maldotti M, Anselmi F, Oliviero S.
Intragenic DNA methylation prevents spurious transcription initiation.
Nature 2017, *543(7643)*, 72-7.

Ripa R, Dolfi L, Terrigno M, Pandolfini L, Savino A, Arcucci V, Groth M, Terzibasi Tozzini E, Baumgart M, Cellerino A.
MicroRNA miR-29 controls a compensatory response to limit neuronal iron accumulation during adult life and aging.
BMC Biol 2017, *15(1)*, 9.

Sahm A, Bens M, Platzer M, Szafranski K.
PosiGene: automated and easy-to-use pipeline for genome-wide detection of positively selected genes.
Nucleic Acids Res 2017, *45(11)*, e100.

Schuhwerk H, Bruhn C, Siniuk K, Min W, Erener S, Grigaravicius P, Krüger A, Ferrari E, Zubel T, Lazaro D, Monajembashi S, Kiesow K, Kroll T, Bürkle A, Mangerich A, Hottiger M, Wang ZQ.
Kinetics of poly(ADP-ribosyl)ation, but not PARP1 itself, determines the cell fate in response to DNA damage *in vitro* and *in vivo*.
Nucleic Acids Res 2017, *45(19)*, 11174-92.

Szambowska A, Tessmer I, Prus P, Schlott B, Pospiech H, Grosse F.
Cdc45-induced loading of human RPA onto single-stranded DNA.
Nucleic Acids Res 2017, *45(6)*, 3217-30.

2016

Avila AI, Illing A, Becker F, Maerz LD, Morita Y, Philipp M, Burkhalter MD.
Xpg limits the expansion of haematopoietic stem and progenitor cells after ionising radiation.
Nucleic Acids Res 2016, *44(13)*, 6252-61.

Dahms* SO, Arciniega* M, Steinmetzer T, Huber** R, Than** ME.
Structure of the unliganded form of the proprotein convertase furin suggests activation by a substrate-induced mechanism.
Proc Natl Acad Sci USA 2016, *113(40)*, 11196-201. * equal contribution, ** co-corresponding authors

Hartmann K, Illing A, Leithäuser F, Baisantry A, Quintanilla-Fend L, Rudolph KL.
Gene dosage reductions of Trf1 and/or Tin2 induce telomere DNA damage and lymphoma formation in aging mice.
Leukemia 2016, *30(3)*, 749-53.

In K, Zaini MA, Müller C, Warren AJ, von Lindern M, Calkhoven CF.
Shwachman-Bodian-Diamond syndrome (SBDS) protein deficiency impairs translation re-initiation from C/EBPα and C/EBPβ mRNAs.
Nucleic Acids Res 2016, *44(9)*, 4134-46.

Li H, Frappart* L, Moll* J, Winkler* A, Kroll T, Hamann J, Kufferath I, Groth M, Taudien S, Schütte M, Yaspo ML, Heuer H, Lange BMH, Platzer M, Zatloukal K, Herrlich P, Ploubidou A.
Impaired planar germ cell division in the testis, caused by dissociation of RHAMM from the spindle, results in hypofertility and seminoma.
Cancer Res 2016, *76(21)*, 6382-95. * equal contribution

Lukjanenko L, Jung MJ, Hegde N, Perruisseau-Carrier C, Migliavacca E, Rozo M, Karaz S, Jacot G, Schmidt M, Li L, Metairon S, Raymond F, Lee U, Sizzano F, Wilson DH, Dumont NA, Palini A, Fässler R, Steiner P, Descombes P, Rudnicki MA, Fan CM, von Maltzahn J, Feige JN, Bentzinger CF.
Loss of fibronectin from the aged stem cell niche affects the regenerative capacity of skeletal muscle in mice.
Nat Med 2016, *22(8)*, 897-905.

Ori A, Iskar M, Buczak K, Kastritis P, Parca L, Andrés-Pons A, Singer S, Bork P, Beck M.
Spatiotemporal variation of mammalian protein complex stoichiometries.
Genome Biol 2016, *17(1)*, 47 (featured in *Research Highlights* by Michael P. Washburn: There is no human interactome.
Genome Biology 2016, 17, 48).

Sahm A, Platzer M, Cellerino A.
Outgroups and positive selection: the *Nothobranchius furzeri* case.
Trends Genet 2016, *32(9)*, 523-5.

Schulz A, Büttner R, Hagel C, Baader SL, Kluwe L, Salamon J, Mautner VF, Mindos T, Parkinson DB, Gehlhausen JR, Clapp DW, Morrison H.
The importance of nerve microenvironment for schwannoma development.
Acta Neuropathol 2016, *132(2)*, 289-307.

Tang D, Tao S, Chen Z, Koliesnik IO, Calmes PG, Hoerr V, Han B, Gebert N, Zörnig M, Löffler B, Morita** Y, Rudolph** KL.
Dietary restriction improves repopulation but impairs lymphoid differentiation capacity of hematopoietic stem cells in early aging.
J Exp Med 2016, *213(4)*, 535-53. ** co-corresponding authors

Selected Awards 2016 – 2018

2018

Dr. Arne Sahm was awarded with the Campus Award **“Life Science and Physics”** of Beutenberg Campus Jena e.V. for the best doctoral thesis in the field.

Prof. Dr. Alessandro Cellerino, Prof. Dr. Christoph Englert, PD Dr. Matthias Platzer, Dr. Bryan R. Downie, Dr. Nils Hartmann, Dr. Philipp Koch, Dr. Andreas Petzold and Dr. Kathrin Reichwald were honored with the **Thüringer Forschungspreis** in the category basic research for establishing the fish *Nothobranchius furzeri* as innovative animal model in aging research.

As one of 10 participants of the Leibniz Association, Dr. Danny Schnerwitzki was selected to participate in the **68th Lindau Nobel Laureate Meeting** dedicated to physiology and medicine.

2017

The FLI was awarded the certificate **“Swallow-friendly House”** by NABU Germany (Nature And Biodiversity Conservation Union). The institute has been installing artificial swallow nests on its roof ridges for many years.

Dr. Francesco Neri receives the **GSCN 2017 Young Investigator Award** of the German Stem Cell Network (GSCN) for his excellent research as a junior scientist.

During the **2nd International Symposium Healthy Ageing**, the Poster as well as the Presentation Award were awarded to Nadja Gebert and Nicolas Huber.

2016

FLI Junior Group Leader Dr. Francesco Neri was awarded the renowned **“Sofja Kovalevskaja Award”** in acknowledgement of his outstanding academic achievements. It is the highest endowed award for young scientists in Germany.

Dr. Ronny Hänold and colleagues received the “Outstanding Poster Award” at the **Second International Conference on Aging and Disease** in Stanford, USA, for the most outstanding poster in terms of content and appearance.

In recognition of its excellent equal opportunities policies, the FLI received the **“Total E-Quality Award”** for the second time, this time with the Add-on **“Diversity”**.

FLI Researchers awarded with Thüringer Forschungspreis

Aging in fast-motion: *Nothobranchius furzeri* as new model in aging research

Researchers are often dependent on animal models to investigate the biological principles of aging. To date, established animal models like invertebrates often differ from humans in terms of physiology or genetics or have as vertebrates a relatively long life span. In contrast, the turquoise killifish from the Southeast African savannah ages similar to humans but significantly faster.
Even under ideal laboratory conditions, the turquoise killifish (*N. furzeri*) lives only from 4 to 12 months and ages in fast motion. This is why in 2005, a team of researchers from FLI decided to bring the fish into the laboratories to establish an innovative model in aging research.

The team sequenced and analyzed the genome of the fish and achieved a breakthrough at the end of 2015 by completely deciphering the genome of the short-lived fish and identifying genes with relevance for the evolution of the aging process. On basis of the freely available genome data, aging researchers worldwide can now, for example, selectively switch on or off genes and thus investigate the influence of individual genes on aging or age-related diseases.

Short-lived strain of the *N. furzeri*.

In the context of demographic change, increasing life expectancy and an increasingly longer phase of illness in old age, the establishment of *N. furzeri* as an aging model is a milestone in aging research, which is also impressively reflected in numerous high-ranking *N. furzeri* publications of the research team. This opens up new possibilities for further research on the molecular basis of aging in vertebrates.

For this outstanding achievement, the FLI research team was awarded the 23rd Thüringer Forschungspreis 2018 in the category of basic research. The award was presented on April 24, 2018 by the Thuringian minister of science Wolfgang Tiefensee.

Research Team:

Prof. Dr. Alessandro Cellerino, Prof. Dr. Christoph Englert, PD Dr. Matthias Platzer, Dr. Bryan R. Downie, Dr. Nils Hartmann, Dr. Philipp Koch, Dr. Andreas Petzold, Dr. Kathrin Reichwald

Honored FLI-researchers together with the Thuringian minister of science Wolfgang Tiefensee (1st from right) at the award ceremony.

Since 1995, the Thüringer Forschungspreis has been awarded once a year by the state of Thuringia for outstanding achievements in research at universities and non-university research institutions. The award is assigned in the categories basic research and applied research.

Invited Speeches and Talks 2016 – 2018

Invited International Guest Speakers at FLI

2016 (total: 58)				
Germany	Europe	Asia	America	
32	13	4	9	
2017 (total: 40)				
Germany	Europe	Asia	America	Australia
24	13	1	1	1
2018 (total: 28)				
Germany	Europe	Asia	America	
14	6	3	5	

Talks of FLI-Scientists

2016 (total: 78)		
International conferences	Seminar talks in scientific institutions	Talks in other institutions
58	14	6
2017 (total: 130)		
International conferences	Seminar talks in scientific institutions	Talks in other institutions
86	37	7
2018 (total: 107)		
International conferences	Seminar talks in scientific institutions	Talks in other institutions
67	35	5

Academic Events 2016 – 2018

02.06.2016 – 04.06.2016	2nd Nothobranchius Symposium, Jena, organized by: Christoph Englert (FLI), Alessandro Cellerino (Scuola Normale Superiore di Pisa, Pisa, Italy), Matthias Platzer (FLI) and Dario Valenzano (Max Planck Institute for Biology of Ageing, Köln, Germany)
16.08.2016 – 24.08.2016	International Summer School 2016 – EMBO Workshop: Molecular mechanisms of ageing and regeneration – From pluripotency to senescence, Spetses, Greece, organized by: Christoph Englert (FLI), Alejandro Sanchez-Alvarado (Howard Hughes Medical Institute & Stowers Institute for Medical Research, Chevy Chase, MD, USA) and Julia von Maltzahn (FLI)
14.10.2016 – 17.10.2016	icBEST/isDDRHD-2016, Chengdu, China, organized by: Zhao-Qi Wang (FLI) and Xingzhi Xu (Beijing Key Lab of DNA Damage Response, Beijing, China)
11.02.2017 – 12.02.2017	Stem Cells and Cancer Gordon Research Seminar (GRS), Lucca (Barga), Italy, organized by: Seerat Bajwa (FLI) and Jeevisha Bajaj (University of California, San Diego, USA)
12.02.2017 – 17.02.2017	Gordon Research Conference – Stem Cells & Cancer, Lucca (Barga), Italy, organized by: K. Lenhard Rudolph (FLI) and Amy J. Wagers (Harvard University, Boston, USA)
27.02.2017 – 28.02.2017	2nd International Symposium Healthy Ageing, Magdeburg, Germany, organized by: Astrid van der Wall (FLI) and LFV Healthy Ageing
11.09.2017 – 13.09.2017	5th Annual Conference of the German Stem Cell Network (GSCN), Jena, Germany, organized by: K. Lenhard Rudolph (FLI) and Daniel Besser (GSCN, Berlin, Germany)
14.09.2017	Non PI-Meeting of the 5th Annual Conference of the German Stem Cell Network (GSCN), Jena, Germany, organized by: Marie Juliane Jung (FLI) and Daniel Besser (GSCN, Berlin, Germany)
30.09.2017 – 02.10.2017	7th International Meeting Jena - Beijing - Molecular Signatures of Adaptive Stress Responses, Erfurt, Germany, organized by: Zhao-Qi Wang (FLI)
27.10.2017 – 29.10.2017	8th International Symposium on DNA Damage, Response & Human Disease (isDDRHD-2017), Shenzhen, China, organized by: Zhao-Qi Wang (FLI)
06.09.2018	Jena Aging Seminar (JAS): Non-PI Meeting, Jena, Germany, organized by: Marie Juliane Jung (FLI), Tom Bates (FLI), Thomas Mindos (FLI) and Omid Omrani (FLI)
06.09.2018 – 08.09.2018	Jena Aging Meeting (JAM), Jena, Germany organized by: Helen Morrison (FLI) and K. Lenhard Rudolph (FLI)
26.09.2018 – 28.09.2018	Leibniz PhD Network “General Assembly”, Jena, Germany, organized by: Tetiana Poliezhaieva (FLI) and IPHT Jena PhD Representatives
31.10.2018 – 04.11.2018	icBEST/isDDRHD Meeting 2018, Shenzhen, China organized by: Zhao-Qi Wang (FLI), Xingzhi Xu (Shenzhen University) and Zhenkun Luo (Mayo Clinics, USA)
06.12.2018 – 07.12.2018	DGfA 2018 - Annual Conference of German Association for Aging Research, Jena, Germany, organized by: Maria Ermolaeva (FLI) and Christian Kosan (Center for Molecular Biomedicine, Friedrich Schiller University Jena)

Jena Aging Meeting (JAM) 2018

The first international conference on the issue of aging took place in Jena; the "Jena Aging Meeting (JAM)" from September 6–8, 2018. About 200 participants from 16 countries met to discuss the latest research results, methods and developments in the field of aging research. Topics included the gene- and protein-related mechanisms in aging, DNA damage response in cancer and aging, metabolism in health, disease and aging, genomic instability and senescence in aging and stem cells in tissue homeostasis, regeneration and aging.

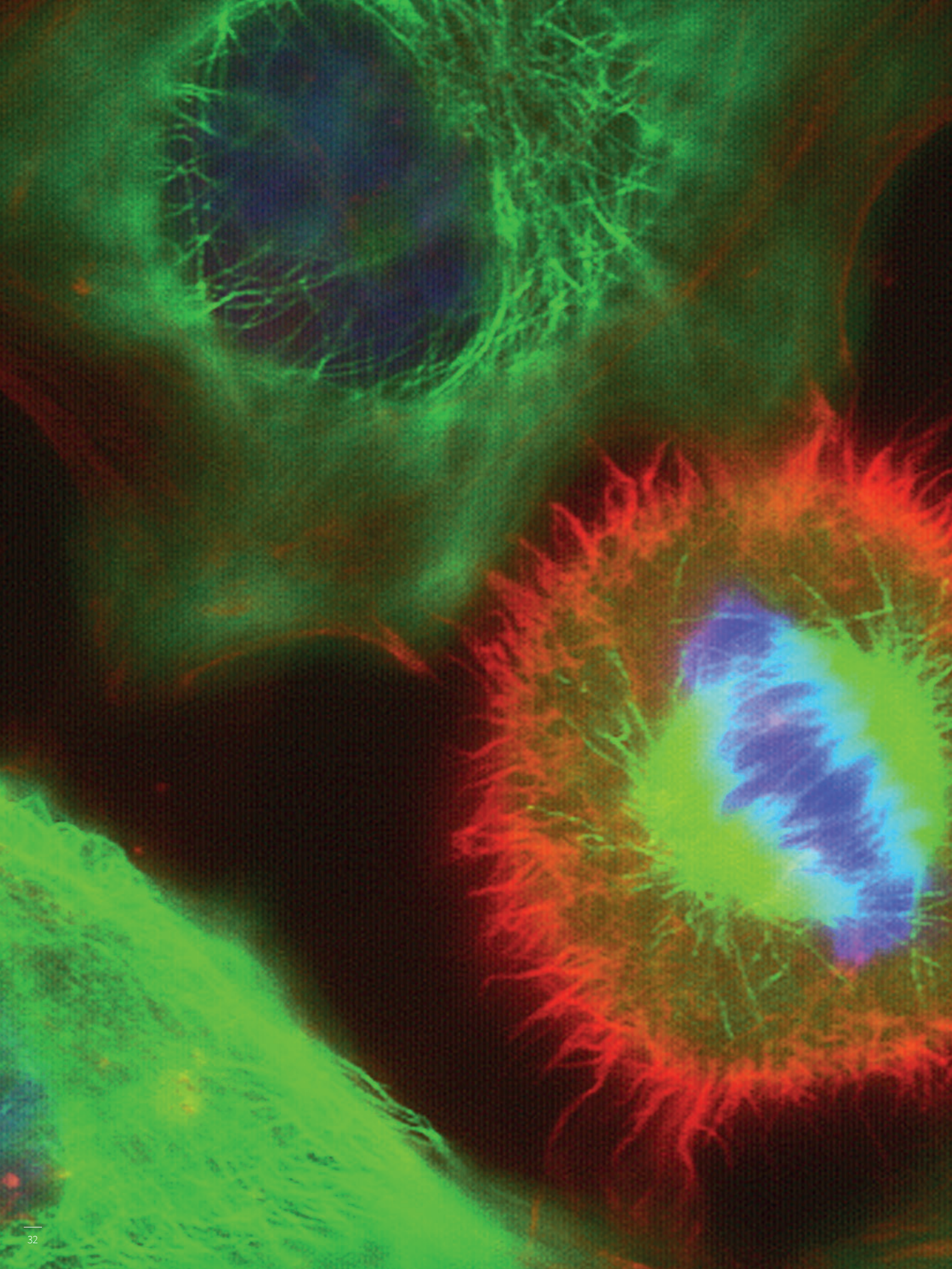
More than 20 internationally renowned speakers gave insights into their field of expertise in aging research. To foster scientific exchange at every level, the three-day conference offered much space to socialize in addition to numerous lectures and poster sessions.

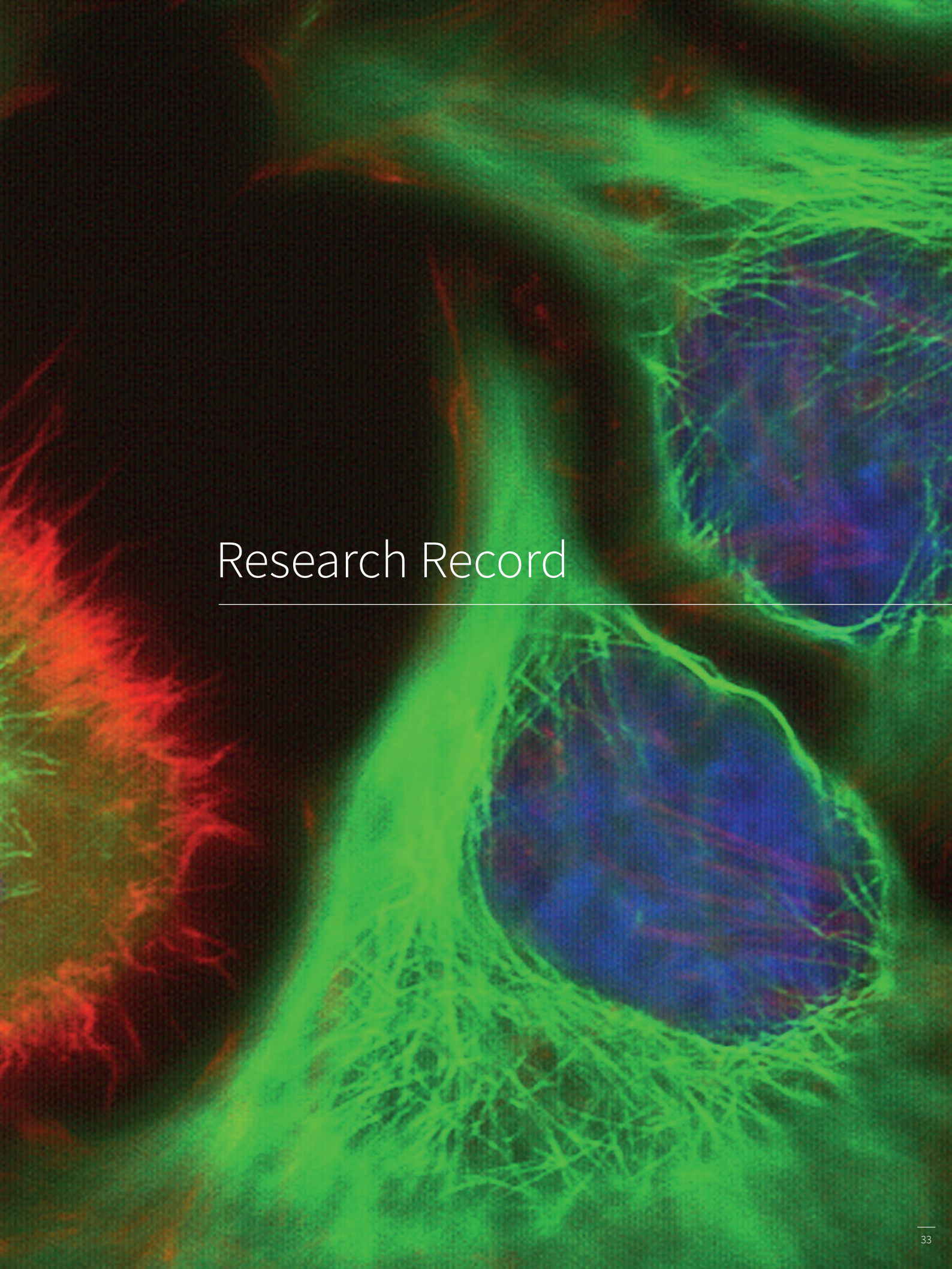
The second Jena Aging Meeting (JAM) will take place from September 17–19, 2020 in Jena.

Together with its partners including the FSU and the Jena University Hospital, research on aging has a special significance for the city: The common goal is to bolster aging research in Jena with a combined basic and translational research approach in order to understand the mechanisms that contribute to aging and aging-related diseases.

Keynote speakers at the JAM were the stem cell researcher Prof. Dr. Emmanuelle Passegué from the Columbia University, New York, USA and the molecular biologist Prof. Dr. Jan Hoeijmakers from the Erasmus Medical Center in Rotterdam, Netherlands.

About 200 participants came to Jena to take part in the first Jena Aging Meeting (JAM).





Research Record

Research Record

Focus of Research

To provide a rational basis for the development of therapies aimed at improving health in the elderly – and backed by a strong expertise in systems biology – research at the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) in Jena focuses on two Areas:

I.

Stem Cells, Regeneration and Organ Homeostasis in Aging

Stem Cells, Regeneration and Organ Homeostasis in Aging

Organ maintenance (homeostasis) and regenerative capacity decrease during aging. This leads to impairments in organ function and to an increased risk of disease development. One reason for this is the reduced performance of the adult stem cells responsible for the lifelong self-renewal and regeneration of organs and tissues. We investigate the causes of this aging-associated inhibition of stem cell function and its effects on organ maintenance. Our research should facilitate the development of therapies to help maintain the function of endogenous stem cells and thus reduce the risk of malfunctions and diseases in old age. Subareas 1 and 2 are allocated to this Research Area.

II.

Genetics, Epigenetics and Molecular Cell Dynamics of Aging

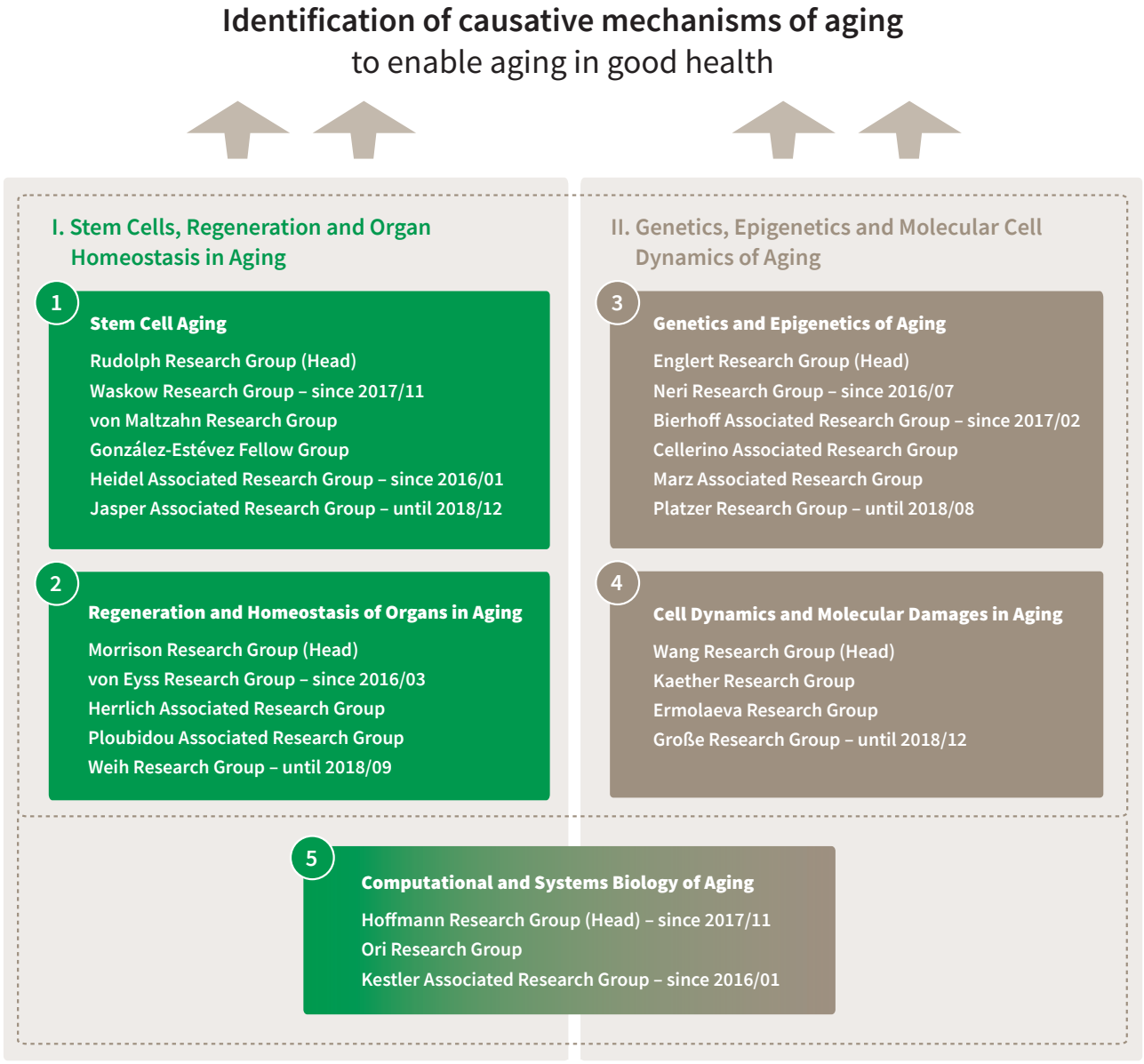
Genetics, Epigenetics and Molecular Cell Dynamics of Aging

A central phenomenon of aging is the accumulation of damage in the molecular building blocks of cells. This applies also to proteins and the genetic information DNA. There is growing evidence that the impairment of proteins and DNA contributes to the malfunctioning of stem cells and tissue maintenance. But the causes of the aging-associated accumulation of protein and DNA damage are still largely unknown. Additionally, the question arises as to which genetic factors have an influence on the speed of aging in molecular components. To address these questions, we are employing comparative analyses and targeted manipulations of the genome or transcriptome in short- and long-lived model organisms, to learn more about the genetic factors influencing the aging process. The objective is to identify genetic and epigenetic variations, which in humans also determine the individual predisposition for healthy aging or the development of aging-related diseases. This Research Area includes Subareas 3 and 4.

Computational and Systems Biology of Aging

Computational and Systems Biology of Aging

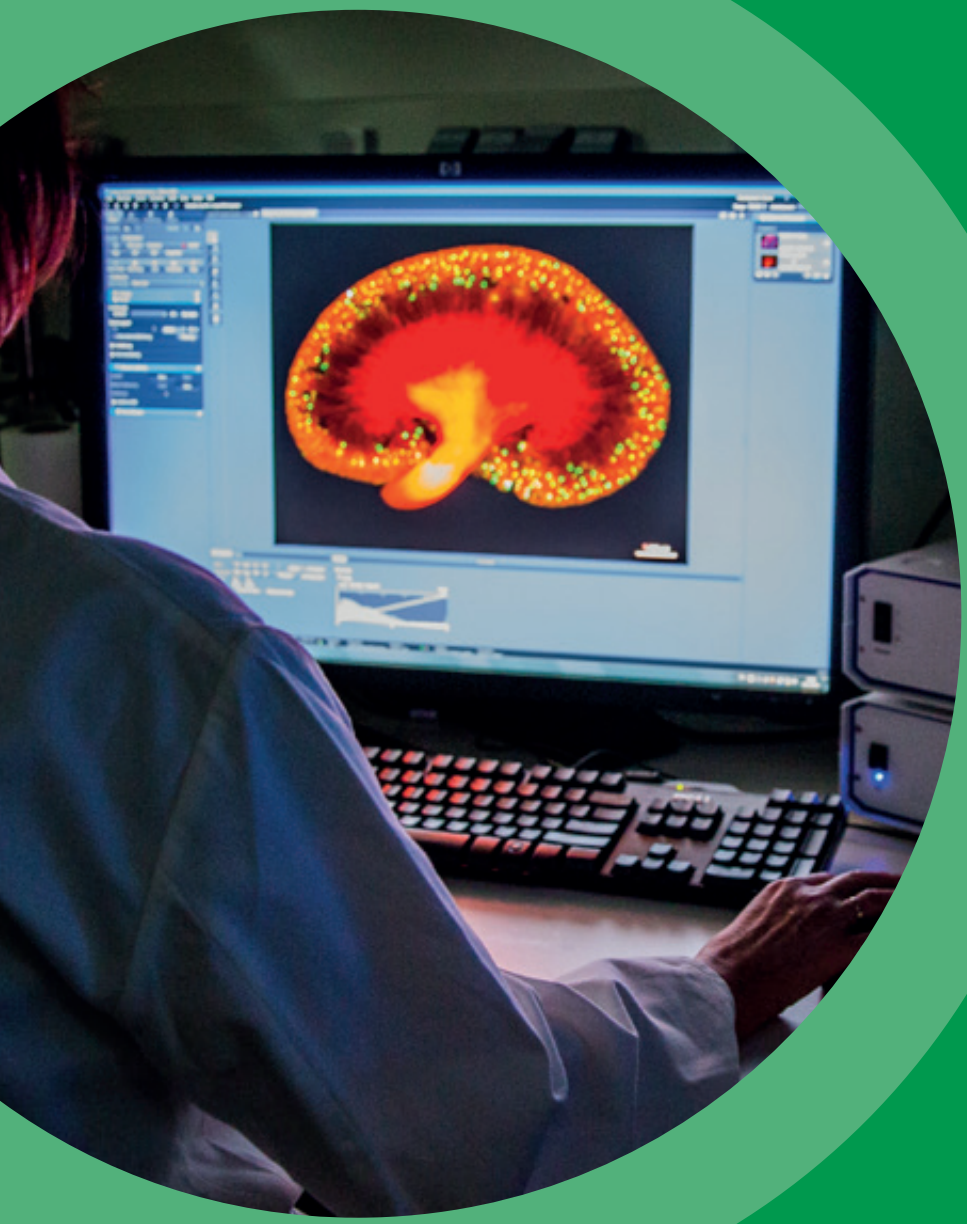
Systems biology and bioinformatics analyses are employed to compare research results from model organisms with human aging, to develop models and predictions for causative molecular mechanisms and circuits that influence human aging. In cooperation with physicians, these assumptions are tested with regard to their significance for disease development in advanced age. Systems biology at the FLI serves as an interface between Research Areas I and II and is identical with Subarea 5.



Research Groups at FLI. Includes all research groups doing research at FLI from 2016–2018.

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 QUESTION:

Why does stem cell functionality decline during aging – and how can we prevent it?

Focus of Research

The research group "Stem Cell Aging" focuses on (epi)genetic and molecular mechanisms of stem cell aging. Adult tissue stem cells have a pivotal role in lifelong maintenance of organ homeostasis and regeneration in response to injury. There is experimental and clinical evidence that the functional capacity of stem cells declines during aging. Stem cell aging involves cell intrinsic accumulation of molecular damages as well as stem cell extrinsic alteration in stem cell niches and in the blood circulation. Causal mechanisms underlying these alterations in stem cells and the stem cell environment as well as its consequences for stem cell function and organism aging remain incompletely understood.

Current Projects

The research group focuses on 3 main areas:

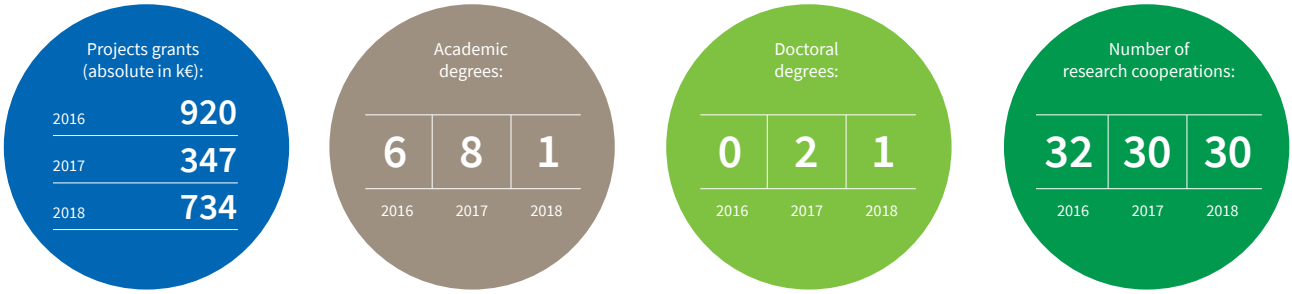
(A) Molecular damages and checkpoint/quality control pathways

(B) Systemic factors, metabolism and inflammation

(C) (Epi)Genetic factors and clonal selection

The group aims to delineate how mechanisms in these 3 areas interact: How do molecular damages impinge on metabolism and epigenetic modification in aging stem cells and *vice versa*. They wish to analyze how these interactions drive the selection of aberrant or mutant stem cells and what are the consequences of these interaction and selection processes on organism aging. The goal is to identify major mechanisms and interactions that drive the decrease in stem cell function and organ maintenance during aging. The group will conduct proof of concept experiment to test if the inhibition of specific mechanisms of stem cell aging can improve stem cell function and organ maintenance in the aging organism.

Numbers 2016 – 2018



Selected Publications 2016 – 2018

Hartmann K, Illing A, Leithäuser F, Baisantry A, Quintanilla-Fend L, Rudolph KL. (2016).
Gene dosage reductions of Trf1 and/or Tin2 induce telomere DNA damage and lymphoma formation in aging mice.
Leukemia. *30(3)*, 749-53.

Schwörer S, Becker F, Feller C, Baig AH, Köber U, Henze H, Kraus JM, Xin B, Lechel A, Lipka DB, Varghese CS, Schmidt M, Rohs R, Aebersold R, Medina KL, Kestler HA, Neri F, von Maltzahn** J, Tümpel** S, Rudolph** KL. (2016).
Epigenetic stress responses induce muscle stem-cell ageing by Hoxa9 developmental signals.
Nature. *540(7633)*, 428-32 (** co-corresponding authors).

Tang D, Tao S, Chen Z, Koliesnik IO, Calmes PG, Hoerr V, Han B, Gebert N, Zörnig M, Löffler B, Morita** Y, Rudolph** KL. (2016).
Dietary restriction improves repopulation but impairs lymphoid differentiation capacity of hematopoietic stem cells in early aging.
J Exp Med. *213(4)*, 535-53 (** co-corresponding authors).

Wang J, Morita Y, Han B, Niemann S, Löffler B, Rudolph KL. (2016).
Per2 induction limits lymphoid-biased hematopoietic stem cells and lymphopoiesis in the context of DNA damage and ageing.
Nat Cell Biol. *18(5)*, 480-90 (recommended by "Faculty of 1000" - Prime).

Cooperation Partners (Selection)

- Friedrich Schiller University Jena (FSU), Germany
- University of Bergen, Norway
- Ulm University, Germany
- Jena University Hospital, Germany

Funding (Selection)

Prof. Dr. Claudia Waskow
Group Leader

Waskow Research Group:
Regeneration in Hematopoiesis
(since 2017/11)

1

CENTRAL RESEARCH QUESTION:

How is hematopoiesis controlled on the cellular and molecular level and how and why does it change with aging?

Focus of Research

Stem cell maintenance is essential for continuous tissue formation during steady-state and under stress. The constant supply of *de novo* generated mature cells from adult stem cells is pivotal for the lifelong function of many organs, in particular for tissues with high turn-over rates such as the gut, skin and blood. Understanding the mechanisms of fate choice in stem and progenitor cells holds the promise of replacement of tissues that lost their functionality during aging by engineered tissues in the future.

One of the most thoroughly studied adult stem cell types is the hematopoietic stem cell (HSC) that gives rise to all blood cells through a process called hematopoiesis. Like this, HSC are also fundamental for a functional immune system. HSC can be prospectively isolated to very high purity, and after bone marrow transplantation the infused donor HSCs disclose their amazing regenerative potential and continuously generate blood cells over long periods.

Despite the precise phenotypic description of HSCs the molecular mechanisms, including signaling pathways and receptor interplay, underlying fate-choice decisions are not resolved. Failure of hematopoiesis can lead to life-threatening blood disorders disclosing the need for a tight regulation of fate choices of HSC to ensure welfare of the organism. Further, during aging, loss of HSC functionality leads to the weakening of immune system. The group focuses on cell-intrinsic and extrinsic niche-mediated signals that regulate HSC fate.

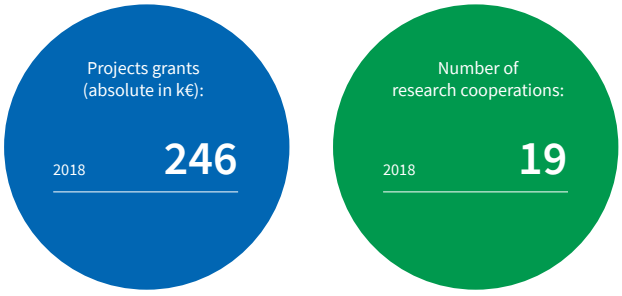
Current Projects

The research group focuses on HSCs and hematopoiesis in mice and humans. The lab uses state-of-the art techniques to understand the effect of cell physiological processes on stem and progenitor cell function with a focus on developing optimized tools to address our questions *in vivo*.

Fundamental research questions include:

- **How is hematopoiesis controlled on the molecular level?**
- **What keeps a stem cell a stem cell? What invites a stem cell to differentiate?**
- **What is the role of growth factors in lineage choice?**
- **How does aging impact hematopoiesis?**

Numbers 2018



Selected Publications 2016 – 2018

Arndt K, Kranz A, Fohgrub J, Jolly A, Bledau AS, Di Virgilio M, Lesche M, Dahl A, Höfer T, Stewart AF, Waskow C. (2018).
SETD1A protects HSCs from activation-induced functional decline *in vivo*.
Blood. *131(12)*, 1311-24.

Percin GI, Eitler J, Kranz A, Fu J, Pollard JW, Naumann R, Waskow C. (2018).
CSF1R regulates the dendritic cell pool size in adult mice via embryo-derived tissue-resident macrophages.
Nat Commun. *9(1)*, 5279.

Schreck C, Istvánffy R, Ziegenhain C, Sippenauer T, Ruf F, Henkel L, Gärtner F, Vieth B, Florian MC, Mende N, Taubenberger A, Prendergast Á, Wagner A, Pagel C, Grziwok S, Götze KS, Guck J, Dean DC, Massberg S, Essers M, Waskow C, Geiger H, Schiemann M, Peschel C, Enard W, Oostendorp RAJ. (2017).
Niche WNT5A regulates the actin cytoskeleton during regeneration of hematopoietic stem cells.
J Exp Med. *214(1)*, 165-81.

Rahmig S, Kronstein-Wiedemann R, Fohgrub J, Kronstein N, Nevmerzhitskaya A, Bornhäuser M, Gassmann M, Platz A, Ordemann R, Tonn T, Waskow C. (2016).
Improved human erythropoiesis and platelet formation in humanized NSGW41 mice.
Stem Cell Reports. *7(4)*, 591-601.

Schoedel KB, Morcos MNF, Zerjatke T, Roeder I, Grinenko T, Voehringer D, Göthert JR, Waskow C, Roers A, Gerbaulet A. (2016).
The bulk of the hematopoietic stem cell population is dispensable for murine steady-state and stress hematopoiesis.
Blood. *128(19)*, 2285-96.

Cooperation Partners (Selection)

- Biotechnology Center of the TU Dresden (BIOTEC), Germany
- Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany
- Memorial Sloan Kettering Cancer Center (MSKCC), New York, USA
- University of Edinburgh, UK
- Vita-Salute San Raffaele University, Milan, Italy

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

DFG SFB 655 Dresden
Cells into tissues

E-Rare

von Maltzahn Research Group: Stem Cells of Skeletal Muscle

Dr. Julia von Maltzahn
Group Leader

1

CENTRAL RESEARCH QUESTION:

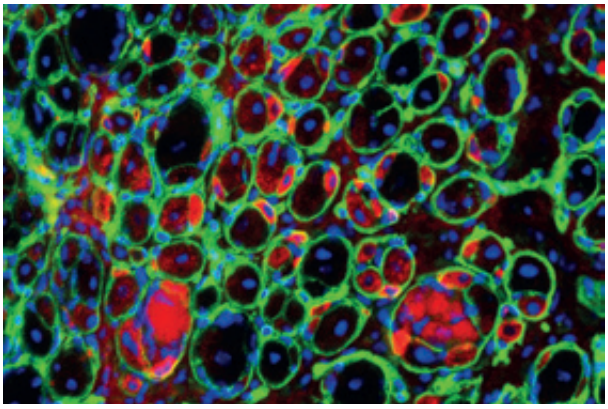
Why does functionality of muscle stem cells decline during aging?

Focus of Research

Skeletal muscle serves a multitude of functions in the organism and exhibits a remarkable ability to adapt to physiological demands and to regenerate. Satellite cells are the stem cells of skeletal muscle and are associated with its growth, maintenance and regeneration. Aged skeletal muscle shows a significantly impaired regenerative potential. Evidence in the literature suggests that functionality of satellite cells in aged skeletal muscle is impaired due to the aged environment, but also due to intrinsic differences between adult and aged satellite cells. The research group “Stem Cells of Skeletal Muscle” investigates the intrinsic differences between adult and aged satellite cells as well as changes in the stem cell niche. This work will provide insights into pathways, which are perturbed in aged satellite cells and allow for modification of these pathways thereby rejuvenating aged muscle.

Methods

To assess the functionality of satellite cells during aging, they analyze injured skeletal muscles from aged and adult mice and investigate the regeneration process at different time points after injury. The group could already show that JAK/STAT-signaling and expression of the transcription factor Hoxa9 is upregulated in aged satellite cells leading to impaired regeneration in aged skeletal muscle. The ultimate goal in the treatment of sarcopenia – the age-related reduction in muscle mass and functionality – is to preserve muscle mass and restore satellite cell homeostasis. When the homeostasis of a tissue is perturbed this likely leads to its degeneration. A factor that can restore the differentiation potential of satellite cells and their ability to self-renew in the aged has the potential to reinstate tissue homeostasis in old skeletal muscle.



Skeletal muscle during regeneration; in green: laminin, in red: developmental myosin; in blue: nuclei.

Numbers 2016 – 2018

Projects grants (absolute in k€):

2016	182
2017	338
2018	354

Academic degrees:

2016	2017	2018
3	1	1

Doctoral degrees:

2016	2017	2018
0	0	1

Number of research cooperations:

2016	2017	2018
10	11	30

Selected Publications 2016 – 2018

Ahrens* HE, Huettemeister* J, Schmidt M, Kaether C, von Maltzahn J. (2018).
Klotho expression is a prerequisite for proper muscle stem cell function and regeneration of skeletal muscle.
Skelet Muscle. *8(1)*, 20 (* equal contribution).

Mayerl S, Schmidt M, Doycheva D, Darras VM, Hüttner SS, Boelen A, Visser TJ, Kaether C, Heuer** H, von Maltzahn** J. (2018).
Thyroid hormone transporters MCT8 and OATP1C1 control skeletal muscle regeneration.
Stem Cell Reports. *10(6)*, 1959-74 (** co-corresponding authors).

Müller* C, Zidek* LM, Ackermann T, de Jong T, Liu P, Kliche V, Zaini MA, Kortman G, Harkema L, Verbeek DS, Tuckermann JP, von Maltzahn J, de Bruin A, Guryev V, Wang ZQ, Calkhoven CF. (2018).
Reduced expression of C/EBPβ-LIP extends health- and lifespan in mice.
Elife. *7*, e34985 (* equal contribution).

Lukjanenko L, Jung MJ, Hegde N, Perruisseau-Carrier C, Migliavacca E, Rozo M, Karaz S, Jacot G, Schmidt M, Li L, Metairon S, Raymond F, Lee U, Sizzano F, Wilson DH, Dumont NA, Palini A, Fässler R, Steiner P, Descombes P, Rudnicki MA, Fan CM, von Maltzahn J, Feige JN, Bentzinger CF. (2016).
Loss of fibronectin from the aged stem cell niche affects the regenerative capacity of skeletal muscle in mice.
Nat Med. *22(8)*, 897-905.

Schwörer S, Becker F, Feller C, Baig AH, Köber U, Henze H, Kraus JM, Xin B, Lechel A, Lipka DB, Varghese CS, Schmidt M, Rohs R, Aebersold R, Medina KL, Kestler HA, Neri F, von Maltzahn** J, Tümpel** S, Rudolph** KL. (2016).
Epigenetic stress responses induce muscle stem-cell ageing by Hoxa9 developmental signals.
Nature. *540(7633)*, 428-32 (** co-corresponding authors).

Cooperation Partners (Selection)

- Essen University Hospital, Germany
- European Research Institute for the Biology of Ageing (ERIBA), Groningen, Netherlands
- Friedrich Schiller University Jena (FSU), Germany
- Leibniz Institute for Farm Animal Biology, Dummerstorf, Germany
- Université de Sherbrooke, Canada
- University Erlangen, Germany
- University of Graz, Austria

Funding (Selection)

Emmy Noether-Programm DFG

DFG Deutsche Forschungsgemeinschaft German Research Foundation

Leibniz Association

González-Estévez Fellow Group: Stem Cells / Regeneration of Planarians

1

Cristina González-Estévez, PhD
Fellow Group Leader

CENTRAL RESEARCH QUESTION:

How does starvation regulate planarian stem cells?

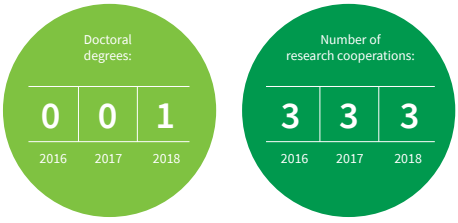
Focus of Research

The fellow group "Stem Cells / Regeneration of Planarians" is interested in understanding how stem cells are regulated during dietary restriction. Caloric restriction is the most powerful anti-aging strategy known that is conserved throughout evolution in the animal kingdom. It is known that caloric restriction extends lifespan of vertebrate and invertebrate animals and protects against age-related diseases such as diabetes, hypertension or cancer. It has been suggested that the beneficial effects of caloric restriction in delaying aging are due, at least in part, to an enhancement in stem cell function. However, little is known about the cellular and molecular mechanisms that caloric restriction uses to regulate stem cell function. The overall objective is the identification of signaling pathways 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 called 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 (cNeoblasts). The proliferative capacity and pluripotency of these stem cells underlies the extreme and renowned tissue plasticity and regeneration capabilities in planarians. Planarians represent an excellent model by which to study stem cells and specifically how caloric restriction regulates them since they are able to withstand long periods of starvation. During this time they can shrink, without showing physiological impairment, and maintain a stable population of proliferating stem cells in detriment of stem cell differentiation.

Current Projects

- High-throughput screening in planarians during starvation. The group aims to find novel genes involved in an enhancement of stem cell function (stem cell maintenance, pluripotency and clonogenecity) and in aging/rejuvenation mechanisms
- Telomere length quantification as a tool to distinguish different populations of planarian stem cells during starvation

Numbers 2016 – 2018



Selected Publications 2016 – 2018

Gutiérrez-Gutiérrez Ó, Felix DA, González-Estévez C. (2017). Planarian finds time(less) to fight infection. Virulence. *8(7)*, 1043-8.

Cooperation Partners (Selection)

- Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain
- University of Oxford, UK
- University of Pisa, Italy

Heidel Associated Research Group:
Stem Cell Aging / Myeloid Neoplasia
(since 2016/01)

1

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

CENTRAL RESEARCH QUESTION:

Which signaling pathways and molecules are involved in self-renewal and differentiation during aging of hematopoietic stem cells and which of them contribute to malignant transformation?

Focus of Research

The group's research interest is the (de-)regulation of signaling pathways and molecules during aging of the hematopoietic system that may eventually contribute to the development of myeloid neoplasia. The researchers employ genetically engineered mouse models and RNAi technology to functionally characterize signaling pathways and molecules involved in self-renewal, differentiation and aging of hematopoietic stem cells. Their overall aim is to identify novel therapeutic targets for clinical therapy of aging associated myeloid cancers.

Numbers 2016 – 2018

Doctoral degrees:

2016	2017	2018
0	1	0

Number of research cooperations:

2016	2017	2018
7	7	7

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Else Kröner Fresenius Stiftung

Current Projects

- Identification of therapeutic targets for aging-associated myeloid neoplasms
- Functional role of evolutionary conserved signaling pathways and cell fate determinants (polarity regulators) in hematopoietic and leukemic stem cell biology
- Biological relevance of PLCgamma1 (PLCg1) signaling in hematopoietic stem cells

Selected Publications 2016 – 2018

Edelmann B, Gupta N, Schnoeder TM, … , Heidel FH, Schraven B, Isermann B, Müller AJ, Fischer T. (2018).
JAK2-V617F promotes venous thrombosis through β1/β2 integrin activation.
J Clin Invest. *128(10)*, 4359-71.

Mohr J, Dash BP, Schnoeder TM, … , Heidel FH. (2018).
The cell fate determinant Scribble is required for maintenance of hematopoietic stem cell function.
Leukemia. *32(5)*, 1211-21.

Prestipino A, Emhardt AJ, Aumann K, … , Heidel FH, Kröger N, Triviai I, Brummer T, Finke J, Illert AL, Ruggiero E, Bonini C, Duyster J, Pahl HL, Lane SW, Hill GR, Blazar BR, von Bubnoff N, Pearce EL, Zeiser R. (2018).
Oncogenic JAK2V617F causes PD-L1 expression, mediating immune escape in myeloproliferative neoplasms.
Sci Transl Med. *10(429)*.

Ranjan S, Goihl A, Kohli S, … , Heidel FH, Isermann B. (2017).
Activated protein C protects from GvHD via PAR2/PAR3 signalling in regulatory T-cells.
Nat Commun. *8(1)*, 311.

Perner F, Schnöder TM, Ranjan S, … , Heidel FH. (2016).
Specificity of JAK-kinase inhibition determines impact on human and murine T-cell function.
Leukemia. *30(4)*, 991-5.

Jasper Associated Research Group: Stem Cell Signaling in Aging & Inflammation (until 2018/12)

1

Dr. Heinrich Jasper
Cooperation with Buck Institute for Research on Aging, Novato, USA

CENTRAL RESEARCH QUESTION:

How do stress, metabolism and other processes affect stem cell function during life?

Focus of Research

Stem cells are an essential part of many adult tissues and make sure that cells are continually replaced in our skin, lungs, intestine and many other tissues. The functional decline of stem cells throughout life is one of the major causes of age-related disease. The group "Stem Cell Signaling in Aging & Inflammation" is interested in how stress, metabolism and other processes affect stem cell function during life. The group uses the intestine of the fruit fly (*Drosophila melanogaster*) as a model system for stem cell biology, taking advantage of the wide array of genetic, molecular and genomic techniques and resources for this model organism. More recently, the lab has been extending its findings in mammalian stem cell systems such as mouse intestinal organoids and the mouse airway system, which is regulated in a highly similar way to the *Drosophila* intestine, both on the functional and regulatory level.

Current Projects

- Influence of growth and stress signaling pathways (e.g. Insulin, JNK), metabolic processes and proteasome stress on stem cells and how this changes during aging
- Research on the intrinsic controls that govern the unique identity of adult stem cells
- Identification of common mechanisms in organismal aging at the stem cell level

Selected Publication 2016 – 2018

Haller S, Jasper H. (2016).
You are what you eat: linking high-fat diet to stem cell dysfunction and tumorigenesis.
Cell Stem Cell. *18(5)*, 564-6.

Luis NM, Wang L, Ortega M, Deng H, Katewa SD, Li PWL, Karpac J, Jasper** H, Kapahi** P. (2016).
Intestinal IRE1 is required for increased triglyceride metabolism and longer lifespan under dietary restriction.
Cell Rep. *17(5)*, 1207-16 (** co-corresponding authors).

Numbers 2016 – 2018

Projects grants (absolute in k€):

2018
20

Number of research cooperations:

2016	2017	2018
0	1	1

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

Laboratory work at the FLI.

Morrison Research Group:
Nerve Regeneration

Dr. Helen Morrison
Group Leader

2

CENTRAL RESEARCH QUESTION:

How does the signaling that underlies maintenance and regeneration of the nervous system impair 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.

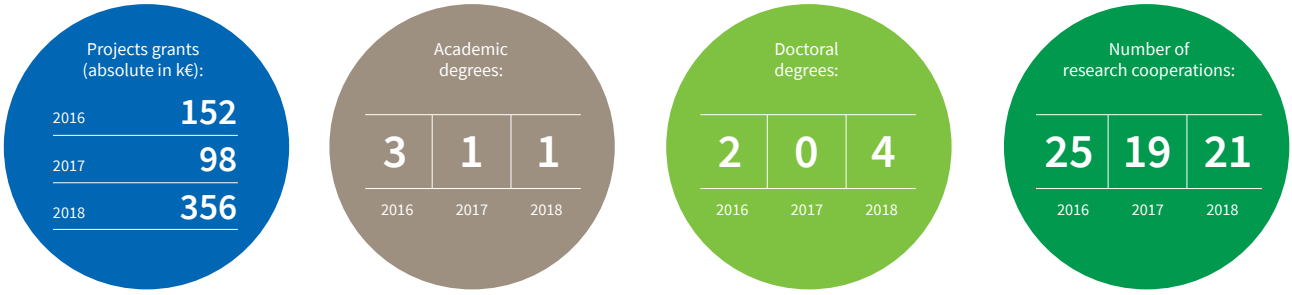
Current Projects

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 its 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 e.g. neural stem cell activity during regeneration to learn about the molecular pathways involved in neuroprotection and repair, to progress towards healthy brain aging as well as brain repair after injury.

Numbers 2016 – 2018



Selected Publications 2016 – 2018

Büttner R, Schulz A, Reuter M, Akula AK, Mindos T, Carlstedt A, Riecken LB, Baader SL, Bauer R, Morrison H. (2018).
Inflammaging impairs peripheral nerve maintenance and regeneration.
Aging Cell. *17(6)*, e12833.

Hagel C, Dornblut C, Schulz A, Wiehl U, Friedrich RE, Huckhagel T, Mautner VF, Morrison H. (2016).
The putative oncogene CPI-17 is up-regulated in schwannoma.
Neuropathol Appl Neurobiol. *42(7)*, 664-8.

Riecken LB, Zoch A, Wiehl U, Reichert S, Scholl I, Cui Y, Ziemer M, Anderegg U, Hagel C, Morrison H. (2016).
CPI-17 drives oncogenic Ras signaling in human melanomas via Ezrin-Radixin-Moesin family proteins.
Oncotarget. *7(48)*, 78242-54.

Schulz A, Büttner R, Hagel C, Baader SL, Kluwe L, Salamon J, Mautner VF, Mindos T, Parkinson DB, Gehlhausen JR, Clapp DW, Morrison H. (2016).
The importance of nerve microenvironment for schwannoma development.
Acta Neuropathol. *132(2)*, 289-307.

Schulz A, Büttner R, Toledo A, Baader SL, von Maltzahn J, Irintchev A, Bauer R, Morrison H. (2016).
Neuron-specific deletion of the Nf2 tumor suppressor impairs functional nerve regeneration.
PLoS One. *11(7)*, e0159718.

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

Leibniz Association

DFG Research Training Group 1715
Molecular Signatures of Adaptive Stress Responses

NF BUNDESVERBAND NEUROFIBROMATOSE

Dr. Björn von Eyss
Group Leader

von Eyss Research Group: Transcriptional Control of Tissue Homeostasis (since 2016/03)

2

CENTRAL RESEARCH QUESTION:

What is the role of transcriptional co-activators YAP and TAZ during tissue homeostasis, regeneration and cancer?

Focus of Research

Every day, the adult organism turns over billions of cells. Since “old” cells constantly get replaced by “new” ones, it is crucial for a given tissue to tightly co-ordinate processes like proliferation, differentiation and apoptosis. Even the slightest imbalance in the homeostasis of tissues will have severe consequences for a long-lived organism leading to development of cancer or premature aging.

One key pathway that acts as a central regulator of tissue homeostasis under physiological conditions and during tissue regeneration is the so-called “Hippo pathway”. The Hippo pathway impinges upon two downstream transducers, the transcriptional co-activators YAP and TAZ.

The research group “Transcriptional Control of Tissue Homeostasis ” focuses on several aspects of YAP/TAZ biology since a comprehensive understanding for the regulation of this pathway will yield new insights into stem cell biology and tissue homeostasis.

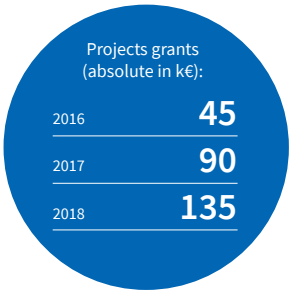
To this end, the researchers aim to identify new pathways that act upstream of YAP/TAZ and to identify downstream YAP/TAZ target genes that are indispensable for its biological output. Furthermore, they wish to elucidate its *in vivo* functions for regeneration, stem cell biology and cancer using appropriate mouse models.

Tools and Methods

Since the lab is mainly interested in transcriptional regulation, they use state-of-the-art methods to investigate YAP/TAZ-mediated transcription:

- Genome-wide transcriptomics: ChIP-Seq, RNA-Seq, 4SU-Seq, 4C-Seq, Capture Hi-C
- High-throughput genetic screens: CRISPR, shRNA, SAM and siRNA
- Proteome-wide interactomics
- *In vitro* stem cell assays
- Inducible mouse models

Numbers 2016 – 2018



Selected Publications 2016 – 2018

Elster* D, Tollot* M, Schlegelmilch K, Ori A, Rosenwald A, Sahai E, von Eyss B. (2018).
TRPS1 shapes YAP/TEAD-dependent transcription in breast cancer cells.
Nat Commun. *9(1)*, 3115 (* equal contribution).

Stopp S, Gründl M, Fackler M, Malkmus J, Leone M, Naumann R, Frantz S, Wolf E, von Eyss B, Engel FB, Gaubatz S. (2017).
Deletion of Gas2l3 in mice leads to specific defects in cardiomyocyte cytokinesis during development.
Proc Natl Acad Sci USA. *114(30)*, 8029-34 (published during change of institution).

Elster D, Jaenicke LA, Eilers M, von Eyss B. (2016).
TEAD activity is restrained by MYC and stratifies human breast cancer subtypes.
Cell Cycle. *15(19)*, 2551-6.

Jaenicke* LA, von Eyss* B, Carstensen A, Wolf E, Xu W, Greifenberg AK, Geyer M, Eilers M, Popov N. (2016).
Ubiquitin-dependent turnover of MYC antagonizes MYC/PAF1C complex accumulation to drive transcriptional elongation.
Mol Cell. *61(1)*, 54-67. (* equal contribution)

Cooperation Partners (Selection)

- Francis Crick Institute, London, UK
- Julius-Maximilians-Universität (JMU), Würzburg, Germany

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

Else Kröner Fresenius Stiftung

Alexander von Humboldt Stiftung/Foundation

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Herrlich Associated Research Group (Emeritus PI): Cancer Cell Biology

2

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

CENTRAL RESEARCH QUESTION:

How does the stem cell gene CD44 affect the formation of tumor metastases?

Focus of Research

The associated research group "Cancer Cell Biology" has been focusing on the tumor protein CD44 that had been discovered by the lab many years ago. The protein has been identified as a marker of so-called tumor stem cells and of tumor cells with the ability to metastasize. Its relevant molecular functions are not yet understood. Further, the lab has developed interest in two genes with presumed function in stem cells, and has generated two mouse lines mutated in these genes, those encoding the protein assembly factor TRIP6 and the centrosomal protein RHAMM whose impact specifically on neural progenitors and brain development is being analyzed.

Numbers 2016 – 2018

Cooperation Partners (Selection)

- Alacris Theranostics GmbH, Berlin, Germany
- Boehringer-Ingelheim RCV & Co KG, Vienna, Austria
- Medical University of Graz, Graz, Austria
- Washington University School of Medicine, Renal Division, St. Louis, MO, USA

Current Projects

- Molecular mechanisms of CD44 in metastasis formation
- Regulation of the proteolytic release of growth factors and cytokines
- Differentiation of *choroid plexus* in the brain and the formation of a *hydrocephalus*

Selected Publications 2016 – 2018

Schultz* K, Grieger (Lindner)* C, Li Y, Urbánek P, Ruschel A, Minnich K, Bruder D, Gereke M, Sechi A, Herrlich P. (2018).
Gamma secretase dependent release of the CD44 cytoplasmic tail upregulates IFI16 in cd44-/- tumor cells, MEFs and macrophages.
PLoS One. *13(12)*, e0207358 (* equal contribution).

Li H, Kroll T, Moll J, Frappart L, Herrlich P, Heuer H, Ploubidou A. (2017).
Spindle misorientation of cerebral and cerebellar progenitors is a mechanistic cause of megalencephaly.
Stem Cell Reports. *9(4)*, 1071-80.

Li H, Frappart* L, Moll* J, Winkler* A, Kroll T, Hamann J, Kufferath I, Groth M, Taudien S, Schütte M, Yaspo ML, Heuer H, Lange BMH, Platzer M, Zatloukal K, Herrlich P, Ploubidou A. (2016).
Impaired planar germ cell division in the testis, caused by dissociation of RHAMM from the spindle, results in hypofertility and seminoma.
Cancer Res. *76(21)*, 6382-95 (* equal contribution).

Parra* LM, Hartmann* M, Schubach S, Ma J, Herrlich** P, Herrlich** A. (2016).
Growth factor and co-receptor release by structural regulation of substrate metalloprotease accessibility.
Sci Rep. *6*, 37464 (** co-senior authors, * equal contribution).

Funding (Selection)

JUNG-Stiftung für Wissenschaft und Forschung

Aspasia Ploubidou, PhD
Associated Group Leader

Ploubidou Associated Research Group: Virus-induced Oncogenesis

2

CENTRAL RESEARCH QUESTION:

How does centrosome activity contribute to cell renewal and oncogenesis?

Focus of Research

Cancer, a major age-related pathology, is the research topic of the group. Cancer encompasses several diseases, which have in common an etiology of genetic defects and two prominent features: altered molecular signaling circuitry and disruption of tissue microarchitecture.

Cancer cells subvert the microarchitecture of the tissue into which they develop, creating the tumor. A major regulator of cellular and tissue architecture is the cytoskeleton, which fulfills its diverse functions by converting intra- and extra-cellular signaling into structures and structure remodeling. The group aims to understand how cytoskeletal signaling, in particular centrosome activity, contributes to cell renewal or commitment to differentiation and how this signaling is subverted in cancer. They have identified mechanisms that induce misplacement of cells from stem cell compartments and epithelia, with oncogenic consequences, provoking the hypothesis that subversion of tissue microarchitecture may be oncogenic *per se*.

The number and complexity of genetic defects encoded by cancer cells make it difficult to identify and target particular driver/s of tumor growth. Unraveling this complexity necessitates development of methodologies that compute the contribution of multiple genetic defects to the overall cell signaling. The group initiated such an interdisciplinary approach, with a consortium of mathematicians, bioinformatics-, cell- & systems-biologists, and clinicians (CanPathPro.eu). It utilizes deep molecular analysis of cancer cells/ organoids/ tumors of lung and breast cancer, to build increasingly complex computational models of signaling and to subsequently validate *in vivo* the *in silico*-made predictions. The aim is to identify signaling events that drive disease development and to build a platform for *in silico* predictive modeling of cancer signaling.

Current Projects

- Mechanisms and oncogenic consequences of centrosome inactivation
- Mitotic functions of RHAMM
- Development & validation of predictive modeling applied to cancer signaling

Selected Publications 2016 – 2018

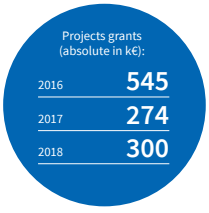
Connell M, Chen H, Jiang J, Kuan CW, Fotovati A, Chu T, He Z, Lengyell TC, Li H, Kroll T, Li AM, Goldowitz D, Frappart L, Ploubidou A, Patel M, Pilarski LM, Simpson EM, Lange P, Allan DW, Maxwell CA. (2017). HMMR acts in the PLK1-dependent spindle positioning pathway and supports neural development. Elife. *6*, e28672.

Li H, Kroll T, Moll J, Frappart L, Herrlich P, Heuer H, Ploubidou A. (2017). Spindle misorientation of cerebral and cerebellar progenitors is a mechanistic cause of megalencephaly. Stem Cell Reports. *9(4)*, 1071-80.

Kroll* T, Schmidt* D, Schwanitz G, Ahmad M, Hamann J, Schlosser C, Lin YC, Böhm KJ, Tuckermann J, Ploubidou A. (2016). High-content microscopy analysis of subcellular structures: assay development and application to focal adhesion quantification. Curr Protoc Cytom. 77, 12.43.1-12.43.44 (* equal contribution).

Li H, Frappart* L, Moll* J, Winkler* A, Kroll T, Hamann J, Kufferath I, Groth M, Taudien S, Schütte M, Yaspo ML, Heuer H, Lange BMH, Platzer M, Zatloukal K, Herrlich P, Ploubidou A. (2016). Impaired planar germ cell division in the testis, caused by dissociation of RHAMM from the spindle, results in hypofertility and seminoma. Cancer Res. *76(21)*, 6382-95 (* equal contribution).

Numbers 2016 – 2018



Funding (Selection)

Weih Research Group:
Immunology (until 2018/09)

2

Prof. Dr. Falk Weih
Group Leader until 2014

Dr. Ronny Hänold
Acting Group Leader

CENTRAL RESEARCH QUESTION:

Which impact does gene regulator NF-kappaB have on the aging immune system?

Focus of Research

An intact immune system is crucial for health, especially in older age. The former research group of Falk Weih "Immunology", headed by Ronny Hänold since 2014/10, lays its research focus on the impact of gene regulator NF-kappaB (NF-κB) on the immune system. This transcription factor is a protein complex that can switch gene transcription on or off. Further, the lab investigates how NF-κB is involved in the emergence of inflammations and autoimmune diseases. One of the lab's goals is to understand how modulation of NF-κB affects the development of age-associated deficiencies and diseases of the immune and nervous system.

Current Projects

- NF-κB-mediated self-tolerance and autoimmunity
- NF-κB signaling pathways in lymphopoiesis, inflammation, and organ maintenance
- The aging brain: ambivalent functions of NF-κB for neuronal plasticity and neurosenescence

Selected Publications 2016 – 2018

Andreas N, Riemann M, Castro CN, Groth M, Koliesnik I, Engelmann C, Sparwasser T, Kamradt T, Haenold R, Weih F. (2018).
A new RelB-dependent CD117+ CD172a+ murine dendritic cell subset preferentially induces Th2 differentiation and supports airway hyperresponses *in vivo*.
Eur J Immunol. *48(6)*, 923-36.

Koliesnik IO, Andreas N, Romanov VS, Sreekantapuram S, Krljanac B, Haenold R, Weih F. (2018).
RelB regulates Th17 differentiation in a cell-intrinsic manner.
Immunobiology. *223(2)*, 191-9.

Riemann M, Andreas N, Fedoseeva M, Meier E, Weih D, Freytag H, Schmidt-Ullrich R, Klein U, Wang ZQ, Weih F. (2017).
Central immune tolerance depends on crosstalk between the classical and alternative NF-κB pathways in medullary thymic epithelial cells.
J Autoimmun. 81, 56-67.

Engelmann C, Haenold R. (2016).
Transcriptional control of synaptic plasticity by transcription factor NF-κB.
Neural Plast. *2016*, 7027949.

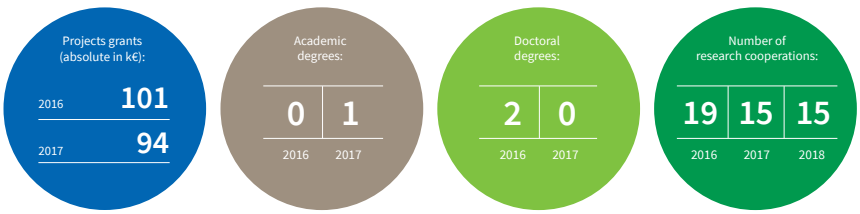
Weidemann A, Lovas A, Rauch A, Andreas N, von Maltzahn J, Riemann M, Weih F. (2016).
Classical and alternative NF-κB signaling cooperate in regulating adipocyte differentiation and function.
Int J Obes Relat Metab Disord. *40(3)*, 452-9.

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

VELUX STIFTUNG

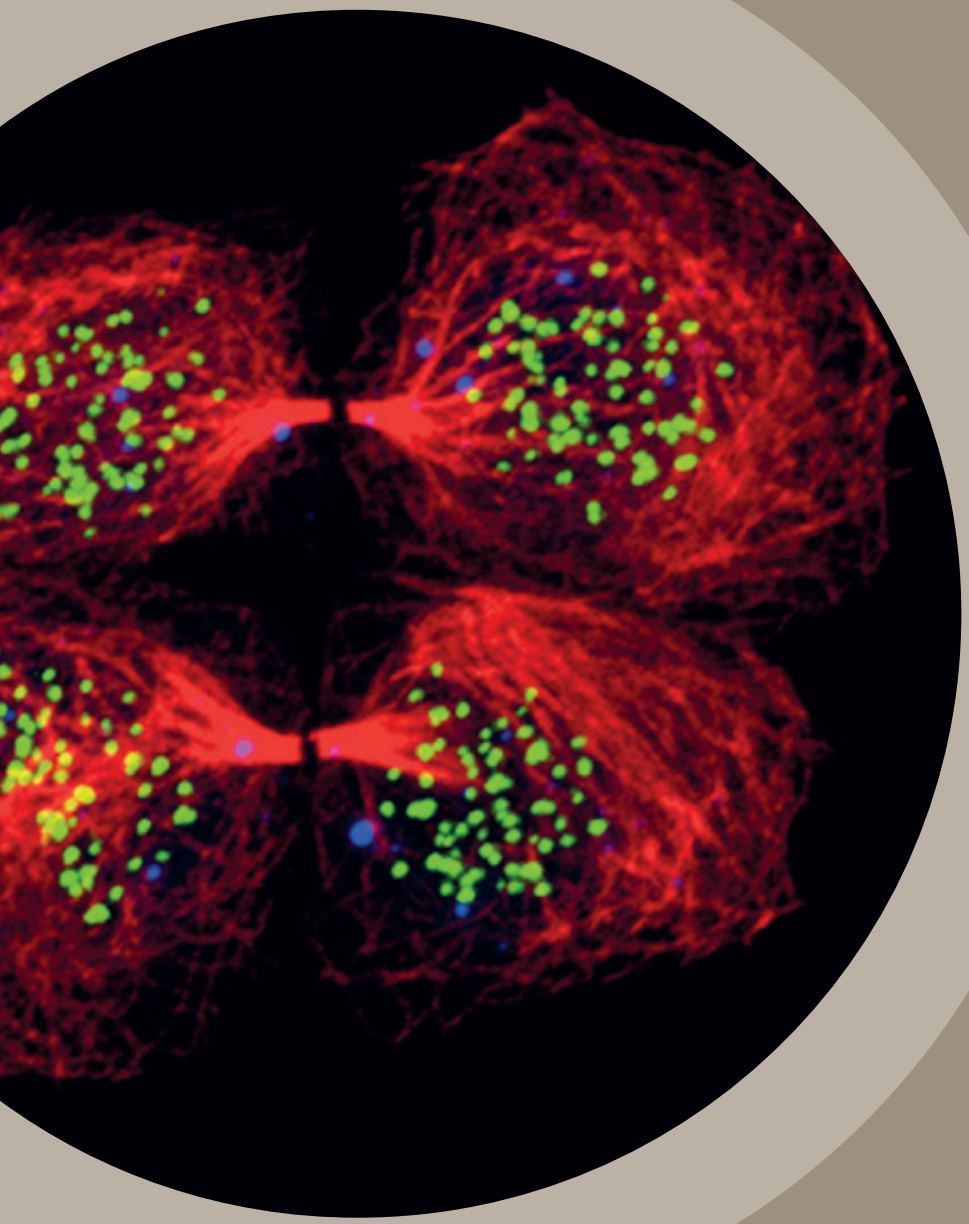
Numbers 2016 – 2018



Insights into the lab.

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 regulate organ development and regeneration as well as aging?

Focus of Research

Molecular Basis of the Urogenital Development | Many "disease" genes in humans play essential roles in the development of specific organs. One example is the Wilms' tumor suppressor gene Wt1 that, in its mutated form, causes a pediatric kidney cancer; yet is indispensable for gonad and kidney development in humans and mice. In order to understand how mutations of this gene cause malformations in humans, the research group "Molecular Genetics" endeavors to explore the molecular mechanisms by which the respective gene product exerts its function. To this end, they are employing biochemistry, cell biology and animal models.

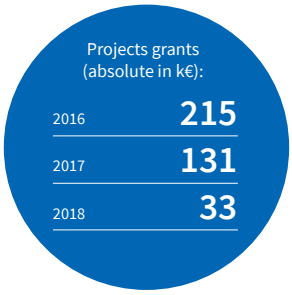
Signaling Pathways Regulating Aging and Lifespan in Short-Lived Vertebrates | The identification of vertebrate genes, which control aging is hampered by the lifespan of available animal models. In 2004, a species of annual fish with an exceptionally short lifespan was described. This species is named *Nothobranchius furzeri* and has a maximum life expectancy in captivity of just a few months. Using CRISPR/Cas9 technology, it is possible to switch genes on and off in *N. furzeri*, thereby allowing the genetic programs and biochemical pathways that regulate aging in vertebrates to be identified and characterized.

Regeneration of Organs | The regenerative capability of human organs differs considerably. While blood cells and skin cells own a high regenerative potential, neurons or kidney cells can only barely regenerate. In contrast, almost all organs of fish and amphibians have a high regenerative potential. The Englert group mainly uses the zebrafish as animal model to analyze the regeneration processes of caudal fins and kidneys. The scientists are especially interested in understanding how age impacts the regenerative capacity and why the regenerative potential is so different across different species. The ultimate goal is to contribute to an increase in the regenerative potential e.g. of the human kidney.

Current Projects

- Identification of targets of the Wilms tumor protein Wt1 in tissue development and homeostasis
- Characterization of Wt1's function in the central nervous system
- Analysis of the age-dependency of kidney and heart regeneration
- Analysis of biochemical signaling pathways that regulate the aging process of the short-lived vertebrate *Nothobranchius furzeri*
- Generation of *N. furzeri* and zebrafish mutants regarding age-associated genes using CRISPR/Cas9

Numbers 2016 – 2018



Selected Publications 2016 – 2018

Aramillo Irizar P, Schäuble S, Esser D, Groth M, Frahm C, Priebe S, Baumgart M, Hartmann N, Marthandan S, Menzel U, Müller J, Schmidt S, Ast V, Caliebe A, König R, Krawczak M, Ristow M, Schuster S, Cellerino A, Diekmann S, Englert C, Hemmerich P, Sühnel J, Guthke R, Witte OW, Platzer M, Ruppin E, Kaleta C. (2018).
Transcriptomic alterations during ageing reflect the shift from cancer to degenerative diseases in the elderly.
Nat Commun. *9(1)*, 327.

Englert C. (2018).
Temperature throws a developmental switch.
Proc Natl Acad Sci USA. *115(50)*, 12553-5.

Schnerwitzki D, Perry S, Ivanova A, Viegas Caixeta F, Cramer P, Guenther S, Weber K, Tafreshiha A, Becker L, Vargas Panesso IL, Klopstock T, Hrabe de Angelis M, Schmidt M, Kullander K, Englert C. (2018).
Neuron-specific inactivation of Wt1 alters locomotion in mice and changes interneuron composition in the spinal cord.
Life Science Alliance. *1(4)*, e201800106.

Nathan A, Reinhardt P, Kruspe D, Jörß T, Groth M, Nolte H, Habenicht A, Herrmann J, Holschbach V, Toth B, Krüger M, Wang ZQ, Platzer M, Englert C. (2017).
The Wilms tumor protein Wt1 contributes to female fertility by regulating oviductal proteostasis.
Hum Mol Genet. *26(9)*, 1694-705.

Baumgart* M, Priebe* S, Groth* M, Hartmann* N, Menzel U, Pandolfini L, Koch P, Felder M, Ristow M, Englert C, Guthke R, Platzer M, Cellerino A. (2016).
Longitudinal RNA-Seq analysis of vertebrate aging identifies mitochondrial complex I as a small-molecule-sensitive modifier of lifespan.
Cell Syst. *2(2)*, 122-32 (* equal contribution).

Cooperation Partners (Selection)

- Brown University, Providence, USA
- University of Bern, Switzerland
- University of Auckland, New Zealand
- Uppsala University, Sweden

Funding (Selection)

Francesco Neri, PhD
Group Leader

Neri Research Group:
Epigenetics of Aging / Damage Accumulation

(since 2016/07)

3

CENTRAL RESEARCH QUESTION:

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

Focus of Research

Aging associates with defective organ maintenance and increased tissue dysfunction as well as with a higher risk for pathological conditions development, including cancers. Colorectal cancers and leukemias are two of the most frequent and lethal neoplasms and their incidence is exponentially increasing during aging. Several studies demonstrated that intestinal stem cells as well as hematopoietic stem cells often represent the cell 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, favoring in this way the selective advantage of dominant clones and the cancer onset. 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 the TET proteins (ten-eleven-translocation) has pointed out the importance of this epigenetic modification in several biological models. Interestingly, two of the principal enzymes responsible for the establishment/removing of DNA methylation (DNMT3A and TET2) are the principal targets of genetic mutations during aging and cancer development.

Research Objectives

The focus of the Neri lab is the functional characterization of epigenome alterations that occur during adult stem cell aging. The main aims are:

- to define epigenetic alterations of stem cells during aging (focusing on DNA methylation changes together with principal histone modifications),
- to characterize the mechanistic basis of the evolution of these changes, and
- 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 research group carries out studies in several model systems including intestinal and hematopoietic stem cells both from mouse and human. They use cutting-edge technologies for the isolation of primary cells, culturing by using organoids or *in vivo* systems, generation of stable cell lines, genome-wide experiments (e.g. total and polyA RNA-seq, ChIP-seq, ATAC-seq, MeDIP-seq, Bisulfite-seq, TAB-seq, MAB-seq).

Numbers 2016 – 2018

Selected Publications 2016 – 2018

Ermolaeva** M, Neri** F, Ori** A, Rudolph** KL. (2018).
Cellular and epigenetic drivers of stem cell ageing.
Nat Rev Mol Cell Biol. *19(9)*, 594-610 (** co-corresponding authors).

Neri F, Rapelli S, Krepelova A, Incarnato D, Parlato C, Basile G, Maldotti M, Anselmi F, Oliviero S. (2017).
Intragenic DNA methylation prevents spurious transcription initiation.
Nature. *543(7643)*, 72-7.

Neri F, Incarnato D, Krepelova A, Parlato C, Oliviero S. (2016).
Methylation-assisted bisulfite sequencing to simultaneously map 5fC and 5caC on a genome-wide scale for DNA demethylation analysis.
Nat Protoc. *11(7)*, 1191-205 (published during change of institution).

Schwörer S, Becker F, Feller C, Baig AH, Köber U, Henze H, Kraus JM, Xin B, Lechel A, Lipka DB, Varghese CS, Schmidt M, Rohs R, Aebersold R, Medina KL, Kestler HA, Neri F, von Maltzahn** J, Tümpel** S, Rudolph** KL. (2016).
Epigenetic stress responses induce muscle stem-cell ageing by Hoxa9 developmental signals.
Nature. *540(7633)*, 428-32 (** co-corresponding authors).

Funding (Selection)

Alexander von Humboldt Stiftung/Foundation
DFG Deutsche Forschungsgemeinschaft German Research Foundation
Leibniz Association
Fritz Thyssen Stiftung für Wissenschaftsförderung

Bierhoff Associated Research Group:
Epigenetics of Aging / Chromatin Landscape (since 2017/02)

3

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

CENTRAL RESEARCH QUESTION:

How do aging-induced epigenetic changes, especially those mediated by non-coding RNAs, contribute to misexpression and destabilization of the genome?

Focus of Research

Our genetic information is stored in the cell nucleus as chromatin, a macromolecular complex in which DNA is associated with proteins and non-coding RNAs. The chromatin structure facilitates packaging of the DNA and regulation of gene expression. The group investigates these epigenetic mechanisms especially in the case of the highly active genes encoding ribosomal RNA (rRNA), that exist in multiple copies. Moreover, the lab is interested in the function of non-coding RNAs and how they can directly interact with the genome by forming RNA:DNA triplexes.

The group hopes that their work leads to a broader understanding of "epigenetic aging". They aim to elucidate the aging-dependent mechanisms that lead to deregulation of rRNA genes and to the loss of function or malfunction of non-coding RNAs.

Current Projects

- Impact of rRNA synthesis on the life span of *C. elegans*
- Regulation of rRNA genes by the non-coding RNA *PAPAS*
- Control of the proto-oncogene *Kras* by an RNA:DNA triple helix
- Genome-wide identification of RNA:DNA triplexes

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

Selected Publications 2016 – 2018

Kosan C, Heidel FH, Godmann M, Bierhoff H. (2018).
Epigenetic erosion in adult stem cells: drivers and passengers of aging.
Cells. *7(12)*, E237.

Sharifi S, Bierhoff H. (2018).
Regulation of RNA Polymerase I transcription in development, disease, and aging.
Annu Rev Biochem. *87*, 51-73.

Brocks D, Schmidt CR, Daskalakis M, Jang HS, Shah NM, Li D, Li J, Zhang B, Hou Y, Laudato S, Lipka DB, Schott J, Bierhoff H, Assenov Y, Helf M, Ressnerova A, Islam MS, Lindroth AM, Haas S, Essers M, Imbusch CD, Brors B, Oehme I, Witt O, Lübbert M, Mallm JP, Rippe K, Will R, Weichenhan D, Stoecklin G, Gerhäuser C, Oakes CC, Wang T, Plass C. (2017).
DNMT and HDAC inhibitors induce cryptic transcription start sites encoded in long terminal repeats.
Nat Genet. *49(7)*, 1052-60 (published during change of institution).

Zhao Z, Dammert MA, Hoppe S, Bierhoff H, Grummt I. (2016).
Heat shock represses rRNA synthesis by inactivation of TIF-IA and lncRNA-dependent changes in nucleosome positioning.
Nucleic Acids Res. *44(17)*, 8144-52.

Zhao Z, Dammert MA, Grummt I, Bierhoff H. (2016).
lncRNA-induced nucleosome repositioning reinforces transcriptional repression of rRNA genes upon hypotonic stress.
Cell Rep. *14(8)*, 1876-82.

Cooperation Partners (Selection)

- Jena University Hospital, Germany

Numbers 2016 – 2018

Cellerino Associated Research Group: Biology of Aging

3

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

CENTRAL RESEARCH QUESTION:

Which affect do microRNAs, gene regulation and mild stress on aging and lifespan?

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-transcriptome Decoupling during Aging |** Investigation of posttranscriptional mechanisms that are responsible for proteome changes during aging.
- **Aging of Neuronal Stem Cells |** Investigation of newly identified genes expressed in the neuronal stem cells and regulated similarly in *N. furzeri* and humans, with regard to the way these genes regulate neuronal stem cell function.
- **Longitudinal Studies of Aging |** Identification of early molecular markers that are predictors of longevity.

Numbers 2016 – 2018

Selected Publications 2016 – 2018

Baumgart* M, Barth* E, Savino A, Groth M, Koch P, Petzold A, Arisi I, Platzer M, Marz* M, Cellerino* A. (2017).
A miRNA catalogue and ncRNA annotation of the short-living fish *Nothobranchius furzeri*.
BMC Genomics. *18(1)*, 693 (* equal contribution).

Heid* J, Cencioni* C, Ripa* R, Baumgart* M, Atlante S, Milano G, Scopece A, Kuenne C, Guenther S, Azzimato V, Farsetti A, Rossi G, Braun T, Pompilio G, Martelli F, Zeiher AM, Cellerino** A, Gaetano** C, Spallotta** F. (2017).
Age-dependent increase of oxidative stress regulates microRNA-29 family preserving cardiac health.
Sci Rep. *7(1)*, 16839 (** co-senior authors, * equal contribution).

Ripa R, Dolfi L, Terrigno M, Pandolfini L, Savino A, Arcucci V, Groth M, Terzibasi Tozzini E, Baumgart M, Cellerino A. (2017).
MicroRNA miR-29 controls a compensatory response to limit neuronal iron accumulation during adult life and aging.
BMC Biol. *15(1)*, 9.

Sahm A, Bens M, Platzer M, Cellerino A. (2017).
Parallel evolution of genes controlling mitonuclear balance in short-lived annual fishes.
Aging Cell. *16(3)*, 488-96.

Baumgart* M, Priebe* S, Groth* M, Hartmann* N, Menzel U, Pandolfini L, Koch P, Felder M, Ristow M, Englert C, Guthke R, Platzer M, Cellerino A. (2016).
Longitudinal RNA-Seq analysis of vertebrate aging identifies mitochondrial complex I as a small-molecule-sensitive modifier of lifespan.
Cell Syst. *2(2)*, 122-32 (* equal contribution).

Cooperation Partners (Selection)

- ETH Zurich, Switzerland
- Goethe University Frankfurt, Germany
- Institute of Vertebrate Biology, Czech Academy of Sciences, Brno, Czech Republic
- Max Planck for Biology of Ageing, Cologne, Germany

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

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:

How do non-coding RNAs impact the process of aging?

Focus of Research

A vast amount of the known vertebrate genes are transcribed as non-coding RNAs (ncRNAs), small molecules playing an important role in the regulation of all kinds of biological pathways. Micro-RNAs (miRNAs) are a well-known example of such small genetic regulators. Currently, around 2,400 families of ncRNAs are known; however, their functions remain unclear: Which kind of ncRNAs are involved in the processes of aging? What are their exact functions and how big is their influence on different stages of aging? What is the correlation of ncRNAs and age-dependent diseases, such as neurodegenerative diseases? The associated research group "Non-coding RNAs in Aging" tries to tackle these questions in an interdisciplinary way by combining state-of-the-art high-throughput bioinformatics with modern wetlab approaches. The group has an excellent expertise in the in-depth analysis of RNA-Seq data, *in silico* ncRNA identification and characterization, as well as virus-bioinformatics.

Additionally, the group investigates RNA:DNA triplex and G-quadruplex formations, representing a new level of genomic regulation by controlling chromatin organization.

Numbers 2016 – 2018

Current Projects

- Tissue specific aging in mice
- Micro-RNA regulation of aging processes
- Age-relevant RNA:DNA-triplex structures
- Non-coding RNA elements causing X-linked Dystonia-Parkinsonism
- Alteration of alternative splicing during aging
- Expression change of inflammatory and immune system genes during aging
- Influence of age on circadian rhythms
- Change in hematopoiesis in old age

Selected Publications 2016 – 2018

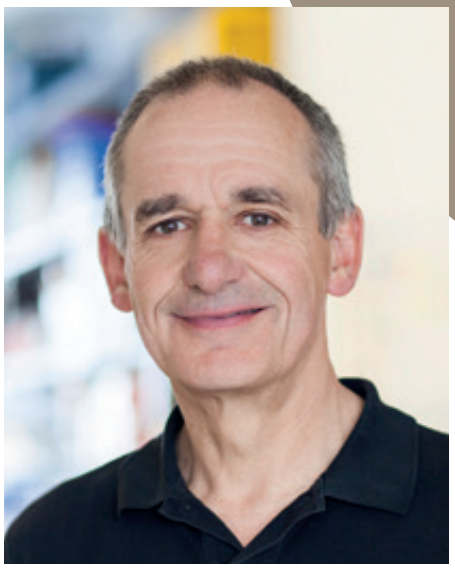
Morales-Prieto* DM, Stojiljkovic* M, Diezel C, Streicher PE, Roestel F, Lindner J, Weis S, Schmeer* C, Marz* M. (2018).
Peripheral blood exosomes pass blood-brain-barrier and induce glial cell activation.
Pre-print Repository. bioRxiv (* equal contribution).

Baumgart* M, Barth* E, Savino A, Groth M, Koch P, Petzold A, Arisi I, Platzer M, Marz* M, Cellerino* A. (2017).
A miRNA catalogue and ncRNA annotation of the short-living fish *Nothobranchius furzeri.*
BMC Genomics. *18(1)*, 693 (* equal contribution).

N. furzeri – fish with an extremely short lifespan.

Platzer Research Group:
Genome Analysis
(until 2018/08)

3



PD Dr. Matthias Platzer
Group Leader

CENTRAL RESEARCH QUESTION:

What is the (epi)genetic information underpinning gene expression and what alterations occur during aging?

Focus of Research

The research group "Genome Analysis" is focused on genetic and epigenetic aspects of aging. By employing state-of-the-art methods and tools, the information stored in DNA can be read out and the sequence of millions and millions of DNA building blocks determined within a short time.

These methods are used to describe the genetic information as well as the processes underpinning e.g. the production of proteins and the alterations of these processes during aging.

The group works on the functional and comparative analysis of genomes and transcriptomes of short- and long-lived model organisms in aging research. In collaboration with clinical partners, the researchers search for genetic and epigenetic variations determining the individual predisposition to healthy aging and complex aging-related diseases.

Current Projects

- Towards a novel model for aging research: Genome analysis of the short-lived seasonal fish *Nothobranchius furzeri*
- Investigating natural ways to exceptional long healthspan – The mole-rats (*Bathyergidae*) (SAW, DFG)
- Impact of DNA methylation on the aging of the brain (EU/BrainAGE)
- Effect of (epi)genetic variations on sepsis susceptibility and outcome (CSCC)
- Development of bioinformatics approaches for assembly and repeat annotation of complex genomes

Offspring of two crossed genetic lines of *N. furzeri* strains.

Numbers 2016 – 2018

Selected Publications 2016 – 2018

Bens* M, Szafranski* K, Holtze S, Sahm A, Groth M, Kestler HA, Hildebrandt** TB, Platzer** M. (2018).
Naked mole-rat transcriptome signatures of socially suppressed sexual maturation and links of reproduction to aging.
BMC Biol. *16(1)*, 77 (** co-senior authors, * equal contribution).

Sahm A, Bens M, Szafranski K, Holtze S, Groth M, Görlach M, Calkhoven C, Müller C, Schwab M, Kraus J, Kestler HA, Cellerino A, Burda H, Hildebrandt T, Dammann P, Platzer M. (2018).
Long-lived rodents reveal signatures of positive selection in genes associated with lifespan.
PLoS Genet. *14(3)*, e1007272.

Mascher M, Gundlach H, Himmelbach A, Beier S, Twardziok SO, Wicker T, Radchuk V, Dockter C, Hedley PE, Russell J, Bayer M, Ramsay L, Liu H, Haberer G, Zhang XQ, Zhang Q, Barrero RA, Li L, Taudien S, Groth M, Felder M, Hastie A, Šimková H, Staňková H, Vrána J, Chan S, Muñoz-Amatriaín M, Ounit R, Wanamaker S, Bolser D, Colmsee C, Schmutzer T, Aliyeva-Schnorr L, Grasso S, Tanskanen J, Chailyan A, Sampath D, Heavens D, Clissold L, Cao S, Chapman B, Dai F, Han Y, Li H, Li X, Lin C, McCooke JK, Tan C, Wang P, Wang S, Yin S, Zhou G, Poland JA, Bellgard MI, Borisjuk L, Houben A, Doležel J, Ayling S, Lonardi S, Kersey P, Langridge P, Muehlbauer GJ, Clark MD, Caccamo M, Schulman AH, Mayer KFX, Platzer M, Close TJ, Scholz U, Hansson M, Zhang G, Braumann I, Spannagl M, Li C, Waugh R, Stein N. (2017).
A chromosome conformation capture ordered sequence of the barley genome.
Nature. *544(7651)*, 427-33.

Dziegelewska M, Holtze S, Vole C, Wachter U, Menzel U, Morhart M, Groth M, Szafranski K, Sahm A, Sponholz C, Dammann P, Huse K, Hildebrandt** T, Platzer** M. (2016).
Low sulfide levels and a high degree of cystathionine β-synthase (CBS) activation by S-adenosylmethionine (SAM) in the long-lived naked mole-rat.
Redox Biol. *8*, 192-8 (** co-senior authors).

Taudien* S, Lausser* L, Giamarellos-Bourboulis EJ, Sponholz C, Schöneweck F, Felder M, Schirra LR, Schmid F, Gogos C, Groth S, Petersen BS, Franke A, Lieb W, Huse K, Zipfel PF, Kurzai O, Moepps B, Gierschik P, Bauer M, Scherag A, Kestler** HA, Platzer** M. (2016).
Genetic factors of the disease course after sepsis: rare deleterious variants are predictive.
EBioMedicine. *12*, 227-38 (** co-senior authors, * equal contribution).

Funding (Selection)

Wang Research Group:
Genome Stability

4

Prof. Dr. Zhao-Qi Wang
Group Leader

CENTRAL RESEARCH QUESTION:

How does the dysfunction of DNA damage signaling and repair pathways affect aging in humans?

Focus of Research

When DNA is damaged through 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 will advance the understanding of fundamental cellular processes, the maintenance of stem cell competence and proper tissue homeostasis. The research group "Genome Stability" uses cellular and molecular tools as well as animal models to dissect the dysfunction of DDR pathways. Their work provides insights into premature aging and age-related pathogenesis (such as cancer and neurodegeneration) in humans.

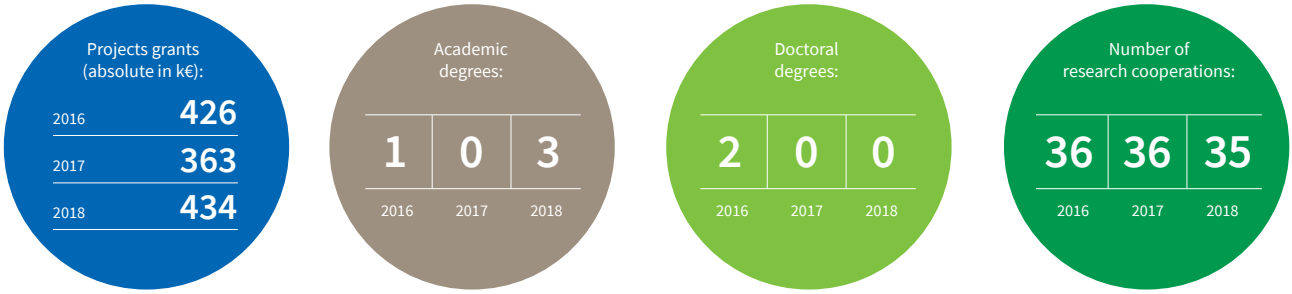
Current Projects

The Cellular Response on DNA Damage |
The two protein kinases ATM and ATR are key regulators of the cellular response in the case 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, the protein complex MRN (MRE11/RAD50/NBS1) detects DSBs, initiates DNA repair and, hence, helps to maintain the genome stable. The Wang group's research aims at understanding the function of molecules involved in DDR.

The Function of Poly(ADP-Ribosyl)ation |
Poly(ADP-Ribosyl)ation – also called PARylation – is the fastest reaction on DNA damage, especially on 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's research aims at elucidating how target proteins sense the PAR signal and regulate DDR.

Neurogenesis and Neurodegeneration |
For brain development, neural stem cells have to be strictly controlled. The remodeling of chromatin (the material which chromosomes consist of) through epigenetic mechanisms is crucial for stem cell profileration and differentiation (neurogenesis) as well as the maintenance of neurons (to prevent neurodegeneration). For histone acetylation, the DNA strand is "unfastened" for transcription factors to bind and dictates gene expression. The research objective of the Wang Lab is to understand the epigenetic modification of histones, thus laying the fundamentals for the development of new therapies to improve cognitive capabilities in the elderly.

Numbers 2016 – 2018



Selected Publication 2016 – 2018

Hartleben G, Müller C, Krämer A, Schimmel H, Zidek LM, Dornblut C, Winkler R, Eichwald S, Kortman G, Kosan C, Kluiver J, Petersen I, van den Berg A, Wang ZQ, Calkhoven CF. (2018).
Tuberous sclerosis complex is required for tumor maintenance in MYC-driven Burkitt's lymphoma.
EMBO J. *37(21)*, e98589.

Hoch NC, Hanzlikova H, Rulten SL, Tétreault M, Komulainen E, Ju L, Hornyak P, Zeng Z, Gittens W, Rey SA, Staras K, Mancini GMS, McKinnon PJ, Wang ZQ, Wagner JD, Care4Rare Canada Consortium, Yoon G, Caldecott KW. (2017).
XRCC1 mutation is associated with PARP1 hyperactivation and cerebellar ataxia.
Nature. *541(7635)*, 87-91.

Liu X, Zong W, Li T, Wang Y, Xu X, Zhou** ZW, Wang** ZQ. (2017).
The E3 ubiquitin ligase APC/C(C)(dh1) degrades MCPH1 after MCPH1-βTrCP2-Cdc25A-mediated mitotic entry to ensure neurogenesis.
EMBO J. *36(24)*, 3666-81 (** co-corresponding authors).

Schuhwerk H, Bruhn C, Siniuk K, Min W, Erener S, Grigaravicius P, Krüger A, Ferrari E, Zubel T, Lazaro D, Monajembashi S, Kiesow K, Kroll T, Bürkle A, Mangerich A, Hottiger M, Wang ZQ. (2017).
Kinetics of poly(ADP-ribosyl)ation, but not PARP1 itself, determines the cell fate in response to DNA damage *in vitro* and *in vivo*.
Nucleic Acids Res. *45(19)*, 11174-92.

Hoa NN, Shimizu T, Zhou ZW, Wang ZQ, Deshpande RA, Paull TT, Akter S, Tsuda M, Furuta R, Tsusui K, Takeda S, Sasanuma H. (2016).
Mre11 is essential for the removal of lethal topoisomerase 2 covalent cleavage complexes.
Mol Cell. *64(3)*, 580-92.

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft German Research Foundation
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
GIF German-Israeli Foundation for Scientific Research and Development
Leibniz Association
DFG Research Training Group 1715 Molecular Signatures of Adaptive Stress Responses

Kaether Research Group:
Membrane Trafficking in Aging

4

Dr. Christoph Kaether
Group Leader

CENTRAL RESEARCH QUESTION:

How are membrane proteins trafficked and localized within cells?

Focus of Research

The research group “Membrane Trafficking in Aging” lays its focus on the trafficking and localization of membrane proteins within cells. These membrane proteins include receptors responsible for correct protein trafficking and transmembrane signal transduction as well as proteins that are involved in aging. All research foci aim at identifying the basic cell biological processes as possible targets for therapies of age-related diseases.

Current Projects

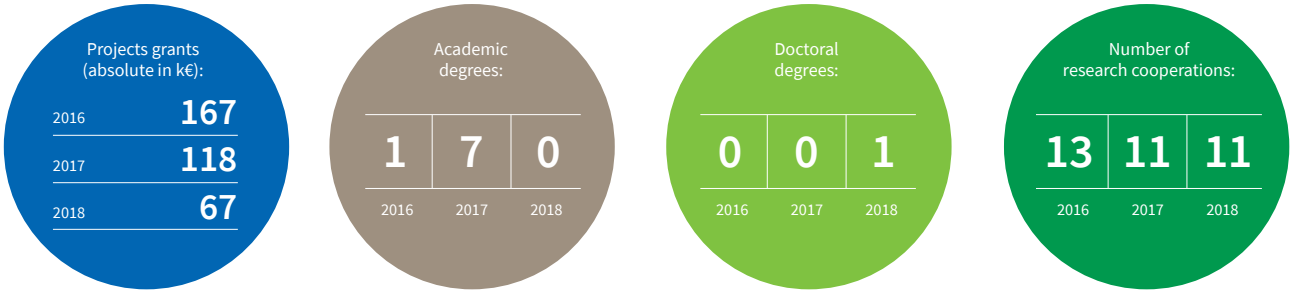
“Anti-Aging” Hormone Klotho | The membrane protein “Klotho” can circulate as “anti-aging” hormone. In mice lacking Klotho, an accelerated aging can be observed. Already at young age, they show age-related symptoms similar to human aging. In contrast, mice with an excess of Klotho live longer. Also in humans, Klotho was shown to be linked to a prolonged lifespan and improved cognitive abilities. Produced in the kidney and brain, it is responsible for several (hormonal) regulatory processes. The group investigates the role of Klotho in the brain.

Rer1, a new Type of Retrieval Receptor | One of the most important functions of endoplasmic reticulum (ER) is to guarantee the trafficking of correctly folded protein complexes. The Kaether Group works on the retrieval receptor Rer1, that transports escaped proteins back from the cis-Golgi to the ER. The group wants to study the molecular details of transmembrane domain mediated sorting and the role of Rer1 therein.

Regulation of Notch and Leukemia | The Notch receptor is essential for development. However, its hyper activation leads to carcinogenesis, for example in a certain T-cell leukemia, T-ALL. The research group studies how the Notch signal transduction is regulated at the level of nuclear import/export and how this contributes to leukemia.

Axonopathies and the Endoplasmic Reticulum | Membrane proteins of the ER are mutated in a number of sensory and motor neuropathies. These membrane proteins structure the ER, but it is unclear how mutations in them can lead to degeneration of the longest axons in our body. The group investigates basic transport mechanisms at the ER and wants to find out how axonopathie-causing mutations act on the molecular level.

Numbers 2016 – 2018



Selected Publications 2016 – 2018

Ahrens* HE, Huettemeister* J, Schmidt M, Kaether C, von Maltzahn J. (2018).
Klotho expression is a prerequisite for proper muscle stem cell function and regeneration of skeletal muscle.
Skelet Muscle. *8(1)*, 20 (* equal contribution).

Valkova C, Liebmann L, Krämer A, Hübner CA, Kaether C. (2017).
The sorting receptor Rer1 controls Purkinje cell function via voltage gated sodium channels.
Sci Rep. *7*, 41248.

Yonemura Y, Li X, Müller K, Krämer A, Atigbire P, Mentrup T, Feuerhake T, Kroll T, Shomron O, Nohl R, Arndt HD, Hoischen C, Hemmerich P, Hirschberg K, Kaether C. (2016).
Inhibition of cargo export at ER-exit sites and the trans-Golgi network by the secretion inhibitor FLI-06.
J Cell Sci. *129(20)*, 3868-77.

Funding (Selection)

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 nematode *C. elegans*, mammalian cell and organoid cultures to identify changes of metabolism and stress responses which occur during aging. The group studies connections between such changes and tissue degeneration during aging with the specific focus on neuronal aging and protein aggregation disorders and with the outlook of attenuating these detrimental processes.

The group performs mutagenesis based forward genetic screens in nematodes and human cells to identify gene changes, which confer protection from aging-relevant cellular stresses such as mitochondrial stress and protein folding stress in the endoplasmic reticulum. This is done with the outlook of developing inhibitors to be used as stress-protective treatments ensuring cell survival and organ maintenance during aging.

The group has a large agenda on using nematodes as alternative model hosts for studying host-microbiome interactions at a mechanistic level and in a high-throughput manner. In this scientific area host effects of both environmental and human (commensal and pathogenic) microbes are researched. The goal of this research is to develop new probiotics and identify microbial metabolites with pro-longevity effects and understand how specific constituents of human microbiome affect host homeostasis and the process of aging.

Current Projects

The group uses nematodes and human cells to study alterations of energy homeostasis and lipid turnover during aging. This is done by use of longevity tests, stress reporters and high-throughput methods such as proteomics and lipidomics (performed in cooperation with the proteomic core facility at FLI and the Friedrich Schiller University Jena). With these methods and additional cell culture and nematode tests they study connections between metabolism, proteostasis and epigenetic alterations during aging.

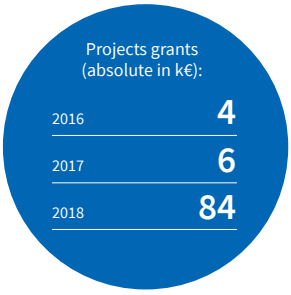
The lab studies effects of natural stress factors such as environmental DNA damage, sleep deprivation and heavy metal exposure on systemic proteostasis, neuronal integrity, cognition and aging in nematodes.

The group performed CRISPR/Cas9 mutagenesis based genetic screen in human skin fibroblasts searching for gene changes which protect against endoplasmic reticulum stress and identified a number of promising candidates which are currently analyzed in detail.

The group is interested in the role of mitochondria and mitochondrial inhibitors in longevity assurance. For this, they perform tests in nematodes at different stages of aging and in a human cell culture model of replicative senescence.

With longevity tests, proteomics and reporter analysis in nematodes the group studies effects of environmental and human-intrinsic microbiota on aging and homeostasis of metazoan hosts.

Numbers 2016 – 2018



Selected Publications 2016 – 2018

Ermolaeva** M, Neri** F, Ori** A, Rudolph** KL. (2018).
Cellular and epigenetic drivers of stem cell ageing.
Nat Rev Mol Cell Biol. *19(9)*, 594-610 (** co-corresponding authors).

Heinze* I, Bens* M, Calzia* E, Holtze S, Dakhovnik O, Sahm A, Kirkpatrick JM, Szafranski K, Romanov N, Sama SN, Holzer K, Singer S, Ermolaeva M, Platzer** M, Hildebrandt** T, Ori** A. (2018).
Species comparison of liver proteomes reveals links to naked mole-rat longevity and human aging.
BMC Biol. *16(1)*, 82 (** co-senior authors, * equal contribution).

Espada L, Ermolaeva MA. (2016).
DNA damage as a critical factor of stem cell aging and organ homeostasis.
Curr Stem Cell Rep. *2*, 290-8.

Cooperation Partners (Selection)

- Center for Sepsis Control and Care (CSCC), Jena, Germany
- Friedrich Schiller University Jena (FSU), Germany
- Jena University Hospital, Germany
- Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute (HKI), Jena, Germany

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

DFG Research Training Group 1715
Molecular Signatures of Adaptive Stress Responses

CONACYT

DAAD
Deutscher Akademischer Austauschdienst
German Academic Exchange Service

Große Research Group:
Biochemistry (until 2018/12)

4

Prof. Dr. Frank Große
Group Leader until 2018

Dr. Helmut Pospiech
Acting Group Leader

The Group and the Institute mourn the loss of Frank Große, who passed away in June 2018.

CENTRAL RESEARCH QUESTION:

How is DNA replication regulated and how are errors during this process prevented?

Focus of Research

The doubling of genetic information, namely DNA replication, is a central aspect of all living organisms. Errors occurring during DNA replication may lead to cancer or premature aging of the cell and/or the whole organism. The Große research group "Biochemistry", headed by Helmut Pospiech since 2016/05, is interested in basic aspects of DNA replication, its regulation and the prevention of errors that might occur during this process.

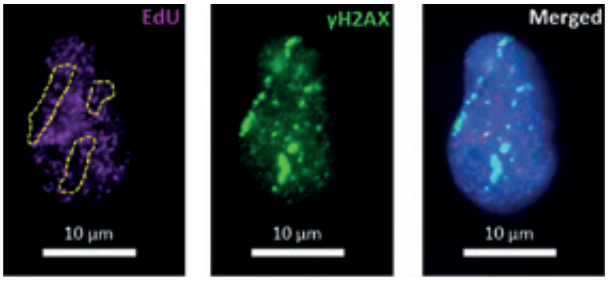
The questions the group is addressing are:

- How is the initiation of replication regulated and how is it stopped when something goes awry?
- What happens to errors that are introduced during this process?
- What happens to replication forks that are stalled and how are they started again?
- What are the signals that cause cell death when damaged sites are irreparable?
- How can these processes be exploited for intervention of aging and age-related disease?

The group intends that its research contributes to a better understanding of how cells prevent replication errors and thereby avoid premature senescence and ultimately cell death.

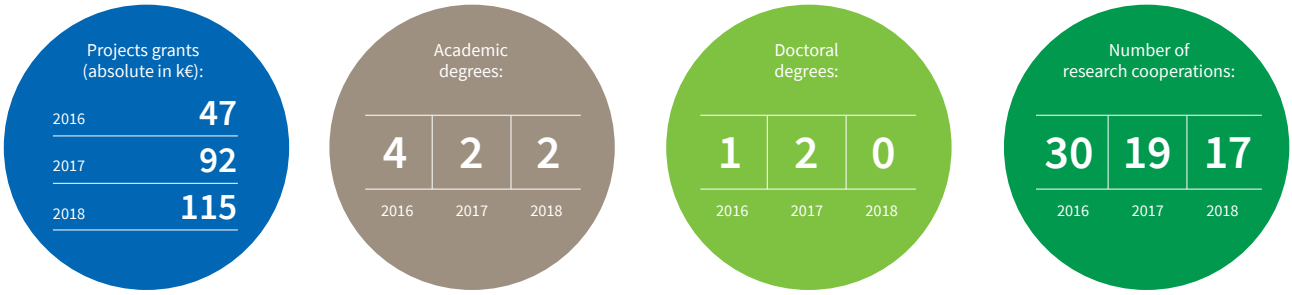
Current Projects

- Initiation of human DNA replication – from protein to function
- DNA replication stress as a cause of genomic instability
- DNA replication fidelity, cancer and aging
- Proteins that interact with replication factors and with p53



Damage due to irradiation with heavy ions.
Damages (visible as green stripes in nucleus) lead to the suppression of DNA synthesis in the affected areas (violet).

Numbers 2016 – 2018



Selected Publications 2016 – 2018

Sokka* M, Koalick* D, Hemmerich P, Syväoja JE, Pospiech H. (2018).
The ATR-activation domain of TopBP1 is required for the suppression of origin firing during the S phase.
Int J Mol Sci. *19(8)* (* equal contribution).

Szambowska A, Tessmer I, Prus P, Schlott B, Pospiech H, Grosse F. (2017).
Cdc45-induced loading of human RPA onto single-stranded DNA.
Nucleic Acids Res. *45(6)*, 3217-30.

Hampp S, Kiessling T, Buechle K, Mansilla SF, Thomale J, Rall M, Ahn J, Pospiech H, Gottifredi V, Wiesmüller L. (2016).
DNA damage tolerance pathway involving DNA polymerase ι and the tumor suppressor p53 regulates DNA replication fork progression.
Proc Natl Acad Sci USA. *113(30)*, E4311-9.

Itkonen HM, Kantelinen J, Vaara M, Parkkinen S, Schlott B, Grosse F, Nyström M, Syväoja JE, Pospiech H. (2016).
Human DNA polymerase α interacts with mismatch repair proteins MSH2 and MSH6.
FEBS Lett. *590(23)*, 4233-41.

Köhler C, Koalick D, Fabricius A, Parplys AC, Borgmann K, Pospiech** H, Grosse** F. (2016).
Cdc45 is limiting for replication initiation in humans.
Cell Cycle. *15(7)*, 974-85 (** co-senior authors).

Cooperation Partners (Selection)

- University of Oulu, Finland
- University Medical Center Hamburg-Eppendorf, Germany
- Ulm University, Germany

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

DAAD Deutscher Akademischer Austauschdienst
German Academic Exchange Service

Studienstiftung des deutschen Volkes

Interconnecting Subarea

Computational and Systems Biology of Aging

Computational and Systems Biology of Aging

Prof. Dr. Dr. Steve Hoffmann
Group Leader

Hoffmann Research Group:
Computational Biology of Aging

(since 2017/09)

5

CENTRAL RESEARCH QUESTION:

How does the epigenome control gene transcription and maturation?

Focus of Research

The research group “Computational Biology of Aging” has been doing research at FLI since November 2017. One of their primary interests is to contribute to a better understanding of the epigenetic control of transcription. To do this, the Hoffmann group is developing methods for the analysis of big and multidimensional biological data sets. The group is and has been member of several high-profile national and international consortia such as the International Cancer Genome Consortium (ICGC) or the BLUEPRINT Consortium.

Current Projects

Data Integration | The integration of epigenetic information including DNA-methylation and histone modification data with transcriptomics, provides new insights into the mechanisms of epigenetic control. As a part of the German ICGC-MMMLSeq and ICGC-DE-mining consortia as well as the HNPCCSys and BLUEPRINT consortia, the group helps to analyze hundreds of datasets from various tumor types. The goal is to identify common epigenomic mechanisms shared by many tissues, e.g. differentially methylated regions (DMRs).

DNA Methylation Analysis | Methylated DNA is one of the main epigenetic modifications. The group implemented the functionality to map bisulfite sequencing derived reads into their alignment software *Segemehl*. This enables easy translation of read numbers into methylation levels. To identify significantly different methylation levels between certain conditions and among larger numbers of samples, the group developed a program called *metilene*. This software is able to rapidly identify differentially methylated regions (DMRs) with high confidence.

RNA Splicing in RNA Sequencing Data | In RNA-Sequencing, reads originate from mRNAs or ncRNAs and can span exon junctions. The biological process leading to exon junctions is called splicing. The Hoffmann Group has extended their alignment software *Segemehl* with an algorithm to handle and to report splicing events. To detect alternative splicing events that play a major role in differentiation and diseases, they developed the software *DIEGO*. The results of *DIEGO* have been crucial for a number of our publications on lymphoma.

Epigenetic Regulation of Transcription | In a recent project the group analyzes bivalent chromatin states in cancer. This bivalent (poised or paused) chromatin comprises activating and repressing histone modifications at the same location i.e. promoter or enhancer regions. Specific combinations of epigenetic marks keep gene expression low but poise genes for rapid activation. Typically, DNA at bivalent promoters is lowly methylated in normal cells, but frequently show elevated methylation levels in cancer samples. The research group proposed an universal classifier built from chromatin data that is able to identify cancer samples solely from hypermethylation of bivalent chromatin.

Numbers 2018

Selected Publications 2016 – 2018

Doose G, Bernhart SH, Wagener R, Hoffmann S. (2018).
DIEGO: detection of differential alternative splicing using Aitchison's geometry.
Bioinformatics. *34(6)*, 1066-8.

Quentmeier H, Pommerenke C, Bernhart SH, Dirks WG, Hauer V, Hoffmann S, Nagel S, Siebert R, Uphoff CC, Zaborski M, Drexler HG, ICGC MMML-Seq Consortium. (2018).
RBFOX2 and alternative splicing in B-cell lymphoma.
Blood Cancer J. *8(8)*, 77.

Grüning BA, Fallmann J, Yusuf D, Will S, Erxleben A, Eggenhofer F, Houwaart T, Batut B, Videm P, Bagnacani A, Wolfien M, Lott SC, Hoogstrate Y, Hess WR, Wolkenhauer O, Hoffmann S, Akalin A, Ohler U, Stadler PF, Backofen R. (2017).
The RNA workbench: best practices for RNA and high-throughput sequencing bioinformatics in Galaxy.
Nucleic Acids Res. 45(W1), W560–W566.

Bernhart SH, Kretzmer H, Holdt LM, Jühling F, Ammerpohl O, Bergmann AK, Northoff BH, Doose G, Siebert R, Stadler PF, Hoffmann S. (2016).
Changes of bivalent chromatin coincide with increased expression of developmental genes in cancer.
Sci Rep. 6, 37393.

Jühling F, Kretzmer H, Bernhart SH, Otto C, Stadler PF, Hoffmann S. (2016).
metilene: fast and sensitive calling of differentially methylated regions from bisulfite sequencing data.
Genome Res. *26(2)*, 256-62.

Funding (Selection)

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

Ori Research Group:
Aging of Protein Complexes

5

Alessandro Ori, PhD
Group Leader

CENTRAL RESEARCH QUESTION:

How do age and environmental factors affect our organs at the molecular level?

Focus of Research

The research group "Aging of Protein Complexes" is interested in studying how age and environmental factors affect our organs at the molecular level. The group employs ultra-sensitive approaches allowing the quantification of thousands of proteins in tissues as well as in rare cell populations. The group's goal is to identify, in an unbiased way, functionally relevant alterations of the proteome that will enable the researchers to understand the mechanisms of organ deterioration that impact on healthy lifespan.

Current Projects

Stem Cell Aging | Adult (somatic) stem cells play a crucial role in maintaining and regenerating our 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 regenerative capacity of adult stem cells. Focusing on different organs, the group employs state-of-the-art mass spectrometry based proteomics to obtain proteome profiles of stem cells and the surrounding tissue (stem cell niche) across age groups and genetic backgrounds, as well as to evaluate the consequences of environmental factors such as stress, calorie restriction and exercise.

Protein Interactions and Post-Translational Modifications in Aging | The group and others have previously shown that multiple mechanisms can influence the availability of functional proteins during aging. These include changes in protein synthesis, intra-cellular localization and post-translational modifications. Currently, the group applies and develops novel approaches that use mass spectrometry to study protein interactions, stability, organelle composition and different types of post-translation modification in the context of aging. Current major focuses are protein-protein interactions in the proteostasis network and non-enzymatic post-translational modifications such as Advanced Glycation End products (AGEs).

Multiomics Analysis of exceptionally short- and long-lived Model Organisms | By taking advantage of the natural variability in lifespan between species, the research group aims to identify key determinants of longevity and bring these in the context of human aging. Thanks to internal and external collaborations, the group has access to multiple model organisms ranging from the short-lived fish *Nothobranchius furzeri*, which has a lifespan of approx. 40 weeks, to the long lived rodent naked-mole rat, that can live up to 30 years. The majority of the lab's studies are based on unbiased integrated omics approaches, bioinformatic analysis, and follow up studies in established model organisms of aging.

Numbers 2016 – 2018

Selected Publications 2016 – 2018

Heinze* I, Bens* M, Calzia* E, Holtze S, Dakhovnik O, Sahm A, Kirkpatrick JM, Szafranski K, Romanov N, Sama SN, Holzer K, Singer S, Ermolaeva M, Platzer** M, Hildebrandt** T, Ori** A. (2018).
Species comparison of liver proteomes reveals links to naked mole-rat longevity and human aging.
BMC Biol. *16(1)*, 82 (** co-senior authors, * equal contribution).

Parca L, Beck M, Bork P, Ori A. (2018).
Quantifying compartment-associated variations of protein abundance in proteomics data.
Mol Syst Biol. *14(7)*, e8131.

Wyant* GA, Abu-Remaileh* M, Frenkel EM, Laqtom NN, Dharamdasani V, Lewis CA, Chan SH, Heinze I, Ori** A, Sabatini** DM. (2018).
NUFIP1 is a ribosome receptor for starvation-induced ribophagy.
Science. *360(6390)*, 751-8 (* equal contribution, ** co-corresponding authors).

Mackmull MT, Klaus B, Heinze I, Chokkalingam M, Beyer A, Russell RB, Ori** A, Beck** M. (2017).
Landscape of nuclear transport receptor cargo specificity.
Mol Syst Biol. *13(12)*, 962 (** co-corresponding authors, highlighted in the "Principle of Systems Biology" - Cell Systems 6 - 2018).

Ori A, Iskar M, Buczak K, Kastritis P, Parca L, Andrés-Pons A, Singer S, Bork P, Beck M. (2016).
Spatiotemporal variation of mammalian protein complex stoichiometries.
Genome Biol. *17(1)*, 47 (featured in Research Highlights by Michael P. Washburn: There is no human interactome. Genome Biology 2016 17:48).

Cooperation Partners (Selection)

- Buck Institute for Research on Aging, Novato, CA, USA
- Francis Crick Institute, London, UK
- Karolinska Institute, Stockholm, Sweden
- Leibniz Institute for Zoo and Wildlife Research (IZW), Berlin, Germany
- MIT, Whitehead Institute, Cambridge, MA, USA
- Scuola Normale Superiore di Pisa, Italy
- University of Helsinki, Finland

Funding (Selection)

ProMoAge

Kestler Associated Research Group: Bioinformatics and Systems Biology of Aging

(since 2016/01)

5

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

CENTRAL RESEARCH QUESTION:

How can computational and mathematical approaches help to analyze and understand molecular-biological data?

Focus of Research

The rapid development of molecular biology has given rise to an increasing demand for computational and mathematical approaches to analyze and understand the resulting data. In particular, advanced methods from bioinformatics are required to extract, investigate, and integrate the essential information from high-throughput experiments, such as microarrays or "Next Generation Sequencing". The emerging field of systems biology provides formal approaches to (temporal) modeling and simulating regulatory processes in biological systems. The research focus of the associated research group "Bioinformatics and Systems Biology of Aging" is at the interface of computer science, statistics and life sciences and covers the following main aspects:

- Statistical and data mining approaches for high-throughput data, with an emphasis on feature selection, classification and clustering
- Modeling, simulating and analysis of regulatory networks, in particular ODE, Boolean, and rule based approaches
- Visualization and functional annotation.

Selected Publications 2016 – 2018

Hühne* R, Kessler* V, Fürstberger* A, Kühlwein S, Platzer M, Sühnel J, Lausser L, Kestler HA. (2018).
3D Network exploration and visualisation for lifespan data.
BMC Bioinformatics. *19(1)*, 390 (* equal contribution).

Schwab J, Burkovski A, Siegle L, Müssel** C, Kestler** HA. (2017).
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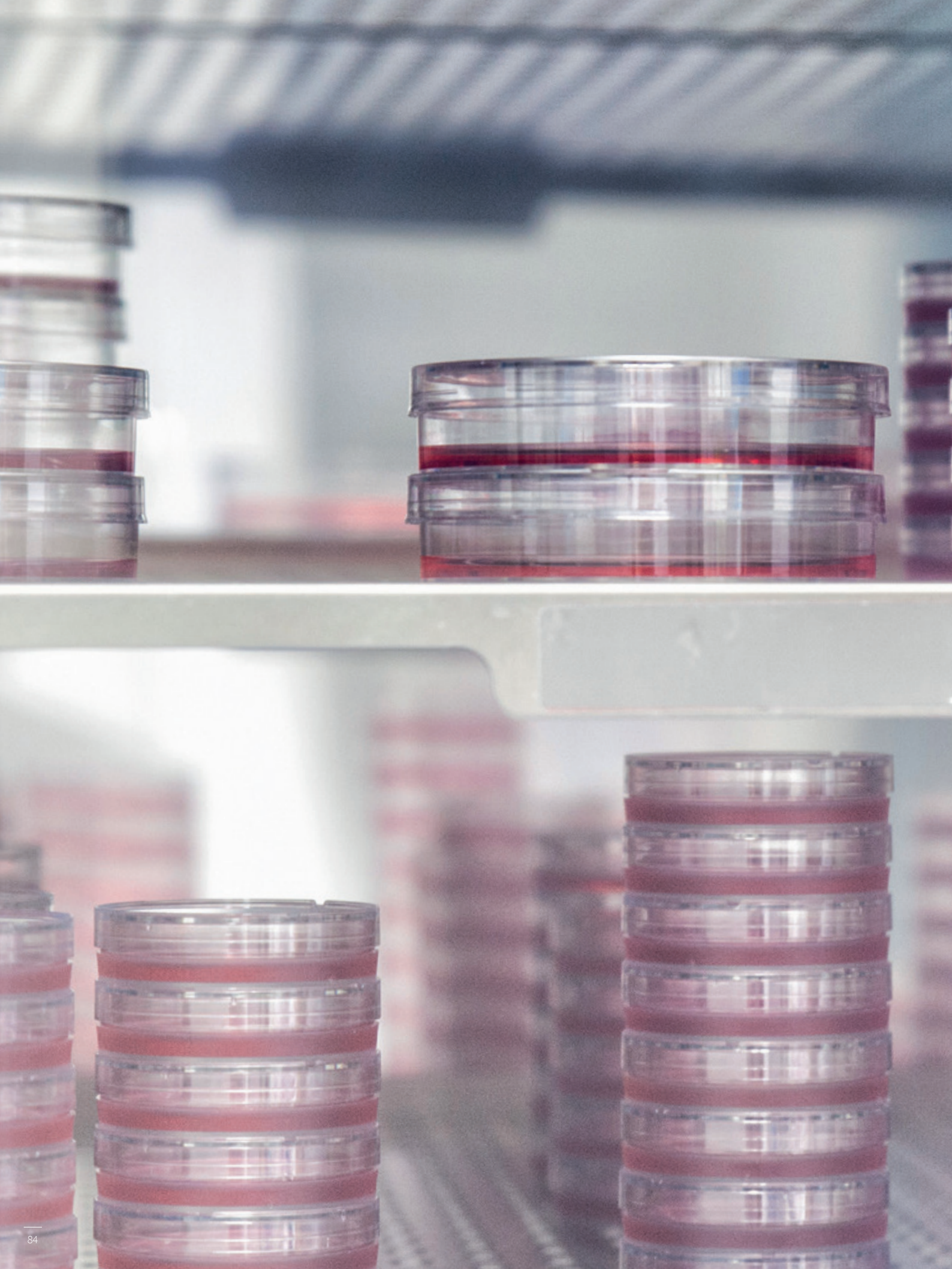
View of the server.



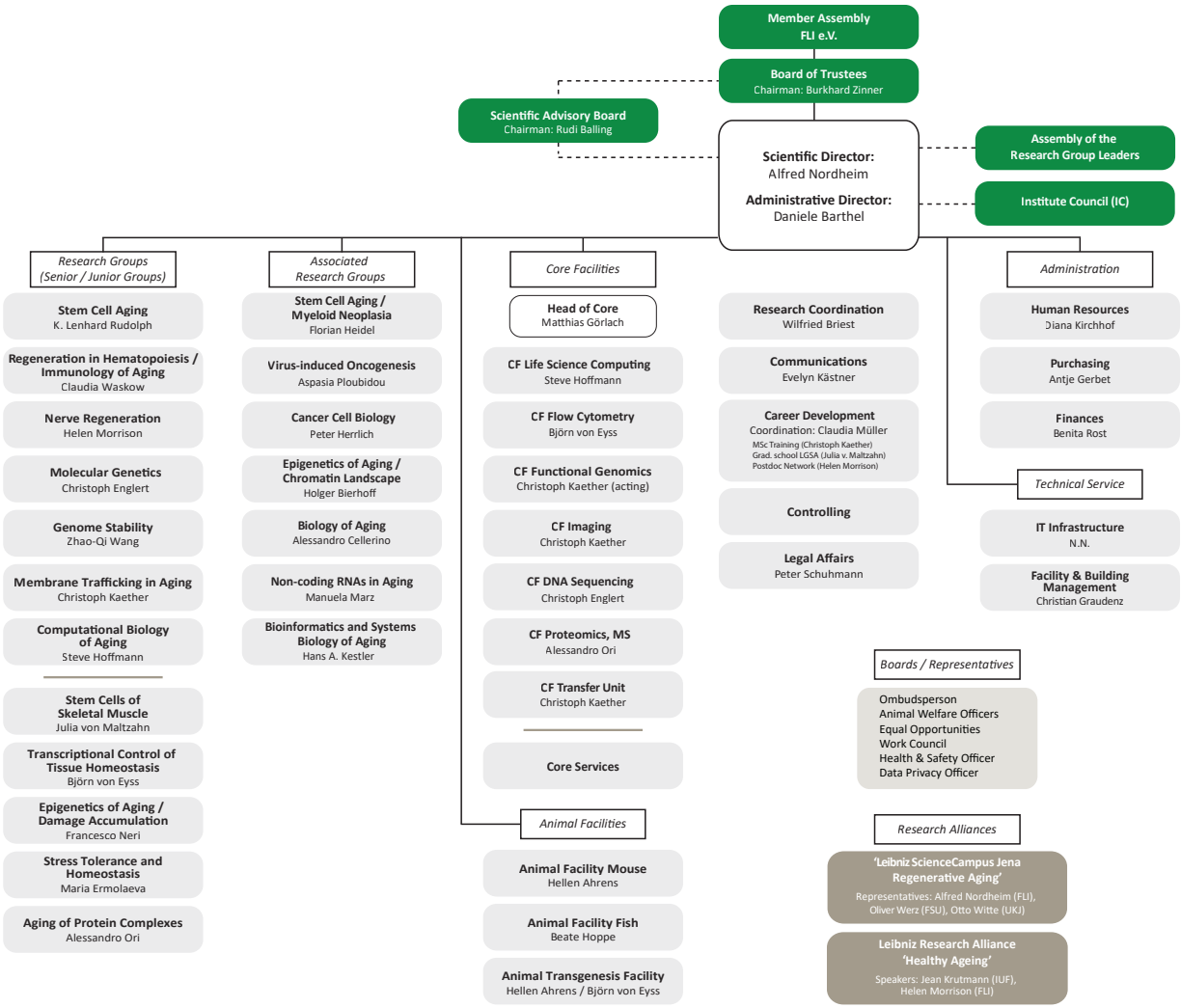
Organization

Organization

Organizational Structure

The FLI is one of the 95 institutes that constitute the Leibniz Association, and as such is funded by the German Federal Ministry of Education and Research (BMBF) and the State of Thuringia. Since 1992, the legal status of the FLI has been that of a registered association (e.V.). The Institute's objective since 2004 has been to promote research and science, education and training in the academic field of research on aging.

A flat hierarchy characterizes the FLI. One Scientific and one Administrative Director are heading the Institute. Research groups represent the basic organization structure, which does not include intermediate hierarchy levels, such as Departments. Group Leaders include Senior (tenured) Group Leaders and Junior Group Leaders at tenure track, ideally at 1:1 ratio, who all have equal voting rights at the monthly Group Leader meetings to discuss the Institute's scientific orientation. The Scientific Director appoints up to four Senior Group Leaders, along with a representative of the Junior Group Leaders and the Head of Core Facilities, to form the Institute Council (IC), which pre-discusses important matters of the Institute with the Directors. An international Scientific Advisory Board (SAB) and the Board of Trustees represent the Institutes' advisory and control boards, respectively. Additional structural elements include staff positions, the Core Administration, as well was a service sector comprised of technical services, scientific services and scientific coordinators.



Organizational Chart of FLI. (as of July 2019)

Executive Bodies

Board of Trustees

Member	
Burkhard Zinner (Chairman)	Thuringian Ministry for Economic Affairs, Science and Digital Society (TMWWDG), Ref. 51 Grundsatzangelegenheiten der Forschungspolitik, Erfurt, Germany
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Prof. Dr. Magdalena Götz (Head of Scientific Advisory Board)	Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Stem Cell Research, Neuherberg, Germany
Prof. Dr. Rudi Balling (Deputy Head of Scientific Advisory Board)	University of Luxembourg, Luxembourg Centre for Systems Biomedicine, Belval, Luxembourg

Scientific Advisory Board

Member	
Prof. Dr. Magdalena Götz (Head)	Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Stem Cell Research, Munich, Germany
Prof. Dr. Rudi Balling (Deputy Head)	University of Luxembourg, Luxembourg Centre for Systems Biomedicine, Belval, Luxembourg
Dr. Asifa Akhtar	MPI of Immunobiology and Epigenetics, Freiburg, Germany
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Prof. Dr. med. Christian Hübner	Institute of Human Genetics, Friedrich Schiller University Jena (FSU), Jena, Germany
Prof. Dr. Stephan Sigrist	Freie Universität Berlin, Berlin, Germany
Prof. Dr. Didier Stainier	Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany
PhD Sir Richard Treisman	The Francis Crick Institute, London, UK
Prof. Dr. med. Lars Zender	University of Tübingen, Faculty of Medicine, Head of Section Oncology, Tübingen, Germany

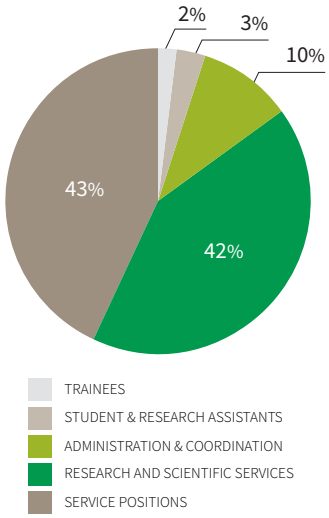
Members Assembly

Member	Represented by
Ernst-Abbe-Hochschule Jena, University of Applied Sciences, Jena	Prof. Dr. Steffen Teichert, Rector
Thüringer Ministerium für Wirtschaft, Wissenschaft und Digitale Gesellschaft, Erfurt	Dr. Ute Zopf, Ref. 54 Institutionelle Forschung
Friedrich Schiller University Jena (FSU), Jena	Prof. Dr. Thorsten Heinzel, Vice President for Research
City of Jena, Jena	Dr. Thomas Nitzsche, Mayor

(As of November 2018)

Staff Development

Over the last ten years, the Leibniz Institute on Aging (FLI) has experienced a rapid development. The number of staff members has increased from 263 (2008) to 309 (2018). In 2018, another 47 people were working as guests with their workplaces at the FLI.
Useable space has more than doubled from 4,500 to approx. 10,000 sqm through the addition of the new laboratory building in 2013. In 2017, reconstruction measures started in the older buildings of the institute.



as of December 31, 2018

Equality & Family-Friendliness

Equal opportunities and a family-friendly working environment are part of a modern personnel policy at the FLI. The percentage of women among all staff members was 56.3% and 41% among the scientific personnel.

The institute follows the equality standards of the DFG and the Leibniz Association in recruiting and personnel development. The FLI supports its employees, through numerous activities in integrating career and family as well as career and caring. These include a modernly equipped parent-child workroom, cooperation agreements with nearby Kindergartens, the implementation of health days/weeks and (care)workshops, various mentoring programs and employment agreements, which, for example, provide the necessary framework conditions for flexible working hours and workplace arrangements. “PhD funding for female doctoral students” and the “Welcome-Back-Fellowship (Betriebsvereinbarung zur Wiedereingliederung von Wissenschaftlerinnen)” support reintegration to work after a parental leave.

The FLI is a member of “Jenaer Bündnis für Familie” and takes part in several other task groups for “Reconciling work and family life”, “Leaders and families” and “Diversity in Education”, which meet regularly to exchange information. When recruiting, the support of the employees’ partners is becoming more and more important. As a member of several regional and supra-regional dual career networks as the Dual-Career-Network of the “Jenaer Bündnis für Familie“, the FLI supports new employees to find an adequate job for their partners in and around Jena.

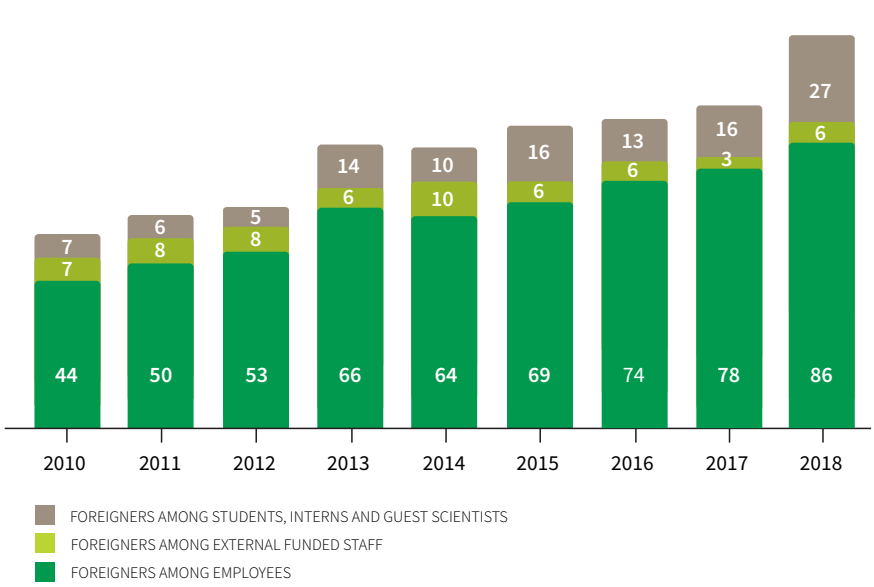
The “Diversity Charter” serves the FLI as a model for its organizational culture of diversity, fairness, tolerance and appreciation at the institute. The FLI openly acknowledges this on its homepage and regularly takes part in the Diversity Days as a representative of the Charter. Flexible target rates to increase the proportion of female scientists based on the cascade model of DFG’s “Forschungsorientierte Gleichstellungsstandards” (research-oriented equality standards) are defined in FLI’s Equal Opportunities plan (2016-2019) and since 2015 they are fixed in the programme budget. The target rates are reviewed annually. The appointment of a W3 professorship with a woman was successfully realized in 2017.

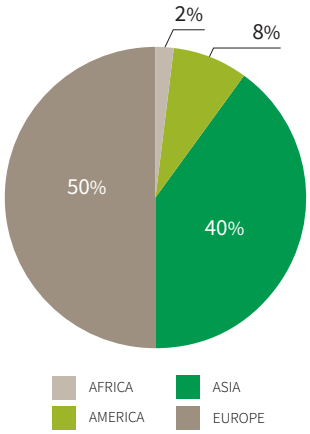
Like in 2013, the FLI was re-awarded the “Total E-Quality” Award (TEQ) in 2016, including the add-on “Diversity” for extraordinary diversity-fostering working conditions. Furthermore, the Institute was awarded with the regional “Jenaer Familiensiegel” in 2018. Both awards honor the wide range of equal opportunity and family-friendly activities implemented at the FLI.

Internationalization

The FLI is an institute of the Leibniz Association. It hosts a significant number of scientists from abroad on all levels (employees, students, guest scientists) – they come from 40 (2018) different countries. The percentage of international co-workers stands at 54.3% among scientists at FLI, 27.8% among all co-workers financed by the FLI and 33.4% among all people working or studying at FLI (2018-12-31). The Institute is bilingual (English/German). The scientific language is English. The FLI increased the ratio of co-workers financed by the FLI from abroad from 16% in 2008 to 28% in 2018. The ratio amongst PhD students increased from 28% to 72% during the same period. Since 2010, the Leibniz Graduate School on Aging (LGSA) has been a service point of the EURAXESS Germany network to help international mobile researchers. As such, the LGSA provides free and personalized assistance for the challenges faced by international researchers and their families when relocating. In 2015, the Institute signed the declaration of commitment to become a member of the European EURAXESS Service Network. To respond to the growing need for assistance for foreign employees a position for a relocation assistant integrated into the "Career development" staff section was set up in 2015.

FLI's Coworkers from Abroad





as of December 31, 2018

Third-Party Funded Projects (Selection)

Sofja Kovalevskaja Award / Alexander von Humboldt Foundation	The Alexander von Humboldt Foundation awarded Dr. Francesco Neri the Sofja Kovalevskaja Award, to investigate the molecular causes of cancer development in old age (2016-2021).	
erc / European Union	ERC Advanced Grant for the Characterization of Gerontogenes (StemCellGerontoGenes, 2013–2018, Prof. K. Lenhard Rudolph)	
Emmy Noether Programme / DFG	Emmy Noether Programme of DFG for the Analysis of Muscle Regeneration (2013-2020, Dr. Julia von Maltzahn)	
RegenerAging / State of Thuringia	The project “Aging-induced impairments in organ regeneration and homeostasis (RegenerAging)” of FSU Jena, UKJ and the FLI is funded within the „ProExzellenz-Initiative” of the State of Thuringia (2015-2020). One of the three new research groups is located at the FLI.	
Leibniz ScienceCampus / Leibniz Association	The Leibniz Association promotes the Leibniz ScienceCampus “Regenerative Aging” to enhance the expertise of aging research in Jena. The research groups of the project “RegenerAging” are integrated into the Leibniz ScienceCampus.	
DFG Research Unit	The FLI participates in the DFG-funded Research Unit “Heme and heme degradation products” (HHDP) investigating the generation of HHDPs, their functions and signaling mechanisms (2016-2019).	
RTG 1715 & RTG 2155 / DFG	Several FLI research projects are involved in the Research Training Group “Molecular Signatures of Adaptive Stress Responses” (RTG 1715) and “Protein Modification: A Key Mechanism for Ageing (ProMoAge)” (RTG 2155) (2016-2020).	
DFG	In the reporting period 2016-2018, the German Research Foundation (DFG) funded 22 additional individual projects at FLI.	

BrainAge / 7th Framework Programme of the European Union	With participation of the FLI in the “Brainage” project, the effects of prenatal stress on brain aging were analyzed; an international project within the 7th Framework Programme of the EU (2012-2017).	
CanPathPro / Horizon 2020 Framework Programme of the European Union	The project, supported by the EU within the Horizon 2020 programme, brings together the resources and expertise of scientists from 6 countries to develop a new systems biology platform for the predictive modeling of cancer-associated signaling processes (2016-2021, www.canpathpro.eu).	
PostDocNetwork / Leibniz Association	The first Leibniz PostDoc Network on the topic of “Aging induced impairments of regeneration and stem cell functionality (RegenerAging)” was established at the FLI to improve PostDoc training (2015-2019).	
Foundations & Associations	Several projects of the FLI are funded by foundations and associations, e.g. by:	
	• Bundesverband Neurofibromatose (Germany)	
	• Children's Tumor Foundation (USA)	
	• Else Kröner-Fresenius-Stiftung (Germany)	
	• German-Israeli Foundation for Scientific Research and Development (Germany, Israel)	
	• Jung Foundation for Science and Research (Germany)	
	• Prof. Dr. Dieter Platt-Stiftung (Germany)	
	• Stiftung Deutsche Krebshilfe (Germany)	
	• Stiftung Sibylle Assmus (Germany)	
	• Velux Stiftung (Switzerland)	

Outlook

During the last years, the research focus of the FLI has been further sharpened through intensive restructuring.

With the successful approval of a “Sondertatbestand” (Temporary Extraordinary Item of Expenditure), which the FLI had applied for in the context of the Evaluation, it will be possible to build up a new Research Program on “Microbiome and Aging” within the coming years. There is increasing evidence that the composition of commensal bacteria on body surfaces, such as the intestine and the skin, changes during aging. *Vice versa*, this aging-associated change in the microbiome influences the way we age. These processes are controlled by bacterial metabolite signaling and epigenetic responses to it in target tissues. With the new Research Programme, the FLI aims to understand microbiome aging and its consequences for organismal aging as a whole.

The continuously growing Subarea “Computational and Systems Biology of Aging” helps to conduct interspecies comparisons between vertebrates and humans to enable new insights into the aging process and to better analyze large data sets. This expertise will help to develop new therapeutic approaches to improve health of the elderly.

With regard to the institute’s infrastructure, reconstruction and modernization works are conducted in FLI’s older buildings from the 1950s.

With the appointment of the position of the future Scientific Director, the long-term perspective of the institute in terms of the research strategy will be promoted and further developed. The FLI will thus be able to maintain and further refine its unique and excellent international position in the area of aging research.

The FLI is on a mission to delineate major factors underlying stem cell aging and impairments in organ maintenance during aging. We are thus contributing to the future development of therapeutic approaches aimed at improving health in old age.

PHOTOGRAPHS:
Anna Schroll Fotografie: 18, 20, 25, 48, 52, 53, 66 (top), 76, 83, 84/85 · Augenwerke Fotografie Nadine Grimm: 4, 28 (left), 36, 38, 42 (top), 44, 45, 47, 50, 55, 58, 60, 61, 62, 66 (bottom), 68, 70, 72, 74 (left), 78, 80, 94/95 · Buck Institute: 46 · FLI/Diekmann Lab: 56 · FLI/Große Lab: 74 (bottom) · FLI/Hartmann: 65 · FLI/Kästner: U2, 29, 54 (right) · FLI/Ploubidou Lab: 32/33 · FLI/Rudolph Lab: U1 · FLI/Wagner: 27 (3, 4), 82 · FLI/Voll: 27 (1, 2), 28 (right), 31, 74 (right) · FLI/von Maltzahn Lab: 42 (bottom) · GSCN/Arne Sattler: 27 (5) · Humboldt-Stiftung/David Ausserhofer: 27 (7) · ICAD Organizing Commitee 2016: 29 (8) · Jörg Hempel: U1, 92/93 · LIN/Blumenstein: 27 (6) · Manja Marz (private): 64 · Sven Döhring: 54 (left) · TOTAL E-QUALITY Deutschland e.V./Giulia Iannicelli: 27 (9) · TU Dresden/Stephan Wiegand: 40

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Edition: 500
Editorial deadline: July 2019
Design: timespin - Digital Communication GmbH, www.timespin.de

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