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Board of Directors at FLI.
Dr. Daniele Barthel and Prof. Dr. K. Lenhard Rudolph
During 2014 and 2015, the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) refined 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. These are the major causes for decreases in quality of life, and increasing vulnerability to the development of diseases in elderly persons. Our research aims to delineate the genetic, epigenetic and molecular processes that underlie these aging-induced impairments.

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

Understanding aging and probing new interventions to increase healthy aging has one major bottleneck: Experiments on aging can take a long time - depending on the lifespan of the organisms investigated. Since 2006, the FLI has spearheaded the development of a new model organism for aging research: Killifish Nothobranchius furzeri, the shortest living vertebrate that can be kept under laboratory conditions. Last year, the FLI succeeded in disclosing the genome of this fish - its publication in December 2015 will help to further speed up future aging research and therapy development.

Aging affects all of us – We believe that aging research can make an important contribution to shaping the demographic change in a positive way, both for the society and the individual, by increasing health during aging.

We wish you an enlightening read and fascinating insights into research and work at the FLI.

Prof. Dr. K. Lenhard Rudolph
Scientific Director of FLI

Dr. Daniele Barthel
Administrative Director of FLI
The Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) was the first national research institute in Germany to focus on biomedical research on human aging, a multifactorial process controlled by environmental and genetic factors.

Declines in stem cell function and organ maintenance are regarded as major factors limiting organismal functionalities and the quality of life during aging; both processes represent major reasons for increases in organismal vulnerability and disease initiation during aging. Since 2004, the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) has focused on impairments in stem cell function and organ maintenance during aging, concentrating on the molecular, genetic, and epigenetic causes leading to these deficiencies.

Other institutes in Germany that have followed the FLI in working on aging, focus on distinct research areas. They concentrate on cellular stress responses; on demographic aspects of population research; on neurodegenerative or metabolic age pathologies; on cardiovascular diseases, or on environmental factors – however, research work in Jena with its focus on the maintenance of stem cells and tissues in the context of aging remains unique at national and international level. There are also a lot of approaches tackling aging research at European level.

The mission of the FLI is to disclose the basic mechanisms that lead to impairments in stem cell function and organ maintenance during aging, thus increasing organismal dysfunction, vulnerability and the risk of disease development.

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Mission & Vision

Unique Research Focus

Declines in stem cell function and organ maintenance are regarded as major factors limiting organismal functionalities and the quality of life during aging; both processes represent major reasons for increases in organismal vulnerability and disease initiation during aging. Since 2004, the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) has focused on impairments in stem cell function and organ maintenance during aging, concentrating on the molecular, genetic, and epigenetic causes leading to these deficiencies.

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Successful Restructuring at FLI

Following the recruitment of Lenhard Rudolph as the new Scientific Director in 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 Cell Aging and Organ Maintenance and
(II) Accumulation of Molecular Damages and (Epi)Genetics of Aging.

Research groups at the FLI work collaboratively in several research projects. Therefore, five main project Subdivisions were installed in 2015 in order to institutionalize the cooperative cross-group research.

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

I. Stem Cell Aging and Organ Maintenance

1. Stem Cell Aging

2. Organ Maintenance in Aging

5. Systems Biology of Aging

II. Accumulation of Molecular Damages and (Epi)Genetics of Aging

4. (Epi)Genetics and Models of Aging

3. Molecular Damages in Aging

Bioinformatics
Flow Cytometry
Functional Genomics
Imaging
DNA Sequencing
Proteomics
Transfer Unit
Animal Facilities (Mouse/Fish)
Core Services

Restructured research focus at FLI. FLI research is structured in five Subdivisions that cooperate closely. These are supported by a wide range of technical Core Facilities and Core Services.
Subdivision 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 Subdivision on “Stem Cell Aging” began its work at FLI in 2013, with the establishment of the research groups of Lenhard Rudolph (hematopoietic and intestinal stem cell aging), Julia von Maltzahn (muscle stem cell aging) and Cristina González-Estévez (Planarian neoblast stem cells); a third-party funded professorship for Claudia Waskow (human hematopoietic stem cells in mouse models) is expected to commence in Spring 2017. 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) have established collaboration 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 Subdivision investigates stem cell-intrinsic and extrinsic mechanisms that limit the function of stem cells and is focusing on the following topics:

- cell-intrinsic and extrinsic alterations that limit stem cell function in aging in response to DNA damage and metabolic changes (Lenhard Rudolph)
- intrinsic and extrinsic changes in aged muscle stem cells (Julia von Maltzahn)
- clonal dominance of mutant hematopoietic stem cells in aging (Florian Heidel, Lenhard Rudolph)
- mechanisms of immortal maintenance of pluripotent stem cells in Planarians (Cristina González-Estévez)
- signaling pathways that control stem cell division (Peter Herrlich)
- signaling pathways that disturb stem cell maintenance and function in the context of inflammation and aging (Heinrich Jasper).

Overall, the “Stem Cell Aging” Subdivision aims to study basic concepts and consequences of stem cell aging in the context of an aging organism. The Subdivision is strongly connected to the Subdivision on “Organ Maintenance 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 bidirectional interactions represent a strong basis for intense collaboration between the two Subdivisions.
Research focus of Subdivision 1. 

a. It is currently not well understood what mechanisms impair cellular functions in aging, or at what level of stem and progenitor cell hierarchies in different tissues. 

b. The relative contribution of niche cells and systemic 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 evidence indicates that aging-associated alterations in microbiota influence stem cell function and vice versa.
Subdivision 2: 
Organ Maintenance in Aging

The functionality of all organs and tissues declines during aging. As such, this deteriorative process represents a major contributory factor 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 is equally important. Research in this Subdivision 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 “Organ Maintenance in Aging” Subdivision has been very successful in recent years – as indicated by the promotion of three former Group Leaders into tenured positions at other institutions. Helen Morrison was promoted into a tenured position at FLI based on the enthusiastic support of external evaluators in 2015 and her excellent research results in the context of neuronal aging. The Subdivision focuses on the following main topics:

- aging-related impairments of cell-to-cell communication in regeneration and disease (Helen Morrison)
- drifts in developmental pathways (Christoph Englert)
- immune aging and inflammation in organ maintenance and regeneration (Ronny Hänold).

Together, the “Organ Maintenance in Aging” Subdivision studies cell-intrinsic and inter-cellular signals and networks that regulate organ maintenance and regeneration. As mentioned earlier, this work is closely related to the newly formed Subdivision on “Stem Cell Aging” and both Subdivisions combine to form Program Area I: “Stem Cell Aging and Organ Maintenance”. This Program Area strongly benefits from the newly built Subdivision on “Systems Biology of Aging”, which fosters the interconnection between Program Areas I and II at multiple levels.
Research focus of Subdivision 2. Organ maintenance is regulated by cell-intrinsic, local and systemic factors, which are subject to aging-associated changes. a. Genetic and epigenetic modulation of developmental pathways has been shown to contribute to aging and disease. It is critical to delineate mechanisms and consequences of aging-associated drifts in developmental pathways to understand defects in organ maintenance during aging. b. Immune aging has complex negative effects on organ maintenance involving tissue-destructive processes, such as the chronic elevation in inflammatory signals, as well as the reduction in protective immune functions, such as the clearance of senescent cells. c. Aging-associated alterations in systemic circulating factors and in local extracellular factors in the micro-milieu of tissues derive from metabolic changes, microbiota alterations, chronic inflammation, and senescent cells, and promote disease and tumor development.
Subdivision 3:  
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.

Since 2004, research at FLI has focused on the analysis of mechanisms that contribute to the accumulation of molecular damages in aging cells and tissues. The main aim of the subunit 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)
- mechanisms of DNA replication, damage response and repair in aging (Frank Große)
- protein trafficking, proteostasis and protein segregation in aging (Christoph Kaether)
- consequences of senescence for tissue and organismal aging (Christoph Kaether).

In order to understand the basic cellular and organismal malfunctions of aging, it is of key importance to analyze aging-associated induction of molecular damages and responses to it - including damage repair. *Vice versa*, aging-associated impairments in stem cell and tissue function can impinge on the accumulation of molecular damages. Examples include aging-associated decreases in immune functions contributing to the reduced removal of damaged and senescent cells, or alterations in metabolism that lead to increased induction of molecular damages. Given these functional and bidirectional interactions, the Subdivision on “Molecular Damages in Aging” is tightly linked to the aforementioned “Stem Cell Aging and Organ Maintenance” Program Area and of central importance to the overall research mission at the FLI. In addition, the functional analysis of molecular damages at FLI has successfully fostered collaboration with the Friedrich Schiller University (FSU) in Jena and contributed to the establishment of two DFG funded research training groups on stress response (RTG 1715) and protein modifications in aging (RTG 2155).

The Subunit is in the process of restructuring, cognizant of the retirement of Senior Group Leaders (Stephan Diekmann in 2015, Frank Große in 2018) and the discontinuation of NMR and X-ray-based structural biology in 2015. The Institute is preparing a call for a senior recruitment during 2017, given the imminent retirement of Frank Große.
Research focus of Subdivision 3. 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.
Subdivision 4: (Epi)Genetics and Models 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 our long-standing track record in genomic research, the newly focused research at FLI implemented a research program on “Genomics of Aging” back in 2004.

- The “Genome Analysis” group of Matthias Platzer and Christoph Englert’s “Molecular Genetics” group (Subdivision 2 on “Organ Maintenance in Aging”) spearheaded, with the newly recruited group of Alessandro Cellerino (Junior Group on Models of Aging since 2005 and now heading a Cooperating Group with Pisa University, Italy), the genomic and functional analysis of the short-lived fish *N. furzeri* as a new model for research on aging.

- Functional genetics analysis of aging was further strengthened by the recruitment of Maria Ermolaeva - using *C. elegans* to identify genetic factors that influence proteostasis, stress responses, and organ maintenance - thus linking Subdivisions 4 and 2.

- In addition to the strong impact of genetics on aging, emerging evidence indicated a significant influence of epigenetic alteration, such as global decreases in DNA methylation and changes in histone modification, on cellular and organismal aging. Collaboration with Alessandro Cellerino from Pisa University and Manja Marz from the FSU in Jena concentrates on the role of long non-coding RNAs and micro RNAs in influencing gene regulation in aging.

Subdivision 4 employs comparative genomics and functional genetics to identify genetic and epigenetic factors; as well as higher order gene regulatory mechanisms that influence the accumulation of molecular damages, stem cell function and organ maintenance during organismal aging. This research is tightly connected to research in Subdivisions 1–3 and strongly benefits from the implementation of the new Subdivision on “Systems Biology of Aging”.

—
Research focus of Subdivision 4. 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 that contribute to aging of an organism and to validate the functional relevance of (epi)genetic changes that occur during aging. Furthermore, genetic risk factors for aging-related diseases are identified and functionally tested. The future development of the Subdivision aims to investigate changes in host-microbiota interactions during aging, and how these influence clonal mutation and epigenetic alterations through metabolites and other signals. The combination of these approaches will help to determine the consequences of such alterations for impairments in stem cell function, organ maintenance and disease development during aging.
Subdivision 5: 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 has developed a unique position 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 a new Subdivision on "Systems Biology of Aging".

The building of the Subdivision on "Systems Biology of Aging" began in 2009 with the GerontoSys program of the Federal Ministry of Science and Education (BMBF), funding for a collaborative project on computational analysis of aging, which continued until 2014 (JenAge). 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 into a new Subunit at the Institute.

The resultant development of Subdivision 5 on “Systems Biology of Aging” is instrumental in understanding the complexity of aging at multi-scale levels of the organism and will boost the interconnection between all 4 current Subdivisions of the FLI’s research program.
Research focus of Subdivision 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 Subdivision on “Systems Biology of Aging”. The overall goal is to interconnect research at different scales, taking place in Subdivisions 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

In October 2014, the FLI began to restructure its central technology platforms and services into a “core” structure of facility and service units separate from FLI’s research groups. The new structure came into effect at the end of 2015. A number of technology platforms (e.g. sequencing, mass spectrometry) had grown out of individual methodological requirements for single research groups in the past but had developed into semiautonomous substructures. As a consequence of refocussed research activities and the concomitant advent of new research groups at FLI, those units increasingly had to serve multiple 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 became necessary 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 Facilities (AF) comprising fish and mouse facilities are run separately, as they involve 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. 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. Facilities and Services, including Animal Facilities, have contributed to a significant 61% of FLI’s 256 peer reviewed research publications during 2013-2015.
Core Facilities:

- Bioinformatics
- Flow Cytometry
- Functional Genomics
- DNA Sequencing
- Proteomics
- Imaging
- Technology Transfer (SPARK)
- Histology, Pathology, and Electron Microscopy
- Protein Production
- Isotope Laboratory
- Gamma Irradiation Chamber
- Small Animal CT
- S2-Safety Level Laboratories
- Media Preparation
- Photo Laboratory

Animal Facilities:

- Mice
- Fish (Zebrafish/Turquoise killifish)
Changes at Group Level

The research focusing of the FLI came along with a successful re-structuring at group level. At the end of 2015, the FLI had 7 Senior Group Leaders, and 5 Junior Group Leaders. Two additional Senior Groups are currently recruited. From the total number of 14 Group Leaders, which are expected to do research at the FLI in 2017, only 6 (ca. 40%) were Group Leaders before the year 2012. Moreover, 8 out of 10 former Junior Group Leaders were successfully recruited into senior positions at other institutes; and two Junior Groups continued their research at FLI as Senior Groups. The refocusing and attraction of a new team of Group Leaders invigorated innovation and collaboration at the FLI and beyond. There exists a strong tense that this has just started and has yet to reach its peak. For example, collaboration with the Friedrich Schiller University, the University Hospital Jena and neighboring institutes at Beutenberg Campus was strengthened, and third-party funding for the installment of a Leibniz ScienceCampus on “Regenerative Aging” was successfully applied for.

Legend Fluctuation

Program Area I:
Subdivisions 1+2 active
Subdivisions 1+2 assoc./cooper.

Program Area II:
Subdivisions 3+4 active
Subdivisions 3+4 assoc./cooper.

Interconnecting Subdivision 5 active
Subdivisions 5 assoc./cooper.
<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
</tr>
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<tbody>
<tr>
<td>2014</td>
<td>K. Lenhard Rudolph</td>
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<tr>
<td>2014</td>
<td>Julia von Maltzahn</td>
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<tr>
<td>2014</td>
<td>Cristina González-Estévez (Fellow)</td>
</tr>
<tr>
<td>2014</td>
<td>Peter Herrlich (associated)</td>
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<tr>
<td>2014</td>
<td>Aspasia Ploubidou (associated)</td>
</tr>
<tr>
<td>2014</td>
<td>Christoph Englert</td>
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<tr>
<td>2014</td>
<td>Helen Morrison</td>
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<tr>
<td>2014</td>
<td>Heike Heuer (associated)</td>
</tr>
<tr>
<td>2014</td>
<td>Falk Weih/Ronny Hänold (associated)</td>
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<tr>
<td>2014</td>
<td>Stephan Diekmann</td>
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<td>2014</td>
<td>Matthias Görlach</td>
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<td>2014</td>
<td>Frank Große</td>
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<td>2014</td>
<td>Christoph Kaether</td>
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<td>2014</td>
<td>Manuel Than</td>
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<td>2014</td>
<td>Zhao-Qi Wang</td>
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<tr>
<td>2015</td>
<td>Maria Ermolaeva</td>
</tr>
<tr>
<td>2015</td>
<td>Matthias Platzer</td>
</tr>
<tr>
<td>2015</td>
<td>Alessandro Cellerino (cooperating)</td>
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<tr>
<td>2015</td>
<td>Ion C. Cirstea (Fellow)</td>
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<tr>
<td>2015</td>
<td>Manja Marz (cooperating)</td>
</tr>
<tr>
<td>2015</td>
<td>Hans Kestler</td>
</tr>
<tr>
<td>2015</td>
<td>Alessandro Ori</td>
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</table>

Development of FLI research groups in 2014 and 2015.
To stay abreast of the accelerating development of technology and research, it is of utmost importance to engage in scientific networks and joint research projects. 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 collaboration with Friedrich Schiller University and Jena University Hospital, we are engaged in 250 joint research projects and associations at national level as well as in collaborating projects with institutes from 30 nations worldwide. In doing so, we provide ourselves with a state-of-the-art international knowledge that enables us 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 characterize the future are the subject of the **LRA Healthy Ageing**, which is coordinated at FLI. Since 2012, the LRA Healthy Ageing has successfully bundled 21 Leibniz Institutes from the fields of Biology, Medicine, Psychology, Education, Sociology and Economy. Collaboration between these diverse scientific disciplines includes research on the biological and social foundations of aging, as well as applications 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. Alongside 16 other Leibniz Institutes, the 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 (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 “RegenerAging” research project was developed by members of the Aging Research Center Jena (ARC). It is a close cooperation between FLI, the Jena University Hospital (UKJ) and Faculties of Medicine, Biology & Pharmacy and Mathematics & Computer Sciences at the Friedrich Schiller University Jena; as well as the developers from Carl Zeiss Microscopy GmbH. The project is funded within the “ProExzellenz Initiative 2” of the State of Thuringia from 2015-19, to the sum of 3.9 million euro. The main focus within the “RegenerAging” project is the functional analysis of the underlying molecular mechanisms of aging-associated impairments. 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 in age. Research focuses on the “Epigenetics of Aging”, “Stem Cell Aging” and “Immunology of Aging”. To our knowledge, there is currently no other national initiative in Germany focusing on aging-induced impairments in the functionality of stem cells and differentiated cells in regeneration and organ homeostasis.

**Leibniz ScienceCampus “Regenerative Aging”**

To further enhance the expertise and networking of aging research in Jena, the FLI has received funding from the Leibniz Association to set up a Leibniz ScienceCampus “Regenerative Aging”. It is funded initially for four years and co-financed by the “ProExzellenz Initiative” of the State of Thuringia.
Further New Joint Projects

In 2015, FLI began its participation in a DFG-funded research network “Heme and heme degradation products” (hhdp) as well as in the BMBF-funded project “Model-based optimisation and individualisation of treatment strategies in haematology” (HaematoOpt). Furthermore, in 2015 we were successful in joint applications for two projects with the Martin Luther University Halle-Wittenberg and the Friedrich Schiller University for the research training group “Protein Modification: A Key Mechanism for Aging – ProMoAge” (RTG 2155).

International Talks and Presentations

In order to foster international visibility and scientific exchange, our researchers are encouraged to visit internationally recognized meetings and present their data. Between 2013 and 2015, 208 oral presentations were given by our scientists on scientific meetings.
### Numbers & Facts

#### 2014 – 2015 at a Glance

<table>
<thead>
<tr>
<th>Category</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Associated Groups</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Articles in Peer-Reviewed Journals</td>
<td>112</td>
<td>100</td>
</tr>
<tr>
<td>Cumulative Impact Factor of FLI Publications</td>
<td>755</td>
<td>801</td>
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<tr>
<td>Number of Established Groups</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Employees*</td>
<td>292</td>
<td>312</td>
</tr>
<tr>
<td>Research Awards for FLI Scientists</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Number of Collaborating Institutions</td>
<td>372</td>
<td>353</td>
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<tr>
<td>Third-Party Funding (in k€)</td>
<td>3,868</td>
<td>4,149</td>
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Development of Publications

Although the number of publications has remained almost constant in recent years, the quality has increased considerably – corresponding with FLI's general strategy to increase the quality, rather than quantity, of research publications. The cumulative impact factor of all publications has doubled since 2008 and further increased in latter years. Setting a cut-off for the impact factor (≥7), 34% of all FLI publications in 2013–2015 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 2014–2015

2015

Insights into sex chromosome evolution and aging from the genome of a short-lived fish.
Cell 2015, 163, 1527-38.

Branch-chain amino acid catabolism is a conserved regulator of physiological ageing.
Not Commun 2015, 6, 10043.

Artery tertiary lymphoid organs control host-aorta immunity and protect against atherosclerosis via vascular smooth muscle cell lymphotoxin B receptors.
Immunity 2015, 42(6), 1100-15 (* equal contribution).

Gene dosage reductions of Trf1 and/or Tin2 induce telomere DNA damage and lymphoma formation in aging mice.
Leukemia 2015, doi: 10.1038/leu.2015.173.

Smg6/Est1 licenses embryonic stem cell differentiation via non-sense-mediated mRNA decay via non-sense-mediated mRNA decay.
EMBO J 2015, 34(12), 1630-47.

Telomerase abrogates aneuploidy-induced telomere replication stress, senescence and cell depletion.
EMBO J 2015, 34(10), 1791-84 (* co-corresponding author).


2014


### Awards 2014–2015

<table>
<thead>
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<th>Year</th>
<th>Award Description</th>
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<tr>
<td>2015</td>
<td>In recognition of his outstanding international research accomplishments in aging research, Prof. K. Lenhard Rudolph was awarded the SENECA Medal for Aging Research, granted by the Industrial Club of Düsseldorf.</td>
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<td></td>
<td>FLI was awarded the Jenaer Familiensiegel in recognition of the institute’s outstanding performance with regard to a family-friendly work environment.</td>
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<td></td>
<td>FLI’s new laboratory building was awarded the architecture prize “eins:eins” by the German Association of Architects (BDA).</td>
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<td></td>
<td>Dr. Dr. Alexander Schulz was honored with the Campus Prize of Beutenberg Campus Jena for the best doctoral thesis as well as with the Promotionspreis of Friedrich Schiller University for the best doctoral graduation at the Faculty of Medicine.</td>
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<tr>
<td></td>
<td>Prof. K. Lenhard Rudolph was awarded the Deutscher Krebspreis 2015 in the category of “Experimental Research”, granted by the German Cancer Society and the German Cancer Foundation.</td>
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Invited Speeches and Talks by FLI-Scientists

Invited International Guest Speakers at FLI

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Invited Speeches and Talks of FLI-Scientists

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### Academic Events 2014–2015

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<td>2014-09-08 – 2014-09-09</td>
<td>Workshop – Systems Biology of Ageing, Jena (Germany), organized by: Jürgen Sühnel (FLI) and JenAge</td>
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<td>2014-09-14 – 2014-09-23</td>
<td>Sino-German Summer School – Cellular Stress Responses, Beijing (China), organized by: Zhao-Qi Wang (FLI) and Quan Chen (China)</td>
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<td>2014-12-05 – 2014-12-06</td>
<td>Annual Meeting of the German Foundation for Aging Research (DGfA) 2014, Cologne (Germany), organized by: Karl Lenhard Rudolph (FLI) and Björn Schumacher (CECAD, Cologne, Germany)</td>
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<td>2015-01-16</td>
<td>Symposium on Molecular Signaling in Health and Disease in Memory of Falk Weih, Jena (Germany), organized by: Ronny Hänold (FLI) and Debra Weih, Christoph Englert, Marc Riemann (FLI)</td>
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<tr>
<td>2015-02-15 – 2015-02-20</td>
<td>Gordon Research Conference – Stem Cells &amp; Cancer, Ventura (United States of America), organized by: Karl Lenhard Rudolph (FLI) and Leonard I Zon (HHMI/Boston Children's Hospital, Boston, United States of America)</td>
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<td>2015-02-25 – 2015-02-26</td>
<td>Interdisciplinary Symposium LRA Healthy Ageing - Better understanding healthy ageing: A trans- and interdisciplinary research approach, Mannheim (Germany), organized by: Astrid van der Wall (FLI)</td>
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<td>2015-05-31 – 2015-06-03</td>
<td>VII. Else Kröner-Fresenius Symposium on Adult Stem Cells in Aging, Diseases and Cancer, Erice/Sicily (Italy), organized by: Karl Lenhard Rudolph (FLI)</td>
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<td>2015-07-19 – 2015-07-22</td>
<td>Statistical Computing 2015 – 47th Meeting of the Working Groups “Statistical Computing” (GMDS/IBS-DR) and “Biostatistics” (GfKI), Günzburg (Germany), organized by: Hans Kestler (FLI) along with Axel Fürstberger and Johann Kraus (Ulm University, Ulm, Germany)</td>
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<td>2015-09-10 – 2015-09-15</td>
<td>Sino-German Symposium: Development and Maintenance of Brain Function: from Basic Mechanisms to Disease, Beijing (China), organized by: Zhao-Qi Wang (FLI) and Zhiheng Xu (Chinese Academy of Sciences, Institute of Genetics and Developmental Biology, Beijing, China)</td>
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<td>2015-09-19 – 2015-09-23</td>
<td>4th International Meeting Jena-Beijing (RTG 1715) – Molecular Signatures of Adaptive Stress Responses, Jena and Dresden, organized by: Zhao-Qi Wang (FLI)</td>
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<td>2015-10-11 – 2015-10-14</td>
<td>16th Ataxia-Telangiectasia Workshop (ATW), Beijing (China), organized by: Zhao-Qi Wang (FLI) and Xingzhi Xu (Beijing Key Laboratory of DNA Damage Response, CNU, Beijing, China)</td>
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<td>2015-12-04 – 2015-12-05</td>
<td>DGfA meeting 2015, Jena (Germany), organized by: Karl Lenhard Rudolph (FLI) and Björn Schumacher (CECAD Research Center – University of Cologne, Cologne, Germany)</td>
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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:

- **Program Area I.**
  - **Stem Cell Aging and Organ Maintenance**

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. Subdivisions 1 and 2 are allocated to this research area.

- **Program Area II.**
  - **Accumulation of Molecular Damages and (Epi)Genetics 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 remain 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 and to learn more about the genetic factors influencing the aging process, we are employing comparative analyses and targeted manipulations of the genome or transcriptome in short- and long-lived model organisms. 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 Subdivisions 3 and 4.

Interconnecting Subdivision
- **Bioinformatics and Systems Biology of Aging**

**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 Program Areas I and II and is identical to Subdivision 5.
Identification of causative mechanisms of aging
to enable aging in good health

I. Stem Cell Aging and Organ Maintenance

1. I. Stem Cell Aging
   Active: Karl Lenhard Rudolph (Head)
   Julia von Maltzahn
   Fellow: Cristina González-Estévez
   Associated: Peter Herrlich
   Cooperating: Heinrich Jasper (since 2015/12)

2. Organ Maintenance in Aging
   Active: Christoph Englert
   Helen Morrison (Head)
   Associated: Heike Heuer (until 2014/12)
   Falk Weih/Ronny Hänold

Bioinformatics and Systems Biology of Aging

3. II. Molecular Damages in Aging
   Active: Stephan Diekmann (until 2014/09)
   Matthias Görlich (until 2015/12)
   Frank Große
   Christoph Kaether
   Manuel Than (until 2015/12)
   Zhao-Qi Wang (Head)

4. (Epi)Genetics and Models of Aging
   Active: Matthias Platzer (Head)
   Maria Ermolaeva (since 2015/04)
   Fellow: Ion Cirstea (until 2015/12)
   Cooperating: Alessandro Cellerino
   Manja Marz (since 2015/02)

5. Systems Biology of Aging
   Active: Hans A. Kestler (until 2015/12)
   Alessandro Ori (since 2015/10)
   Associated: Jürgen Sühnel (until 2014/12)

Research Groups at FLI. Includes all research groups doing research at FLI in 2014 and 2015.
Program Area I

Stem Cell Aging and Organ Maintenance
Stem Cell Aging and Organ Maintenance

Subdivision 1: Stem Cell Aging .............................................................
38 Rudolph Research Group
40 von Maltzahn Research Group
42 González-Estévez Fellow Group
43 Herrlich Associated Group
44 Ploubidou Associated Group
45 Jasper Cooperating Group

Subdivision 2: Organ Maintenance in Aging ........................................
46 Englert Research Group
48 Morrison Research Group
50 Heuer Associated Group
51 Weih/Hänold Associated Group
Focus of Research

The research group of K. Lenhard Rudolph, Scientific Director at FLI, is engaged in investigating the antecedents, processes and consequences of stem cell aging. Adult stem cells are essential for the lifelong maintenance and regeneration of various organs and tissues. Experimental and clinical data indicate that the functional capacity of adult stem cells in organ regeneration declines during aging. Molecular mechanisms that cause impairments in stem cell function during aging are still not completely understood.

Genetic analyses have identified a growing number of genes and genetic loci that are associated with longevity and aging in model organisms and humans. For most of these associations, the molecular mechanisms and their functional relevance for mammalian aging remain unknown. In many cases of genetic loci associations, the responsible genes have not even been identified. Emerging experimental data indicate that at least some of the aging/longevity-associated genes influence the functional reserve of adult stem cells.

Current Projects

Genes in Adult Stem Cell Aging | The research project “Longevity and Aging-Associated Genes in Adult Stem Cell Aging” (ERC Advanced Grant) determines the influence of longevity and aging-associated genes on stem cell aging by employing reverse genetic screening approaches. The overall goal of the studies is to delineate novel mechanisms of stem cell aging and its implication for defects in organ homeostasis and regeneration during aging.

Telomere Dysfunction | A second project deals with checkpoints and stem cell function upon telomere dysfunction. This project is part of the Marie Curie Initial Training Network “Chronic DNA damage in Ageing” (CodeAge) of the EU 7th Framework Programme. The aim is to identify novel checkpoints that limit maintenance and function of adult stem cells in response to telomere dysfunction. We intend to generate a rational basis by which to select novel targets for compound screens aiming to identify novel compounds for regenerative therapies.

Aging Immune System | In late life, hematopoietic stem cells partly lose their functionality, especially the capability to build immune cells, which is thought to contribute to the development of immune defects and increased risk of infections in the elderly. At the same time, a weakened immune system can accelerate aging, since damaged body cells are no longer detected and eliminated by the immune cells, leading to organ and tissue dysfunction or an increasing risk of cancer.
**Numbers 2014 – 2015**

**Selected Publications**

**2015**

Adams* PD, Jasper* H, Rudolph* KL. Aging-Induced Stem Cell Mutations as Drivers for Disease and Cancer. Cell Stem Cell 2015, 16(6), 601-12 (*co-corresponding authors). (Review)


**2014**


**Team (as of 31.12.2015)**

- **Staff Scientist:** Cagatay Günes
- **Postdocs:** Daniel Andre Felix, Yohei Morita, Sonja Schätzlein, Tobias Sperka, Duozhuang Tang, Stefan Tümpel, Mei-Fang Wu, Jianwei Wang, Vasily Romanov (external)
- **Doctoral Students:** Alush Irene Avila, Ali Hyder Baig, Seerat Bajwa, Phillip Gerald Calmes, Yulin Chen, Zhiyang Chen, Sarmistha Deb, George Garside, Bing Han, Ilwook Kim, Sospeter Ngoci Njeru, Omid Omrani, Simon Schwörer, Miaomiao Suo, Jiangnan Yang
- **Research Engineer:** Melanie Kettering
- **Technical Assistants:** Sebastian Berkhoff, Sabrina Eichwald, Antje Vester
- **Master Students:** Elias Amro, Amama Kanwal, Ute Köber, Sachin Sridharan, Christy Susan Varghese, Sarah von Löhneysen
- **Bachelor Student:** Daniel Whisenant

**Funding**

![Funding Logos]
Focus of Research

Skeletal muscle serves a multitude of functions in the organism and exhibits a remarkable ability to adapt to physiological demands. 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. Our lab 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, we analyze injured skeletal muscles from aged and adult mice and investigate the regeneration process at different time points after injury. We could already show that JAK/STAT-signaling 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.
Numbers 2014 – 2015

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Selected Publications

2015


2014


Team (as of 31.12.2015)

- Postdocs: Marie Juliane Jung, Hellen Elisa Ahrens, Laura Zidek
- Doctoral Student: Manuel Schmidt
- Technical Assistants: Sabine Landmann, Christine Poser

Selected Cooperation Partners

- Ottawa Hospital Research Institute (OHIRI), Ottawa, Canada
- Nestlé Institute of Health Sciences, Lausanne, Switzerland
- European Research Institute for the Biology of Ageing (ERIBA), Groningen, Netherlands

Satellite cells (stained in red) are the skeleton muscle’s stem cells.
Focus of Research

The lab of Cristina González-Estévez 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 life span of vertebrate and invertebrate animals. Moreover, caloric restriction 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 in Cristina’s lab 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. We aim to find novel genes involved in an enhancement of stem cell function (stem cell maintenance, pluripotency and clonogenecity) and in aging/rejuvenation mechanisms.
- Study of autophagy in the regulation of stem cells in planarians.
- Telomere length quantification as a tool to distinguish different populations of planarian stem cells during starvation.

Numbers 2014 – 2015

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Team (as of 31.12.2015)

Doctoral Student: Oscar Gutierrez-Gutierrez
Technical Assistant: Marta Iglesias Garcia
Focus of Research

Peter Herrlich, Scientific Director Emeritus of FLI, and his research group have 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 generated two mouse lines, in the genes encoding protein assembly factor TRIP6 and the centrosomal protein RHAMM whose impact on neural progenitors and brain development is being analyzed.

Current Projects

• Role of CD44 in metastasis formation and molecular mechanisms of co-receptor functions of CD44 splice variants
• Regulation of the proteolytic release of growth factors and cytokines
• Differentiation of choroid plexus in brain and the formation of a hydrocephalus

Selected Publications

2015


2014

Focus of Research
Cancer, a major age-related pathology is the research topic of Aspasia Ploubidou’s lab. It is well established, in different systems, that cytoskeleton deregulation is associated with oncogenic cell growth. The cytoskeleton fulfills its diverse functions by converting intra- and extra-cellular signals into structures and structure remodeling. The group’s primary aim is 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.

Current Projects
- Mechanisms and consequences of centrosome inactivation to answer the long-standing key question of whether centrosome inactivation is oncogenic in human cells
- Mitotic functions of RHAMM, a multifunctional protein, which is deregulated in human cancers

Individual Contributions to Edited Volume
2015

Selected Publications
2015

Team (as of 31.12.2015)
Postdocs: Manmeet Sakshi Bedi, Huaibiao Li
Focus of Research
Stem cells are an essential part of many adult tissues and ensure 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 Jasper Cooperation Group 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 are 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 Publications without FLI Contribution
2015
Adams* PD, Jasper* H, Rudolph* KL. Aging-Induced Stem Cell Mutations as Drivers for Disease and Cancer. Cell Stem Cell 2015, 16(6), 601-12 (*co-corresponding authors). (Review)


2014

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 Englert group 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. Recently, 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
• Establishment of zebrafish models to analyze Wilms’ tumor protein Wtx
• Analysis of the age-dependency of kidney regeneration
• Analysis of biochemical signaling pathways that regulate the aging process of the short-lived vertebrate *N. furzeri*
**Numbers 2014 – 2015**

**Project grants (absolute in k€):**

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**Postdocs:**

- Thomas James David Bates
- Lihua Dong
- Nils Hartmann
- Abinaya Nathan
- Birgit Perner

**Doctoral Students:**

- Andreas Große
- Uta Naumann
- Stefan Pietsch
- Danny Schnerwitzki
- Peter Singer

**Scientific Staff:**

- Eric Kegan Donahue (Fulbright-Stipendiat)

**Research Engineer:**

- Dagmar Kruspe

**Technician:**

- Gabriele Günther

**Master Students:**

- Paul Cramer
- Johannes Krug

**Guest:**

- Bingjue Li

**Selected Publications 2015**


**Team (as of 31.12.2015)**

- Postdocs: Thomas James David Bates, Lihua Dong, Nils Hartmann, Abinaya Nathan, Birgit Perner
- Doctoral Students: Andreas Große, Uta Naumann, Stefan Pietsch, Danny Schnerwitzki, Peter Singer
- Scientific Staff: Eric Kegan Donahue (Fulbright-Stipendiat)
- Research Engineer: Dagmar Kruspe
- Technician: Gabriele Günther
- Master Students: Paul Cramer, Johannes Krug
- Guest: Bingjue Li

**Funding**

[DFG Deutsche Forschungsgemeinschaft]

[Deutsche Krebshilfe]

[Fonds der Chemischen Industrie]

**Selected Cooperation Partners**

- Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany
- University of Würzburg, Würzburg, Germany
Focus of Research

Helen Morrison's research lab 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 Morrison 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 her laboratory, Morrison and her team are 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 Morrison 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.
RSW 2014 – 2015

```plaintext
2014 2015
288 € 225 €
```

**Selected Publications**

**2015**

Inside-out Regulation of Ectodomain Cleavage of Cluster-of-Differentiation-44 (CD44) and of Neuregulin-1 requires Substrate Dimerization. 
*J Biol Chem* 2015, 290(28), 17041-54 (*co-senior authors, 2015 Best of JBC Papers of the Week Winner).

Inhibition of RAS Activation Due to a Homozygous Ezrin Variant in Patients with Profound Intellectual Disability. 
*Hum Mutat* 2015, 36(2), 270-8 (* equal contribution).

Merlin Isoforms 1 and 2 Both Act as Tumour Suppressors and Are Required for Optimal Sperm Maturation. 
*PLoS One* 2015, 10(8), e0129151.

**2014**

Neuronal merlin influences ERBB2 receptor expression on Schwann cells through neuregulin 1 type III signalling. 
*Brain* 2014, 137(2), 420-32 (* equal contribution).

Schulz A, Walther C, Morrison H, Bauer R. 
In vivo electrophysiological measurements on mouse sciatic nerves. 
*J Vis Exp* 2014 (Author-Produced Video).

**Team (as of 31.12.2015)**

- **Postdocs:** Yan Cui, Susann Groth, Lars Björn Riecken, Alexander Schulz, Ansgar Zoch
- **Doctoral Students:** Robert Büttner, Annemarie Carlstedt, Cansten Dornblut, Frederike Kramer, Stephan Schacke, Kassandra Walluks
- **Scientist:** Junzhi Ma
- **Technicians:** Birgit Pavelka, Uta Petz, Christin Ritter
- **Master Student:** Lin Ma

**Funding**

- [Children’s Cancer Research Foundation](#)
- [DFG – Deutsche Forschungsgemeinschaft](#)
- [Deutsche Krebshilfe](#)
Focus of Research
Thyroid hormones (TH) are essential for proper brain development and the metabolic homeostasis of the organism. While in the adult TH deficiency is associated with dementia, neurological symptoms and depression, untreated congenital hypothyroidism leads to irreversible brain damage characterized by mental retardation, deafness and severe motor defects. Surprisingly, the molecular mechanisms underlying these deficits are poorly understood as yet. The group’s aim is to define the mechanisms of TH action in the developing as well as in the adult brain.

Current Projects
- Functions of thyroid hormone in brain development and aging
- (Patho-) Physiological role of murine thyroid hormone transporters
- Development of therapeutic strategies for patients with Allan-Herndon-Dudley Syndrome
- Impact of thyroid hormone in ischemic brain injury
- Role of the anti-aging hormone klotho in the neuroendocrine system

Selected Publications
2015

2014


Numbers 2014 – 2015

Project grants (absolute in k€)

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Number of joint research projects

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Focus of Research
An intact immune system is crucial for health, especially in older age. The former research group of Falk Weih, now provisionally led by Ronny Häneld, lays its research focus on the impact of gene regulator NF-κB (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 a better understanding of NF-κB function in age-related immune deficiencies and disease.

Current Projects
- NF-κB-induced autoimmunity as reason for inflammatory aging
- NF-κB signaling pathways in lymphopoiesis, inflammation, and organ maintenance
- The aging brain: Neuro-immunological studies of NF-κB’s role in the injured and aged brain.

Selected Publications
2015


Team (as of 31.12.2015)
Postdocs: Ievgen Kolesnik, Marc Riemann
Doctoral Student: Christian Engelmann
Research Engineers: Nico Andreas, Debra Weih
Technical Assistants: Elke Meier, Heike Dittmar
Program Area II

Accumulation of Molecular Damages and (Epi)Genetics of Aging
Accumulation of Molecular Damages and (Epi)Genetics of Aging

Subdivision 3: Molecular Damages in Aging

54  Diekmann Research Group
56  Görlach Research Group
58  Große Research Group
60  Kaether Research Group
62  Than Research Group
64  Wang Research Group

Subdivision 4: (Epi)Genetics and Models of Aging

66  Ermolaeva Research Group
68  Platzer Research Group
70  Cirstea Fellow Group
71  Cellerino Cooperating Group
72  Marz Cooperating Group
Focus of Research

Stephan Diekmann, former Professor of Biophysical Chemistry, retired as FLI Group Leader in September 2014. Up until then, he focused his research on the structure/function relationship of the human centromere/kinetochore complex. The centromere is a chromosomal substructure responsible for DNA segregation. The kinetochore protein complex settles at the centromere and, during mitosis, attaches the centromere to spindle microtubuli. Microtubule attachment is regulated by the mitotic checkpoint. Faithful chromosome segregation is essential for genome integrity; malfunction of this structure leads to aneuploidy. The group studied the proteins involved in kinetochore and checkpoint function by investigating their assembly and complex binding behavior in time and space in living human cells, increasingly also in vitro and by pull-down analyses.

Diekmann also studied cellular senescence. He carried out deep transcriptome analyses of cellular senescence within the BMBF-funded JenAge research consortium. In primary human fibroblasts, he studied the effects of mild stress. Based on these studies, he established a quantitative model for the cellular transition from proliferation to senescence.

Current Projects

- **The centromere/kinetochore complex** | Analysis of the properties of the human inner kinetochore complex
- **Mechanisms of cellular senescence** | Development of a systems-biology cellular senescence model establishing a new mathematical model which quantitatively describes the aging process of human fibroblast during replicative senescence (JenAge)

The kinetochore imaging studies in living human cells of the Diekmann group resulted (i) in the binding dynamics of all kinetochore proteins over the entire cell cycle and (ii) in the first overall architecture of the complex.
Numbers 2014 – 2015

Project grants (absolute in k€):

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Number of joint research projects:

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Selected Publications

2015


2014


Funding

Carl Zeiss Stiftung

Selected Cooperation Partners

- National Institutes of Health (NIH), Washington, USA
- National University of Ireland Galway, Ireland
- Ludwig-Maximilians-Universität München (LMU), Munich, Germany
- Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute (HKI), Jena, Germany
- Leibniz Institute of Photonic Technology (IPHT), Jena, Germany
Focus of Research

Accumulation of molecular damage and decreasing repair capacity constitutes a typical phenotype of aging cells and tissues. The group focuses on structural integrity of and specific recognition mechanisms between biomolecules. Deficiency in proteins involved in DNA replication or repair causes genomic damage and may lead to premature aging syndromes. Moreover, protein damage accumulation via stochastic chemical modifications (e.g. by reactive oxygen species) and/or proteolytic (mis-)processing may promote ill-folding and/or aggregation of proteins. This in turn may trigger pleiotropic responses such as a compromised general capacity of protein turn-over and/or compromised signaling pathways. As a consequence, cellular malfunction and eventually tissue degeneration are observed. The aim is to mechanistically understand the consequences of molecular damage and the related mechanisms of genome maintenance and repair as well as of protein aggregation. To this end, the three-dimensional structure and function of DNA replication and repair proteins of heme-binding proteins and of Alzheimer’s associated amyloid aggregates are addressed.

Current Projects

Biomolecules under analysis in recent years:
- Proteins active in the maintenance and the repair of genomic information
- Heme-binding motifs and proteins
- Oligomeric amyloid β peptides as agents in Alzheimer’s pathogenesis

In this context the group also develops techniques for NMR spectroscopy, which is a powerful tool for the structural characterization of biomolecules and their interaction in solution and in the solid state.

First complete experimental data based model of the archaeal minichromosome maintenance complex as derived from the group’s experimental results and published structural data. It shows the hexameric MCM complex. One subunit is highlighted in orange. The blue and yellow colored parts indicate the C-terminal, truncated winged helix domains of MCM. This domain controls the activity of the ATPase center of MCM.

CENTRAL RESEARCH QUESTION:
What are the consequences of molecular damage and what do the related mechanisms of genome maintenance and repair look like?
Selected Publications

2015

Kumar ST, Leppert J, Bellstedt P, Wiedemann C, Fändrich M, Görlach M.
Solvent Removal Induces a Reversible β-to-α Switch in Oligomeric Aβ Peptide.


Wiedemann C, Szambowska A, Häfner S, Ohlenschläger O, Guhrs KH, Görlach M.

2014


Team (as of 31.12.2015)

Senior Scientist: Ramadurai Ramachandran
Staff Scientist: Oliver Ohlenschläger
Doctoral Students: Nishit Bharat Goradia, Amit Kumar
Research Engineer: Georg Peter
Technical Assistants: Sabine Häfner, Angelika Heller

Funding

Deutsche Forschungsgemeinschaft

Selection Cooperation Partners

- Friedrich Schiller University Jena, Jena, Germany
- University of Bonn, Bonn, Germany
- Ulm University, Ulm, Germany
- Bauhaus University Weimar, Weimar, Germany
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 group 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 these 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
• Microtubules and kinesin

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 2014 – 2015

- Project grants (absolute in k€):
  - 2014: 51 €
  - 2015: 5 €

- Academic degrees:
  - 2014: 0
  - 2015: 1

- Number of joint research projects:
  - 2014: 34
  - 2015: 34

Selected Publications 2015


Team (as of 31.12.2015)

- Staff Scientists: Konrad Böhm, Helmut Pospiech, Bernhard Schlott
- Postdoc: Anna Szambowska
- Doctoral Students: Yasser Said Helmy Aly (external, DAAD), Heidi Keller, Julia Kutz (external)
- Technical Assistants: Annette Gleiche, Anita Willitzer, Marina Wallmann
- Master Students: Isabell Küffner, Vera Tröster

Funding

Selected Cooperation Partners

- Friedrich Schiller University Jena (FSU), Germany
- University Hospital Hamburg-Eppendorf (UKE), Hamburg, Germany
- University of Oulu, Finland
- Ulm University, Germany
Focus of Research

Christoph Kaether’s research group on “Membrane Trafficking” lays its focus on the trafficking and localization of proteins within cells, mainly of membrane proteins. 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 | When the ectodomain of the membrane protein “Klotho” is enzymatically cleaved, Klotho circulates as an “anti-aging” hormone in blood circulation. In mice lacking Klotho, an accelerated aging can be observed. Already at a young age, they show age-related symptoms such as osteoporosis, atherosclerosis, deposition of calcium e.g. in the arterial wall, or loss of fatty tissue – all of which usually occur only in very old animals. 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. In mouse models, the group tries to establish how Klotho prevents aging and which role it plays in the brain, by genetically inactivating Klotho in different tissues and analyzing changes in behavior, lifespan and physique of the mice.

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 recently identified a mammalian retrieval receptor, Rer1, that transports escaped proteins back from the cis-Golgi to the ER. What’s special about Rer1 is that it recognizes sorting signals in transmembrane domains and is responsible only for specific membrane protein complexes, of which not all are known as yet. The group wants to study the molecular details of transmembrane domain mediated sorting and the role of Rer1 therein.

Notch in Neurons | The Notch receptor is essential for development, but also involved in learning and memory. However, it’s also known that its hyper activation leads to carcinogenesis. The Kaether lab studies where and how in neurons Notch is processed and how the signal transduction is mediated. Moreover, the group has found Notch-inhibitors, which it is trying to deeply understand, in order to improve their effect. The lab has also conducted a high-throughput screening of chemical compounds and the human genome to find compounds and further proteins involved in the Notch signal transduction. One of the identified compounds in which the group is currently interested is FLI-06. FLI-06 inhibits the protein export from ER, targeting an unknown mechanism which the team wants to identify.
Numbers 2014 – 2015

Selected Publications

2015


2014


Team (as of 31.12.2015)

Postdocs: Hellen Elisa Ahrens, Shivashankar Marthandan, Sigrun Nagel, Malle Soom, Christina Valkova, Yoji Yonemura
Doctoral Students: Bastian Kindermann, Mandy Rothe, Denica Doycheva (external)
Technical Assistant: Jana Hamann
Master Students: Paul Aigbire, Talitha Feuerhake, Anne Heiner

Funding
Focus of Research

The highly resolved three-dimensional structure of proteins is the key to understanding their biological function and their biomolecular interactions at the atomic level. It provides the structural details crucial for the rational development of interacting molecules as drug candidates. That is why Manuel E. Than’s research group concentrates on investigating the structure function relationship of proteins central to neurodegenerative diseases, aging and proteolytic proprotein processing. Using X-ray crystallographic, biochemical and biophysical methods, the group has investigated soluble and transmembrane proteins as well as protein complexes involved in the development of Alzheimer’s Disease and the proteolytic proprotein activation during secretion. The work also focusses on other neurodegenerative diseases and aging related processes.

Current Projects

Alzheimer’s Disease and the Large Type I Transmembrane Protein β-Amyloid Precursor Protein (APP) | Alzheimer’s Disease is characterized by senile plaques in the patient’s brain. These plaques contain as the main component the neurotoxic amyloid β-peptide (Aβ), which is derived from the large type I transmembrane protein β-amyloid precursor protein (APP). Little is known about the detailed atomic structures of many molecules involved in the building of Aβ, or their interactions and physiologic functions – therein setting the starting point for many research projects in the Than lab.

PC-Inhibitors | Many secreted proteins and peptides are excised from larger precursors by a specific class of serine proteases, the Proprotein/Prohormone Convertases (PCs). This cleavage is essential for the activation of the respective substrates, ranging from peptide hormones (such as insulin), extracellular proteases, growth and differentiation factors (implicated in neurodegenerative diseases, tumor growth and metastasis) to bacterial toxins and viral coat proteins, making the PCs a very interesting pharmacological target. One PC is Furin, whose crystal structure has been newly described by the Than group. The group also developed a novel expression and crystallization system to study the interaction between human furin and pharmaceutically very important non-covalent inhibitors – an important step towards pharmaceutical application.

Methodological Developments | The focus on protein target oriented research often results in the necessity to establish, extend or adapt new protein-crystallographic methods. Methods from the Than lab include, for example, the development of an element-specific electron density map, a novel approach for the experimental phase determination in protein crystallography, and the transformation of protein crystals by tightly controlled humidity changes.
PROGRAM AREA II: ACCUMULATION OF MOLECULAR DAMAGES AND (EPI)GENETICS OF AGING

Numbers 2014 – 2015

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Selected Publications

2015


2014


Team (as of 31.12.2015)

- Postdoc: Sven Dahms
- Technical Assistant: Sabine Gallert
- Bachelor Student: Oliver Waldmann

Selected Cooperation Partners

- Several Universities and Research institutions in Germany, Austria, Belgium, Denmark, the Netherlands, Poland, Canada, and the USA
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 work in Zhao-Qi Wang’s laboratory will provide insights into premature aging and age-related pathogenesis (such as cancer and neurodegeneration). The lab uses cellular and molecular tools as well as animal models to dissect how the dysfunction of DNA damage signaling and repair pathways causes pathological changes and aging in humans.

Current Projects

The Cellular Response on DNA Damage | Two key enzymes – protein kinases ATM and ATR – regulate the cellular response in the case of DNA damage. ATM is primarily activated through DNA double-strand break (DSB), ATR through DNA single-strand break 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 keep 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 single-strand breaks and replication stress. Poly(ADP-Ribose) 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 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 | For brain development, neural stem cells have to be strictly controlled. The modeling of chromatin (the material which chromosomes consist of) through epigenetic mechanisms is crucial for stem cell differentiation and the development of neurons (neurogenesis). For histone acetylation, the DNA strand is “unfastened” for transcription factors to bind and decipher genes. The research objective of the Wang laboratory is to understand the epigenetic modeling of histone status, thus laying the fundamentals for the development of new therapies to improve cognitive capabilities in the elderly.
Selected Publications

2015


2014


Team (as of 31.12.2015)

**Postdocs:** Paulius Grigatavicius, Xiaojian Liu, Nadine Schneble, Alicia Tapias Soler, Zhongwei Zhou

**Doctoral Students:** Reham Mohamed Mahmoud Atteya, Sören Hüttner, David Lazaro Pellon, Gabriela Pereira Carvalho Guerra, Harald Schuhwerk, Konstantin Siniuk

**Scientist:** Christian Marx

**Research Engineer:** Tina Rüdiger

**Technical Assistants:** Tjard Jörß, Chris Meesezahl
Focus of Research

Maria Ermolaeva’s research group centers its research focus on counteracting cell death caused by physiological stress as a major cause of tissue dysfunction and organ failure during diseases and aging. Emerging as a dangerous byproduct of normal metabolism or as a consequence of external inputs such as sunlight, high fat diet or environmental pollution, physiological stress becomes virtually inevitable. With age, the stringency of metabolic regulation, immune regulation and organelle function progressively declines leading to age-related accumulation of stress-producing entities. Also stress-induced damage accumulates due to decline in repair capacities leading to eventual malfunction of organs. Finding means of battling stress is therefore a major challenge having key scientific and clinical relevance especially in connection with aging. Research in the Ermolaeva lab is focused on the discovery of novel genetic factors and chemical (or natural) compounds with the capacity to improve cell survival and organ homeostasis under different stress conditions. As a long term goal the group aims to convert its findings into therapies used to enhance tissue integrity and performance during normal aging and age-related degenerative diseases.

Current Projects

Recently, the group discovered that transient activation of innate immune response by DNA damage or probiotic feeding leads to elevated systemic stress resistance in the nematode C. elegans. Stress resistance is achieved through increased activity of the ubiquitin proteasome system (UPS) which maintains cellular proteomes in a “healthier” state prior to stress exposure. These exciting findings indicate that simple cost effective interventions could be used to promote cell maintenance and survival during stress. Looking ahead, the Ermolaeva lab aims at a deeper understanding of the molecular mechanisms linking protective stimuli to organ maintenance; thereby identifying potential molecular targets for stress-protective therapeutic modulation. Another aim is to search for novel compounds and genetic pathways linked to improved tissue homeostasis under stress in two model systems: C. elegans and mammalian primary cells. The group will address the interplay between immunity and protein quality control in nematodes and cell culture. Results will be validated in mouse models of tissue degeneration, potentially leading to first steps in creating stress-protective human therapies.

Current Projects are:

• Studying effects of radiation hormesis in murine models of organ degeneration
• High throughput screens for mediators of stress tolerance in human cells
• Genome wide stress tolerance screens in C. elegans
• Studying effects of diet, exercise and inflammation on metazoan longevity and homeostasis (using C. elegans as a model organism)
Numbers 2014 – 2015

Selected Publications

2015

- Ermolaeva MA, Dakhovnik A, Schumacher B. Quality control mechanisms in cellular and systemic DNA damage responses. *Aging Res Rev* 2015, 23(Pt A), 3-11 (*co-corresponding authors).*


2014

- Ermolaeva MA, Schumacher B. Quality control mechanisms in cellular and systemic DNA damage responses. *Aging Res Rev* 2014, 23(Pt A), 3-11 (*co-corresponding authors).*

Team (as of 31.12.2015)

Postdoc: Lilia Pinela Soares Espada
Doctoral Students: Oleksandr Dakhovnik
Technical Assistant: Yvonne Schaub
Guest: Tetiana Polezhaeva

Funding

**Selected Cooperation Partners**

- Jena University Hospital (UKJ), Jena, Germany
- Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute (HKI), Jena, Germany
Focus of Research

The "Genome Analysis" research group led by Matthias Platzer is focused on genetic and epi-genetic 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. Aided by clinical partners, 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 2012)
- Impact of DNA methylation on the aging of the brain (EU/BrainAGE)
- Effect of genetic variations on sepsis susceptibility and outcome (CSCC)
- Development of bioinformatics approaches for assembly and repeat annotation of complex genomes


Cooperation Partners

- Leibniz Institute for Zoo and Wildlife Research (IZW), Berlin, Germany
- University Duisburg-Essen, Germany
- Center for Sepsis Control and Care (CSCC), Jena, Germany
- Jena University Hospital (UKJ), Jena, Germany
- TU Dresden - University Hospital I, Dresden, Germany
- Leibniz Institute of Plant Genetics and Crop Plant Research (IPK), Gatersleben, Germany
- National and Kapodistrian University of Athens, Athens, Greece
- Tilburg University, Tilburg, The Netherlands
Focus of Research
The RAS superfamily of small GTPases act as molecular switches in several signaling pathways, cycling between an active GTP-bound, and an inactive GDP-bound form. In its GTP-bound form, RAS interacts with and regulates a vast spectrum of functionally diverse downstream effectors, controlling many biological processes such as proliferation, differentiation, apoptosis, and migration.

Somatic mutations in the HRAS gene (codons 12, 13 and 61) lead to cancer, whereas germline mutations (most frequent at codon 12) lead to the Costello Syndrome (CS), a rare human disease leading to premature aging. Although the mutations affect the same residues as RAS oncogenic mutations, CS patients only occasionally develop cancer, albeit at a younger age when compared to the general population. Combining these observations, we hypothesize that HRAS hyperactivation in CS through unknown mechanisms leads to a premature aging program, as well as to a resistance to oncogenic transformation.

Current Projects
• Tumor prevention and tumor escape molecular mechanisms in CS
• Age-associated changes in the RAS signalosome in animal models
• Minor project: The role of HRAS alternative splicing product (p19HRAS) in preventing oncogenic transformation

Selected Publications
2015

2014


Numbers 2014 – 2015

![Academic degrees:](Image)  
2014: 1  
2015: 2  

![Number of joint research projects:](Image)  
2014: 2  
2015: 3
Focus of Research
The main interest of Alessandro Cellerino’s group is to use the annual fish *Notobranchius furzeri* to study the biology of aging. Research activity has been performed in the framework of the "Jena Center for Systems Biology of Ageing - JenAge".

Current Projects
- **MicroRNAs and Aging** | Investigation of the regulation of microRNAs during aging via next-generation sequencing and functional tests of gene activity
- **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
- **Effects of Mild Stress (Hormesis)** | Investigation in *N. furzeri* of how mild stress can contrast the effects of aging and promote longevity

Selected Publications

**2015**

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: What 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 Cooperating Marz Group 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.

Current Projects

- Understanding the regulation of aging
- The role of micro-RNAs in aging
- RNA:DNA triplexes involved in aging
- Non-coding RNA elements causing X-linked Dystonia-Parkinsonism

Selected Publications

2015


2014


N. furzeri – fish with an extremely short lifespan.
Interconnecting Subdivision

Bioinformatics and Systems Biology of Aging
Bioinformatics and Systems Biology of Aging

Subdivision 5: Systems Biology of Aging

76 Kestler Research Group
78 Ori Research Group
80 Sühnel Associated Group
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 of Hans A. Kestler’s group at the FLI 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.

Current Projects
Bioinformatics | The advent of high-throughput biomolecular technologies has made high-dimensional biological data available for the investigation of many clinical settings. The large numbers of features and low numbers of probes in such data sets pose many challenges for their analysis. Machine learning approaches and statistical methods are essential for the interpretation of the data. For example, clustering methods can detect groups of similar probes. Feature selection techniques are employed to identify features (e.g. marker genes) that are relevant to distinguish certain phenotypes. Classification algorithms can predict the phenotype of a probe according to the measurements.

Systems Biology | Interactions of genes and gene products, as well as cross-talk between individual pathways, make up complex networks that preclude an intuitive understanding. Along with the increase in knowledge on genetic interactions, mathematical modeling and simulation have become indispensable tools for the analysis of regulatory networks. Modeling approaches vary in the degree of abstraction, which influences the level of detail, but also comprehensibility and the amount of information required to specify the model parameters. The Kestler group’s research covers the highly abstract Boolean models, as well as comprehensive models based on differential equations or intermediate rule-based approaches.
Numbers 2014 – 2015

Number of joint research projects:

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Selected Publications

2015


Team (as of 31.12.2015)

Postdocs: Ludwig Maximilian Lausser, Alexander Groß, Stefan Taudien

Funding
Focus of Research

Alessandro Ori’s lab is interested in studying how age, mutations 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

**Functional Proteomics of Aging** | Mammalian cells are made up of >10,000 different protein species. The abundance of these proteins is tightly regulated in a cell-type specific manner so that specialized cells such as muscle cells and neurons can be made using the same genetic information. Measuring protein abundance is therefore crucial for understanding the molecular alterations that lead to the dysfunction of a specific organ or cell type. The group employs state-of-the-art mass spectrometry based proteomics to obtain proteome profiles of tissues and cell types across age groups and genetic backgrounds as well as to evaluate the consequences of environmental factors such as stress, calorie restriction and exercise.

**Protein Complexes with Variable Composition** | Proteins do not work alone; rather, they engage in physical interactions with other proteins to form protein complexes. Protein complexes are the molecular machines that carry out essential functions inside our cells such as production of energy, replication of genetic material and transport of molecules. The Ori group has previously shown that certain protein complexes, such as the nuclear pore complex, adapt their composition to fulfill cell-type specific needs. This is a clever way that cells use to switch the function of a protein complex by changing only a few, critical components. For the purpose of studying how age and age-associated mutations affect the structure and function of protein complexes, the Ori lab uses computational approaches that allow comparison of the composition of protein complexes across different proteome profiles. In addition, the group uses biochemical approaches to isolate protein complexes with a definite composition and study their interactions with other proteins.

**Novel Approaches for Proteomic Data Analysis and Integration** | Protein abundance can be regulated by different means including transcription, translation and degradation. In order to understand at which level of regulation the impact of aging manifests, it is necessary to integrate proteomic data with complementary information such as measurements of transcript abundance or translation rate. The Ori Group works in close collaboration with leading computational biologists to develop tools for the analysis of large proteomic datasets and their integration with genomic information.
Numbers 2014 – 2015

Number of joint research projects:

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Selected Publications 2015


Selected Publications without FLI Contribution 2015


Team (as of 31.12.2015)

- Doctoral Student: Nadja Gebert
- Technical Assistant: Ivonne Heinze

Cooperation Partners

- Biognosys AG, Zurich, Switzerland
- ETH Zurich: Institute of Molecular Systems Biology, Zurich, Switzerland
- European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
- Leibniz-Institut für Analytische Wissenschaften – ISAS – e.V., Berlin and Dortmund, Germany
- University Basel: Biozentrum - Proteomics Core Facility (PCF), Switzerland
- University Hospital Heidelberg, Germany
- University of Oxford: Department of Biochemistry, United Kingdom
- University of Oxford: Institute of Reproductive Sciences, United Kingdom
Focus of Research
The Sühnel group has conducted research in the field of bioinformatics and computational biology with an emphasis on structural biology and computational genomics. In the structural biology field, the researchers were interested in the identification and analysis of unusual motifs and interactions in three-dimensional structures of proteins and nucleic acids. Research involved different techniques including quantum-chemical calculations, molecular dynamics simulations and structural bioinformatics approaches. All analyses are closely linked to the “Jena Centre for Systems Biology of Ageing – JenAge”, which was funded by the BMBF from 2009 until 2014.

Current Projects
• Development of tools for an accelerated and improved annotation and analysis of prokaryotic genomes computational in the group’s genomics work
• Development of a new genome browser type
• Development and maintenance of a variety of widely used databases and webtools

Selected Publications
2015


2014
Project Review: JenAge
(BMBF-funded until September 30, 2014)

Aging and the development of age-related diseases are extremely complex phenomena. In recent years, a multidisciplinary approach known as systems biology has emerged that analyzes the interactions between the components of biological systems in a systemic way. At the end of 2009, following the successful acquisition of external BMBF-funding, the "Jena Centre for Systems Biology of Ageing (JenAge)" was established in Jena. The center’s objective was to identify evolutionarily old transcriptional and signaling networks activated by mild stress, and to investigate their role in preserving body function in old age.

Approach
A multi-species approach was adopted to investigate network modulations due to the influence of environment, pharmacological intervention and lifestyle – in humans (ex vivo and in vivo) as well as in nematodes (C. elegans), the Turquoise killifish (N. furzeri), zebrafish (D. rerio) and mice (M. musculus). The experimental data obtained were mathematically analyzed, modeled in an iterative process and validated in model organisms. For the effective use of the large amounts of data, a data management system was established. In addition, a new database of aging factors has been set up, which integrates data from various existing databases and also includes new information obtained within the JenAge project and extracted from the scientific literature.

Results
The interdisciplinary work in the JenAge center has so far resulted in 79 publications, including 28 under FLI-participation. The JenAge center also maintains three public information platforms:

• The research center’s website includes data and facts about the JenAge research project.
• The information centre provides general information on aging and systems biology for scientists working in these areas.
• The aging factor database AgeFactDB aims at data integration in aging research.

Although JenAge funding expired in the end of 2014, further JenAge-related work continues, for example on the experimental validation of hypotheses and also on new computational studies. The roughly 2,500 next generation sequencing data sets are available for further analysis, both in the JenAge data management system and, after use in JenAge publications, also in public databases.

In addition, biological samples not yet used in experiment have been stored in the JenAge biobank.
Organization
The FLI is 1 of the 88 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.

FLI is characterized by a flat hierarchy. 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, all with equal voting rights at Group Leader meetings. Decisions on the future direction of the Institute and about major investments are taken after discussion and in concordance with the Group Leader panel, which assembles once per month.

The Scientific Director appoints four Senior Group Leaders, along with a representative of the Junior Group Leaders and the Head of Core Facilities, to form the Institute Council, 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 as a service sector comprised of technical services, scientific services and scientific coordinators.
## Executive Bodies

### Board of Trustees

<table>
<thead>
<tr>
<th>Member</th>
<th>Institution</th>
<th>Address</th>
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<tbody>
<tr>
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### Scientific Advisory Board (SAB)

<table>
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<tbody>
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### Members Assembly

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<th>Member</th>
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<tbody>
<tr>
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<td>Prof. Dr. Gabriele Beibst Rector</td>
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<td>Robert Fetter, Ref. 54 Institutionelle Forschung</td>
</tr>
<tr>
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<td>Prof. Dr. Thorsten Heinzel Vice President for Research</td>
</tr>
<tr>
<td>City of Jena</td>
<td>Am Anger 15 07743 Jena, Germany</td>
<td>Dr. Albrecht Schrotter Mayor</td>
</tr>
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</table>
Over the last ten years, the FLI has experienced rapid development. The number of staff members has doubled; the Institute’s official language is now English; the proportion of staff members from abroad has grown to 25.7% (2015-12-31) and useable space has more than doubled from 4,500 to approx. 10,000 sqm through the addition of a new building in 2013. All of this represents continuing challenges for all employees at the FLI. Huge efforts will also have to be made to meet future requirements, as we continue to progress.

Equality & Family-Friendliness
On December 31, 2015, the FLI had 312 staff members financed by FLI, thereof 27.6% scientists and board, 18.6% in the science supporting sector, 24.7% students, 6.1% in the administrative sector, 10.0% working in the infrastructure sector, and 10.5% guests. The percentage of women was 54.8%.

In terms of personnel procurement and staffing procedures, FLI follows the principle of equality. The FLI supports its employees, through numerous activities, in integrating career and family. For example, employment agreements have been put in place; female scientists are supported through the Leibniz mentoring program; flexible working time is common; child-care is facilitated; and the Institute supports international scientists in their welcome to Jena as well as parents (to be) in preparing a parental leave or returning to work after the event. 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 equalization plan (2013-2017) and reviewed annually. In 2015, a new female Junior Group Leader was recruited, and a female former Junior Group Leader was tenured as Senior Group Leader.

In 2013, the FLI successfully applied for the Total E-Quality Award (TEQ). Furthermore, the Institute was awarded the regional “Jenaer Familiensiegel” in 2015. Both awards honor the wide range of equality and family-friendly activities implemented at the FLI, e.g. the memberships in “Jenaer Bündnis für Familie” and in several other task groups. To support parents at the FLI, the Institute holds cooperation agreements with two nearby kindergartens, offering places for 15 children of FLI-employees. Moreover, all employees have the opportunity to use FLI’s parent-child-workroom to cover gaps in childcare e.g. due to kindergarten closures. As a member of several regional and trans-regional dual career networks, the FLI supports new employees in bringing spouses and family to Jena and by helping the partner to find an adequate job offer in and around Jena.

Internationalization
The FLI is one of the most international research institutes within the Leibniz Association. The percentage of international co-workers stands at 45% among scientists and 22% among all co-workers at FLI. The Institute is strictly bilingual (English/German) and has one of the highest percentages of international Group Leaders (38%) across all institutes of the Leibniz Association. The FLI increased the ratio of employees from abroad from 16% in 2008 to 22% in 2015. The ratio amongst PhD students increased from 28% to 52% during the same period. The FLI employs a significant number of scientists from abroad at all levels, including professors. As of December 31st, 2015 employees and students from abroad represented 31 different nationalities.

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. The Institute’s increasing attractiveness abroad resulted in a strengthening of the internal relocation management in 2012; a student assistant was enlisted, which has developed into a half-time position for a relocation assistant integrated into the “Career development” staff section.
Origin of FLI's Employees from Abroad

Numbers 2014 – 2015

* Numbers based on FLI-financed employees.
# Third-Party Funded Projects

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<thead>
<tr>
<th>Programme</th>
<th>Description</th>
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<tr>
<td><strong>erc</strong></td>
<td>ERC Advanced Grant for the Characterization of Geronto-genes (StemCellGerontoGenes, 2013–2018, Prof. K. Lenhard Rudolph)</td>
</tr>
<tr>
<td><strong>Emmy Noether Program</strong></td>
<td>Emmy Noether Program of DFG for the Analysis of Muscle Regeneration (2013-2018, Dr. Julia von Maltzahn)</td>
</tr>
<tr>
<td><strong>RegenerAging/ Freistaat Thüringen</strong></td>
<td>The first project “Aging induced impairments in organ regeneration and homeostasis” (RegenerAging) of the interdisciplinary Aging Research Center (ARC) Jena is co-financed by the “ProExzellenz” Initiative of Thuringia (2015–2019, headed by Prof. K. Lenhard Rudolph).</td>
</tr>
<tr>
<td><strong>hhdp/DFG</strong></td>
<td>The FLI participates in the DFG-funded research network “Heme and heme degradation products” (hhdp) investigating the generation of HHDPs and their alternative functions and signaling mechanisms (2015–2018, Dr. Oliver Ohlenschläger)</td>
</tr>
<tr>
<td><strong>RTG 1715/DFG</strong></td>
<td>The FLI participates in the Research Training Group “Molecular Signatures of Adaptive Stress Responses” (RTG 1715), funded by DFG.</td>
</tr>
<tr>
<td><strong>eMed/BMBF</strong></td>
<td>The FLI is a research member of the BMBF-funded project “Model-based optimisation and individualisation of treatment strategies in haematology” within the interdisciplinary research consortium “eMed Systems Medicine” (HaematoOpt, 2015-2018, Dr. Matthias Platzer; together with Prof. K. Lenhard Rudolph and Prof. Andreas Hochhaus, UKJ).</td>
</tr>
<tr>
<td><strong>Leibniz ScienceCampus</strong></td>
<td>To enhance the expertise of aging research in Jena, the FLI receives funding from the Leibniz Association to set up a Leibniz ScienceCampus “Regenerative Aging”.</td>
</tr>
<tr>
<td><strong>JenAge/BMBF</strong></td>
<td>The BMBF-supported “Jena Centre for Systems Biology of Ageing (JenAge)” analyzes the effect of mild stress on lifespan in a multi-species approach.</td>
</tr>
<tr>
<td><strong>BrainAge/7th Framework Programme</strong></td>
<td>The FLI participates in the “BrainAge” project, where the effect of maternal stress during pregnancy on brain aging is analyzed. This international project is supported through the 7th Framework Programme of the EU.</td>
</tr>
<tr>
<td><strong>CodeAge/ 7th Framework Programme/ Marie Curie</strong></td>
<td>The FLI participates in two International Training Networks: “MARRIAGE” and “CodeAge”. Both projects are supported through the 7th Framework Programme Marie Curie of the EU.</td>
</tr>
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Outlook

After years of fundamental restructuring, FLI’s research focus has become deeper, more targeted, and unique at both, national and international level.

During 2016 and 2017, we will further strengthen our research focus by building a research pipeline on stem cell aging and organ maintenance spanning from flies to humans. In addition, the newly developed short-lived killifish model will help us to bridge the gap between basic discoveries in lower models (e.g. worm or fly) towards the identification of therapeutic targets that may help to prevent disease development in human aging.

The Institute plans to expand into the field of epigenetics and to incorporate a new Research Program on microbiota and aging. 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. This is controlled by bacterial metabolite signaling and epigenetic responses to it in target tissues. The FLI intends to incorporate a new Research Program aiming to understand “Microbiome Aging and its Consequences for Organismal Aging”. We also see the opportunity to interconnect with other research activities in this new field both in Jena and at national and international level. To integrate the different effectors that influence the aging process, the FLI has begun to build up a new Subdivision on “Systems Biology of Aging”. This will include the development of a state-of-the-art proteome analysis Core Facility and research group. We envision the recruitment of a senior scientist in “Computational Biology” integrating new approaches such as deep learning and artificial intelligence in order to predict network interactions at multiple scales and the implications for the biology of aging.

With regard to the Institute’s infrastructure, reconstruction works are planned for the FLI’s older buildings, some of which were built back in the 1950’s. By installing state-of-the-art technologies and working conditions, the enhanced research environment will foster further recruitments and boost the scientific excellence of the Institute.

The FLI is on a mission to delineate major factors underlying stem cell aging and impairments in organ maintenance during aging. Our program is unique and at the cutting edge in the international arena of research on aging, and aims to enable the future development of therapies to increase health in the elderly. As such, we are proud of our achievements thus far and we are looking forward to the upcoming evaluation of our Institute in October 2016 – hoping to fully convince our reviewers and our funding bodies to continue the support of our work.
25% of planarian mesenchymal cells are adult stem cells – in humans less than 1%.