Welcome to a voyage of discovery into the world of age research in Jena.
Welcome remarks from Prof. Wanka

Our society is undergoing a significant transformation. The demographic changes pose great challenges in all areas of our relationships with one another. In order to successfully rise to the challenge, we need science and research to propose solutions. We are looking to health science for answers as well. New research approaches in the life sciences, such as systems biology and personalized medicine, can improve prevention, diagnosis and therapy for age-related diseases.

The German federal government has laid the foundation for efficient and sustainable support of research on aging by declaring “Health and Nutrition” a high-priority area in its High-Tech Strategy 2020 program, together with passing legislation for the “Program Framework for Health Research” in 2011 and the “Research Agenda for Demographic Transition—Aging with a Future.”

During the last ten years, a prominent institution in Germany has dedicated itself to research on aging and successfully established itself as a leader in the field by concentrating on the topics of “Mechanisms of Aging and Senescence” and “Age-associated Diseases”: the Fritz Lipmann Institute (FLI). By integrating various research disciplines and developing an outstanding international network, as well as providing targeted support for junior scientists, FLI has distinguished itself in a variety of ways.

The German Federal Ministry of Education and Research (BMBF) is pleased to support the FLI and its important work through institutional and third-party funding. Citing an excellent example, I would like to refer here to the energetic activities that are part of GerontoSys—Systems Biology for Healthy Aging program [GerontoSy—Systembiologie für Gesundheit im Alter], which is supported by the BMBF. Together with the research campuses in Ulm and Cologne, which are also supported as part of GerontoSys, the “JenAge” research core at the FLI no doubt represents one of the most important campuses for age-related research in Germany.

The new FLI research building fosters successful scientific work by creating a state-of-the-art research environment. It is my hope that the momentum it creates will provide new impulses for age-related research in Jena and beyond.

“By integrating various research disciplines and developing an outstanding international network, as well as providing targeted support for junior scientists, FLI has distinguished itself in a variety of ways.”

Professor Johanna Wanka, German Federal Minister of Education and Research
Welcome remarks from Christoph Matschie

at the dedication of the new research building, August 28, 2013

Europe in 2040. What will our lives be like? Numerous studies address this question and even though future prognoses are generally associated with considerable uncertainty, the challenges of our time can nevertheless be clearly outlined. Global megatrends for which we will have to find solutions include climate change, scarcity of natural resources and an aging society.

One hundred years ago, the average life expectancy in Europe was forty-seven years. By the middle of the 21st century, it will climb to significantly over eighty years of age. The downside of this happy prospect is that an increasing segment of the population will be suffering from age-related diseases. And yet, our knowledge about medical approaches for the prevention or treatment of many aging-associated diseases is very limited.

Researchers at the Leibniz Institute for Age Research—Fritz Lipmann Institute (FLI) are some of the pioneers in this field. The molecular mechanisms and genetic factors contributing to the development of cellular and organism dysfunction in the course of human aging are being researched here in Jena. The State of Thuringia turned its attention to this important field of the future early on and brought together partners, whose strengths complement each other. Today, the Fritz Lipmann Institute, the Friedrich Schiller University Jena and the University Hospital Jena are joint, international leaders in the field of aging research. The Aging Research Center Jena, recently founded by the university, will extend this lead.

The research building we dedicate today is an important pillar of support for the outstanding research on aging conducted at the Fritz Lipmann Institute. The state and the federal government supported the new building’s construction, its connection to the existing infrastructure and provision with equipment with almost 38 million EUR in funding. The building offers the best environment for interdisciplinary science. It is simultaneously an essential prerequisite for advancing strategic development and a prerequisite for attracting outstanding scientists and junior scientists as well as providing support for additional third-party projects. The new facility enables the FLI to build on recent scientific advances. As an example, the Scientific Director of the Institute, Professor Rudolph, was recognized for his highly innovative approaches to researching the aging process in adult stem cells with a European Research Council (ERC) Advanced Grant of 2.5 million EUR at the end of 2012.

I am pleased that the Fritz Lipmann Institute has undergone such a successful development in the past years. Important answers to crucial questions for the future are being discovered here in Jena through the support of the federal and state governments.

Christoph Matschie,
Minister of Education, Science, and Culture of the State of Thuringia
“It is not a matter of adding years to life, but rather one of adding life to years.”

Alexis Carrel (1873–1944) was a French surgeon, anatomist, and biologist. He received the Nobel Prize for Physiology or Medicine in 1912.
The demographic transformation in Germany is without question one of the major social challenges of the present. The Leibniz Institute for Age Research—Fritz Lipmann Institute (FLI) in Jena, Germany, dedicates itself to aging as a specific aspect of this process: it is a fact that we are all living longer. While that is a happy prospect in principle, we also know that at an advanced age certain diseases occur with high frequency. We therefore need to conduct health research that concentrates especially on the molecular mechanisms and genetic factors that give rise to age-related diseases.

"The Leibniz Association is happy that such a well positioned and successful institute is included in its ranks."

FLI recognized this early on and was the first national institute in Germany to focus its activity on researching the biomedical causes of aging under the aegis of Professor Peter Herrlich. Through his applications-oriented basic research—under the motto theoria cum praxi—FLI continues to enjoy high international visibility as well.

I am pleased that the Leibniz Institute for Age Research has been able to attract professor Karl Lenhard Rudolph as the new Scientific Director this past year. Lenhard Rudolph is an outstanding scientist—he is the recipient of the 2009 Leibniz Prize, an ERC Advanced Grant from the EU, as well as the 2012 Science Prize from the Stifterverband, the innovation agency of Germany’s business community in support of science. In addition, he is active within the Leibniz Association as spokesperson of the Leibniz Research Alliance on Healthy Ageing.

This research network dedicates itself to the interrelationship of biological and social factors in aging in order to develop new strategies for intervention and adaptation. The participants include institutes conducting medical research in its narrowest sense but also sociologists conducting research on work, economic research institutes and regional planners. I am hopeful that new answers to the challenges of demographic change and the question of how we can remain healthy as we age will result from a symbiosis of concentrated expertise.

Likewise, I am pleased that the Fritz Lipmann Institute has taken the initiative in setting up the international science campus “Leibniz Link on Healthy Aging” in conjunction with leading institutes in China. FLI is thereby also supporting the internationalization strategy of the Leibniz Association helping to make the “Leibniz” trademark more recognizable world-wide.

The Leibniz Association is pleased to include such a well positioned and successful institute in its ranks. I wish FLI all the best for its activities and would like to sincerely thank all of the staff members for their dedication and energy.
Dear readers,

We focus on biomedical research on aging to decode the molecular mechanisms that promote age-related biological malfunctions and diseases thus creating the basis for new therapies designed to improve health at advanced age. To this end, scientists at the Leibniz Institute for Age Research—Fritz Lipmann Institute (FLI) in Jena are concentrating on two core areas:

I. Regeneration and stem cell aging—Organ maintenance [homeostasis] and regenerative capacity decrease during aging. This leads to impairments in organ function and to an increased risk of disease development. This phenomenon is compensated by regeneration—a process that facilitates the preservation of tissue function in multi-cellular organisms. Adult stem cells are essential for the maintenance and regeneration of organs and tissue. However, this regenerative capability declines with age. We investigate the causes for this decline with the goal to uncover new approaches to therapies that aim to preserve the functioning of the body’s own stem cells and organs during aging.

II. Accumulation of molecular damages and (epi)genetics of aging—A central phenomenon that accompanies aging is the accumulation of damages. This is at the same time cause and consequence of the decreasing capacity of organisms to repair biological molecules and/or to renew faulty tissues and organs. The molecular factors that contribute to the age-dependent increase in damage accumulation are still largely unknown. Therefore, the FLI focuses on the origin of the increasing damage and tries to elucidate how it contributes to diseases such as cancer. We are conducting comparative analyses and are making selected changes to genomes and transcriptomes in short- and long-lived model organisms to learn more about the genetic factors influencing the aging process. At the same time, we are looking for genetic and epigenetic variations that are specific for individual predispositions toward healthy aging or the development of age-related diseases in people as well.
New research groups are being recruited for both core areas. Group leaders work in teams to develop novel concepts and perform cutting-edge research in each of the core areas. Transparent performance criteria for budgetary allocations enable the research structure to flexibly and efficiently adapt to changing demands and thus increase its effectiveness. The internationalization of the institute and the incorporation of women into management positions will sustainably increase the capabilities of the FLI.

The FLI has played an integral part in the establishment of the Aging Research Center Jena at the Friedrich Schiller University and University Hospital, which includes researchers from different faculties. The planned founding of a Center for the Medical Study of Aging at the University Hospital would help to speed up the translation of research findings into practical applications so that patients can benefit as quickly as possible.

Demographic change is one of the great challenges of our time but it offers great opportunities as well. If we succeed in extending the healthy lifespan, the strains on society can be minimized and our society’s future development will be enriched by the wealth of knowledge and experience older people possess.

With this brochure we want to introduce you to the core areas of our research. We wish you an exciting and entertaining voyage of discovery into the world of age research at FLI.

Sincerely,

Professor K. Lenhard Rudolph,
Scientific Director of the Leibniz Institute for Age Research — Fritz Lipmann Institute (FLI)

“Demographic change is one of the great challenges of our time but it offers great opportunities as well. If we succeed in extending the healthy lifespan, the strains on society can be minimized and our society’s future development will be enriched by the wealth of knowledge and experience older people possess.”

K. L. Rudolph has been Scientific Director of the Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI) since the beginning of 2012 and also a professor at FSU in Jena since October 2012. His group investigates the molecular and genetic causes of stem cell aging. Prior to this, he was Chairman of the Department of Molecular Medicine and of the Max Planck research group at the University of Ulm. Before, he held a Heisenberg professorial chair at the Hannover University Medical School and headed an Emmy Noether Research Group.
The research program of the Leibniz Institute for Age Research – Fritz Lipmann Institute (FLI) focuses on two main areas. The work on regeneration and stem cell aging (Core Area I) is particularly important as the aging process reduces the ability of cells to regenerate and, at the same time, increases the risk of cancer. The accumulation of uncorrected DNA damage and the genetics of aging are at the center of Core Area II.

Systems-oriented biological analyses and bioinformatics are used to compare findings obtained in model organisms to data from people suffering from age-related dysfunctions and disorders to generate hypotheses about the underlying causes of aging in humans. These hypotheses will be tested experimentally and refined by experts in mathematical modeling as part of an iterative process.

The goal is to decode the causative mechanisms of human aging. Molecular therapies to improve health during old age (our healthspan) will be developed based upon this knowledge.
Preface: Daniele Barthel, Administrative Director of the Leibniz Institute for Age Research

Administrating science at FLI – a catalyst for research

Administration at the FLI is an integral part of the institute’s affairs and research activities. The administration creates and maintains a professional working environment and thereby not only fosters an atmosphere that makes it possible for scientists to conduct world-class research, but also achieves a reputation that attracts national and international scientists. The administration at the FLI keeps bureaucratic processes from interfering with researchers’ day-to-day activities and provides a general set-up to support science. In contrast to rule-bound administrations, the administration at the FLI flexibly adapts its operations to the non-hierarchical nature of scientific work and the way scientists think removing any barriers between administration and science.

Elements that are important to the internal operations of the FLI include transparency of administrative processes; simplicity of administrative requests; emphasis on providing advice to junior scientists as well as care and attention in dealing with questions of compensation, occupational safety and the buildings’ organization. The administration’s legal expertise helps negotiate contracts for collaborative efforts with partner organizations, as an example. All of this requires enthusiastic and innovative administrative staff on one hand and an efficient and comprehensive IT system on the other. IT does not function in isolation from research, but instead serves the specialized requirements of both the administrative and scientific areas.

Excellence in research is based on the expertise of the researchers. FLI offers a range of advantages to enhance its attractiveness and achieve the goal of drawing outstanding researchers from the national and international arena. These include specific support to promote the careers of staff members; advisors for junior scientific and technical staff members; assistance with external funding applications and bookkeeping; a family-friendly environment through kindergarten placement and a parent/child work room; language courses and various opportunities for advanced training. Assistance for new staff members from foreign countries is especially important to us.

Over the last ten years, the FLI has undergone a rapid development. The number of staff members doubled; the Institute’s official language is now English; the proportion of foreign staff members has grown to 25% at present and useable space has increased from 4,500 sq m to 9,000 sq m through the addition of a new building. All of this represents continuing challenges for the FLI administration. It also means that huge efforts are made to meet the new requirements going forward. This includes an integrated administrative network that establishes a direct, transparent connection between the administration and research groups to facilitate the seamless exchange of information and reports. The continuous developments in research must be reflected in the administration.

The scientific mission has set course for 2023. This mission can only be successful if the FLI administration reaches its goals long before that.

Dr. Daniele Barthel
Administrative Director of the FLI
The first national center for research on aging in Germany

by Kerstin Wagner

Fritz Lipmann – a pioneer of research on aging

The Leibniz Institute for Age Research’s name commemorates Fritz Lipmann, an outstanding German-American biochemist who contributed substantially to our understanding of the foundations of aging.

Fritz Lipmann was born into a Jewish family in Königsberg, East Prussia (now Kaliningrad). He initially studied medicine and later chemistry and pharmacology in Königsberg, Munich, and Berlin. He conducted research in Copenhagen after 1930, then in Boston and New York beginning in 1949.

A considerable part of Lipmann’s work involved the metabolism of energy compounds in cells. He recognized that the ATP molecule (adenosine triphosphate) functions as the main transporter and source of energy in the cell and that coenzyme A was an important intermediary in fat metabolism. Fritz Lipmann was awarded the Nobel Prize for Physiology or Medicine together with the German biochemist Hans Krebs in 1953 for his work on energy metabolism and the discovery of coenzyme A.

His insight into the relationship between metabolism, life expectancy and the reduction in energy production by mitochondria in aging organs laid the foundations for cell-based research on aging.

The origins of today’s FLI go back to the period of the German Democratic Republic (GDR). The “Central Institute for Microbiology and Experimental Therapy—ZIMET”, which existed on the campus at Beutenberg in Jena, Germany, at the time was a non-university research institute of the Academy of Sciences. It comprised about 1,000 staff members in the mid-1980s and was one of the largest biomedical research institutions of the GDR. Its research focused on antimicrobial compounds.

Two research institutes emerged from the Central Institute in 1991: the Hans Knöll Institute for Natural Product Research—HKI, and the Institute for Molecular Biotechnology—IMB, which was placed on the “Blue List”. Since the 1970s, the Blue List included research institutions that were supported jointly by the national and state governments due to their superregional significance.
The institutes on the Blue List constituted the Leibniz Association beginning in 1992. The focus of the IMB centered on basic and translational research in the area of molecular biotechnology with particular emphasis on diagnosis and therapy of human diseases. IMB’s contribution to the world-wide Human Genome Project—IMB had participated in the sequencing of chromosomes 8, 21 and X—made the institute well known domestically and internationally.

New research orientation – and a new name

Professor Peter Herrlich was appointed as the new scientific Director of the IMB in 2003. Together with the scientists at the institute, Herrlich developed a new research mission for the Institute, which centered on the mechanisms of aging and age-related disease. IMB was renamed as Leibniz Institute for Age Research—Fritz Lipmann Institute (FLI) and thereby became the first national research institute in Germany dedicated to broad biomedical research on aging.

330 scientists from 30 countries currently work at the FLI.
The Leibniz Association

The Leibniz Association connects 89 autonomous research institutions whose missions extend from natural and engineering science, through environmental science, economics, land use planning and the social sciences to the humanities. Leibniz Institutes operate in interdisciplinary thematic research alliances on socially important issues. The scientific program covers the whole spectrum from basic to applied research. Implementation of the socially relevant priority program is aided by the creation of scientific services and infrastructure. Due to the significance of the institutes for both levels of government, the federal and state governments each support the institutes of the Leibniz Association in equal proportion. The Leibniz Association occupies a leading position among non-university research institutions in terms of the sums of public funding it receives [see illustration]. Leibniz Institutes employ about 17,000 individuals, including 7,900 scientists. The total budget of the Institutes is 1.5 billion EUR. For more information please visit:

www.leibniz-gemeinschaft.de/en/home
How genes let us age

by Christoph Englert and Matthias Platzer

Yeast, worms and fruit flies are the classic models in research on aging. These model organisms have already revealed a great deal to scientists about how genes influence aging. More recently, fish with exceptionally short lifespans and extremely long-lived naked mole rats have been added to the squad of model organisms. The new recruits will help scientists at the FLI determine the role of genes in aging more precisely.

The giant tortoises of the Galápagos Islands live to be over 200 years old, while humans live to about 80. Compared to these, worms (average lifespan: 2–3 weeks) and fruit flies (average lifespan: barely 45 days) are remarkably short-lived creatures. Life-span varies greatly from species to species and is determined by genetic and environmental factors.

What we know today about the influence of genes on lifespan is largely based on investigations in invertebrate creatures, such as the yeast Saccharomyces cerevisiae, the worm Caenorhabditis elegans and the fruit fly Drosophila melanogaster. Our knowledge about the molecular causes of aging in higher vertebrates is significantly less. What we do know comes for the most part from studies with zebrafish (Danio rerio) and mice (Mus musculus). So far, two major variables that considerably lengthen lifespans of vertebrates have been identified: dietary restriction—i.e. hunger—and the suppression of a protein that acts as a receptor for growth hormone (growth hormone receptor, GHR).

We still know very little about the interaction of genes that regulate the lifespan of humans. Studies thus far indicate that variations in many genes are involved, with each contributing a relatively small effect. The gene APOE, which plays a role in the metabolism of cholesterol and inflammation processes, is important for attaining great age, for instance. Other “longevity genes” in humans include FOXO3, which can intercept harmful...
“Aging is accompanied by – and probably caused by – the loss of the ability to regenerate cells, tissues and organs. Researching how regenerative powers of the organism can be preserved is one of the greatest challenges for research on aging.”

Professor Christoph Englert, head of the Molecular Genetics Research Group

C. Englert has been Professor of Molecular Genetics at Friedrich Schiller University Jena since 2004 and heads a research group of the same name at FLI. His research addresses questions of aging and developmental genetics.

Learning from model organisms

A scientist in aging research who decides to work with vertebrates has a problem: For one, there are only very few model vertebrates with short lifespans. However, these animal models are important for carrying out life history studies within reasonable time frames at affordable costs. For another, the advantages of studies with extremely long-lived vertebrates are also being discussed. The reasoning is that these organisms, including humans, are able to deal very effectively with age-related damages. With their help, it may be possible to demonstrate how to extend the period of health, or “healthspan”, for a given lifespan.

- Oxygen radicals in cells, and EX01, which is important for the correct DNA replication. However, the latter is also involved in the repair of genetic damages and the preservation of the telomeres, protective caps at the end of chromosomes that shield them from deterioration.

Natural life cycle of Nothobranchius furzeri
Fish with short lifespans

The lifespan of *Nothobranchius furzeri*, a fish found in East Africa and also known as turquoise killifish, is extremely short. It is being used at FLI as a new model organism for research on aging. In its natural habitat, the fish lives three to eight months, depending on the availability of water. Even with the best laboratory care including an unlimited water and food supply, it doesn’t exceed the natural lifespan of its cousins in the wild. However, that means the cause of its extremely short lifespan must be encoded somewhere in its genetic make-up (genome).

We have recently taken a big step forward in the search for those areas of the genome that carry the information for life expectancy of the fish. We paired fish with short lifespans (three months) with those having long lifespans (eight months) in the laboratory, recorded the lifespans of their offspring and then analyzed the association of genetic markers with their phenotype. This allowed us to narrow the areas containing genetic determinants for life expectancy to regions on four chromosomes. The fish has thereby become the only vertebrate besides mice for which definite chromosomal areas could be identified that determine lifespan.

The areas identified in the genetic material of the fish are quite large, however: They contain hundreds of genes. Based on the crossbreeding experiments we undertook, though, we predict that about ten genes must play a causative role in the determination of the fish’ lifespan. To identify potential candidates, all genes in the regions are being systematically investigated. As an important prerequisite to locating the genetic determinants of the fish lifespan, we are currently sequencing the genome of *N. furzeri*. Just as important, we also recently succeeded in devising recombinant DNA techniques to produce transgenic *N. furzeri*; this is a method by which we can knock down or alternatively switch on individual genes. We can use this technique in the future to investigate how certain genes contribute to aging or determine lifespan. Since we humans—just like fish—are vertebrates, we expect that we will find human counterparts for most of the genes identified in *N. furzeri*. 
Long-lived African mole rats

In the semi-arid regions of East Africa lives a rodent about the size of a mouse called the naked mole rat. Its Latin name is *Heterocephalus glaber*. This species should assist us in discovering and learning about the molecular mechanisms responsible for an exceptionally long life of excellent health. The naked mole rat not only enjoys an extremely long life, but also a very long healthy lifespan. The animals live up to thirty years without suffering from age-related diseases such as cancer.

Naked mole rats—they belong to the zoological family *Bathyergidae*—have adapted perfectly to a subterranean life style. They construct large communal tunnel systems, in which they spend their whole lives. They have devised a division of labor under these conditions that is familiar to us from insect colonies such as honeybees, ants and termites. It is unique among mammals however. Only a single female procreates in each colony. Caring for the brood, finding food, as well as extending and defending the burrow are undertaken communally.

Astonishingly, the “queen mole rat”, the only female who reproduces, lives much longer that her contemporaries. That is remarkable because this observation contradicts a widespread theory of aging that assumes an organism can invest its energy either in reproduction and propagation or in the maintenance of its own bodily functions. How can the queen mole rat reconcile the extreme physical stress of the many sequential pregnancies with healthy and extreme longevity? Through the support of the Leibniz Association, working together with our colleagues from the Leibniz Institute for Zoo and Wildlife Research (IZW) Berlin, we would like to learn why.

“Aging is a complex process. It involves all the parts of an organism and can be influenced by the interaction of numerous genes and environmental factors.”

PD Dr. Matthias Platzer, head of the Genome Analysis Research Group

M. Platzer has been working in the Genome Analysis Research Group at the Institute since 1993 and has headed the group since 2000. His group participated successfully in the International Human Genome Project and numerous other genome projects.
African mole rats of the genus *Fukomys*, which also belong to the long-lived family *Bathyergidae*, live under conditions similar to naked mole rats. The African mole rats also live in extended family groups and, as a rule, only one pair reproduces and propagates. The other members of the family remain as helpers in the nursery colony and refrain from reproducing. Despite otherwise having the same living conditions, the reproducing animals live about twice as long as the helpers.

Such a dramatic difference in life expectancy within one species is without equal among vertebrates. Thus, the mole rats offer the opportunity to study slow aging compared to rapid aging within a single species. This project, carried out jointly with colleagues from the University of Duisburg-Essen, is being supported by the German Research Foundation (DFG). The investigations with Mechow’s mole rat (*Fukomys mechowii*) and Ansell’s mole rat (*Fukomys anselli*) complement our studies on the naked mole rat.
“We need to look beyond the boundaries of our own discipline. Molecular regulatory mechanisms are not restricted to a single organ, but instead are interconnected with one another in an extremely complex system. These non-linear interactions can only be analyzed by employing mathematical methods and massive computational power. We need doctoral students and postdocs for whom statistical physics, graph theory and linear algebra are as second-nature as DNA, transcription and splicing.”

Professor Rudi Balling, Director of the Luxembourg Centre for Systems Biomedicine, University of Luxembourg

Both projects will use state-of-the-art methods to measure the extent to which individual mole rat genes are being read in different tissues and organs and translated into proteins. That will help us attain new insights into the aging process including humans. In addition, it will allow us to critically examine current theories on the mechanisms of aging. It is our hope that these insights can one day contribute to a long life for humans with the best possible health.

Christoph Englert, Matthias Platzer and Alessandro Cellerino received the 2010 Max-Bürger-Award of the German Society of Gerontology and Geriatrics for the introduction and use of the short lived fish N. furzeri in aging research. It is an innovative model to unravel fundamental mechanisms of aging.
Our powerful cellular repair forces age too

by Frank Große, Zhao-Qi Wang, Matthias Görlach, and Stephan Diekmann

Living is aging. But why do we age? Is it just chance, an accident or predetermined by a genetic program? Scientists today assume that aging is not a process controlled by a genetic program running inexorably to the end. It looks more as though aging may be the result of many small instances of damage that accumulate in cells and molecules over the course of a lifetime. How quickly we age depends for example on how much damage occurs and how many defects can be corrected by the cellular repair service. It is especially important to correct damage to the hereditary DNA molecules. Paradoxically, even the powerful cellular repair forces age.

Scientists at the FLI would like to understand the molecular details of the age-dependent accumulation of DNA damage and discover how incomplete repairs lay the cornerstone for diseases of advanced age like Alzheimer’s and cancer.

Damage to the DNA molecule can be caused by external influences like excessive alcohol and nicotine consum or by ultraviolet rays from the sun. However, changes in our DNA can also occur when our genome is duplicated during cell division. Errors can happen at any time in the course of copying or “replicating” the DNA. To keep this hazard in check, only a few cells in the adult organism still capable of dividing—gametes and stem cells—are long-lived. Most of the body’s cells are in a resting state, referred to as quiescence, from which the cells are only awakened occasionally, such as when it becomes necessary to close a wound or replace peripheral blood. However, this capability deteriorates slowly over the course of time as well.

This is due, among other things, to changes in telomeres, protective caps that sit at the ends of chromosomes. They become shorter by about 50 to 100 DNA building blocks (nucleotides) each
Accumulation of molecular damages

time a cell divides. As a result, each cell in the body can only divide forty to seventy times before its telomeres are used up and the cell falls into a state known as replicative senescence. This does not happen with gametes and stem cells. They possess a special enzyme called telomerase. It makes sure that the telomeres at the end of the chromosomes are replenished after each cell division. Most cells in the body, however, lack the enzyme telomerase.

Part of our research work at FLI focuses on DNA replication at the molecular level in an attempt to understand in detail which factors control the precise and error-free duplication of the hereditary molecule.

Initiator of DNA duplication

We know today that replication can begin at about 300,000 specific locations on the forty-six human chromosomes. Only about ten percent of the starting points are actually used however; the rest is kept as a silent reserve.

Replication is initiated by growth signals that are excreted by cells to heal wounds for example. Receptors that sit like antennas at the surface of cells receive and transmit the signals to the cellular interior. There, the signals terminate the quiescent phase and induce the start of replication at specified starting points.

In order for the hereditary molecule to be able to replicate, a special molecular machine, the "replisome", is required to sit on specific sites, known by its technical name as the "replication fork". The replisome comprises about 50 different proteins. The most important of these are the helicases—proteins that can unwind the two strands of DNA twisted about one another like corkscrews. In addition, they separate the base pairs. The bases can be imagined as the two halves of a ladder that are joined together and thereby connect the outer ladder rails to each other. Separating the base pairs is necessary so exposed bases can pick up other matching bases and complete a new half of the separated DNA strand again, thus replicating the hereditary molecule.
Accumulation of molecular damages

The crucial initiator for the beginning of replication comes from a helicase named CMG. It comprises eleven proteins, of which the Cell Division Cycle Protein 45, abbreviated Cdc45, is especially important. It apparently determines at which starting points replication begins. About 15,000 replication sites are simultaneously opened by about 30,000 Cdc45 proteins within one cell. At the same time, replication bubbles form that protect the DNA from attack by external influences. The DNA can be copied with a very low error rate. Through measurements taken at DESY (the German electron synchrotron center) in Hamburg, we have determined the X-ray small angle structure of the Cdc45 protein.

During our investigations it turned out that very little Cdc45-protein is found in aging cells. Further replications are blocked by the shortage of these proteins and the cell ages. Conversely, if too much Cdc45 is present in the cell, too many replication sites are opened. The copying of the hereditary molecule begins, however, it is not completed. Instead, there are DNA breaks that finally bring about apoptosis, the genetically programmed death of the cell.
“We are decoding the molecular signal pathways that are important for healthy aging. Changes to molecules and signal chains in the interior of the cells are related to development of diseases typical of advanced age, such as cancer and Alzheimer’s. An important goal of our work is to identify molecules that are suitable targets for new medications against cancer and neurodegenerative diseases.”

Dr. Helen Morrison, head of the Tumor Biology Research Group

DNA damage control

With increasing age, copying errors accumulate within cells’ DNA—not only because the replication of the genome becomes more error prone, but because the repair force ages as well. Cells rely on a network of sensors to detect DNA damage. These include two important proteins, ATM and ATR. They control the signals that prevent cells from dividing before the DNA damage is fixed. The ATM protein primarily springs into action when breaks in the DNA double helix have been detected. ATR, by comparison, reacts to breaks in single strands as well as to stalled replication forks.

In order to learn more about the role of proteins that respond to DNA damage in the development of diseases, we disabled the gene for the DNA repair protein in the neurons of mice. In response, the nerve cells perished and the mice developed coordination disorders. Moreover, NBS1 deficiency caused the growth of the nerve cell precursors to cease. This could be the cause behind microcephaly (small head) and malformations of the brain that occur in these diseases.
Further investigations showed that both the NBS1 and ATR proteins are very important for the correct development of nerve cells. The absence of ATR triggers replication stress, which leads directly to cell death. The absence of NBS1 prevents breaks in the DNA double helix from being repaired. The resulting formation of what are referred to as micronuclei led to a second wave of copy errors. These results are surprising. It had long been assumed that ATR and NBS1 acted as protective and signalling proteins for collapsed replication forks. This new discovery shows that the proteins carry out their vital functions through differing mechanisms. Future investigations should reveal how insufficient response to DNA damage allows diseases of the central nervous system and accompanying premature aging to develop.
Ceaseless attacks on the DNA

The DNA of every cell is damaged about 10,000 times daily by a wide range of influences such as the reactive oxygen species that form during normal metabolic processes and cellular respiration. The continuing attacks on DNA place great demands on the repair forces, whose task it is to ensure the dependability of the genetic material. Damage known as a single-strand break, which resembles a crack in one beam of a ladder, occurs every ten seconds. Repairing this kind of damage is undertaken by proteins that divide up the work. Some detect the damage, others repair it and still others monitor the quality of the repair. One of these inspection proteins is named aprataxin. It senses incomplete single-strand repair and makes sure that it is correctly executed. If aprataxin cannot complete its task, nerve cells perish and neurodegenerative diseases arise that are accompanied by a loss of coordination in the movements of extremities, but also loss of coordination between head and eyes.

“The quality of repair processes in a cell is probably genetically determined. A complete understanding of these mechanisms is fundamental to research on the causes of aging.”

Professor Stephan Diekmann, head of the Molecular Biology Research Group

S. Diekmann has been a research group head at FLI since 1992 and a Professor of Biophysical Chemistry at FSU in Jena since 1993. Previously, he conducted research at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, at Harvard University in Cambridge, USA, and at the Deutschen Elektronen Synchrotron DESY in Hamburg.

Proteins of the repair process could be analyzed with microscopes.
Aprataxin comprises several functional parts. One of these is necessary for detecting and removing unproductive repair intermediates. It appears possible that aprataxin also facilitates the removal of incorrect building blocks from DNA that has just been copied.

Only if DNA repair is carried out reliably, can a long and healthy life be ensured. The better we understand these mechanisms, the more likely we are to discover intervention points to sustainably improve the health of older individuals.

“One of the greatest challenges in research on aging is to establish the border between what is ‘normal’ and what is pathologically altered aging.”

Dr. Matthias Görlach, head of the Biomolecular NMR Spectroscopy Research Group

M. Görlach has been working at FLI since 1994 and has headed the Biomolecular NMR Spectroscopy Research Group since 1999. Prior to joining the FLI, he carried out on research at the Howard Hughes Medical Institute at the University of Pennsylvania School of Medicine in Philadelphia, USA.
“There are certainly various causes for the decline of organ condition during aging. The number of stem cells in an organ falls with increasing age, for example. This might be attributable to the necessary niches for creating stem cells gradually losing their support function. Future work will concentrate on slowing these aging processes to the extent possible. Perhaps some day it will be possible to reprogram differentiated cells into stem cells in-vivo to compensate for the loss of the endogenous stem cells.”

“Maintaining our body’s regenerative capacity is important for healthy aging. We are investigating mechanisms that sustain the regenerative capacity in skeletal muscle in the aged.”

Professor Hans R. Schöler, Director of the Max Planck Institute for Molecular Biomedicine in Munster, Germany

Dr. Julia von Maltzahn, head of the Muscle Regeneration Research Group

Age-dependent changes to the make-up of stem cells lead to an altered composition of cells in tissues and organs. This is symbolically illustrated by the paper collage of Japanese artist Maki Yumaachi. If a portion of the stem cell population is lost during aging, it leads to altered tissue that can no longer exercise the same functions.
As stem cells become older

by K. Lenhard Rudolph

Stem cells are found in almost all tissues and organs of human beings. Stem cells in adult tissues, also known as "adult stem cells", are responsible for the preservation of the tissue and organs of our bodies. With increasing age, however, the life-sustaining power of the stem cells declines. Scientists at the FLI are researching the causes of this loss in functionality. Their goal is to develop new therapies for maintaining the performance of the body's own stem cells and increasing the preservation of organs during the aging process.

Adult stem cells contribute in a fundamental way to the daily renewal and regeneration of organs and tissues. However, stem cells lose their regenerative potential as they age. This is illustrated by clinical observations: There are problems in blood regeneration after bone marrow transplantation of patients suffering from leukemia if stem cells from older donors are used for bone marrow transplants. Investigations of aging mice revealed that the proper functioning of adult stem cells in various tissues and organs declines as a function of age. Blood stem cells, muscle stem cells, neuronal stem cells, hepatic stem cells and epidermal stem cells are equally affected.

The age-dependent decline in the proper functioning of stem cells is not always accompanied by a reduction in their numbers. During aging, however, there is an increasing disequilibrium in the ability of stem cells to differentiate, i.e. to mature into cells with defined functionality. In hematopoietic organs, for example, stem cells become increasingly unable to differentiate into lymphocytes—an important cell type of our immune system. The body’s defenses require these cells, however. The age-dependent decline of the blood stem cells’ functioning likely contributes to an increased susceptibility to infections. In addition, the immune system is responsible for removing old and damaged cells from the body. If this capability declines, aging accelerates. Cancer can increasingly develop as well.

"The aging process is certainly one of the main risk factors for cancer development. The causes are complex. There is also an increasing susceptibility to different infections that results from the increase of genetic modifications caused by the failure of the repair processes and the reduction of the immunological defenses against tumors. Above and beyond this, each form of cancer must be individually examined regarding its molecular cause."

Professor Harald zur Hausen, former Scientific Member of the Management Board of the German Cancer Research Center in Heidelberg, who received the 2008 Nobel Prize for Physiology or Medicine for his groundbreaking work on carcinogenesis.
A different make-up of the stem cell pool lies at the root of age-dependent loss of stem cell functioning. The pool of blood-forming, or hematopoietic stem cells (HSCs), consists of stem cells that produce either lymphocytic cells (lymphoid lineage) or other blood cells. During the course of aging, it is primarily the subpopulation of lymphoid-biased HSCs, from which naïve lymphocytes mature, that is lost. We have recently identified a mechanism that likely contributes to the age-dependent loss of HSCs that give rise to the lymphoid lineage.

When stem cells age, cancers develop

Malignant tumors generally develop from cells in which several genetic changes (mutations) have accumulated. Eventually, this leads to the generation of transformed cells, which are multiplying out of control and destroying other organ systems.

Stem cells carry a particularly high risk of accumulating mutations since stem cells have the longest lifespans of actively dividing cells in organs. Interestingly, mutations that accumulate in stem cells are the same ones that arise in malignant tumors.
In the future, it might become possible to detect dangerous mutations in stem cells before full-blown cancers develop; targeted therapy could be developed to remove these pre-cancerous, damaged stem cells. These kinds of approaches could revolutionize cancer therapy.

All in all, our scientific knowledge increasingly points to age-dependent changes in adult stem cells as playing a key role in the loss of function in tissues and organs as well as in the development of cancer. Therefore, one of our most important goals is to understand the molecular mechanisms of stem cell aging. This knowledge will provide a basis for developing medical therapies that help to improve health and reduce the risk of cancer as we age.

“An intact, well functioning immune system is important for maintaining health. However, the functioning of the immune system declines with age. We are investigating the complex molecular signaling pathways that play a role in the normal development of the immune system and pathological changes to it. We are hoping to attain new insights from our investigations as to how to preserve the proper functioning of the immune system and its cells during the aging process.”

Professor Falk Weih, head of the Immunology Research Group
Publications


Projects

(Third party funded)

The project “Aging induced impairments in organ regeneration and homeostasis” (RegenerAging) of the University Center for cross-disciplinary research on aging (ZAJ) is funded by the ProExcellence Initiative of Thuringia (2015-2019, headed by Prof. K. Lenhard Rudolph).

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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 program of the EU.

The FLI participates in two International Training Networks: MARRIAGE and CodeAge. Both projects are supported through the 7th framework program Marie Curie of the EU.

The FLI participates in the Research Training Group Molecular Signatures of Adaptive Stress Responses (RTG 1715), funded by DFG.


Awards

2012 Prof. K. Lenhard Rudolph received the Society Needs Science Award of the “Stifterverband” 2012. 1 Prof. Peter Herrlich received the Ernst Jung Medal of Medicine in Gold as lifetime achievement award 2 2012 Alexander Schulz, PhD student in the group of Helen Morrison, received the Young Investigator Award of the Children’s Tumor Foundation. 3 2010 Three research group leaders received the Max Bürger Award 2010 of the German Society of Gerontology and Geriatrics. 4

Funding Sources:

Certificates:
The aging of living organisms is a process involving multiple factors, one which is influenced by environmental and genetic factors. Our main task is to understand the molecular mechanisms that underlie the human aging process and lead to age-related diseases. We hope that this knowledge can contribute to a healthy process of aging in humans. The main question we are trying to answer:

“What molecular mechanisms and genetic factors contribute to the development of cellular and organism dysfunction in the course of human aging, and how can these be therapeutically influenced?”