Universität zu Köln

CECAD COLOGNE Excellent in Aging Research – Exzellent in Alternsforschung

CECAD Cologne
Annual Report 2009-11

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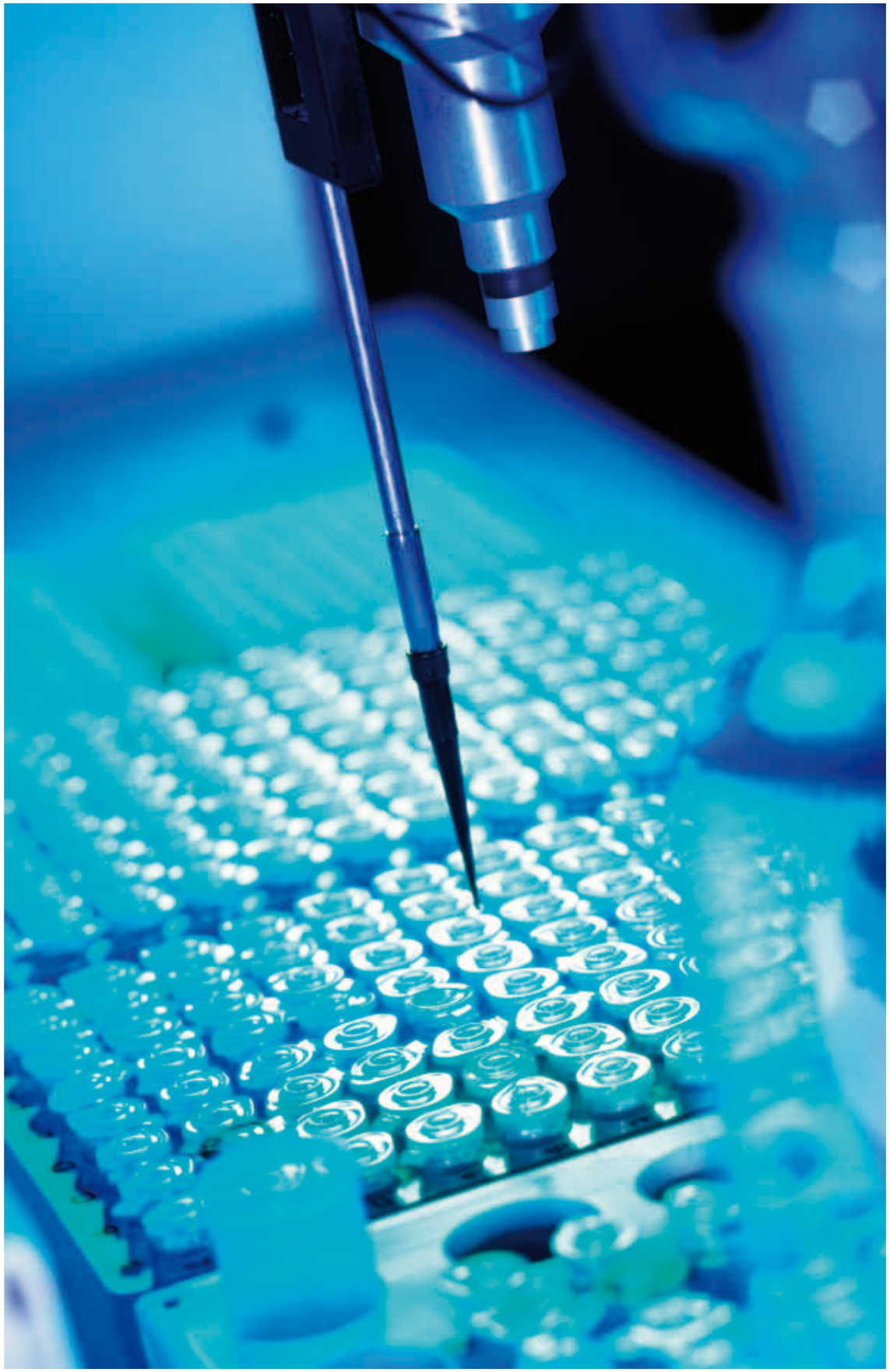

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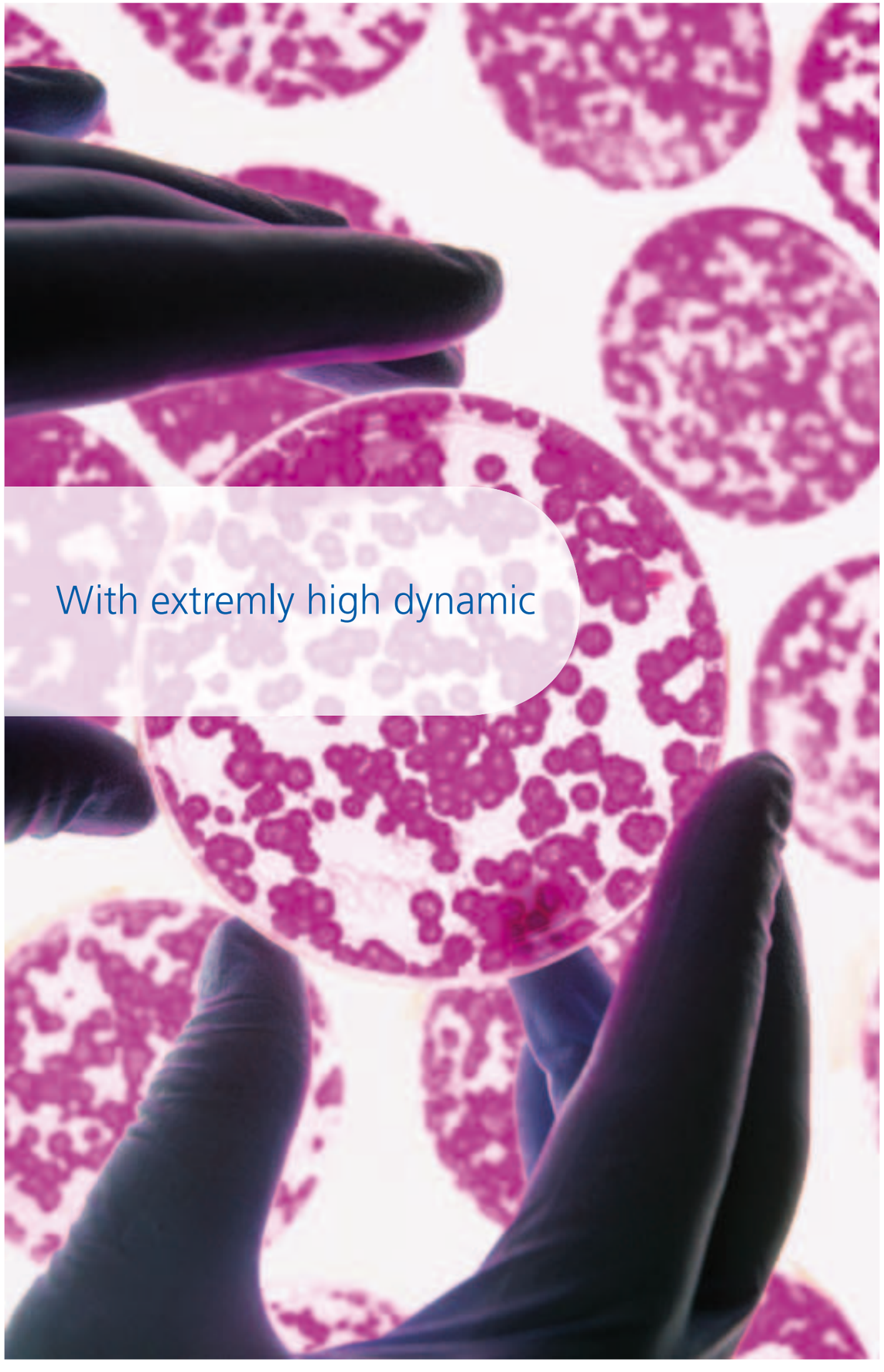
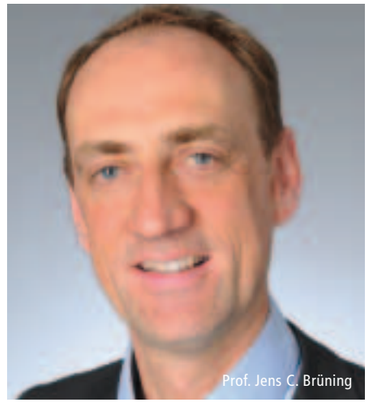


With extremly high dynamic

Editorial


Prof. Jens C. Brüning

Aging – an unfavorable aspect of life?

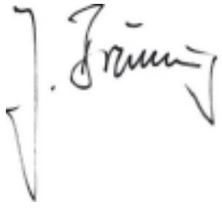
The Cologne Cluster of Excellence in Cellular Stress Responses in Aging-associated Diseases provides an dynamic environment for research into the aging process and related diseases. Our aim is to understand the molecular mechanisms that underlie the aging process and thereby provide a platform for the development of new therapies for aging-associated diseases such as cancer, diabetes and neurodegenerative disorders. CECAD's approach is truly interdisciplinary and international, with groups of outstanding researchers working in four main project areas, and the cluster already holds a leading position in international research on the aging process.

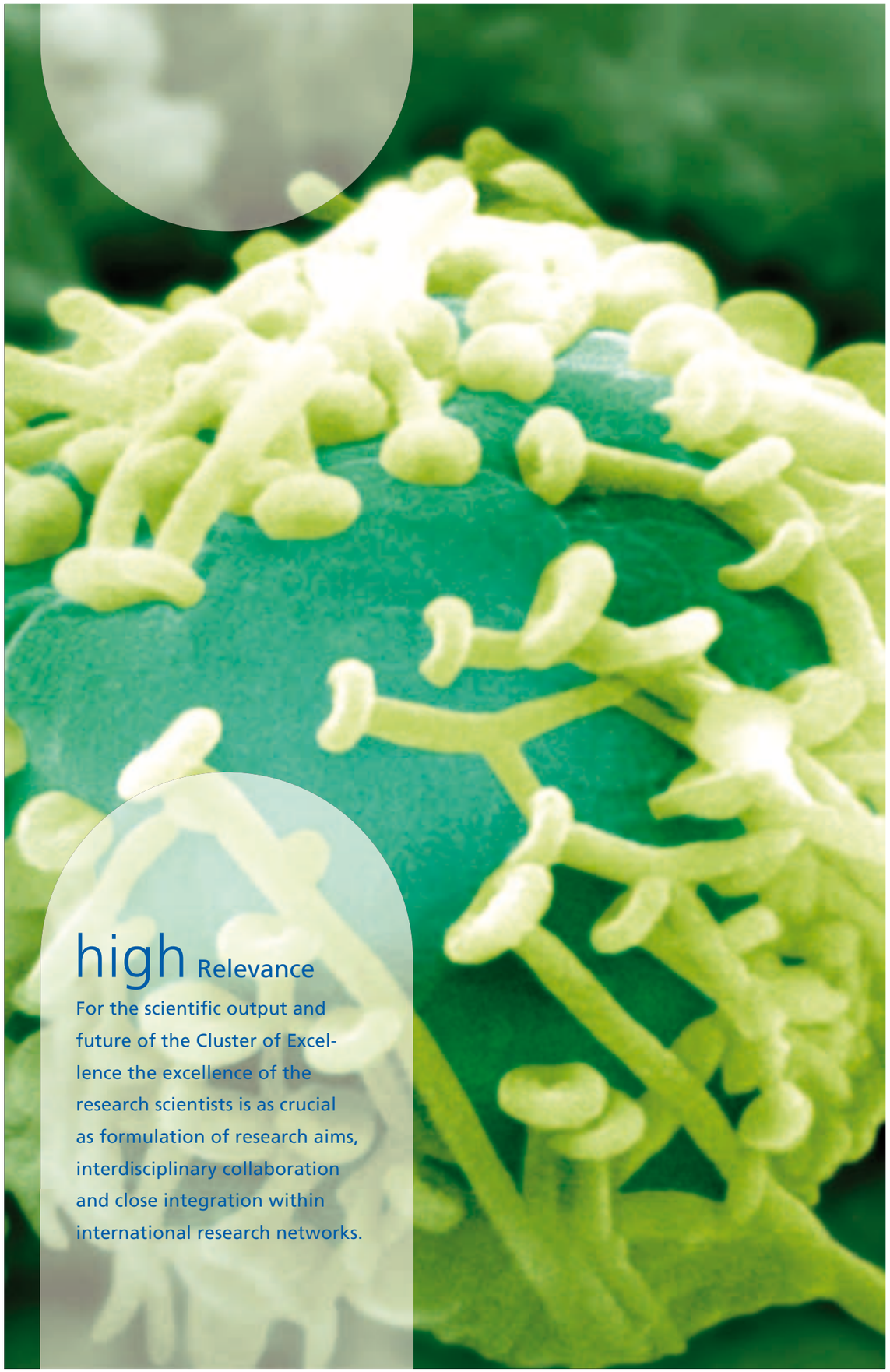
This provides us with many opportunities: Up to now the aging process has been examined from the perspective of separate disciplines, but CECAD's interdisciplinary approach now provides an opportunity to identify the points of overlap between individual research areas and may unearth common underlying causes for age-related diseases. The new laboratory facility is due to be completed by the end of 2012 – an important milestone in the consolidation of the communication network between scientists of the University of Cologne, University Hospital of Cologne and Max Planck Institute for the Biology of Aging.

Research into age-related diseases is of very high social relevance – however, it is not simply about extending people's lifespan but also ensuring that their quality of life remains high. This is an important concern of CECAD but the organization's work is not just a reflection of societal themes in a research context. The demographic change that society is experiencing will continue over the next few decades, and even increase: CECAD's research involves a high level of societal interaction and is positioned at a critical interface between science and society. CECAD is funded via the DFG within the excellence initiative set up by the German federal and state governments.

Vision

It is the vision of this cluster of excellence to be able to define processes where a failure to function triggers the pathogenic mechanisms underlying aging-associated diseases. CECAD seeks to identify key points for therapeutic intervention across the whole spectrum of aging-associated diseases. CECAD at the University of Cologne is committed to realizing this vision, and thus provides a dynamic research environment. CECAD takes an interdisciplinary and international approach, and has excellent researchers working in four main project areas. We are proud to be playing a decisive role in international research into the aging process.





CECAD Cologne
Staff Structure & Funding

The Excellence Cluster CECAD Cologne is supported by the Faculty of Mathematics and Natural Sciences and the Faculty of Medicine of the University of Cologne.

Scientific Coordinator:
Prof. Jens C. Brüning
Institute of Genetics at the University of Cologne, Director of the Center for Diabetology, Endocrinology and Preventative Medicien at the University Hospital of Cologne and Director of the Max-Planck Institut for Neurological Research

Deputy Scientific Coordinators:
Prof. Thomas Langer
Institute of Genetics at the University of Cologne
Prof. Michael Hallek
Director of the Department of Internal Medicine I at Cologne University Hospital

Principal Investigators (PI's):
up to 35

Scientific Members:
over 300

Technology Platform:
Head: Prof. Peter Nürnberg
Genomics Facility, Head: Dr. Peter Frommolt
Proteomics Facility, Head: Dr. Tobias Lamkemeyer
Lipidomics Facility, Head: Dr. Susanne Brodesser
Imaging Facility, Head: Dr. Astrid Schauss
Mouse Phenotyping

Platform for Education, Career Development and Gender Equality:
Head: Prof. Carien Niessen
Coordinator: Dr. Doris Birker
Student Assistant: Julia Panteleit

Translational Platform:
Head: Prof. Oliver Cornely
Navigators: Muriel Freudenberger, Dr. Pauline Schumacher

Managing Director:
Dr. Christopher Schippers
Assistant to Managing Director: Maria Vilgertshofer
Student Assistant: Kai Lichtenberg, Philipp Schreier

Project Management:
Dr. Nora Redemann

PR & Marketing:
Head: Astrid Bergmeister
Editorial Assistant: Andrea Pfennig
Student Assistant: Alana Hönig

Financing:
CECAD is funded by the DFG (German Research Foundation) within the Excellence Initiative by German Federal and State Governments and receives further financel support by the University of Cologne.

What's happening as we get older?

high Relevance

The setting of the Research Areas is based on an understanding that the overall research aim is to identify the underlying molecular mechanisms and central causes of the aging process and of aging-associated disorders.

Research Areas

Is aging an unfavourable concept of life? Understanding the molecular mechanisms underlying the aging process is the key to answering this question. CECAD Cologne has identified the key fields of enquiry in aging research and addresses them in four main research areas:

Research Area A: **Cellular Stress Responses and Dysfunction during the Aging Process**

Research Area B: **Senescence of Membranes and Age-related Impairment of Pathogen Defense**

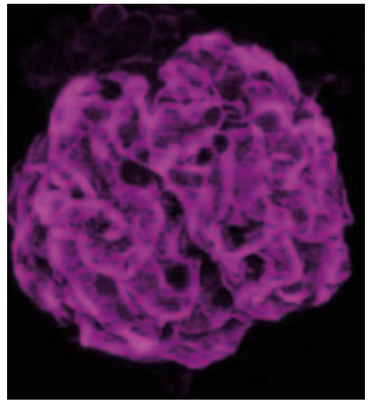
Research Area C: **Inflammation in Aging-associated Diseases**

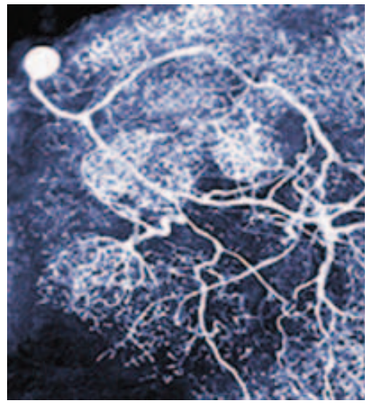
Research Area D: **Metabolic Signaling Pathways in Aging-associated Diseases**

Thus CECAD is playing a key role in pioneering international research. Leading international scientists at CECAD achieve a high level of translation between basic research and clinical application, raising the prospect of therapies for common aging-associated diseases such as cancer, diabetes, and neurodegenerative disorders.

Working with Model Organisms

Models are based on assumptions. Theories are formulated as cognitive constructs are then realized and tested through experimentation. Animal models allow working hypotheses to be verified on a living organism. The goal of this work with so-called ‘model organisms’ such as the mouse, the thread worm C. elegans, the fruitfly Drosophila and the zebrafish, is to gain knowledge about functions and processes which may be transferable to the human sphere: for example, experiments on the signal pathways of insulin in diabetes research, or work on podocytes from knock-out mice in kidney research. Further examples include the investigation into inflammatory regulators and signal cascades in the pathogenesis of diseases, or experiments on thread-worm tissue that could help to answer the question of how far the degradation of proteins can affect life span.





Research Area A: Cellular Stress Responses and Dysfunction during the Aging Process

The overall vision of the excellence cluster is to acquire an understanding of the molecular basis of the aging process. This involves identifying the processes where a failure to function leads to the onset of aging-associated diseases.

The projects in Research Area A focus on the cellular mechanisms responsible for the aging process and aging-associated diseases. The main focus of this CECAD research field is on the stress responses which, for example, can be triggered by ER stress or mitochondrial dysfunction. Here the main aim is to unravel the links between the immune system, metabolic processes and cellular stress responses. This will further our understanding of atherosclerosis, type 2 diabetes, and inflammatory cancer, and provide a platform for the development of new treatments.

There would be no living, growing cells without mitochondria – they are the power source of the cells, generating energy and consuming oxygen. A small amount of oxygen is also altered in this process. When these dangerous reactive oxygen species (ROS) or free radicals converge on other cell constituents such as proteins, lipids or DNA, these can be damaged or even destroyed. As mitochondrial function diminishes, the production of the undesirable oxygen species increases. Young, healthy cells have damage-limiting defense mechanisms and for a while the cell can compensate for the accumulation of damaged molecules but once a certain level has been reached, the damage to the cell is exacerbated.

Some research teams are investigating the role of ROS damage and apoptosis as a consequence of aging-associated mitochondria DNA mutations and impaired mitochondrial morphogenesis during the aging process. The functional state of the mitochondria is related to endocrine and stress signaling cascades that affect the life-span of organisms. There is interplay between this state and stimuli, stress or restriction of caloric intake. The development of aging-associated diseases is connected to dysregulation of these complex regulatory networks.

Parallel to this, research is ongoing into neurodegenerative disorders such as Parkinson's and Alzheimer's disease, which are also associated with aging.

Research Area A takes an integrative approach to cellular dysfunctions related to the aging process and to aging-associated diseases. The research projects employ a wide variety of experimental approaches, cutting-edge technology, and cellular and mouse models.

Research Area B: Senescence of Membranes and Age-related Impairment of Pathogen Defense

The functionality of cell membranes is a key factor in pathogen defense. Research Area B is deepening our understanding of the defense mechanisms of aging membranes.

The immune system becomes weaker with age, thus lowering the ability of an organism to defend itself against pathogens. Aging of the immune system leads to dysfunction of the innate immune system, and is evidenced by lower levels of immunity. Many innate defense mechanisms such as signaling through receptors on the cell surface, phagocytes, phagosomal maturation and fusion with lysosomes, as well as autophagy, are membrane-bound processes. Within the membranes, ceramide functions as the base molecule for the synthesis of complex sphingolipids, which together with sphingolipid-cholesterol create enriched platforms. These not only cluster the receptor molecules but also regulate the uptake of bacterical and viral pathogens. Strikingly, all isoforms of ceramide synthases have been identified as homologs of yeast longevity-assurance genes (LAF), which are proteins that regulate life-span.This discovery led to the hypothesis that aging-related changes in the sphingolipid composition of membranes cause functional deficits in innate immunity.

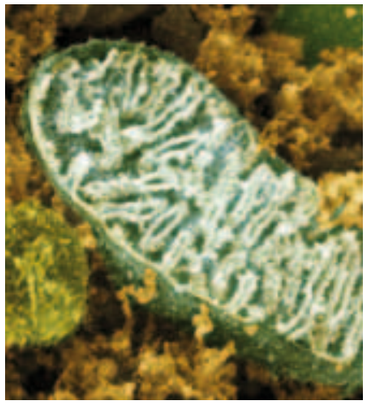
CECAD has chosen to take an integrative experimental approach in which genetically modified mice with inducible, tissue-specific deficencies in ceramide synthesis are exposed to specific pathogens. The ultimate aim is then to develop therapeutic strategies for the treatment of age-related membrane dysfunctions.

Research Area C: Inflammation in Aging-associated Diseases

The goal of Research Area C is to understand which cellular and molecular mechanisms at the interface of the innate immune system with metabolic processes and cellular stress responses lead to inflammation. The area of interest includes the pathogenesis of chronic aging-associated diseases with a particular focus on atherosclerosis, type 2 diabetes and inflammatory cancer. The research involves investigating why the body reacts with inflammatory responses, what triggers the onset of disease, and which aspects are important for disease progress. A complex network of mediators such as potent cytokines regulate the inflammatory responses of cells through the activation of intracellular signaling cascades.

Chronic inflammation is an important trigger factor in the pathogenesis of the aging-associated diseases such as cancer. Research here focuses on investigation of the links between diet, metabolism, cellular stress responses, inherited immune defenses and the resulting tissue damage.

The most important model organism in Research Area C is the mouse. The role of inflammatory mediators and signal pathways in the pathogenesis of diseases is analyzed in vivo. In order to explore the issue of susceptibility to chronic diseases further, CECAD is carrying out studies on the genetic loci associated with these diseases.



Research Area D:
Metabolic Signaling Pathways in Aging-associated Diseases

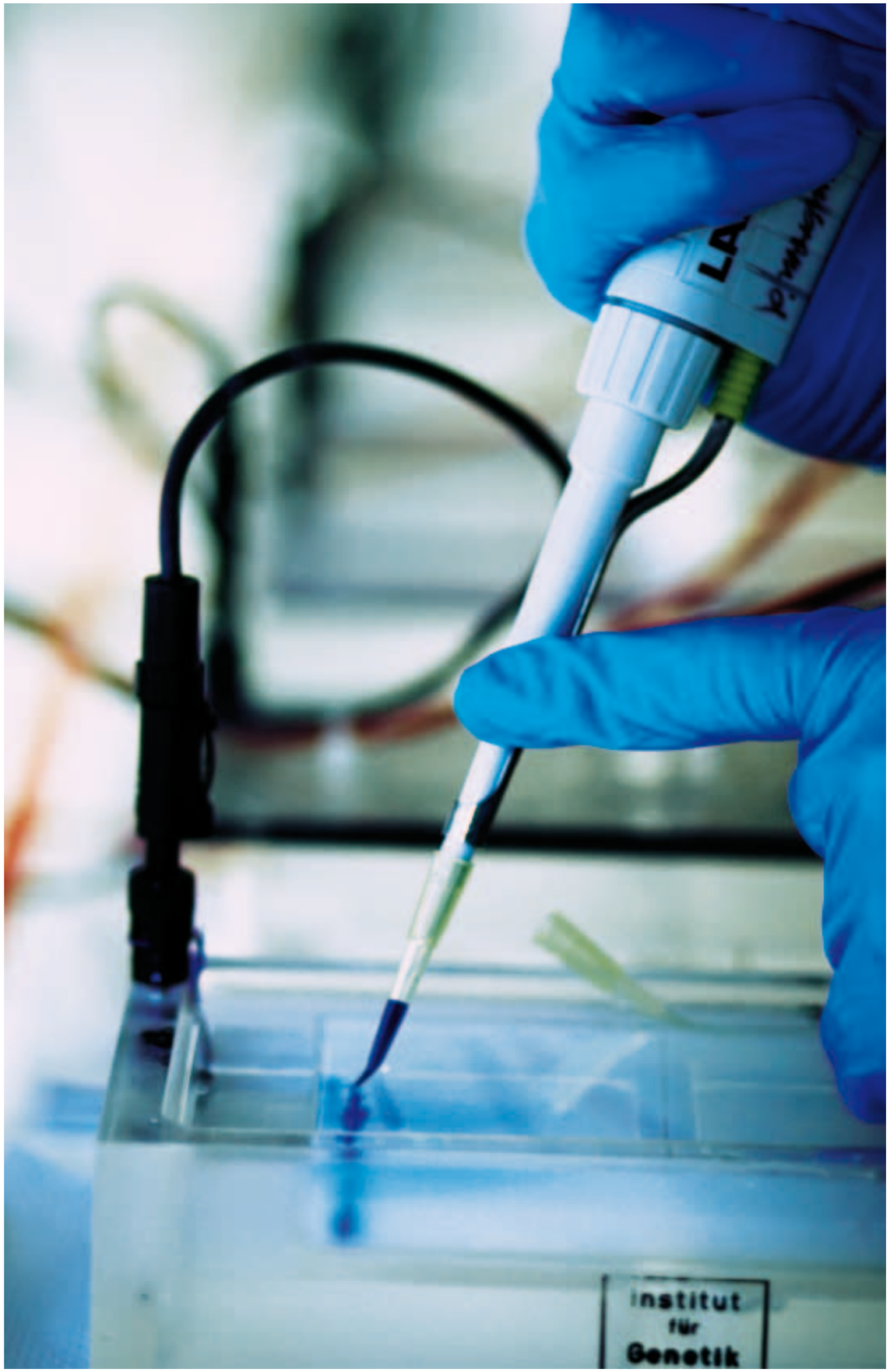
The metabolic signaling pathways play a complex role in the genesis of aging-associated diseases. The goal of Research Area D is to understand the metabolic signaling pathways involved in the development of obesity. The control and dysregulation of energy homeostasis are decisive parameters in this process. A further line of research in Area D is to identify, in both model organisms and human cells, novel genes that carry a predisposition to the development of obesity and type 2 diabetes. A third aspect is the identification of novel pathomechanisms that lead to complications in diabetes.

Processes such as the insulin signaling cascade are critical for the regulation of life-span, and their dysregulation is central to the development of aging-associated diseases such as obesity and type 2 diabetes. Obesity is increasing in western societies, where approximately 30% of the population is overweight. Excessive fat mass and being overweight are directly connected to the onset of insulin resistance, leading to the development of type 2 diabetes and diabetic complications such as retinopathy, nephropathy, and various skin conditions.

Experimental approaches in this CECAD research area have a very high output, owing to the unique availability of model organisms, and also have high translational potential. This means that insights obtained into metabolic processes at different levels of complexity can often be directly adopted for clinical application.

Research into the pathogenesis of neurodegenerative diseases is the key focus of this research area. Overburdened defense systems allow the accumulation of defective proteins that no longer function properly. Certain enzymes exercise a type of quality management in the cell and are responsible for the elimination of these proteins. When this process is compromised, the malformed proteins ‘glue’ together forming protein clumps in the nerve cells, which are the cause of many neurodegenerative diseases. Since such malfunctions increase with age, the incidence of neurodegenerative diseases also rises significantly in the elderly. These diseases include Parkinson’s, Alzheimer’s and Huntington’s chorea. Potentially successful approaches to future treatment of these diseases include suppression of the development of these protein clumps and restoration of the cell’s ‘quality management’ system.

What services do CECAD's Platforms offer?



Technology Platforms


Prof. Peter Nürnberg

An important added value of CECAD is the availability of central facilities in genomics, proteomics, imaging, as well as state-of-the-art platforms for the generation and analysis of a wide spectrum of model organisms including yeast, D. discoideum, D. melanogaster, D. rerio, C. elegans and mice. These facilities currently provide a variety of cutting-edge and sophisticated technologies to the research groups and foster the collaboration between system- and molecularly-oriented research groups.

Genomics Facility
Dr. Peter Frommolt

The Cologne Center for Genomics (CCG) headed by Prof. Peter Nürnberg functions as a Central Facility of the University as well as a Technology Platform of the Cluster of Excellence (CECAD). Over the last years, a high-throughput sequencing platform of the second generation (1 Illumina HiSeq Sequencer, 2 Illumina Genome Analyzer II, 1 Roche-454 FLX Genome Sequencer) has been built up. In addition, a corresponding bioinformatics infrastructure for adequate data management and fully efficient and state-of-the-art statistical analysis of sequences has been established. The latter has been achieved with the support of the university's computing center (RRZK).

The analysis services of the Genomics Facility are provided in combination with methodological support and a newly established bioinformatics service for the analysis of the data, which is run by Dr. Peter Frommolt. Within CECAD, the sequencing platform and bioinformatics service has been used by the Antebi, Hennies, Hoppe, Kubisch, Schumacher, Uhlirova and Wollnik labs over the report period.

The platform for hybridization of Affymetrix and Illumina microarrays is constantly in operation. Combined with bioinformatics support, it has been used by the Benzing, Brüning, Hennies, Herling, Pasparakis, Paulsson, Reinhardt, Schubert, Schumacher and Wunderlich labs.

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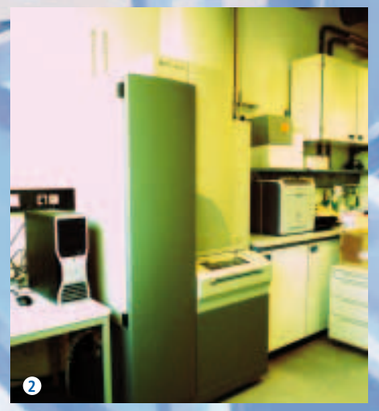


Proteomics Facility
Dr. Tobias Lamkemeyer

Institute for Genetics

1 Orbitrap: The Thermo Scientific LTQ Orbitrap Discovery mass spectrometer is a hybrid system combining the LTQ XL linear ion trap mass spectrometer and the Orbitrap mass analyser. The LTQ Orbitrap Discovery provides fast, sensitive and reliable detection of compounds, supporting a wide range of applications from routine compound identification to the most demanding analysis of trace levels of components in a complex mixture, and PTM identification. Being compatible with fast chromatography, the LTQ Orbitrap Discovery is coupled to a Easy nLCII nanoLC sytem (Proxeon).

2 4800: The AB SCIEX 4800 Plus MALDI TOF/TOF Analyzer features a compact vertical design and OptiBeam on-axis laser providing low attomole sensitivity in MS and MS/MS. The 4800 Plus system offers complete support for LC-MALDI analyses. By decoupling the mass spectral analysis from the chromatography separations, it is possible to perform comprehensive MS and MS/MS analysis without the time constraints of LC. The 4800 Plus system will therefore be coupled to a nanoLC system composed of a PAL autosampler and Eksigent pumps.

3 Surveyor: The modular design of the Thermo Scientific Surveyor Plus HPLC system gives increased application flexibility and efficiency. Three components, the MS Pump Plus, Autosampler Plus and PDA Plus Detector, perform protein and peptide analysis while for detection of neurotransmitters in microdialysates, the system is coupled to an electrochemical detector (Antec).

The Proteomics Facility performs protein analysis in the following core areas:

- Detection of protein regulation (differential protein expression) using stable isotopes/isobaric label (SILAC, TMT)
- Specific analysis of modifications of proteins (post-translational modifications, mainly phosphorylations)
- Detection of neuro-transmitters in microdialysates

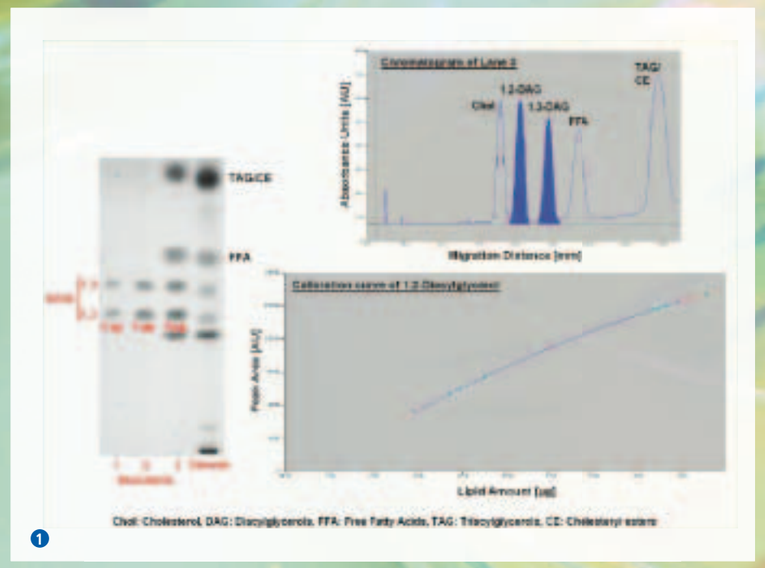
Two highly sensitive mass spectrometers with different ionization techniques, linked to nanoLCs, form the core of the technical equipment. Furthermore, the detection of neuro-transmitters is carried out through LC-coupled electro-chemical detection. The Mascot, Phenyx and Sequest algorithms, as well as ProteomeDiscoverer (Thermo Scientific) and MaxQuant comprise the high-performance software evaluation equipment. The data is managed by the laboratory information management system (LIMS) Proteinscape (Bruker) and is archived in the University of Cologne's computer center.

Facts & Figures:

Two highly sensitive mass spectrometers, linked to nanoLCs:

- MALDI-MS (4800 PLUS TOF/TOF, ABSCIEX)
- ESI-MS (LTQ/Orbitrap Discovery, Thermo Scientific)

Steinfeldt T, Könen-Waisman S, Tong L, Pawlowski N, Lamkemeyer T, Sibley LD, Hunn JP, Howard JC (2010) Phosphorylation of mouse immunity-related GTPase (IRG) resistance proteins is an evasion strategy for virulent Toxoplasma gondii.PLoS Biol. Dec 21;8(12):e1000576



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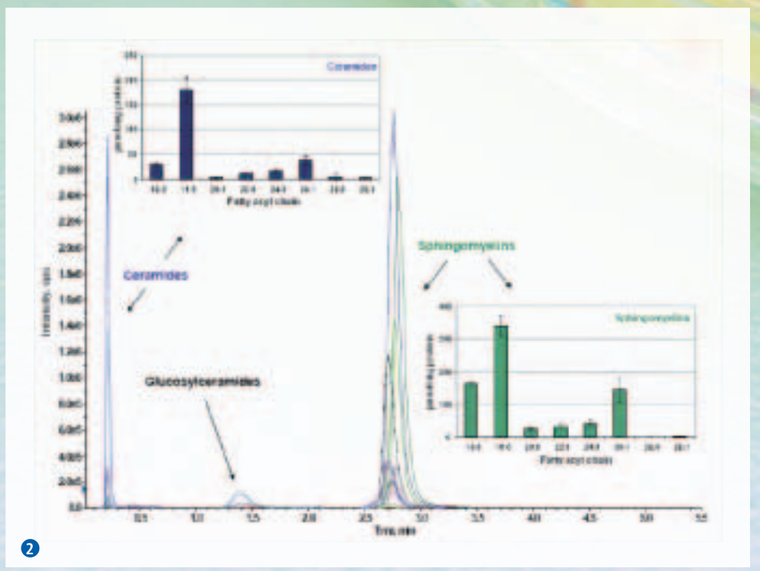

2

1 Quantification of lipids by analytical Thin Layer Chromatography: After separation and derivatization of the lipid bands, the TLC is scanned lane by lane by the TLC Scanner 3 of CAMAG, which produces quantitative data by densitometry. A calibration curve is calculated from the peak areas of standard substances developed together with the sample extract on the same plate. The lipid content of the samples is then calculated on the basis of the calibration curve.

2 LC-MS/MS chromatogram displaying the separation of 39 Sphingolipid species (including subspecies of Ceramide, Glucosylceramide, and Sphingomyelin acylated by fatty acids with 16 to 26 carbon atoms) from mouse skeletal muscle using the Multiple Reaction Monitoring scan mode. The quantification is carried out by correlation of the peak areas of the endogenous lipids with those of appropriate internal standard substances which were added to the sample prior to the lipid extraction.

Lipidomics Facility
Dr. Susanne Brodesser

Institute for Medical Microbiology, Immunology and Hygiene (IMMIH)

The CECAD Lipidomics Facility determines lipid profiles in biological samples, with the goal of linking physiological alterations to changes in the lipid composition. The facility performs analyses in a variety of biological sources (cells, mouse and human tissues, C. elegans, D. melanogaster, zebrafish, blood, isolated cell organelles and bacteria). The analytical service carries out sample preparation, extraction, purification and quantitative analysis of the lipids of interest, as well as data evaluation. All common lipid classes and subclasses are routinely quantified by analytical Thin Layer Chromatography (TLC). With Liquid Chromatography coupled to Tandem Mass Spectrometry (LC/MS/MS) it is possible to discriminate between lipid subspecies differing only in the fatty acyl chain. LC/MS/MS-based methods using the 4000 QTRAP System of AB SCIEX are offered for the quantification of selected sphingolipids (ceramides, glucosylceramides, and sphingomyelins) for example. For the analysis of fatty acids, the Agilent GC/MSD 7890A/5975C, a gas chromatograph coupled to a mass selective detector, is available at the facility.

Facts & Figures:

- Analytical Thin Layer Chromatography (TLC)
- Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS)
- Gas Chromatography-Mass Spectrometry (GC/MSD)
- Quantification of different lipid classes by TLC
- 4000 QTRAP LC/MS/MS System (AB SCIEX) for mass spectrometric analysis of lipid subspecies
- GC/MSD 7890A/5975C (Agilent) for analysis of fatty acids

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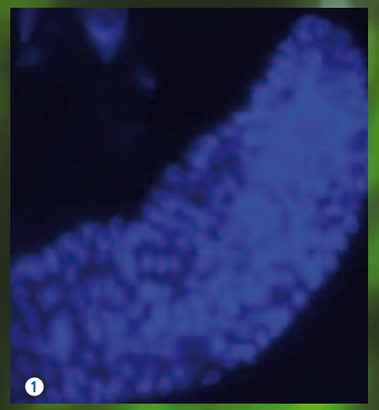
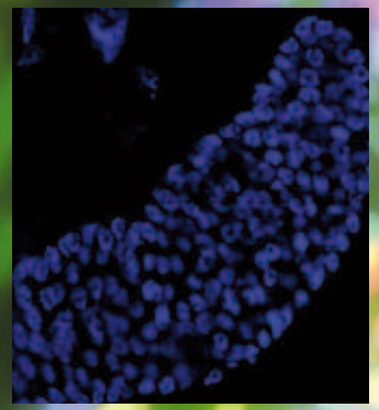
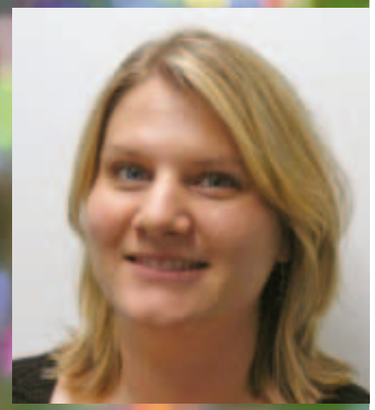






1 Fluorescence image of DAPI stained nuclei (blue) of the worm C.elegans taken with the Deltavision RT Microscope. z-stacks were taken (only one plane shown) and four pictures per plane were stitched together with the Softworx program. On the left, raw data are shown. On the right, the deconvolved image (obtained with the Huygens program) is presented. The data are courtesy from Stefanie Wolters, Schumacher lab.

2 Shown are MEF cells (mouse embryonic fibroblasts) with GFP-labeled mitochondria (green) and peroxisomes highlighted in red. The cells were imaged for 1 min at maximum speed and the movement of peroxisomes was tracked over time. Image analysis was performed with the Volocity software (screen shot shown). The peroxisomes were recognized automatically and their tracks were measured. (own data).

Imaging Facility
Dr. Astrid Schauss

Institute for Genetics

Within the CECAD Platform Imaging, we offer scientists a choice of light microscopes:

Widefield:
- Nikon Eclipse Xi
- Deltavision RT (reconstructive Deconvolution) (Applied Precision)

Confocal:
- Zeiss Meta 510
- Ultraview Spinning Disk (Perkin Elmer)

After a personal training session, users are able to use the microscopes independently and make bookings online:
http://www.imagingfacility.uni-koeln.de

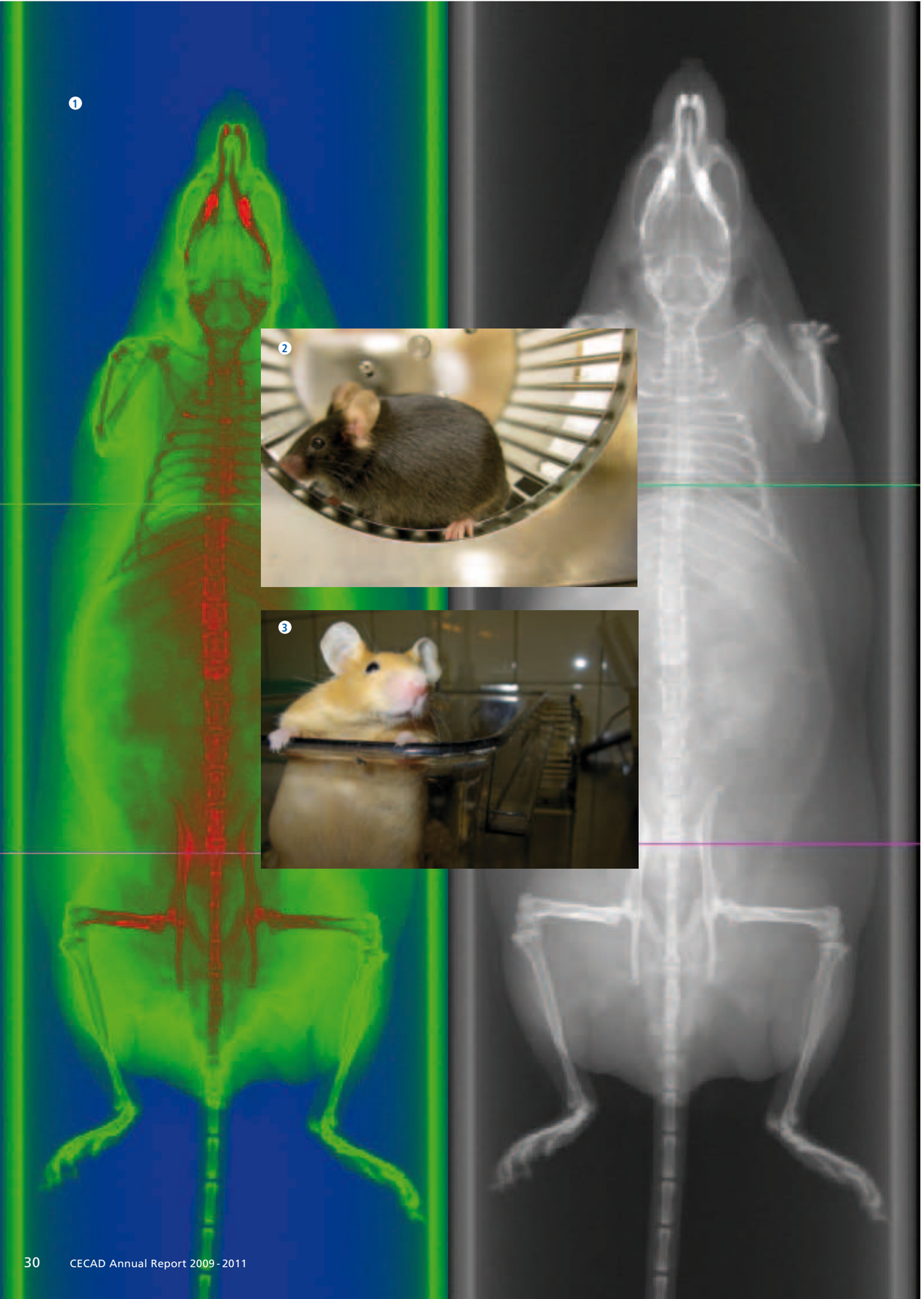
The facility is always there to help with any problems that might arise and assist with the establishment of new light-microscopic methods. Two computers are available for further data analysis, equipped with the following software: Imaris, Volocity , Huygens (deconvolution), Image J and others.

The microscopes are equipped with incubation chambers and CO_2 , allowing live-cell imaging for several days under physiologic conditions. Besides z-stacks for three-dimensional reconstruction, colocalisation and tracking experiments, more specialized techniques like FRAP (Fluorescence Recovery After Photobleaching) and FRET (Foerster Resonance Energy Transfer) to study protein dynamics and interactions can be used.

Data storage is achieved in collaboration with the „Rechenzentrum“, where Imaging users receive their own group account:
https://sofs.uni-koeln.de/projects/CECADImagingfacility

To cover the service contracts, the use of the microscopes is charged by the hour (Widefield microscopes 15 Euros/h, Confocal microscopes 20 Euros/h, training 50 Euros, in groups 30 Euros).

In case of publication, we ask to be mentioned in the acknowledgements. For extended help or method establishment, we kindly ask for authorship.



Mouse Phenotyping

1 Scout image (left: artifical color, right: monochrome) of a mouse taken with an X-ray tomography based imaging system (micro-CT).

2 Mouse in voluntary running wheel.

3 An agouti-coated mouse model of obesity.

The newly established technology platform for mouse phenotyping provides members of the CECAD with access to standardized methods and the latest technologies, which can then be adapted to suit the specific requirements of individual projects. The phenotyping platform is designed in particular for the metabolic characterization of genetically modified mice, as well as for conducting various behavioral tests. If desired, different surgical techniques can be undertaken, e.g. intracerebroventricular cannulation. The current set-up enables the following parameters to be assessed: metabolic rate, food and water intake, activity (home cage, running wheel, treadmill, spontaneously induced, motor dysfunction), body composition (total fat and lean mass, different bone parameters) and fat distribution in the abdominal cavity (visceral/subcutaneous), learning behavior and memory capacity, anxiety, explorative behavior and the reward system.

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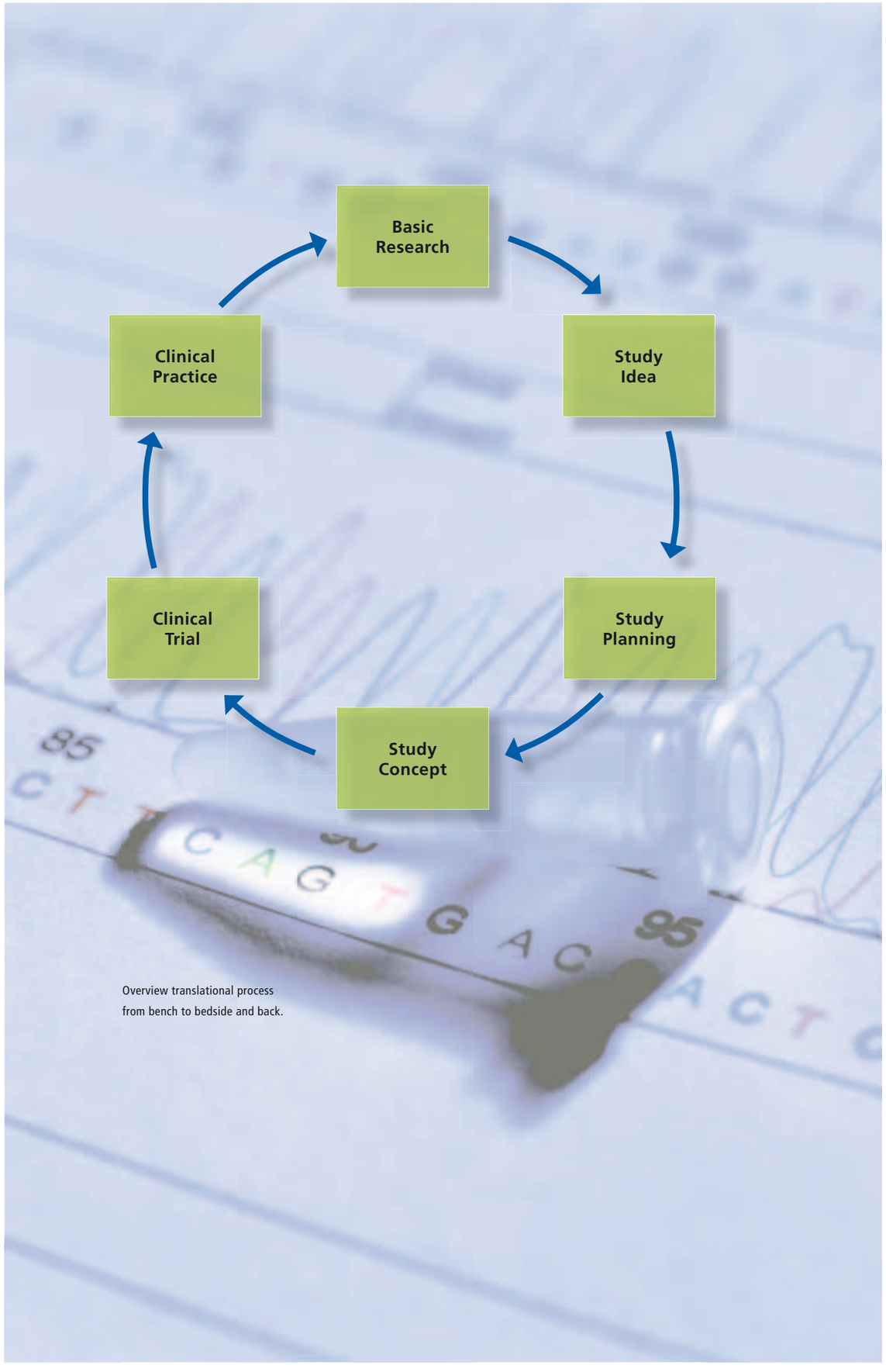


Overview translational process
from bench to bedside and back.

Translational Platform

Prof. Oliver Cornely

Muriel Freudenberger

‚From bench to bedside and back' – CECAD encourages translational activities with the aim of bringing basic research findings of therapeutic benefit to the point of clinical application. Through joint navigation of translational projects the translational platform, directed by Pro. Oliver Cornely will forge effective links between basic research and clinical practice. The structure of these Cologne Navigation Concept (CNC) resulted from the collaboration of CECAD and the Center for Clinical Trials Cologne (CCTC).

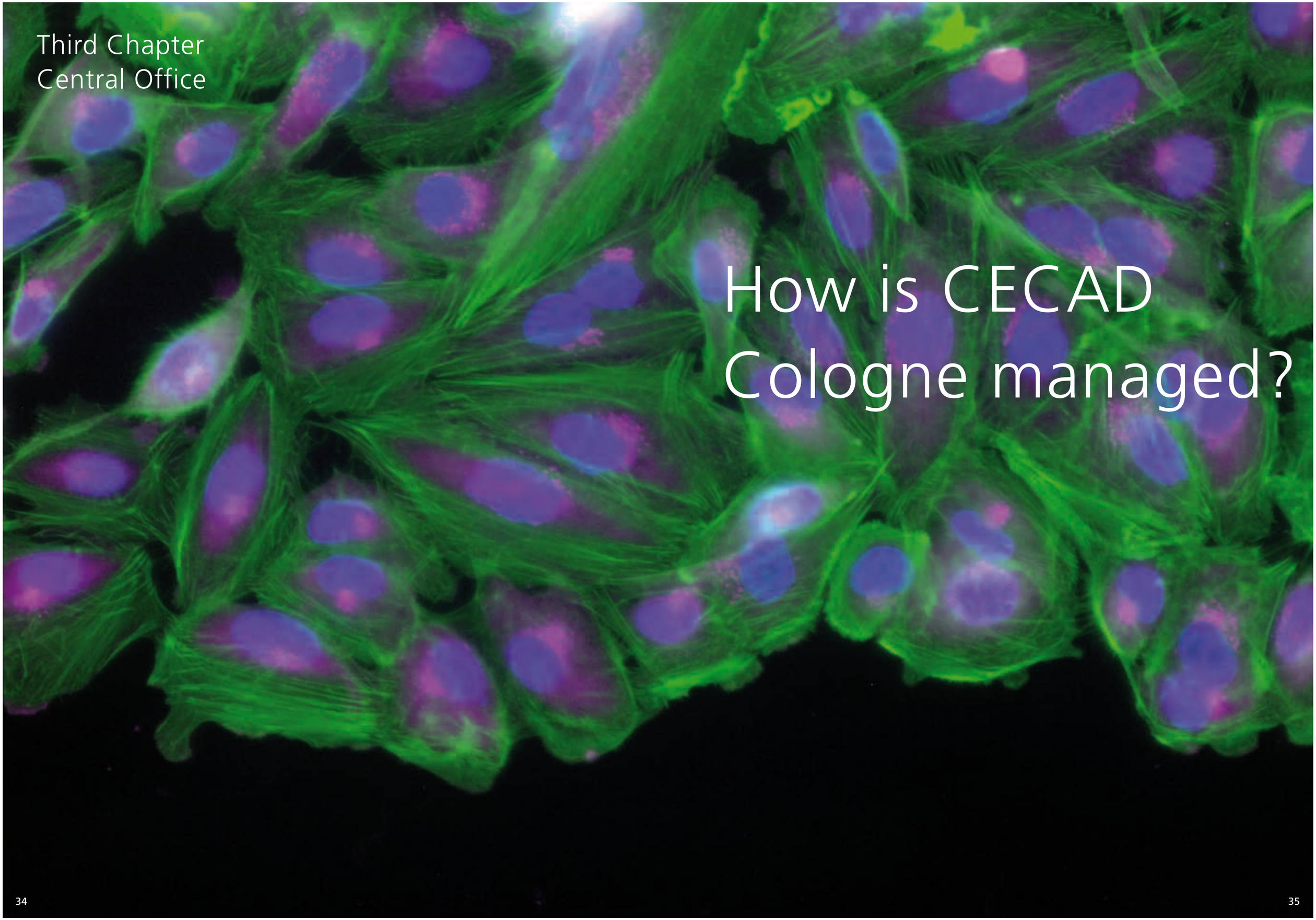
The main goal of the translational platform is to foster a strong interdisciplinary research approach involving both basic researchers and clinicians. To continue to support the academic scientists carrying out basic research in their endeavour to develop products for clinical application, the RP-C has set up an innovative service performed by two navigators (CECAD/CCTC), a navigation tandem, each experienced in basic and clinical research. They frequently meet all PIs and junior groups to discuss results from basic research, to prioritize, in concert with the researcher, potential translational projects, and to find clinical partners. The navigators thus create vertical and horizontal links between basic science and clinical networks, supporting translation from bench to bedside and vice versa, helping to develop clinical trial protocols, and searching for appropriate national/international funding opportunities.

A translational project proceeds through various stages: Phase 1: Basic research findings. Once the initial study idea has been drawn up (Phase 2), the project enters a first planning phase (Phase 3) and is then developed into a concrete study concept (Phase 4) and finally into a clinical trial (Phase 5). If the outcome is positive, the results of the clinical trial are introduced and applied to clinical practice (Phase 6). The return transfer link takes questions arising in clinical practice back to the basic researchers to search for answers (Phase 7).

Proving the efficacy of this innovative navigation concept a total of 17 translational projects was already established 7 month after launching: 15 of these target drug use, and 2 target medical devices. External public funding sought for 7 projects has already been granted for 5 of these. Furthermore, 2 patent applications were submitted.

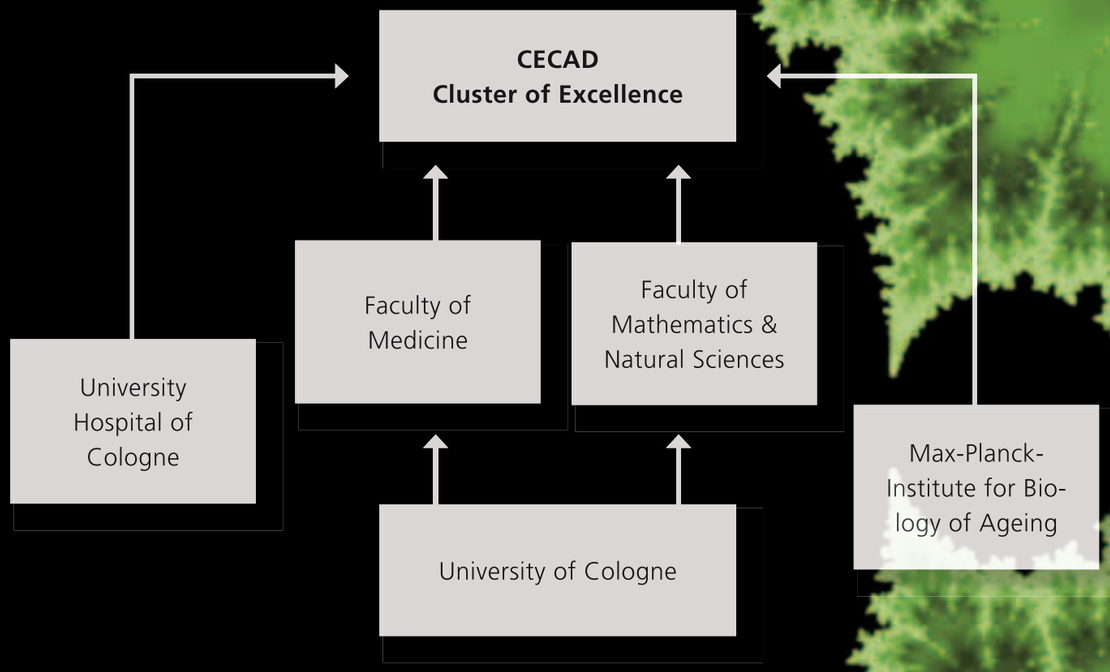
This innovative navigation concept was recently nominated by Cologne University for the regional North Rhine-Westphalian Innovations Award 2011.

How is CECAD Cologne managed?



CECAD Support Structure

The CECAD Cluster of Excellence within the University of Cologne



Dr. Christopher Schippers

Dr. Nora Redemann

high **Relevance**

Research is based on communication. Physical proximity enhances communication, thus promoting collaboration between researchers. From this standpoint, completion of the CECAD laboratory building in early 2013 is of great relevance.

Central Office

Maria Vilgertshofer

Kai Lichtenberg

Philipp Schreier

Offices Mission

To be successful, research must be integrated into the professional structures of a modern scientific administrative organisation. The Central Office sets the optimal conditions for research and disburdens the scientists from administrative work wherever possible.

Research

All CECAD research requires efficient and effective administration as well as financial backing. The Central Office coordinates the finances of the cluster and works in close collaboration with the University, University Hospital and Max-Planck-Institute administrations to secure funding for joint research projects – the CECAD Grants. In the same manner, the newly recruited groups (Uhlirova, Trifunovic, Hoppe, Schumacher) are supported in all respects. To increase cooperation from a structural point of view, CECAD CRC Bridging groups (Iden, Lammers) were set up. They link the cluster with four collaborative research centers also involved in aging research. Management of the research platforms – the Imaging, Lipidomics, Proteomics, Genomics and Mouse Phenoytyping facilities - forms another important aspect of our work. The Technology Platform provides state-of-the-art equipment for performing scientific research and is one of the key benefits the cluster offers to its members. Furthermore, the Translational Platform, which helps to identifiy and develop projects with a view to later clinical application, is supported by the Central Office.

Offices Task Overview
Organisation, Finance and Support in Following Topics:

Research	CECAD Grant Projects
	New CECAD Groups
	CECAD Technology Platform (Facilities)
	CECAD Translational Platform
Promotion of Junior Researchers	Graduate School
	Fellowship Program
	Other Career Development Measures
Gender Equality	Collaboration with Family Support of University of Cologne
	Female Faculty Club
	Maternity Leave Fellowships
	Kindergarten
Facility	New Building
Structure	Executive and Advisory Board Meetings
	Members Assemblies, Retreats, Conferences
PR & Marketing	Marketing
	External Communications
	Internal Communications

Design of the CECAD laboratory building in the Josef-Steltzmann Strasse on the campus of Cologne University Hospital. The building will be ready for occupation in early 2013. Architects: gmp Aachen, Planning and interior construction: medfacilities GmbH Cologne and Dr. Heinekamp Labor-und-Institutsplanung, Karlsfeld.

Promotion of Junior Researchers

Promotion of Junior Reseachers is a matter of highest priority for the cluster (s. Page 55). Through effective management of new CECAD research groups, organisation of a structured postgraduate training programme, and career development schemes, CECAD ensures a steady support of young researchers.

Gender Equality

Gender mainstreaming is a political issue and CECAD actively promotes gender equality for women and men at all levels of research and administration. The compatability of research work and family life and promotion of gender-specific issues in the public arena form the focus of this initiative (for further information see Page 55).

Facility

The new laboratory facility represents a fundamental milestone in CECAD's institutional strategy. Scientific collaboration relies on effective communication and this is injected with a new dynamic through close physical proximity. The scheduled moving-in date into the new CECAD Laboratory Building is early 2013 – a prospect loaded with expectations and requiring intricate planning. Together with two users representatives, CECAD's Managing Director will have been the main sparring partner of the external project

A view of the lighted building at night shows its proportions most clearly.

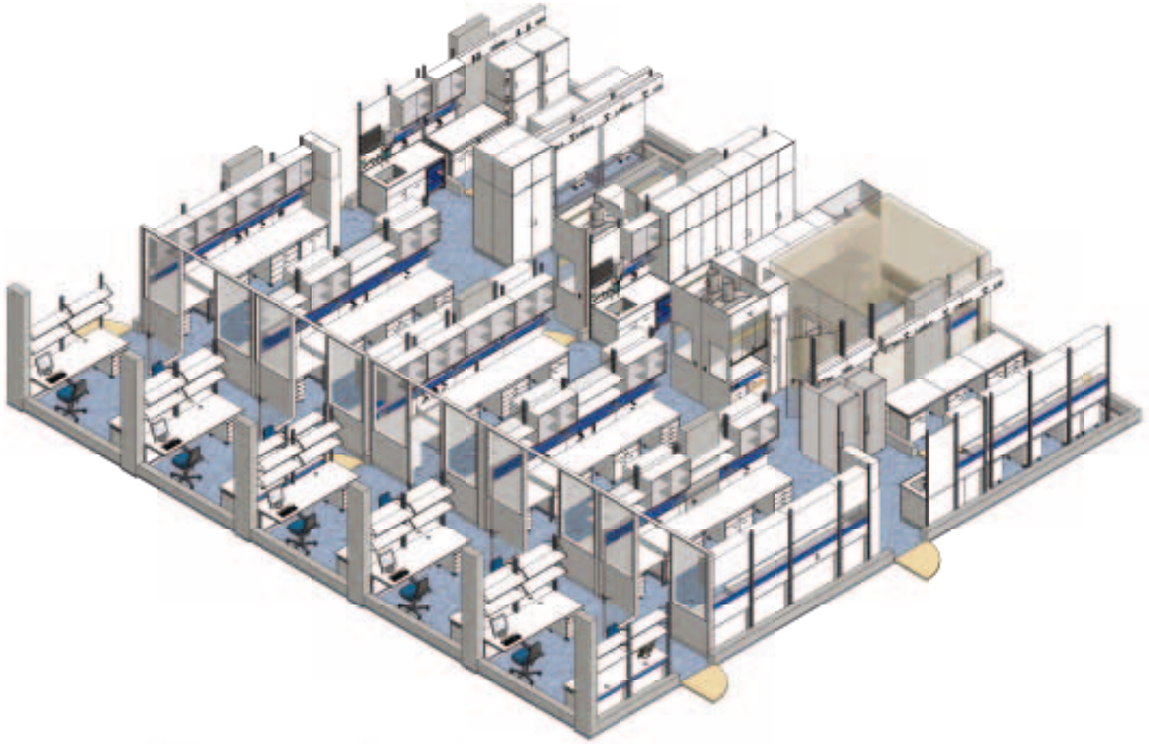
management and planning teams throughout – from the starting phase in 2008 up to moving into the facility in 2013: Establishing the broad layout and critical details while maintaining a user-oriented approach to the construction process is an important project for the whole cluster.

Scientific Communication

By organising seminars, lectures and retreats, CECAD creates a framework for the exchange of scientific ideas and a platform for further knowledge production. Science today takes place within a dense communications network. The CECAD series of seminars is aimed at all research scientists in the cluster and provides an important forum for the exchange of ideas and networking among the next generation of researchers. Besides the Junior Scientists Retreat, a larger retreat is held each year for all CECAD researchers: Two days are set aside for discussion of current research issues, aims and strategies. The Central Office is also active in organising international research conferences such as the Mosbacher Meeting 2010, which it run jointly with the German Society for Biochemistry and Molecular Biology and the Cologne Spring Meeting in March 2011.

PR & Marketing

Through active communication with the relevant stakeholders, CECAD's PR & Marketing team are raising the profile of CECAD as well as an awareness of aging research among the public (further information on Page 49).



Official Ceremony: The dignitaries attending the cut of the spade in October 2009 reflect the considerable scientific and political importance of the new CECAD facility (Prof. Thomas Langer, Prof. Edgar Schömig, Fritz Schramma, Thomas Rachel, Prof. Andreas Pinkwart, Prof. Joachim Klosterkötter, Prof. Axel Freimuth, Prof. Hans-Günther Schmalz).

The internal layout of the new CECAD building is based on an innovative distribution of space for laboratories, documentation and communications. Defined modules differentiate between standard and flexible furnishing and fittings. The plans went through a requirements analysis and operational systems analysis. User involvement is an essential, conceptual aspect of this approach.

1–3 The Mosbacher Meeting 2010 was dedicated to „The Biology of Aging: Mechanisms and Intervention“ and was a convention attended by many of the leading aging experts from all over the world.

3 & 4 The Advisory Board is the highest professional body within the CECAD. Scientists of the highest international standing in their disciplines meet here to make recommendations for the conceptual development of the cluster. On this photo, members of the Advisory Board are: Klaus Rajewsky, Herbert Jäckle, Frances Ashcroft, Tamas Horvath.

5 Official Opening: Vice-Speaker Thomas Langer gives a talk at the opening ceremony of the Nikon Imaging Facility in Cologne.

6 Ernst-Mach Gymnasium: Members of the cluster are also active in schools: Matthias Cramer explains the work of the cluster to pupils.

Structural Overview

High-level decisions e.g. on investments, allocation of funds and appointments are taken by the Executive Board and implemented through the Central Office.

Scientific Coordinator of the Cluster is Leibniz Prizewinner Prof. Jens C. Brüning of the Institute of Genetics, who is also Director of the Max-Planck Institute for Neurological Research and Director of the Center for Diabetology, Endocrinology and Preventative Medicine at the University Hospital of Cologne. The two deputy coordinators are Prof. Thomas Langer from the Institute of Genetics and Prof. Michael Hallek, Director of the Department of Internal Medicine I at Cologne University Hospital.

Members of the Executive Board include the leaders of the CECAD research areas, one director from the Max-Planck-Institute for Biology of Ageing and the heads from the platforms for Technology, Translation and Career Development/Gender Equality as well as a representative of the Junior Research Scientists. The Deans of the Faculty for Mathematics and Natural Sciences (Prof. Karl Schneider) and Faculty of Medicine (Prof. Thomas Krieg) are also members of the Board.

CECAD undertakes continuous scientific assessment and re-evaluation of its research concept. At the Advisory Board Meeting in Autumn 2010, which fell during the first funding period, CECAD submitted itself to scientific evaluation and consultation. The cluster held an open day of talks, poster presentations, advisory panels and discussions. In its résumé, the Advisory Board praised CECAD's strategic vision, an essential element of which focuses on career development for individual researchers in line with the scientific goals of the cluster. Encouraging more physicians to take part in basic research was one aspect of this drive.

CECAD Finances

The launch of CECAD at the end of 2007 was followed by a recruitment drive for new research group leaders and the installation of new technology platforms, which were completed in the first months of 2009. This meant big investments in state-of-the-art technology in the years 2008 and 2009, resulting in research facilities equipped to the highest possible standards. Personnel was recruited in parallel to staff the platforms and the new research groups.

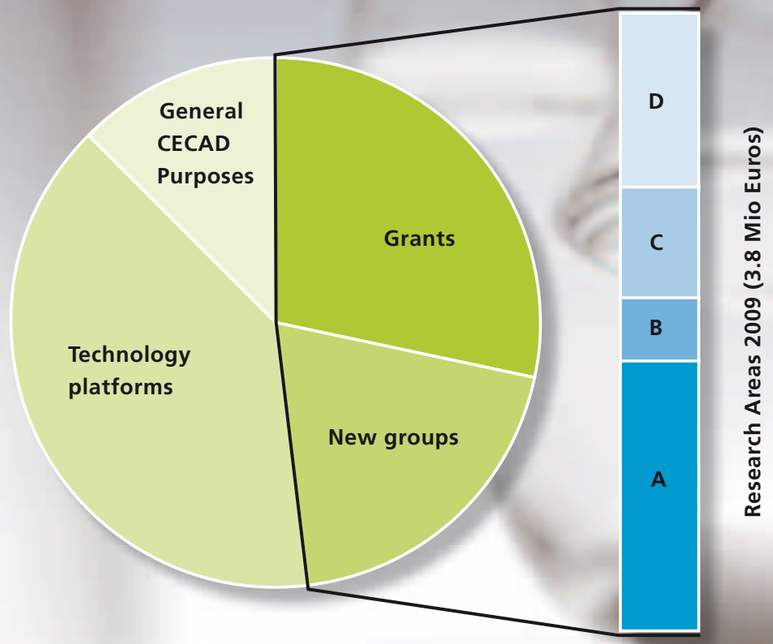
Our financial development is proof of the success and soundness of our conceptual considerations at the investment planning stage: The outlay on equipment has paid off, enabling our research teams to achieve outstanding scientific results. Consequently, investment costs have fallen. Increasing personnel costs reflect the intensity of the cluster's research activities and show that CECAD is committed and focused in pursuing its scientific research goals.

Personnel:	2009	2.7 Mio. Euros
	2010	3.3 Mio. Euros
Running costs and investments:	2009	2.9 Mio. Euros
	2010	2.3 Mio. Euros

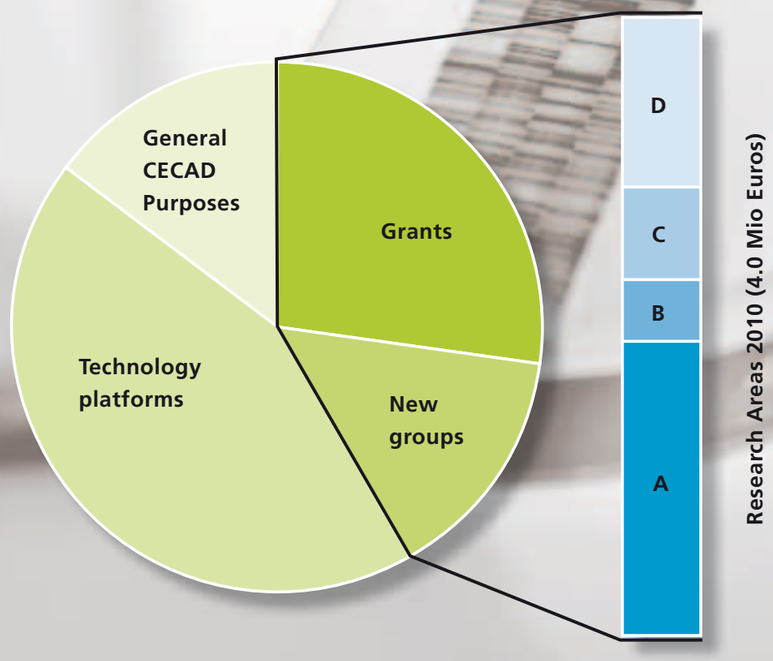
In the years 2009 and 2010, CECAD had a budget of 11.2 Mio. Euros for project funds, which were assigned to the newly installed research groups and technology platforms and general CECAD purposes (e.g. administration, promotion of junior scientists, equal opportunity schemes, PR- and marketing). In addition, already established research groups received grants to intensify their research and collaboration within CECAD. (see figure). The bar inserts illustrate the budget distribution of the four CECAD research areas A-D.

Apart from extensive funding from the DFG, amounting to 5.6 Mio. Euros annually plus overhead funds, the cluster receives substantial support from the University. The main purpose of the University funds is to ensure the continuation of scholarships and junior research groups in the years following the end of the first funding period by the DFG.

Finally, the University and University Hospital of Cologne is receiving substantial support from the federal government and the state of North Rhine-Westphalia to construct and equip the new CECAD Laboratory Building. The construction costs amount to over 85 Mio. Euros, to which will be added funding for initial procurement of equipment.



Budget distribution 2009 (5.6 Mio Euros)



Budget distribution 2010 (5.6 Mio Euros)

The screen shots show the new image as used on CECAD's new website. In conception and user guidance the website is designed to supply essential information meeting the many disparate requirements of the various CECAD stakeholders.

CECAD – excellent in research of molecular mechanisms in aging

The redesign of the CECAD header image shows regularly functioning cell processes and their disruption through erroneous processes occurring in aging-associated disorders.

PR & Marketing


Astrid Bergmeister


Andrea Pfennig

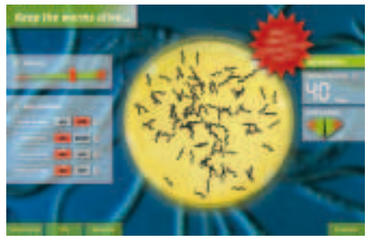

Alana Hönig

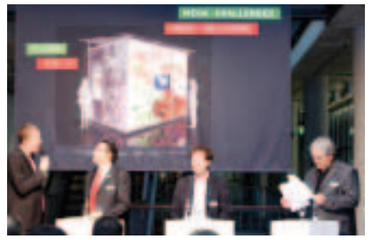
The research of the CECAD has an important social function to fulfil in an aging society. Our aim is to stimulate public awareness of the social as well as individual relevance and benefits of our research. The unique selling point (USP) of the CECAD for research investment is the high level of interdisciplinary work and close networking, combined with a high rate of translation of basic research into clinical applications.

Integrated Communications and Marketing Strategies

CECAD finances its research through public funds. This generates many stakeholders, bound to CECAD through their various requirements and interests. CECAD communicates actively with its partners, both within and outside the organisation. Through integrated communications and marketing strategies in which target groups, news bulletins, aims and key PR topics are aligned, the CECAD provides information specially tailored to the scientific community, political forums, scientific administrative bodies and business. In this process of science-to-science and science-to-public marketing, CECAD has forged many new communication channels in addition to the classic PR media.

The floating Science-Center MS Wissenschaft is cruising down German and Austrian rivers, the theme for 2011 being "Research for our Health". CECAD is taking part with an interactive exhibit. In the game 'Keep the worm alive!', young visitors take on the role of managers of their own metabolism. Alongside, a trailer tailoured to the young audience gives them some background or Edutainment. As 'Talking Heads', CECAD scientists describe the research going on in their particular area.





Urban Future - Future Energy - Understanding Aging: The three North Rhine-Westfalian universities, Dortmund, Münster and Cologne, staged the collaborative project 'Science Container' demonstrating their interdisciplinary approach to research at the tradefair NRW-Länderwoche. CECAD took the lead role in this science-to-science and science-to-public showcase project.

International Marketing: Science-to-Public and Science-to-Science

Examples are the Science-Container at Expo Shanghai and the interactive exhibit on the ship MS Wissenschaft. As a project leader with its Science-Container "Mega Challenges – Mega Solutions" CECAD took a winning place in international marketing, along with two other NRW institutions at Expo 2010 in Shanghai (NRW Länderwoche). The theme for Wissenschaftsjahr 2011 is 'Research for our Health' and CECAD is currently presenting an interactive exhibit on the popular science exhibition ship MS Wissenschaft. What CECAD is offering here is targeted Edutainment, thereby using the PR opportunity to present its unique selling points while addressing the educational and recruitment needs of this specific sector of the public. Aboard MS Wisssenschaft young guests are promoted to Managers of Metabolism in the game 'Keep the Worm Alive' while in 'Talking Heads' CECAD scientists explain in more depth why they are engaged in aging research. The link www.young-cecad.de provides more information and further insights into CECAD's activities as a follow-up medium. In August 2011, when the ship is due to dock in Cologne, CECAD will host an event to bring together internal stakeholders as well as the relevant scientific, political and administrative stakeholders from outside the cluster. Through this networking opportunity CECAD aims to achieve a double-spill-over effect and maximize its outreach potential.

Developing a new CECAD Corporate Image

In 2010 CECAD developed a new image for public and internal communications, reflecting its basic research objective: investigation of the disturbances of cellular activities and molecular mechanisms underlying the aging process. This new image is now projected across all the relevant information media. With regards traditional communications channels, the focus is on CECAD's new website, launched in January 2011, and the new internal newsleter that first appeared in May 2011. While the website is effective for external or internal use, the newsletter is intended chiefly for internal news topics and updates and to intensify links within CECAD. Further projects such as a PR film and trade fair stand are in progress.

Classic public relations is another vital aspect of our work, which may take the form of press releases, in-house publications or contributions to popular science journals and books such as die ZEIT or the Public Service Review of Science and Technology. Another new focus of PR activities is in the pipeline.

CECAD is keen to ensure that the scientific fruits of its high-level research yield high returns for the public financial resources invested and that these funds are applied so as to achieve the highest benefits for society, since the development of new therapeutic approaches to aging-associated disorders is a matter of considerable social relevance in an aging society.

The University of Cologne has CECAD to thank for its high ranking among the universities. The function of PR and Marketing is to highlight CECAD's leading position in the international research arena.

CECAD's external communications are stakeholder-oriented. To give effective publicity to our mission for society, our research vision and our concrete scientific achievements it is absolutely essential to address interest groups in their own language.

Internal communications: The CECAD Cologne newsletter. Who's coming – who's going, who's received an award or a recent grant, what new projects or purchases are in the pipeline, what interesting events are coming up?: The internal CECAD newsletter welds the cluster together and strengthens its identity by keeping all CECAD members up to date and better informed.

CECAD works closely with the Rectorate of Cologne University and recently collaborated over the concept and content of a special supplement for Die Zeit.

CECAD was selected prizewinner for 2009 in the 'Land of Ideas' contest. Professor Brüning receiving the award.

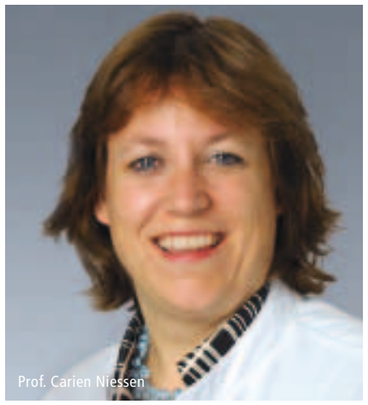
Exhibition of the Cologne Prizewinners from the contest 'Land of Ideas': Lady Mayoress Antwerpes opening the exhibition in January 2011.

Television interview with Professor Brüning on the Tageschau early 2011 on announcement of the DFG Excellence Initiative.

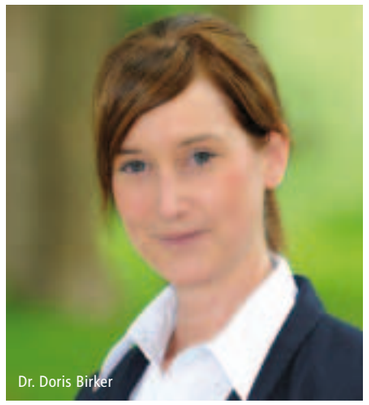
high **Relevance**

Successfull support of the next generation of research scientists is a lasting investment in the cluster's scientific future.

Platform for Education, Career Development and Gender Equality Programs



Prof. Carien Niessen



Dr. Doris Birker

Julia Panteleit

Education & Career Development

The Platform for Education, Career Development and Gender Equality Programs is dedicated to the career development of CECAD young scientists, providing a broad and varied training platform in general scientific and soft skills. This includes the structured program of the CECAD Graduate School as well as the career development of the Bachelor and Master students, PhD students, PostDocs and Junior Group leaders. CECAD's success is dependent on the scientific input and ideas of young, motivated and highly qualified international PhD students and postdoc researchers. The Cluster of Excellence for Aging Research at the University of Cologne offers a challenging environment for young scientists: CECAD identifies the relevant lines of enquiry and drives research at a high level of intensity. In turn, the young scientists benefit from this and from the opportunity to develop their scientific skills and extend their career opportunities.

The CECAD Graduate School

Research requires excellent training. The CECAD Graduate School with its principle of "Creating Sustainable Careers" therefore offers an extensive program for PhD students in the interdisciplinary and future-oriented field of aging and aging-associated diseases research. The three-year international program provides excellent conditions for research with intensive supervision and state-of–the-art technology platforms within an international work setting. English is the mandatory language of the program. The students

receive a full scholarship for the duration of the 3-year program and are further supported with 10,000 Euros bench fees per year. Additionally, they receive an annual sum of 1000 Euros travel money to ensure that no opportunities are missed for international networking through attendance of relevant conferences and summer schools. The graduate programme is completed by seminars and method courses in aging research. Soft skills courses in 2010 and 2011 included „Grant Writing", „Scientific Writing", and „Poster Presentations" and advanced courses in scientific research networking provide the basics for effective communication of research findings. In April 2009, the first five candidates of the CECAD Graduate School were selected from eighty international applicants. In 2010 CECAD could recruit seven international students for the graduate program. The four members of the 2011 class were selected from 220 applicants. The rise in number of international applicants since the start of the program is proof of the increasing attractiveness of the doctoral program and the draw of the cluster itself. Other factors contributing to its success have been the presence of the CECAD Graduate School at recruiting events such as the „Source Event" in Berlin, December 2009, „Nature jobs Career Expo" in London, September 2010 and the „MIT European Career Fair" in Boston January 2011, while announcement of the scholarships through leading print- and internet media also play an important role.

General education and career development

CECAD is dedicated to providing top quality education alongside specialised training at different stages of a researcher's career. To achieve this goal, the cluster has invested in and continues to expand a comprehensive training program.

The annual Master's course „Model systems of Aging and Aging-related Disease" is a key feature, giving CECAD students an introduction to methods and techniques commonly used in aging research.

All CECAD young scientists are invited to take part in the CECAD seminars and soft skills courses. The annual CECAD PhD student and PostDoc retreat offers another opportunity for networking, scientific exchange and cooperation among young CECAD members of the university and researchers from the Max-Planck Institute for the Biology of Aging who also participate.

To encourage international networks of PhD students and PostDocs, five travel grants were awarded in 2010, enabling successful applicants to attend an important meeting in their area of research and explore the possibility of working abroad as a PostDoc.

A further important component of the program was the discussion forum organized in February 2011 by CECAD in collaboration with the MPI for Biology of Aging and the IPMM Program of the University of Cologne. Here external speakers informed the young scientists about sources of funding through associations such as DAAD, DFG or the Marie-Curie Actions.

To encourage the transition of PostDoc researchers into independent group leader positions, CECAD introduced „CECAD senior postdoctoral fellowships". These fellowships have so far been awarded to two CECAD PostDocs who will receive 10,000 Euros bench fees/year for two years as well as a technician position.

CECAD Independent Junior Research Groups

One major goal of CECAD has been to further recruit exceptional Junior Research Group Leaders. In the last four years several excellent international young group leaders have joined CECAD and have supplemented and strengthened the scientific concept of the cluster. CECAD supports these young group leaders with excellent resources and sustained mentoring and training programs. Their success and quality is reflected in the prizes and awards won by these group leaders.

Scientific school activities

To generate enthusiasm for scientific research in the next generation requires a combination of public outreach and furthering of public understanding of science and research' (PUS/PUR). The fascination of teenagers and young adults with processes can be exploited to attract the scientists of tomorrow. In October 2009 sixth-formers from high schools were invited to attend a holiday academy, led by CECAD Professors, where they ran experiments to answer some of the key questions in aging research. Each year, the University of Cologne holds a Children's University with activities including field studies, laboratory experiments, lectures and detailed work in groups. This gives children and teenagers their first experience of scientific work and a taste of the fascination of thinking creatively and formulating questions. CECAD researchers also took part in this program in 2009 and 2011.

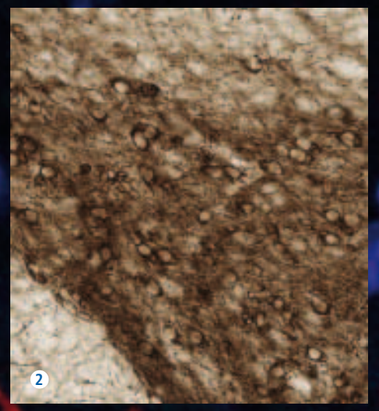
Gender Equality Programs

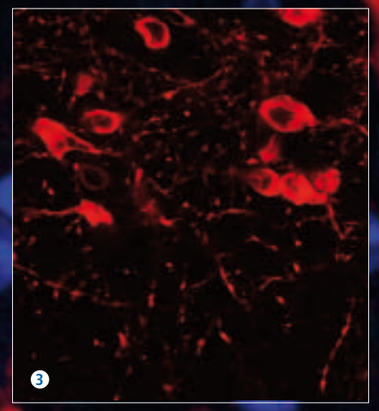
Female participation drops progressively beyond the PhD level and an important priority of CECAD is the advancement of women in science. CECAD has therefore implemented a "Keep Women on the scientific Career Path" program that includes career support, mentoring, family support and information dissemination. This has already borne fruit, since CECAD has been able to recruit a number of excellent female group leaders over the last two years. To achieve some of these goals, the Platform for Education, Career Development and Gender Equality Programs is working closely with the Gender Equality Office and the Family Support and Dual Career Office at the University of Cologne as well as various collaborative research centers.

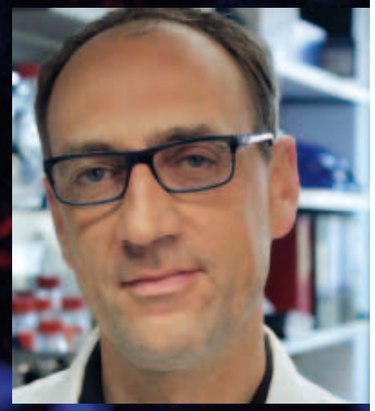
The „CECAD Female Faculty Club" was started in July 2010 to build up vertical communication links between female CECAD researchers from the level of Master's student to Professor. The meetings combine a short informative topic related to women in science and/or family matters with an informal get-together. Topics presented so far have included „how to combine science with being a mother" by our Junior Group Leader Aleksandra Trifunovic, „the legal do's and don't when you get pregnant" by the Family Support of Cologne University and an overview of the different female Cornelia Harte Mentor programs, offered by the Gender Equality Office.

Cologne University's new kindergarten "Paramecium", due to open in Autumn 2011, will give further support to gender equality by offering the option of child care tailored to University working hours. CECAD will salary two full-time child minders in this center so that 8-10 additional children of CECAD parents can be enrolled.

How is research progressing at CECAD Cologne?







1 Staining: Brigitte Hampel, Sulay Tovar. Double immunofluorescence for colocalization of endogenous tyrosine hydroxylase and transgenically expressed β-galactosidase in brain slices of reporter mice. Nuclear staining: blue (DAPI), β-galactosidase staining: green, tyrosine hydroxylase: red.

2 Staining: Brigitte Hampel, Christine Könner. Immunohistochemistry for endogenous tyrosine hydroxylase (brown) in the ventral tegmental area of the brain.

3 Staining: Brigitte Hampel, Sulay Tovar. Immunofluorescence for endogenous tyrosine hydroxylase (red) in the hypothalamic arcuate nucleus.

Prof. Jens C. Brüning

CECAD Coordinator
Head of Research Area D
Principal Investigator
Institute for Genetics

Body weight is tightly controlled within a species-specific range and organisms have developed a complex regulatory network to avoid either excessive weight gain or chronic weight loss. For energy homeostasis, i.e. maintenance of a stable metabolic state, there must be continual communication between the different organs involved: adipose tissue, skeletal muscle, liver, pancreas and the central nervous system (CNS). A tight hormonal network ensures rapid communication to control initiation and cessation of eating, nutrient processing and partitioning of the available energy within different organs and metabolic pathways. Recent experiments indicate that many of these homeostatic signals modulate the neural circuitry of food reward and motivation. Though this cross-talk has been intensively studied for many years, we are far from fully understanding how energy balance is maintained. Our aim is to identify the key neuronal targets of peripheral hormones involved in control of feeding and peripheral glucose metabolism, particularly those of leptin and insulin. We then hope to elucidate the intracellular signaling pathways in such neurons as well as the nature of higher integrating neurocircuits orchestrating the multiple outputs associated with nutrient balance and intraorganismal fuel partitioning. Finally, we aim to define the molecular basis of obesity- and aging-associated alterations in these pathways in order to establish novel molecular targets for the treatment of obesity and diabetes.

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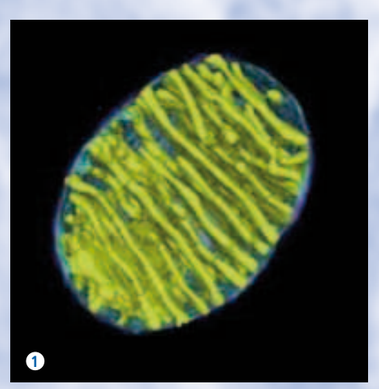

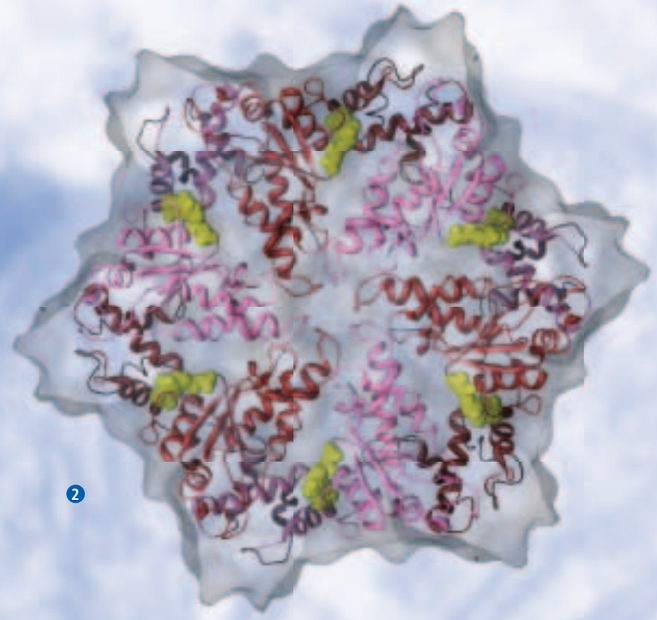

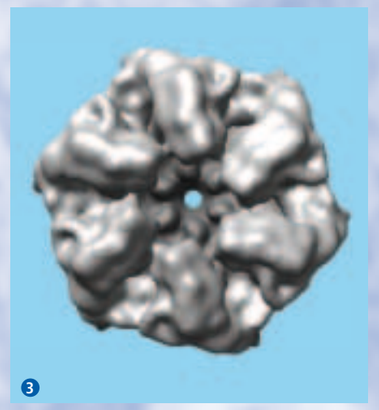

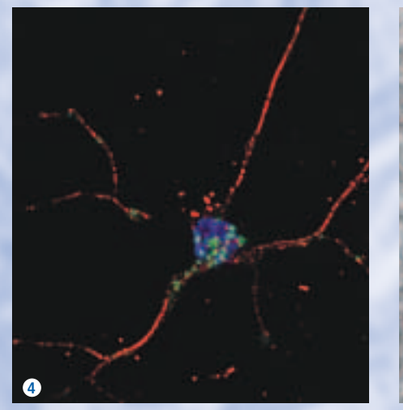

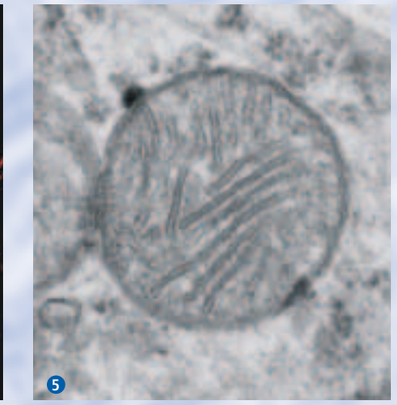

1 3D-reconstruction of *Neurospora crassa* mitochondria by electron microscopy.

2 & 3 Cryo-electron-microscopic reconstructions of hexameric m-AAA proteases (top view).

4 Mitochondrial fragmentation and perinuclear clustering in PHB2-deficient murine hippocampal neurons. Mitochondria were visualized expressing mitochondrially targeted EGFP (green). The nucleus was stained with DAPI (blue) and neuronal βIII-tubulin by immunofluorescence (red).

5 Electron microscopy of murine hippocampal mitochondria.

6 Structural model of the AAA ATPase ring of the yeast m-AAA protease based on the crystal structure of bacterial FtsH. A substrate binding region is highlighted in red.

Prof. Thomas Langer

CECAD Vice Spokesperson
Head of Research Area A
Principal Investigator
Institute for Genetics

A dysfunction of mitochondria, the powerhouses of the cell, has severe cellular consequences and is linked to aging and neurodegeneration. We are interested in cellular surveillance strategies that have evolved to limit mitochondrial damage and ensure cellular integrity. Protein quality control, executed by various intramitochondrial proteases, and the dynamic fusion and fission of mitochondrial membranes are emerging as key processes in the molecular network governing aging and life-span. Impairment of these systems is associated with various neurodegenerative disorders that form the focus of our research. Studies on AAA proteases, energy-dependent quality control enzymes in the inner membrane of mitochondria, and associated prohibitin scaffold complexes have unraveled important regulatory functions for biogenesis and fusion of mitochondrial membranes and highlight the importance of inner membrane integrity for mitochondrial activities and neuronal survival. The stress-induced processing of the dynamin-like GTPase OPA1 by the novel peptidase OMA1 has been identified as a potential sensing mechanism for mitochondrial dysfunction, offering novel approaches for genetic and biochemical interventions.

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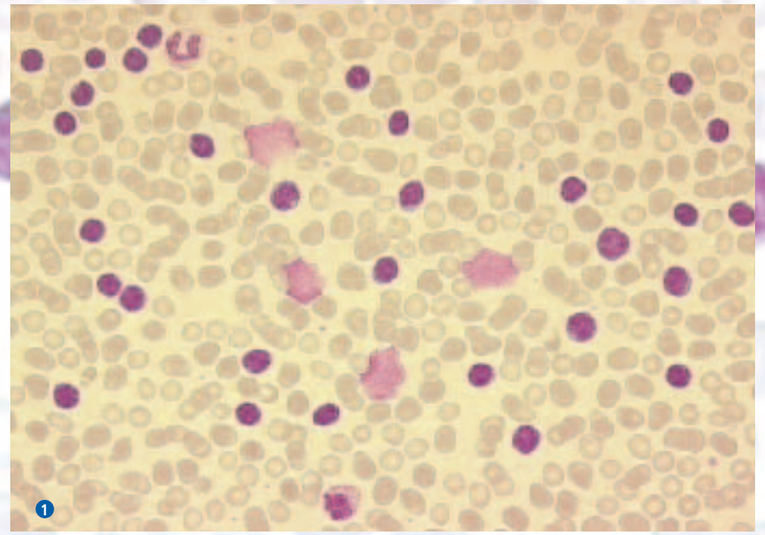

1 Lymphocytic cells: Peripheral blood smear showing chronic lymphocytic leukemia (CLL) with typical Gumprecht's shadows of dark-stained lymphocytes with scant cytoplasm.

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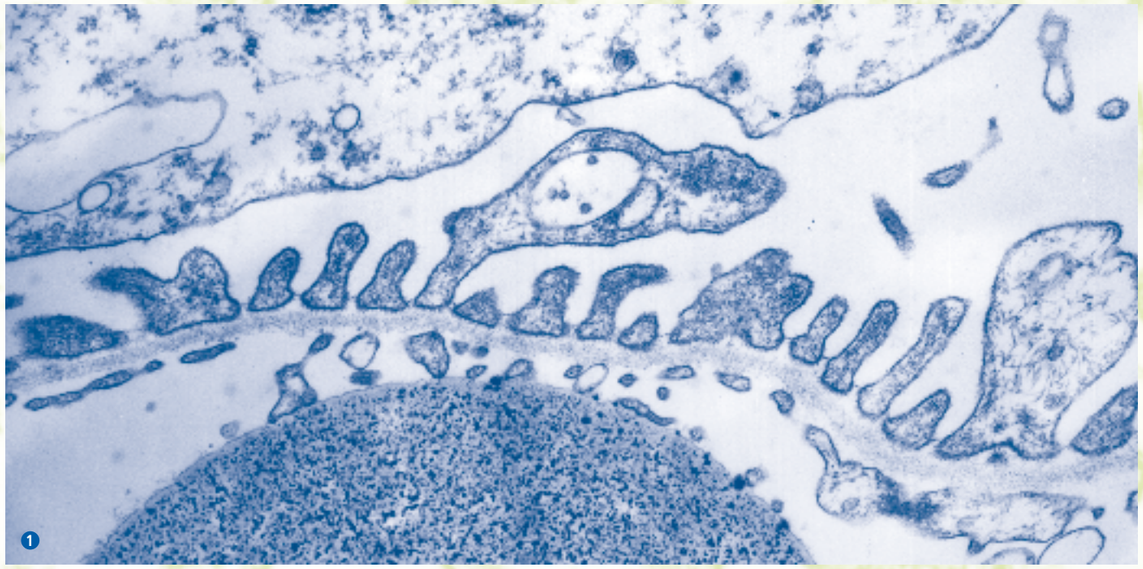
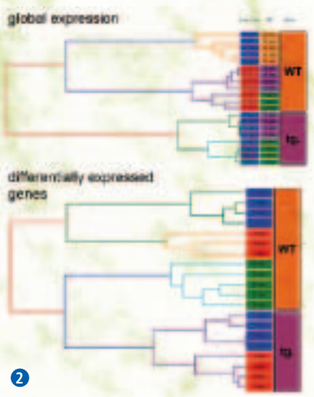
Prof. Michael Hallek

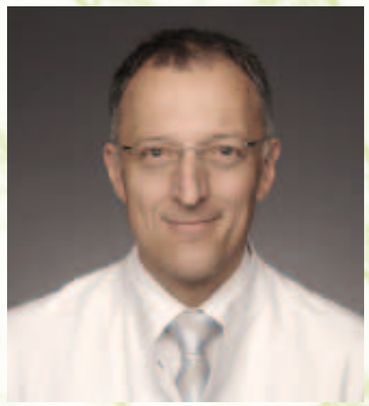
CECAD Vice Spokesperson
Principal Investigator
Department of Internal Medicine
and Center of Integrated Oncology

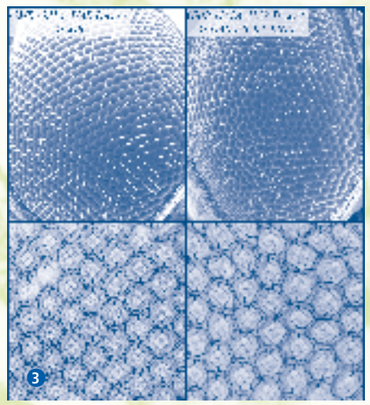
Chronic lymphocytic leukemia (B-CLL) is the most common leukemia in the Western world, occurring predominantly in the elderly. It is characterized by progressive accumulation of long-lived and apoptosis-resistant CD5+ B-cells. CLL cells will only expand in a suitable microenvironment. In our search for molecular modulators of the microenvironment in CLL pathogenesis we study the effects of macrophage migration inhibitory factor (MIF), and its putative receptor complex composed of CD74 and CD44, using targeted gene deletions in mice. To understand the relevance of MIF for the pathogenesis of CLL, we use the Eμ-TCL1 mouse model for human CLL. We have crossed the Eμ-TCL1-transgenic mouse model with MIF, CD74 and CD44 knockout mice and found that in the absence of MIF, the development of leukemia is significantly slower leading to a longer survival of leukemic mice. MIF seems to enhance the homing of macrophages in the typical homing organs (spleen, liver) of CLL cells, which enhance the proliferation and prevent apoptosis of leukemic cells. Our aim is to further dissect the pathways of this important interaction and to use this knowledge for the development of novel therapeutic principles. To this end, we have already used inhibitors of typical signaling pathways of the B-cell receptor to induce the apoptosis of CLL cells. Over the next 5 years, the following questions will be addressed:

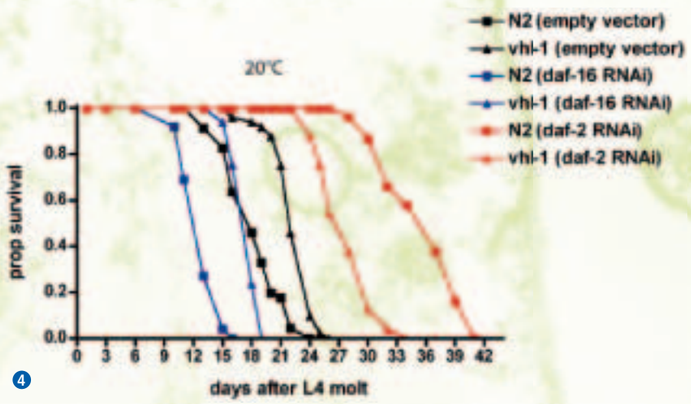
1. What are the key interactions between CLL cells and the (pro-inflammatory) microenvironment that promote aggressive forms of CLL?
2. What is the role of the PI3K pathway for CLL pathogenesis and treatment? A phase II trial with a PI3K inhibitor will be initiated.
3. Which factors govern the late onset of CLL despite its strong genetic predisposition?











1 Ultrastructure of the glomerular filter. The interdigitating foot processes of podocytes determine the architecture of the glomerular filter. Podocytes are terminally differentiated cells that cannot self-renew. Therefore, just like neurons they are predisposed to age-related injuries for a lifetime.

2 A genetic mouse model for age-related kidney disease. Analysis of differentially expressed genes in young mice of the genetic mouse model cluster compared to a group of old wildtype mice indicated that the genetically modified mice might provide a model for age-related kidney disease.

3 Lessons from the fly. The development of the complex symmetry of the fruit fly eye requires proteins and cellular programs highly conserved through evolution. Their mammalian homologs are essential for the integrity of the kidney filtration barrier. Deciphering these programs genetically in flies will help to elucidate the signaling pathways involved in podocyte maintenance and survival.

4 Renal Cell Carcinoma and Longevity. Almost all sporadic renal cell carcinomas are caused by mutations in the tumour suppressor protein VHL. Renal cell carcinoma is the most lethal malignancy of the genito-urinary tract and affects millions of patients worldwide. Interestingly, loss of this protein in the nematode C. elegans results in an increased lifespan. We now aim to identify the cell type responsible for the longevity phenotype and have observed and analysed the signaling pathways involved in stress response and lifetime regulation in these mutants.

Prof. Thomas Benzing

Principal Investigator
Kidney Research Center Cologne (KRCC)

An ever-increasing proportion of the aging population is affected by renal disease and hypertension. Although „normal aging“ does not necessarily cause dramatic changes in kidney function, deterioration of kidney filtration rate, a strongly increased incidence of hypertension and a high susceptibility to acute kidney failure are very common findings. The causes of age-related renal pathologies are poorly understood but genetic as well as environmental factors clearly play a role. Progressive glomerulosclerosis and a decrease in glomerular density through micro-/macrovascular changes as well as tubular atrophy, interstitial fibrosis and a low regenerative capacity of the injured kidney appear to be central to the understanding of this important age-associated disorder. Our lab uses mouse models of renal aging as well as the model organisms C. elegans and Drosophila melanogaster to address the role of genes involved in age-related kidney disease, altered renal repair capacity and stem cell function and the degeneration of the glomerular filtration barrier. We recently showed that deletion of the vhl-1 gene in C. elegans markedly extended lifespan in C. elegans and reduced susceptibility to various insults. pVHL is a major component of a ubiquitin ligase complex that controls stability of hypoxia-inducible transcription factors. Since pVHL is a known kidney disease protein, we are also investigating the role of the VHL gene and pathway in regulating age-related susceptibility to renal injury and stem cell function.

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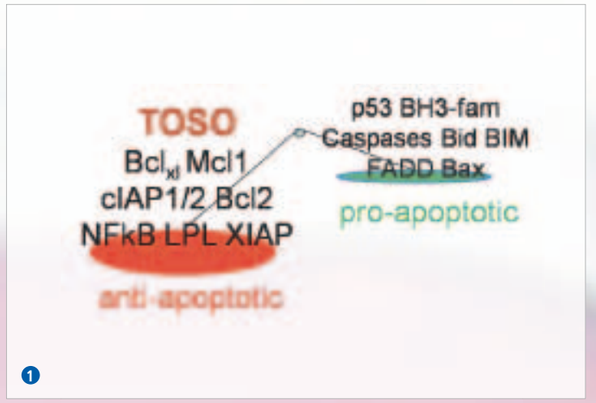
Prof. Oliver Cornely

Head of Translational Platform
Principal Investigator
Clinical Trials Center Cologne (CTCC)

The Clinical Trials Center Cologne (CTCC) plays a role vital in the success of CECAD's research strategy, bridging the gap between basic research and the application of therapeutic advances to clinical practice. The scientific and political goal of transferring results from 'Bench to Bedside and back' is the guiding principle along which Prof. Cornely directs the Medical Division of the Clinical Trials Center Cologne. CTCC was established by the Medical Faculty of the University of Cologne to support clinical trials processes and to further improve the quality of patient-oriented clinical research from the academic side. Over the last 4-year funding period since April 2007, financed by the Federal Ministry of Education and Research (BMBF 01KN1106), nine trial centers were set up within the University Hospital, each with a one-year grant for a principal investigator, and a further three-year grant for a study nurse. CCTC provides structural support, standardized through the laying down of standard operating procedures, for decentralized clinical study centers and further support through all stages of the clinical trial process.

The translation of clinical research findings into practical applications raises the fundamental question of how the insights gained through basic research, e.g. studies on model organisms, can be applied as rapidly and widely as possible to the development of new therapeutic approaches. And how, on the other hand, solutions to problems arising in clinical practice, e.g. in the treatment of neurodegenerative and neuromuscular disorders, can be found through basic laboratory research. CECAD is currently running five clinical trials and the first groups of patients will be enroled in the coming weeks. Establishing an active navigation system as part of the Translational Platform will ensure considerable growth in this area in coming years.



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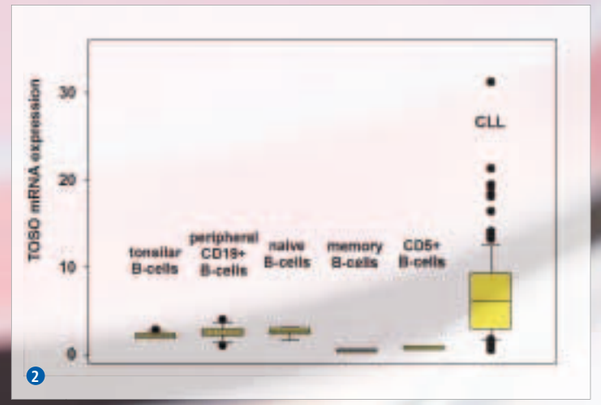

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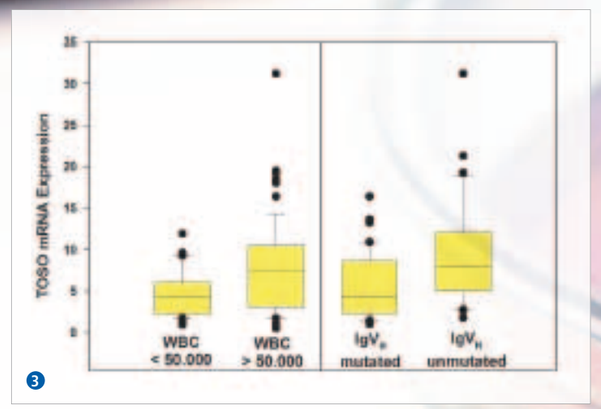

3

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Dr. Lukas P. Frenzel
Prof. Clemens-Martin Wendtner

Principal Investigators
Department of Internal Medicine I


Dr. Lukas P. Frenzel

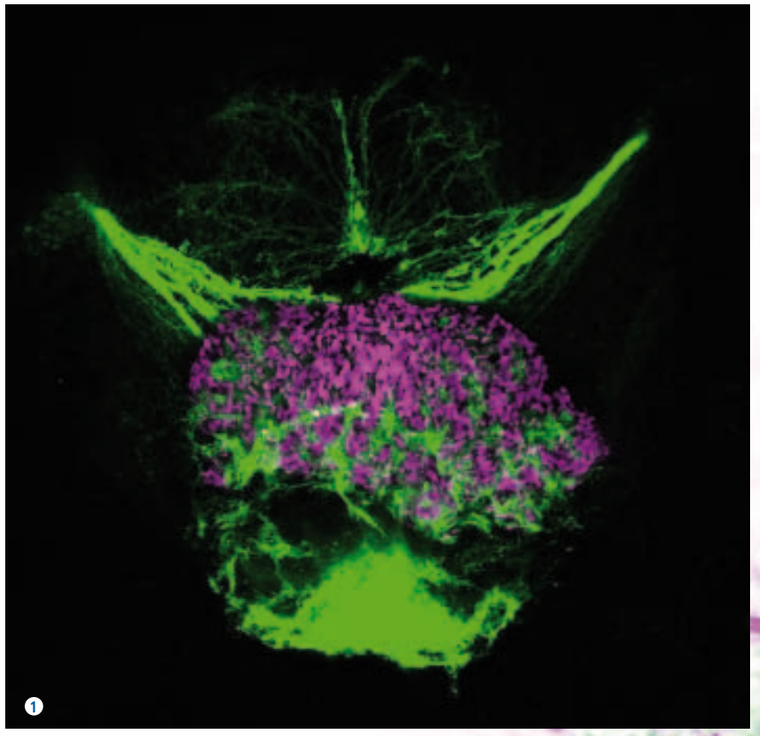

Prof. Clemens-Martin Wendtner

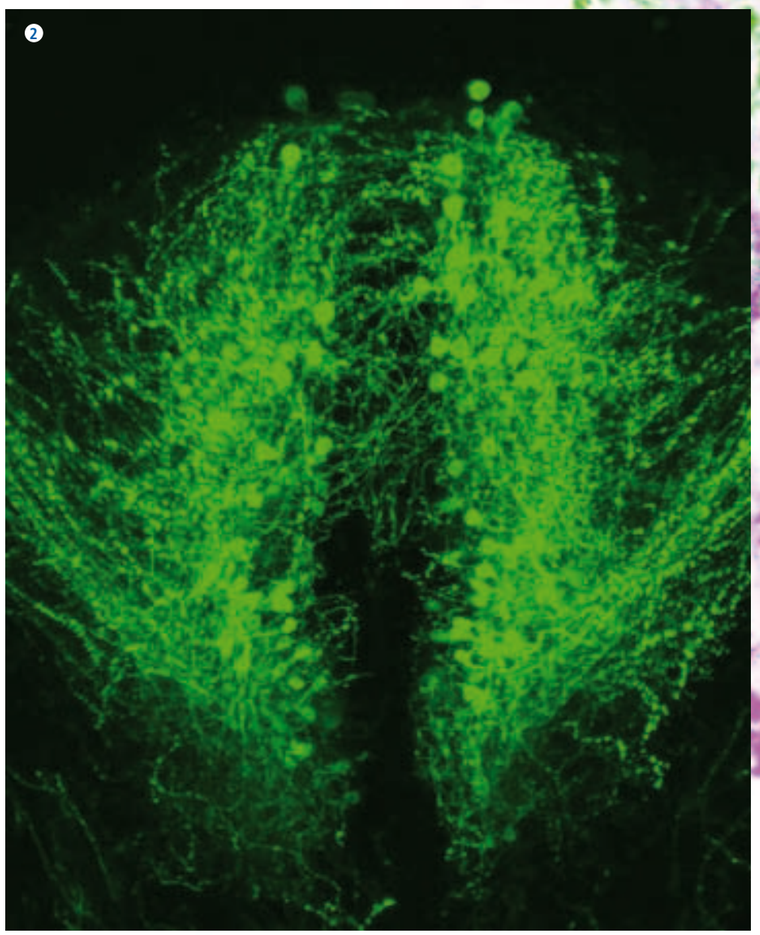
Survival and development of mature B cells and B cell-derived lymphomas depends on a complex network of signaling cascades. B cell antigen receptor (BCR) engagement is a major survival determinant in mature B cells and a central pathogenic force in chronic lymphocytic leukemia (CLL). BCR represents the most uniformly implicated promoter of CLL precursor transformation or clonal sustenance. BCR regulates TOSO, which was identified as a surface molecule with negative regulatory function on lymphocyte apoptosis. Moreover, we were able to show that TOSO is over-expressed on the B-cell subset and especially by CLL cells. Recent data indicate that TOSO deficiency results in reduced B-cell counts. Preliminary gene expression data reveal that TOSO might regulate central developmental and survival pathways in B cells. The research of our group is aimed at identifying the impact of TOSO on major key survival and activation pathways in normal and malignant B-cell development and its impact on the interaction with the microenvironment and metabolic pathways. Finally, we aim to develop strategies to target TOSO in vivo, as it may well have therapeutic potential for the treatment of immunologic disorders and hematologic malignancies.

1 TOSO – major determinant of disrupted balance between anti-apoptotic and pro-apoptotic factors in CLL.

2 TOSO is significantly overexpressed in CLL cells compared with normal B-cell subsets.

3 TOSO is significantly overexpressed in malignant cells from CLL patients with poor-prognosis.





1 Confocal brain section of a double-transgenic juvenile fish tg(otpb1:GFP; prl:RFP). The otpb1 transgene labels hypothalamic somatostatin-, CRH, TRH, vasopressin-like and oxytocin-like neurons or their axons, while the prl transgene labels lactotrophic cells of the anterior pituitary gland.

2 The tg(pomca-mGFP) transgene, which labels the POMC neurons of the arcuate nucleus in the hypothalamus.

Prof. Matthias Hammerschmidt

Principal Investigator
Cologne Biocenter

The genetic and cellular basis of the aging-associated disorders obesity and anorexia is not fully understood. Energy homeostasis in mammals is under the neuroendocrine control of the hypothalamic melanocortin system, comprising antagonistic POMC and AGRP neurons and a whole set of not fully characterized second-order neurons. Little is known about the plasticity of the system in relation to the metabolic state of the animal and possible changes that occur during aging. We address these questions in the zebrafish. We have found that zebrafish obesity becomes more prominent on aging, when somatic growth rates drop, whereas in younger fish the predominant response to ad-libitum feeding is increased growth. This shift coincides with a shift in the expression response of POMCa versus POMCb, the two zebrafish POMC paralogs. We have generated transgenic tools to compare the effects of overexpression of POMCa versus POMCb in young and older zebrafish, to study development and plasticity of the neuronal network via in-vivo imaging of neuronal wiring, synapse density and synaptic activity, to lineage-trace POMC and AGRP neurons at different ages, to study plasticity at the level of neurogenesis, and to conditionally ablate POMCa/b, AGRP and different second-order neurons (GHRH, TRH, HCRT etc.) in young and aged fish. Finally, in our ongoing forward genetic screens for zebrafish regulators of obesity or anorexia, we have isolated 8 confirmed mutants with alterations in the tightly associated somatic growth.

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Dr. Marco Herling

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1 Scenarios for the development of lymphoid malignancies in the background of inherited or acquired ATM inactivation (nach Stankovic et al, Blood 2002) and its potential chronological relationship to TCL1 aberrations (A) Pediatric Ataxia teleangiectasia (AT) patients with inherited inactivation of both ATM alleles develop B- and T-cell lymphoma, but T-cell tumors are largely predominant. ATM-/- mice also develop only T-cell tumors with predominance of chromosome 14 (TCR-locus) and chromosome 12 (murine TCL1 locus) breakpoints. (B) Individuals with both germline ATM alleles in wild type constitution can acquire complete ATM inactivation during lymphoid development and develop TCL1-positive tumors, which are either mature B-cell malignancies (B-CLL or mantle cell lymphoma) or mature T-cell leukemia (T-PLL). Overall, sporadic B-cell tumors are more common than T-cell malignancies in non-A-T individuals. (*) However, patients with sporadic B-CLL, but also T-PLL can be ATM mutation carriers. Thereby, this first (predisposing?) 'hit' can incide at germline, but also at differentiation stages of a hematopoetic precursor prior to the B-cell transformation stage, as shown by comparisons of buccal, non-B-cell leukocyte and tumor DNA. (Stankovic et al., Blood 2002). In support, genotyping 992 CLL pts. compared to 2707 healthy controls revealed variants (nsSNP's) in ATM and BRCA2 genes to be associated with higher risk of CLL (Rudd et al., Blood 2006).

Organismal aging and associated tumorigenesis are intrinsically linked to DNA damage and altered repair mechanisms. In lymphocytes, the molecular relays that govern the thresholds towards senescence vs. lymphomagenesis via shifts in cellular programs of repair vs. tolerance are largely unknown. The T-cell leukemia 1 (TCL1) oncogene, a strong activator of pro-survival AKT, is highly expressed in the lymphatic lineage and is implicated in the pathogenesis of T-cell prolymphocytic leukemia (T-PLL) and its B-cell counterpart chronic lymphocytic leukemia (CLL). A common feature of these tumors of mature lymphocytes is their predominance in the elderly, and a marked association with genomic aberrations / functional deficiencies of the DNA repair regulator ATM. This PI3-like kinase is a crucial regulator of processes involved in aging and cancer susceptibility. We hypothesize a functional link between TCL1 (oncogene) and ATM (tumor suppressor) in genome integrity of lymphocytes and our aim is to understand their oncogenic cooperation. We postulate that by augmenting signals through the antigen-receptor- or IGF-1R fed central PI3K-AKT-mTOR survival pathway, TCL1 'interferes' with an essential genomic integrity / longevity axis of ROS accumulation and Foxo-mediated ATM modulation. Our functional analyses on these molecular relationships tie in with many CECAD focus areas. A first spin-off at the translational level is the set of novel substances designed to sense and fatally potentiate tumor-specific elevated ROS.

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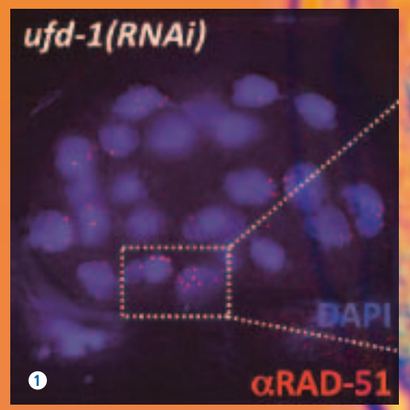

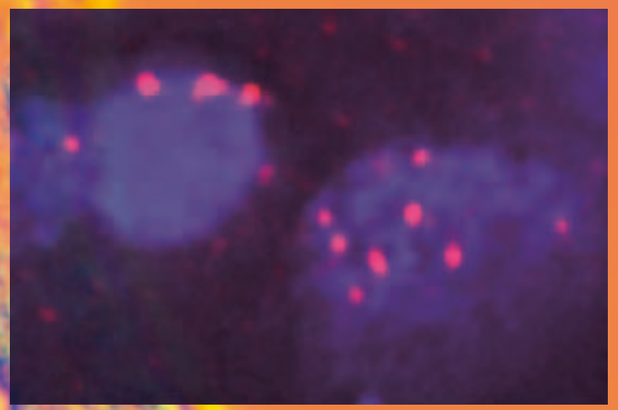

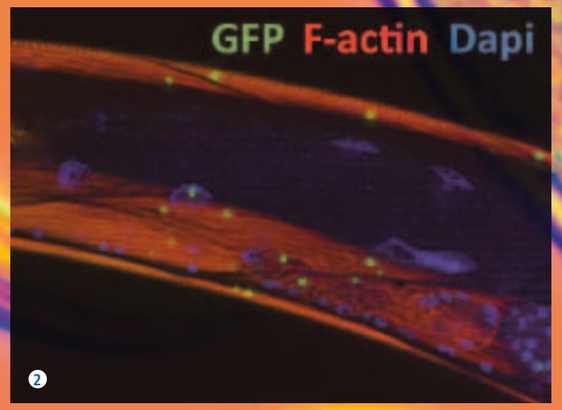

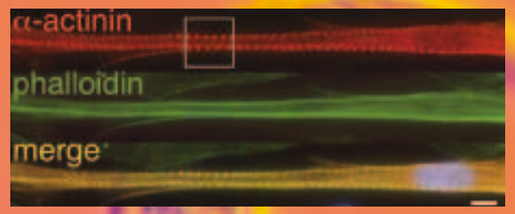

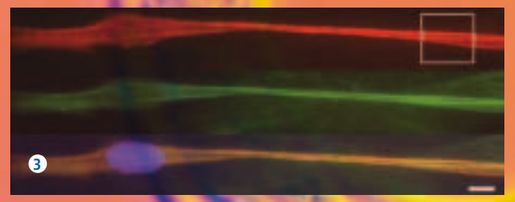

1 CDC-48 associates with various alternative adaptor proteins that modulate its activity. Previously, we investigated the conserved role of the CDC48UFD1/NPL4 complex in ERAD. Interestingly, our new results have identified a specific function of this complex throughout cell cycle control. We have therefore started a detailed analysis of the CDC48UFD1/NPL4 complex using time-lapse DIC microscopy. In early embryos of C. elegans, the first division is unequal and generates an anterior blastomere, AB, and a smaller posterior blastomere, P1, which have different fates and cell division timing, with AB dividing ~2 min before P1. Interestingly, downregulation of the corresponding genes cdc-48., ufd-1 and npl-4 by RNAi in the early embryo specifically increases the time separating the division of AB from that of P1, also called P1 division delay. Furthermore, we were able to show suppression of the RNAi induced P1 division delay phenotype by simultaneous downregulation of the PI-3-like kinase atl-1 and the kinase chk-1. Both kinases activate the DNA replication checkpoint that contributes to asynchrony of cell division in two-cell stage wild-type embryos (Mouysset et al., 2008). Recent work revealed WRN-1 as an additional checkpoint protein for DNA replication. Interestingly, it genetically interacts with CDC-48 in this pathway and human p97 physically associates to the human Werner (WRN) RecQ helicase. Similar to mutations of human WRN, wrn-1(RNAi) phenotypes confer features of accelerated aging in the worm. Thus, the detailed analysis of the WRN-1/CDC-48 interaction, using C. elegans as a model organism, will help us to decipher the relationship between genome stability and aging.

Prof. Thorsten Hoppe

Principal Investigator
CECAD Cologne at the Institute for Genetics

2 & **3** Recently, we revealed a novel functional interaction between UFD-2, the Caenorhabditis elegans ortholog of the yeast E4 enzyme UFD2, and CHN-1, a homolog of the human cochaperone CHIP. CHIP binds to the chaperones Hsc70 and Hsp90 and displays both E3 and E4 activity to mediate the ubiquitylation of a variety of chaperone-bound substrates. We discovered that UFD-2 and CHN-1 form a complex that apparently regulates the protein level of the myosin chaperone UNC-45, which in turn functions as a molecular chaperone to regulate myosin folding and assembly during muscle development. In combination, the E3 enzymes CHN-1 and UFD-2 are able to increase the multiubiquitylation of UNC-45 (Hoppe et al., 2004). Conceptually, these findings support a novel mechanism in which two E3 enzymes, UFD-2 and CHN-1, team up to achieve E4 function.
Our new findings have revealed an unanticipated function of the ubiquitin-selective chaperone CDC-48/p97 in myosin assembly and myofibril organization both in C. elegans and humans. The developmentally regulated assembly of a CDC-48/UFD-2/CHN-1 complex links turnover of the myosin chaperone UNC-45 to functional muscle formation. Our data suggest that a similarly conserved pathway regulating myosin assembly could exist in man. Remarkably, mutations in human p97, known to cause hereditary inclusion body myopathy, abrogate this muscle-specific activity and result in severely disorganized myofibrils. These results identify a key role of CDC-48/p97/VCP in the process of myofiber differentiation and maintenance, which is abolished during pathological conditions leading to protein aggregation and inclusion body formation in human skeletal muscle (Janiesch et al., 2007).

Differentiation, developmental processes and environmental changes challenge the integrity of the proteome in every eukaryotic cell. Proteostasis is maintained by the re-folding or degradation of unfolded and damaged proteins and is essential for cellular function, organismal development and viability. The ability to sustain protein quality control (PQC) is a long-term challenge for individual cells and entire organisms since high levels of damaged proteins accumulate with stress and aging. It is commonly thought that age-related impairment of PQC affects general proteostasis networks, allowing enhanced aggregation of unfolded proteins that can be toxic for cells and eventually shortening lifespan.

Protein ubiquitylation is known to be a key player in posttranslational control mechanisms and recent studies point to an involvement of ubiquitin in the regulation of aging. The main interest of our group is therefore on developmental processes in multicellular organisms that are governed by ubiquitin-mediated proteolysis (using C. elegans as a model). Besides the E1, E2, and E3 enzymes required for ubiquitin-conjugation, we have identified additional modulators involved in substrate recruitment and polyubiquitin chain assembly and we are currently investigating molecular mechanisms of polyubiquitin chain assembly on protein substrates in physiologically relevant pathways. This should provide essential information for research into protein aggregation diseases and throw light on the general interplay between protein homeostasis and aging/longevity.

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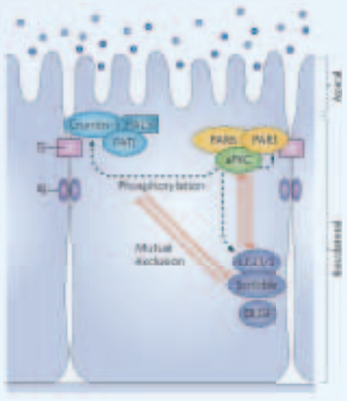
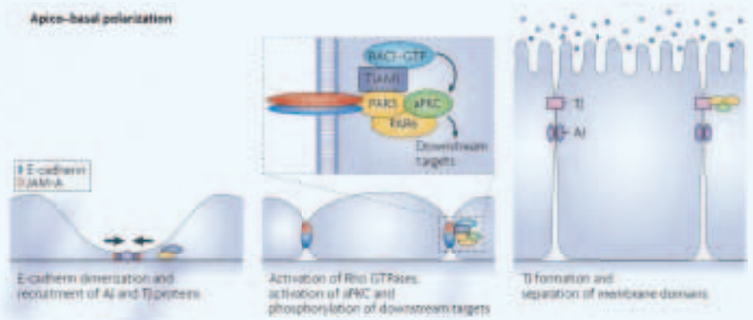


1 Polarity proteins of the Par3, Crumbs and Scribble complexes. Three conserved protein complexes — the partitioning defective (Par), Crumbs and Scribble complexes — control many polarization processes in different organisms. The polarity proteins were initially studied in Drosophila melanogaster and Caenorhabditis elegans, but all of them have at least one homolog in mammals.
The par genes were first identified in C.elegans. Two of these genes encode the PDZ-domain proteins Par3 and Par6 which, together with the Ser/Thr kinase atypical protein kinase C (aPKC), constitute the Par complex. Isoforms of Par3, Par6 and aPKC are ubiquitously expressed and are involved in various cell polarization processes. The kinase activity of aPKC is required for a functional Par complex, and aPKC-mediated phosphorylation of target proteins is a key event of downstream polarity signaling. The Crumbs complex comprises the transmembrane protein Crumbs and the cytoplasmic scaffolding molecules PALS1 and PATJ. A genetic interaction of the cytoplasmic proteins Scribble, Discs large (Dlg) and Lethal giant larvae (Lgl) was first described in D. melanogaster.
In polarized mammalian epithelial cells, the Par3 and Crumbs-3 complexes localize predominantly to TJs, whereas components of the Scribble complex show basolateral localization. Several molecular interactions between the three complexes have been identified. Mutual exclusion of the Scribble complex and the apical junctional complexes controls apico–basal polarity, and aPKC-mediated phosphorylation of Lgl2 and Par1, another conserved polarity protein (not shown) maintains the asymmetric distribution of polarity regulators. AJ, adherens junction, TJ, tight junction. (adapted from Iden & Collard, NRMCB 2008).

2 Crosstalk between Rho GTPases and polarity proteins during the formation of epithelial apico–basal cell polarity. Simplified schematic of apico–basal polarization. Following epithelial (E)-cadherin clustering, structural proteins (those that form AJs and TJs) and signalling proteins, including α-catenin, β-catenin, afadin and ZO-1, are recruited to immature cell–cell contacts. Transmembrane proteins of the junctional adhesion molecule (JAM) and nectin family are implicated in localizing the Par complex to primordial adhesions. Rho GTPases are activated downstream of cadherin clustering by unknown mechanisms. Through association with Par3, T-cell-lymphoma invasion and metastasis-1 (Tiam1) couples E-cadherin-dependent Rac1 activation to activation of aPKC, thereby inducing phosphorylation of downstream targets and subsequent polarization and maturation into fully polarized epithelium. (adapted from Iden & Collard, NRMCB 2008).



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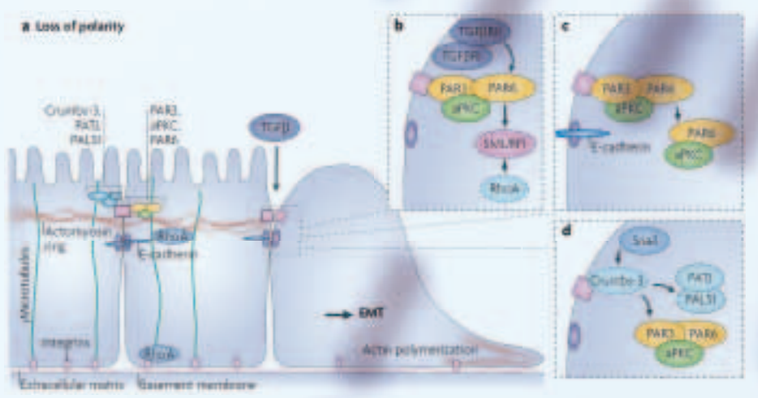

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3 Mechanisms inducing loss of epithelial polarity and EMT. a Transforming growth factor-β (TGFβ) induces epithelial–mesenchymal transition (EMT) through different mechanisms, including targeting of polarity proteins and Rho GTPases. b Ligand-activated TGFβ receptor II (TGFβRII) phosphorylates Par6, which in turn activates the E3 ubiquitin ligase Smurf1 and thereby induces proteasomal degradation of RhoA, loss of the actomyosin ring and breakdown of apico–basal polarity. c TGFβ also induces transcriptional downregulation of Par3, resulting in the cytoplasmic localization of aPKC and Par6, downregulation of E-cadherin and loss of TJs and AJs. d Furthermore, TGFβ activates the transcriptional repressor Snail, which inhibits Crumbs-3 expression, leading to the relocalization of the Crumbs-3 complex proteins PALS1 and PATJ as well as of the Par complex, followed by loss of apico–basal polarity. Another early event during EMT is the loss of basally localized RhoA activity, which results in the disassembly of basal microtubules, disruption of integrin-mediated adhesion and the subsequent breakdown of the basement membrane. (adapted from Iden & Collard, NRMCB 2008).

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Cell polarization is crucial for the development of multicellular organisms and aberrant cell polarization contributes to various diseases. Seminal studies in invertebrates identified proteins that regulate various polarization processes including asymmetric cell division and epithelial cell polarization. Polarity proteins may react to extrinsic polarity cues such as growth factor gradients or extrinsic cues such as the microtubule cytoskeleton. By assembling multiprotein complexes, they induce downstream signaling to establish cellular asymmetry. Of the three polarity protein complexes described so far – Par3, Crumbs and Scribble – the Par3 complex has the broadest function. Furthermore, cross-talk between polarity proteins and Rho GTPase signaling components controls formation of cell-cell contacts and apico-basal polarity in epithelial cells. For decades, loss of apico-basal polarity has been considered a prerequisite for tumor formation and progression.

The research of our junior group focuses on the function of polarity proteins in skin homeostasis and in age-related pathologic conditions including cancer. We are investigating cell type-specific functions of polarity proteins, and studying the consequences of deregulated polarity signaling on cellular architecture, survival mechanisms and cell death. Overall, our aim is to gain a better understanding of aging-associated skin pathologies, which may reveal future directions for targeted therapies.

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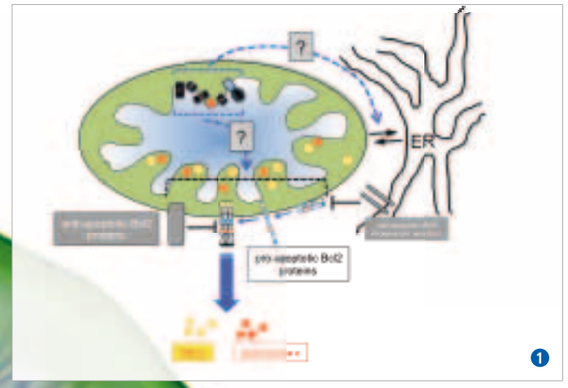

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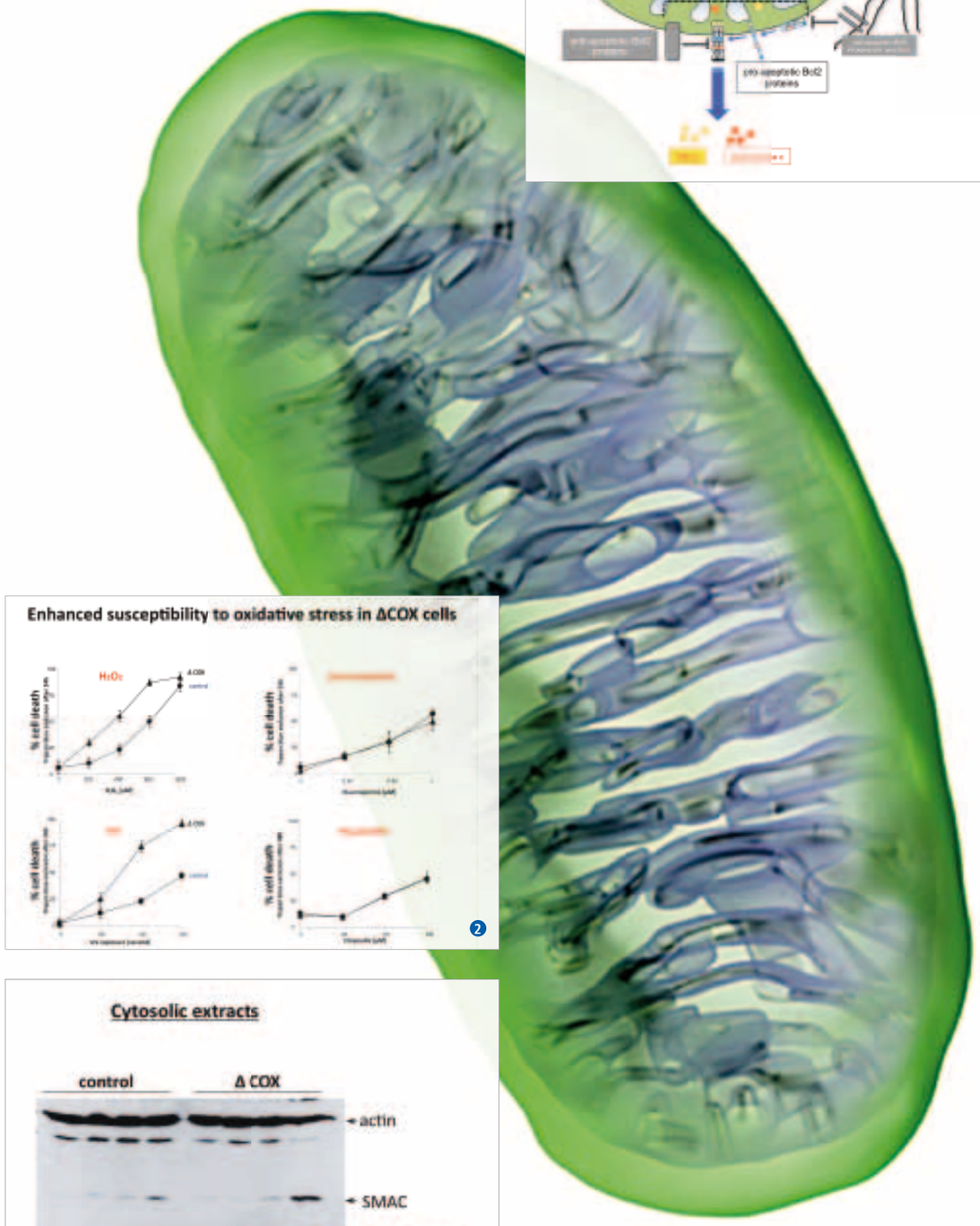

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3

Dr. Hamid Kashkar

Principal Investigator
Institute for Medical Microbiology, Immunology and Hygiene (IMMIH)

There is a general consensus that an accumulation of cellular damage is the initiating event in aging and that mitochondria are the convergence point for signaling cascades triggered by cellular damage. The mitochondrial check point permits cells either to arrest mid-cycle to restore function or to undergo apoptosis when severely damaged. Apoptosis is induced by permeabilization of the mitochondrial outer membrane, releasing pro-apoptotic factors including cytochrome c and SMAC. Whereas cytosolic cytochrome c initiates the proteolytic activation of caspases, cytosolic SMAC potentiates caspase activity by antagonizing the inhibitor of apoptosis proteins (IAPs) family.

Our longstanding interest is in understanding the physiological role of the crosstalk between mitochondria and IAPs in the context of cancer and neurodegenerative diseases and the immediate aim of our research is to establish whether alteration of mitochondrial outer membrane permeabilization contributes to apoptosis dysregulation or immune inflammation in such aging-associated diseases and if so, how. Mechanistically, we will scrutinize the molecular mechanisms controlling the coordinated release of mitochondrial factors in response to cellular damage cues. Unique opportunities will arise from our studies for development of new in-vivo mouse models, the ultimate aim being to create synergies between in-vitro and in-vivo research programs extending from animal models to patients.

1 The apoptotic activity of mitochondria is regulated by the family of Bcl2 proteins consisting of anti- (Bcl2, Bcl-xL, Mcl1, BI1) and pro-apoptotic (Bax and Bak) members. Activation of pro-apoptotic members like Bax (conformational change) has been viewed as an early key regulatory step, which directs the permeabilization of the outer mitochondrial membrane (OMM) and releases multiple death-promoting factors including cytochrome c and SMAC. These in turn induce caspase activity and apoptosis. The objectives of this project are to establish: 1) how alterations of the respiratory chain modulate Bcl2 protein function, 2) the role of mitochondria-ER physical interaction and how it is controlled by mitochondrial RC.

2 A wild-type cell line (wt) and a cybrid line containing mtDNA mutation (a truncation mutation in the cytochrome c oxidase subunit I) (ΔCOX) were treated with different apoptotic stimuli. Cell death was measured after 24 hours.

3 Wt and ΔCOX cells were treated with increasing concentrations of H2O2. Cytosolic fractions were isolated and the amounts of cytosolic SMAC and cytochrome c were analyzed by Western blotting.

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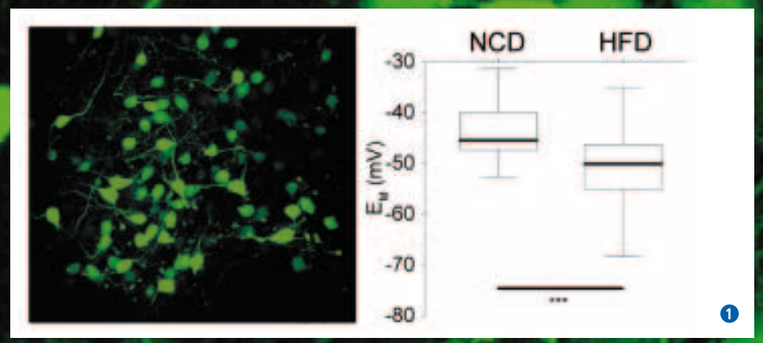

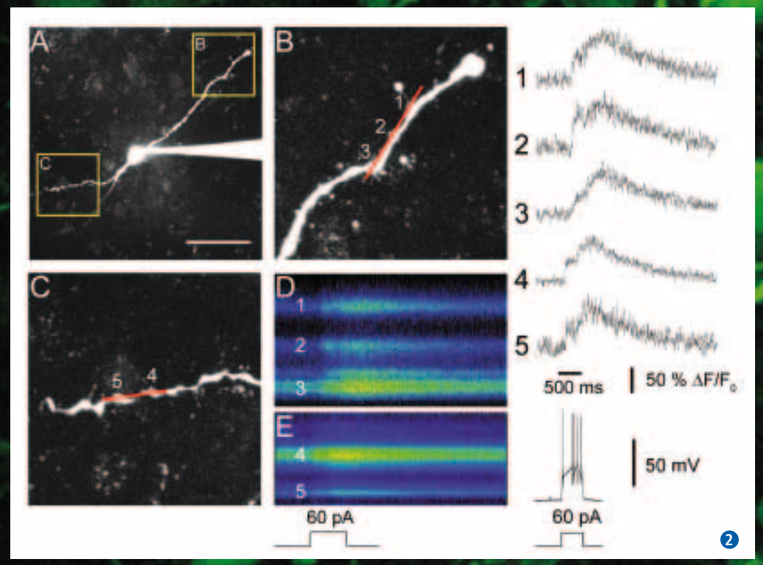

1 Diet-dependent modulation of membrane potential in pro-opiomelanocortin-expressing neurons (POMC neurons). Left: GFP labeled POMC neurons in the arcuate nucleus of the mouse hypothalamus. These neurons are important components of the neuronal circuit that regulates energy homeostasis. Right: High-fat diet (HFD) hyperpolarized the resting membrane potential of POMC neurons (NCD: normal chow diet).

2 Activity dependent Ca^{2+} influx in a POMC neuron. A Calcium Green-1-loaded POMC neuron. B, C Framed regions of A in higher magnification. Positions of the line scans are marked with red lines. The numbers indicate areas of the line scans analyzed. D, E Line scans. Ca^{2+} accumulation was induced by a short burst of action potentials. Numbers correspond to positions in B and C. right panel: extracted fluorescence data from the corresponding line scans in D and E.

Prof. Peter Kloppenburg

Principal Investigator
Cologne Biocenter

Obesity and type 2 diabetes are closely linked diseases that are associated with excessive weight and fat mass, and their prevalence is increasing within Western populations. To better understand and counteract obesity, type 2 diabetes, and associated metabolic disorders, increasing efforts are being made to define the homeostatic control mechanisms that regulate body weight and energy homeostasis. Energy homeostasis is tightly controlled by neuronal circuits in the arcuate nucleus of the hypothalamus to adjust food intake and energy expenditure according to the availability of fuel sources in the periphery of the body. Aging, extreme diets, and diseases can deregulate these neuronal systems. Thus, defining age and diet-associated changes in this network is critical to the understanding of what makes organisms increasingly susceptible to metabolic disorders over their life-span. The long-term goal of our laboratory is to analyze and define the biophysical parameters and cellular mechanisms that cause age- and diet-dependent changes in intrinsic firing characteristics and synaptic properties in the neuronal circuits that control energy homeostasis. To achieve this aim, our group is using a combination of electrophysiological recordings and optical imaging. A detailed understanding of the cellular and molecular mechanisms that promote or prevent deregulation of these neuronal control circuits during aging, extreme diets, and diseases may lead to novel approaches for therapeutic intervention in metabolic and neurological disorders.

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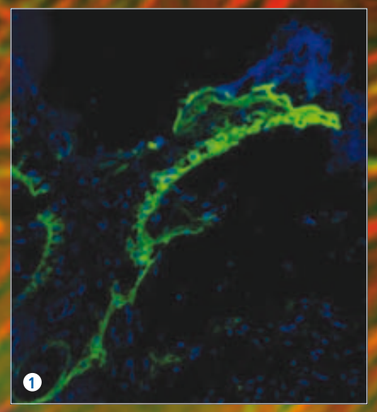
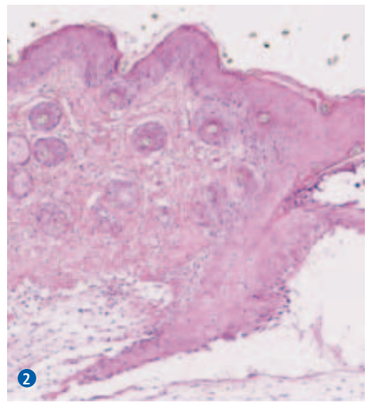
Belgardt BF, Husch A, Rother E, Ernst MB, Wunderlich FT, Hampel B, Klockener T, Alessi D, Kloppenburg P, Brüning JC (2008) PDK1 deficiency in POMC-Expressing cells reveals FOXO1-dependent and -independent pathways in control of energy homeostasis and stress response. Cell Metab 7:291-301



1 - 3 Reciprocal interactions among cells and of cells with the surrounding extracellular matrix are crucial to maintain skin homeostasis. Alterations have been implicated in diseases ranging from skin ulcers to cancer of the skin. Studies to dissect the underlying molecular mechanisms utilize patient skin biopsies, genetic mouse models and complexes in in-vitro cell culture systems.

Prof. Thomas Krieg

Principal Investigator
Department for Dermatology and Venerology



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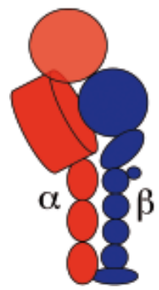

Research in the Department of Dermatology concentrates on severe common skin diseases. Cell-cell and cell-extracellular matrix interactions are crucial for the maintenance of healthy skin functions and disturbed in a number of such diseases, for example in chronic inflammatory processes, autoimmune disorders, non-healing wounds, formation of keloids and other fibrotic disorders, invasive growth and metastasis of common skin tumors, photo-aging and genodermatoses.

Key questions addressed in our laboratory are

- How does the interaction among cells in the epidermis control the barrier functions of the skin?
- What is the relevance of defined inflammatory cells and their secreted mediators for skin diseases and skin aging?
- By which mechanisms do cells interact with the extracellular matrix of skin and how does this communication affect dermal homeostasis, proteostasis and tumor growth/invasion?

The aim of our work is to translate experimental, clinically oriented research into treatments suitable for clinical application.

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Gabrielli A, Avvedimento EV, Krieg T (2009) Scleroderma. N Engl J Med 360: 1989-2003

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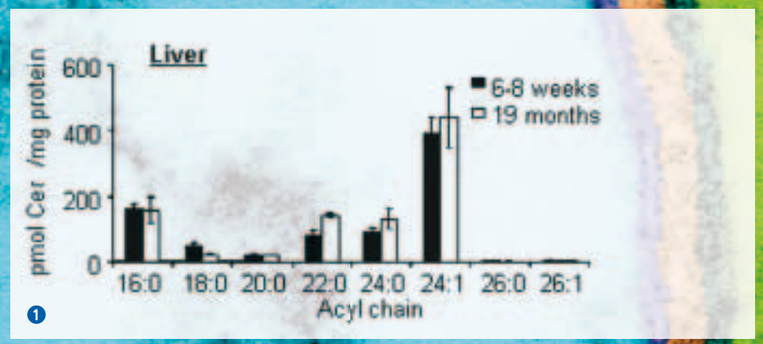

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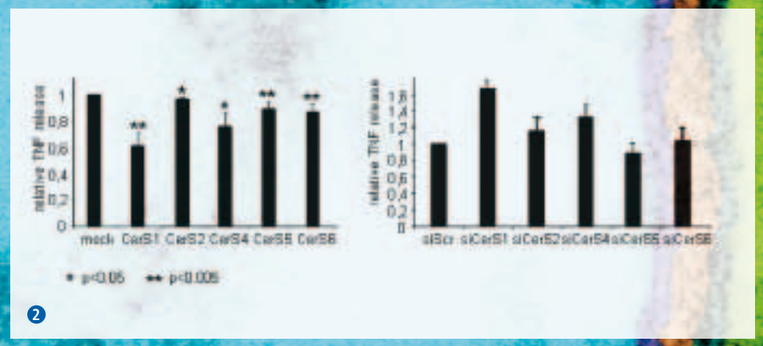

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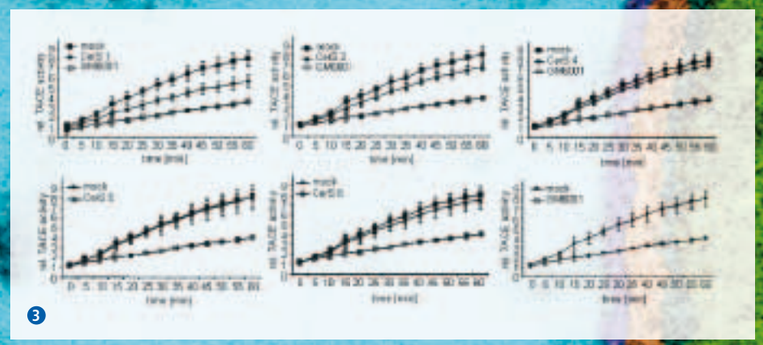

3

Prof. Martin Krönke

Head of Research Area B
Principal Investigator
Institute for Medical Microbiology, Immunology and Hygiene (IMMIH)

Aging of the immune system (immunosenescence) renders the aged less able to mount an immune response following infectious challenge and is mediated by both an impaired adaptive immunity and the dysfunction of the innate immune system. Furthermore, immunosenescence is associated with a pro-inflammatory state characterized by elevated cytokine levels and impaired membrane cytokine receptor function. Many innate defense mechanisms are membrane-bound events and within membranes, ceramides form platforms that cluster receptor molecules and regulate uptake of bacterial and viral pathogens. Changes in ceramide production appear to follow a development-aging continuum and can be generated through different pathways. The de novo synthesis involves ceramide synthases 1-6 (CerS). CerS genes are homologous to the Lass (longevity assurance homolog) gene family in yeast, provoking the hypothesis that age-related changes of membrane sphingolipid composition cause functional deficits of innate immunity.

Our results indicate that i) CerS1 expression is decreased in aged mice, ii) the concomitant decrease of C:18 ceramide leads to a hyperactive TNF-converting enzyme (TACE), and iii) that the enhanced TACE activity in turn causes increased TNF release, which is the hallmark of the hyper-inflammatory state of the elderly. During the next funding period our group aims to identify the molecular basis for the functional link between CerS genes and age-related syndromes such as the pro-inflammatory state and oxidative stress generated by NADPH oxidases.

1 Down-modulation of C18-ceramide in aged mice. The ceramide composition of membranes from liver tissue of old (>19 months) mice exhibited increased C22:0, C24:0, and C24:1 ceramides compared to liver from 6-week-old mice, whereas the C18-ceramide content was significantly lower (Fig. 1). These specific changes in C18-Cer expression were detected in aged mice from three different sources.

2 CerS1-dependent TNF release. Results from TNF ELISAs showing the pronounced effect of overexpression of CerS1, which alters C18:0-ceramide, on TNF release.

3 CerS1 dependent TACE activity. To obtain mechanistic insights into the action of C:18-ceramide on TNF release TACE activity was analysed in HEK293FT cells transfected with either CerS expression plasmids or CerS specific siRNAs, respectively. Overexpression of CerS1 had the most obvious inhibitory effect on TACE. After CerS down-regulation by siRNAs, a significant increase in TACE activity was observed with CerS1siRNA over a 60-minute period compared to cells transfected with the scrambled control siRNA.

Herz J, Pardo J, Kashkar H, Schramm M, Kuzmenkina E, Bos E, Wiegmann K, Wallich R, Peters PJ, Herzig S, Schmelzer E, Krönke M*, Simon MM, Utermöhlen O* (2009) Acid sphingomyelinase is a key regulator of cytotoxic granule secretion by primary T lymphocytes. Nat Immunol. 10: 761-768 (* shared responsible authorship)

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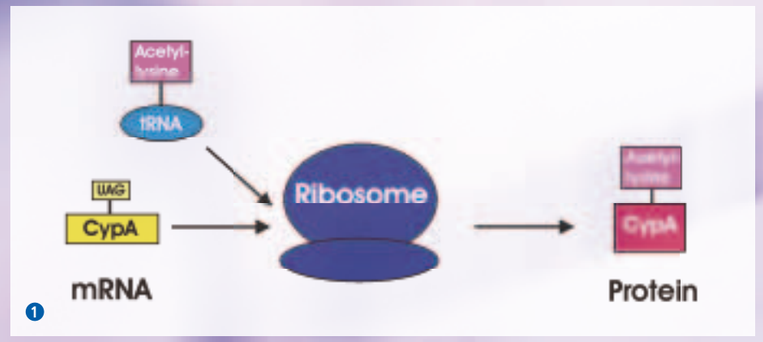

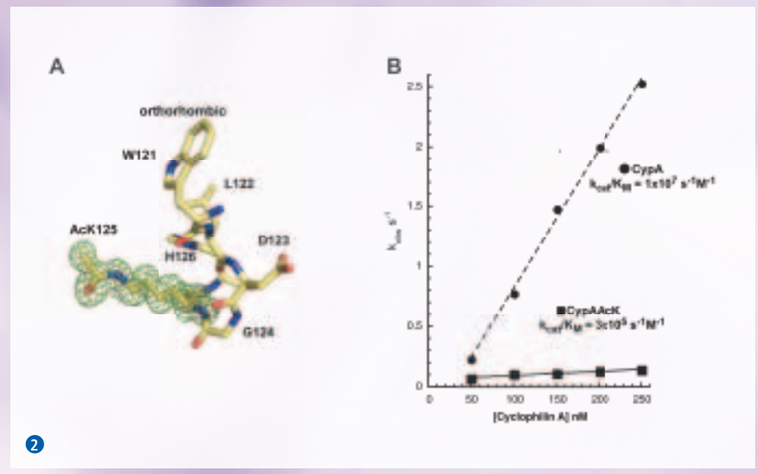

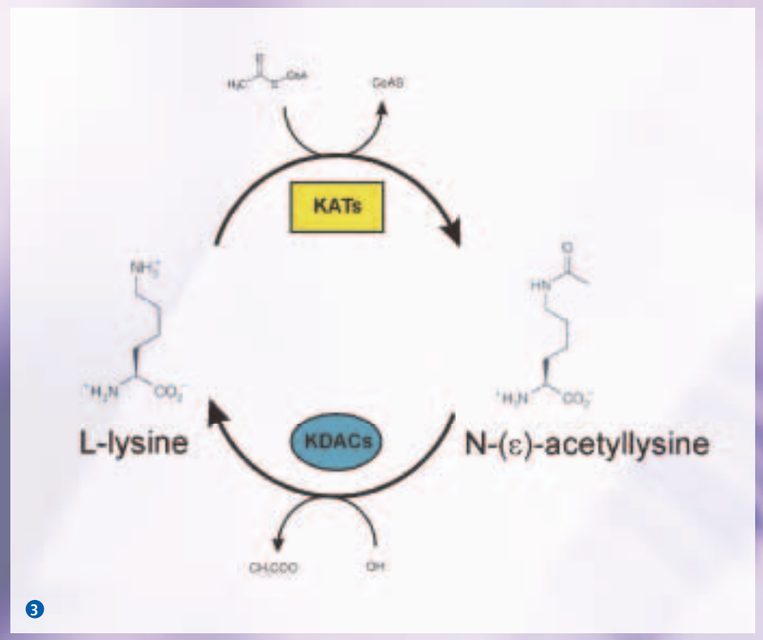

1 The genetic-code expansion concept. Archaea use an expanded-genetic code, i.e. they decode additional proteinogenic amino acids. We use a synthetically evolved orthogonal aminoacyl-tRNA synthetase/$tRNA_{CUA}$ pair from *Methanosarcina bakeri* to specifically charge tRNAs with acetyl-lysine and incorporate it recombinantly into proteins as a response to an amber-stop codon.

2 Functional consequences of K125 acetylation in CypA. (A) Omit map of the acetyl-lysine density for the orthorhombic CypA AcK125 structure contoured at 1 σ. (B) Acetylation decreases CypA-catalysed *cis* to *trans* isomerization. A linked chymotrypsin assay was used to measure the catalytic efficiency of *cis-trans* isomerisation by CypA. The two kinetic rates observed represent a first fast phase showing cleavage of a nitroanilide peptide *trans*-substrate by chymotrypsin and a second slower phase representing *cis-to-trans* isomerization by CypA prior to cleavage by chymotrypsin. Plotting CypA or acetylated CypA against kobs gives k_{cat}/K_M showing that acetylation reduces kcat/KM 35-fold (Lammers et al., 2010).

3 The reversible acetylation/deacetylation cycle of N-(ε)-lysine. KATs catalyse the transfer of the acetyl-moiety from acetyl-CoA to the N-(ε)-amino group of lysine side chains. KDACs remove the acetyl-moiety, reforming the non-acetylated lysine side-chain.

Dr. Michael Lammers

Principal Investigator
CECAD Cologne at the Institute for Genetics

In our group we are interested in the role of post-translational lysine-acetylation in controlling cytoskeletal function. Recent progress in quantitative proteomics has shown that thousands of proteins in all cellular compartments covering all essential cellular functions are lysine-acetylated. This suggests that the function of post-translational lysine-acetylation extends far beyond the control of gene expression as originally thought. Lysine-acetylation could directly influence protein function by a variety of different mechanisms, and dysfunction of the acetylation/deacetylation regulatory system may be involved in the development of cellular disorders.

Using the genetic code expansion concept, our group will study mechanistically how protein lysine-acetylation regulates cytoskeletal function up to atomic resolution. We will synthesize proteins carrying homogenously and site-specifically incorporated acetyl-lysine residues, using a synthetically evolved aminoacyl-tRNA synthetase/$tRNA_{CUA}$ pair from *Methanosarcina bakeri*. To this end, we will use biophysical methods including X-ray-crystallography to determine the effect of lysine-acetylation on protein structure and function.

Quantitative proteomics, using stable-isotope labeling with amino-acids in cell culture (SILAC), will provide a detailed view of how the acetylation patterns of proteins change in aging-associated diseases such as cancer and neurodegenerative disorders. These studies will reveal functional differences between lysine-acetylation and other post-translational modifications such as phosphorylation and ubiquitylation, which may open up new therapeutic strategies for the treatment of aging-associated diseases.

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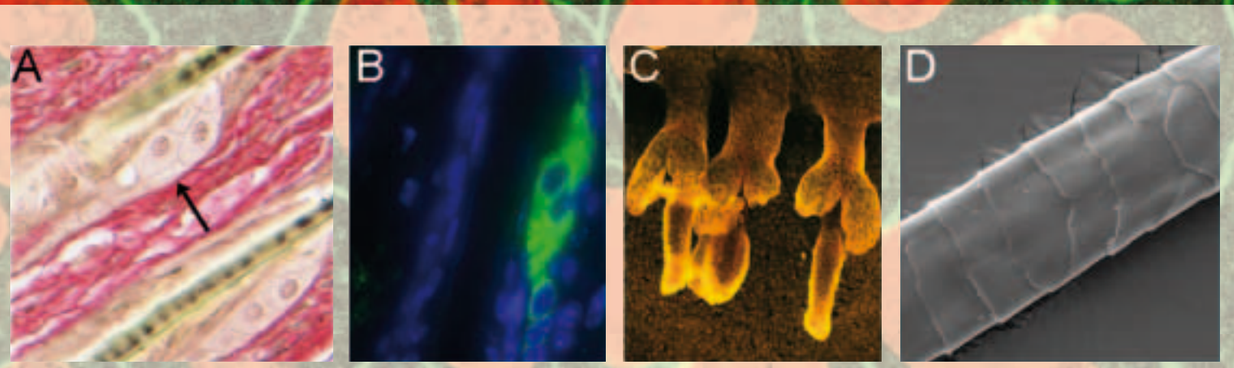

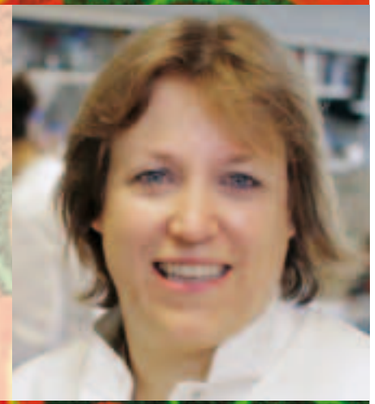

1 Epidermal appendages: (A) The sebecaous gland (arrow) is associated with the hair follicle and (B) characterized by SCD1 as stained for in green. (C) Wole mounts of three hair follicles and their associated sebaceous glands. (D) Scanning electron micrograph of a hair. The background image visualizes the tight junctional barrier in primary keratinocytes stained for the tight junctional marker ZO1-1. Red represents the nucleus.

Prof. Carien Niessen

Head of Platform for Education, Career Development
and Gender Equality Programs
Principal Investigator
Center for Molecular Medicine Cologne (CMMC)

The skin barrier protects organisms from drying out and is the first line of defense against micro-organisms, UV radiation and heat. For organisms to maintain and restore the skin barrier, the interfollicular epidermis (IFE) and its appendages, hair follicles (HF) and sebaceous glands must continously be renewed. Different populations of stem- and progenitor cells guarantee constant self-renewal under steady state conditions and sufficient plasticity for the fast replacement of lost tissue in case of injury. The flexible balance between self-renewal and terminal differentiation is determined by the variable conditions of the extracellular environment. Both barrier integrity and plasticity of the progenitor cell pools decrease during aging. The overall goal of my laboratory is to understand how regulators of cell structure integrate with regulators of metabolic activity, proliferation and inflammation to control skin barrier formation and homeostasis. Finally, our aim is to understand how age associated alterations in molecular regulators of cell architecture alter progenitor cell behavior and result in (age) associated impairment of the skin barrier.

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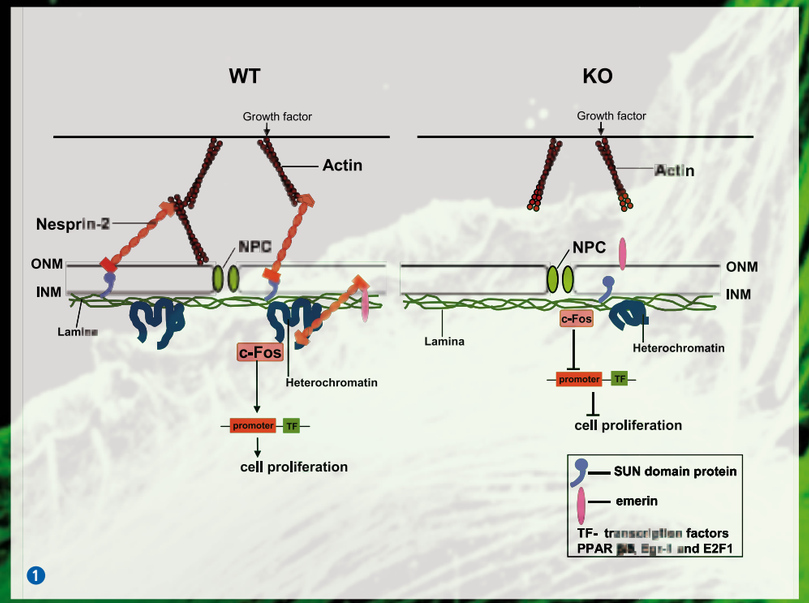
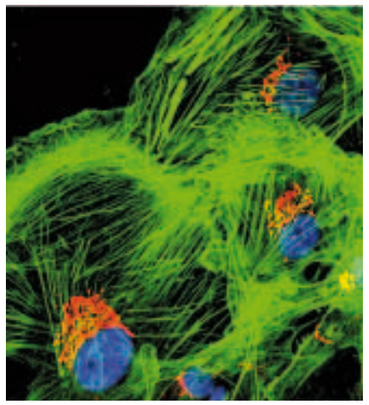
+ Shared last author

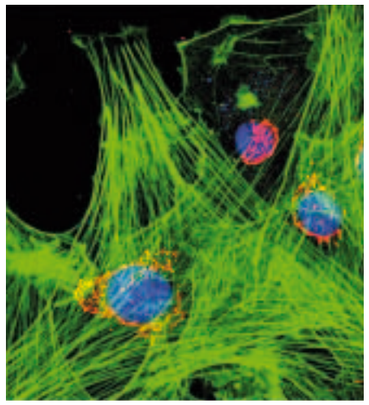


1 Nesprin-2 Giant function in wound healing. Schematic model showing the proposed mechanisms of involvement for Nesprin-2 in cell migration, proliferation and transcription regulation. In wild-type cells Nesprin-2 at the ONM, together with other NE proteins, connects the nucleus to the actin cytoskeleton. Through its association with heterochromatin at the INM, Nesprin-2 affects the proper expression or availability of transcription factors. In cells from knockout animals F-actin distribution and the status of heterochromatin are altered. The expression and availability of transcription factors is reduced and leads to reduced cell proliferation.

Prof. Angelika A. Noegel

Principal Investigator
Institute for Biochemistry I





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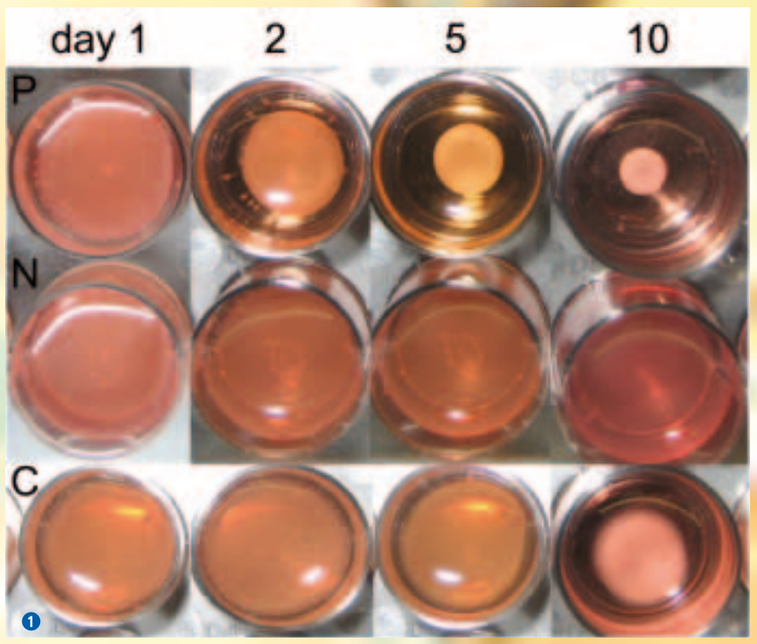
Chromosomes of eukaryotic cells are separated from the cytoplasm by the nuclear envelope and its proteins mediate a variety of key cellular activities. To identify the mechanisms by which the nuclear envelope contributes to aging and disease phenotypes we have investigated the interactions of the nuclear envelope proteins Nesprin-1, -2 and -3 and have searched for other substances that bind to the Nesprins. We have analyzed and characterized primary fibroblasts from patients suffering from muscular dystrophies and continued our analysis of Nesprin-2 giant knockout mice. Our results have revealed a network of interactions among the Nesprins, interconnecting all cytoskeletal filament systems and stabilizing the nucleus and its association with cell components such as the centrosome. Nesprins also affect signal transduction. Nesprin-2 binds directly to α-catenin and controls the access of β-catenin to the nucleus, thereby inhibiting Wnt signaling. In the Nesprin-2 deficient mouse altered expression and localization of transcription factors and changes in the actin cytoskeleton result in impaired wound healing.

Our results suggest that Nesprins play a dual role: they contribute to the mechanical stability of the nucleus and cell, and they influence gene expression through interactions with transcription factors and with chromatin. With involvement in such vital functions, they provide intriguing candidates to control the onset of age-related diseases.



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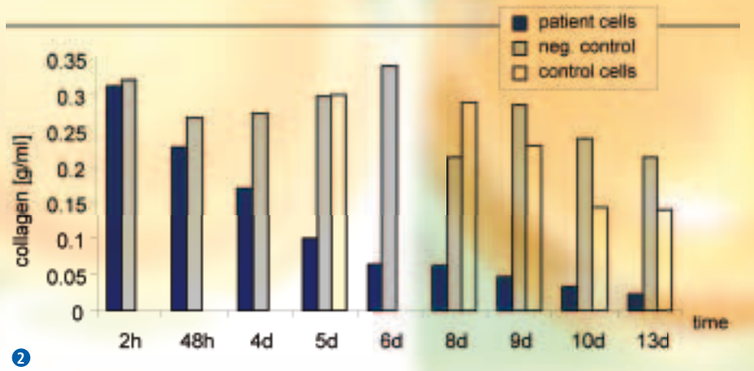

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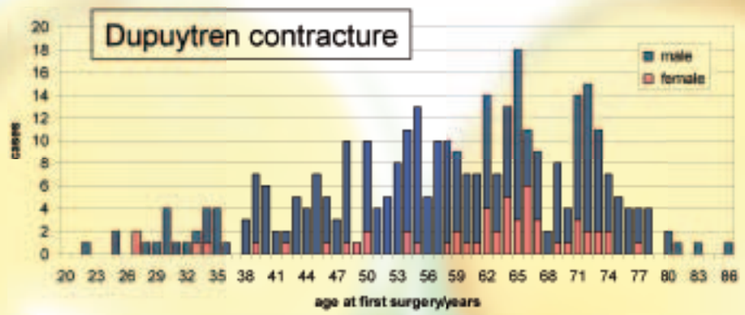

3

1 & 2 Increased contractility of myofibroblasts obtained from Dupuytren disease patients compared to cells from unaffected individuals as shown by floating collagen populated with myofibroblasts.

3 Distribution of age at onset (represented by age at first surgery) of Dupuytren contracture in male and female patients. Materials from a total of 560 clinically characterized cases have been sampled for the study so far.


Prof. Peter Nürnberg


Dr. Hans Christian Hennies

Prof. Peter Nürnberg

Head of Technology Platform
Principal Investigator
Cologne Center for Genomics (CCG)

Dr. Hans Christian Hennies

Principal Investigator
Cologne Center for Genomics (CCG)

Dupuytren contracture (DC; OMIM 126900) is one of the most common genetic disorders of connective tissue. The incidence is strictly age-dependent, peaking in the sixth and seventh decade of life in men and women, respectively. DC is a multifactorial disorder with a strong genetic component. It is characterized by disturbed fibroblast proliferation and extracellular matrix deposition. We are performing a multiple-stage, whole-genome association study to identify common genetic variants associated with the disease. An international Dupuytren disease study group has been established and blood and tissue samples collected from more than 500 patients to date. Our second aim is to generate expression profiles from affected tissues in order to assess differential expression. Finally, we will compare properties of affected cells with those of normal controls. Tools have been set up to determine the contractility of myofibroblasts under various conditions, which will enable us to characterize and distinguish age-dependent and stress-induced changes. Once integrated, the data obtained will further our understanding of the pathology of DC and processes of abnormal fibroblast differentiation.

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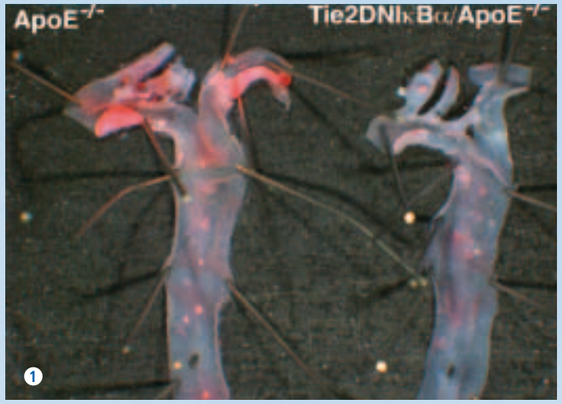

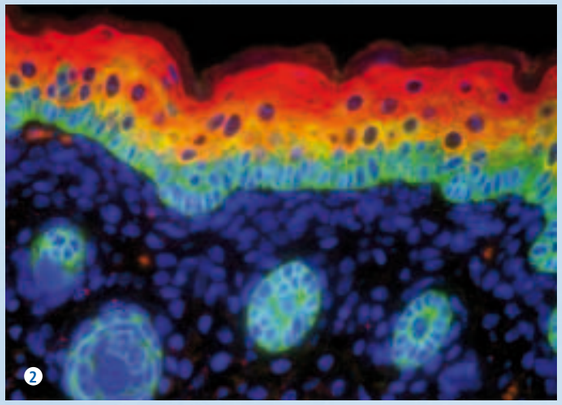

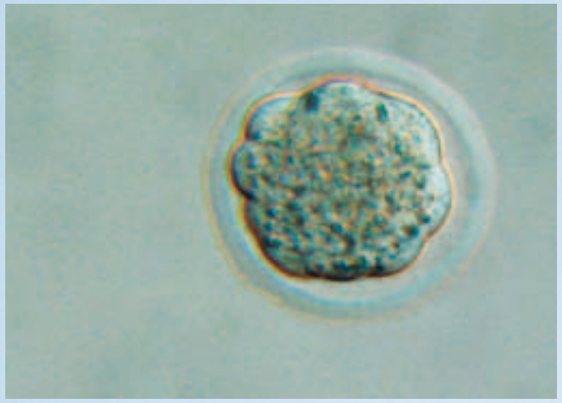

1 Reduced atherosclerosis development in ApoE-/- mice with NF-B inhibition in endothelial cells. En-face staining of dissected aortas with Sudan IV showed that ApoE-/- mice expressing DNIB in endothelial cells were protected from the development of atherosclerotic plaques upon feeding with a high-cholesterol diet for 10 weeks, while ApoE-/- littermate controls showed severe atherosclerosis.

2 Section from mouse skin stained with antibodies recognising keratin 14 (green) that is expressed in basal keratinocytes, and keratin 10 (red) that is expressed in suprabasal keratinocytes. Nuclei are counterstained with DAPI (blue).

Prof. Manolis Pasparakis

Head of Research Area C
Principal Investigator
Institute for Genetics

Inflammation is now recognized as a critical player in the pathogenesis of multiple human diseases and as an important risk factor for cancer development. The IKK/NF-B signaling pathway regulates immune and inflammatory responses and is implicated in the pathogenesis of a number of aging-associated diseases. Our group is studying the mechanisms by which NF-B signaling controls cellular responses to infection and injury and affects the pathogenesis of chronic inflammatory diseases. Using conditional mouse models, we have shown that NF-B signaling in epithelial cells of the skin and the intestine is required for the maintenance of immune homeostasis in these tissues. Our experiments have also revealed an unexpected function of IKK/NF-B signaling in liver parenchymal cells, where it acts to prevent chronic inflammation and the development of hepatocellular carcinoma. In addition, we have shown that NF-B activation is a critical pathogenic factor for atherosclerosis in vascular endothelial cells, as it induces the expression of adhesion molecules and chemo-attractants that recruit monocytes into developing plaques. These signaling pathways therefore continue to show rich potential as targets for clinical intervention with age-related diseases.

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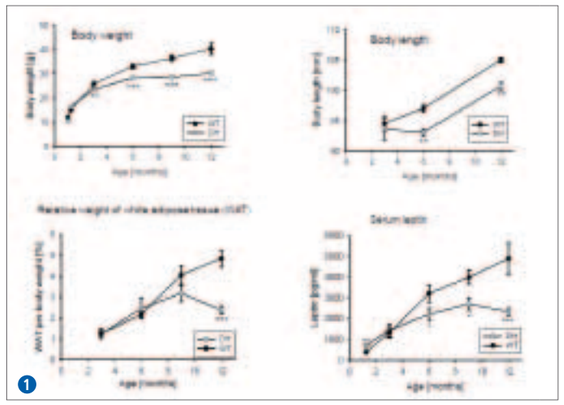
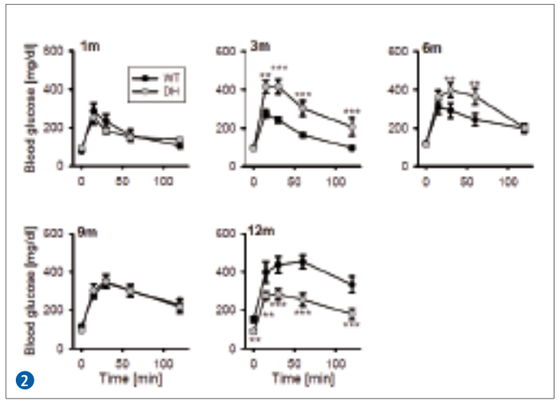
Prof. Mats Paulsson

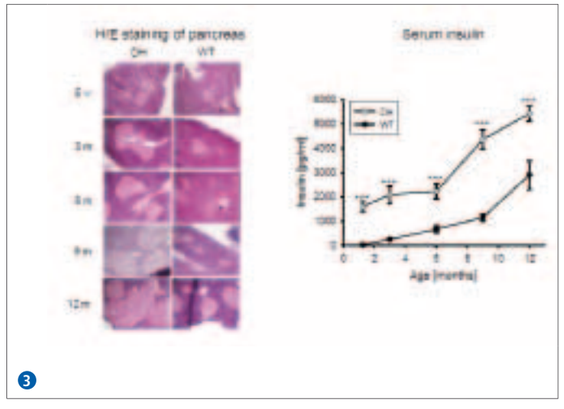
Principal Investigator
Institute for Biochemistry II



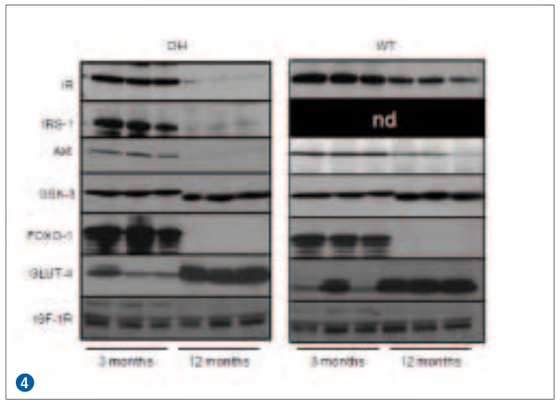
1 Body weight, body length, relative weight of white adipose tissue and serum leptin levels were measured at 1, 3, 6, 9 and 12 months of age. DH: male mice heterozygous null for the insulin receptor and the insulin receptor substrate-1, WT: wildtype littermates. Values represent means +/- SEM.



2 Glucose tolerance tests (GTT). Blood glucose concentrations of 16 h fasted mice were measured before and after intraperitoneal glucose injection. Tests were performed at 1, 3, 6, 9 and 12 months. DH: male mice heterozygous null for the insulin receptor and insulin receptor substrate-1, WT: wildtype littermates. Values represent means +/- SEM.



3 Sections of pancreas of male mice of the indicated age were stained with hematoxylin/ eosin (left panel). Serum insulin levels were measured by ELISA. DH: male mice heterozygous null for the insulin receptor and insulin receptor substrate-1, WT: wildtype littermates. Values represent means +/- SEM.



4 Protein extracts from the livers of 3 mice at the indicated age were resolved on SDS-PAGE, blotted and probed with antibodies against components of the insulin-signaling cascade (insulin receptor (IR), insulin receptor substrate (IRS-1), protein kinase B (Akt), glycogen synthase kinase-3 (GSK-3), transcription factor FOXO1), the insulin-dependent glucose transporter GLUT-4 or the IGF-1 receptor.

Research in our group focuses on the role of extracellular matrix (ECM)-proteins in the development of aging-associated diseases. Within the framework of CECAD, we have specifically addressed the roles of testicans as mainly CNS-expressed ECM-proteins in the central nervous control of energy homeostasis and obesity development. We have demonstrated that mice deficient for all 3 testican isoforms develop an obese phenotype and currently following up on the question, how testicans may regulate extracellular bioavailability of neuropeptides and neurotransmitters, which are critical for control of food intake and energy expenditure. In a second series of experiments we aimed to define alterations in ECM-composition during the development of diabetic retinopathy. Here, we planned to perform longitudinal experiments in a mouse model of genetically determined insulin resistance through combined heterozygous deficiency for the insulin receptor (IR) and the insulin receptor substrate (IRS)-1 protein. Surprisingly, while these animals exhibited the pre-described phenotype of insulin resistance and glucose intolerance at a younger age, they were protected from aging-asscoaited deterioration of glucose metabolism as observed in control animals. Thus, this model sets the ground to resolve the apparent controversy of insulin resistance contributing to diabetes development in mammals and the life-extending effect of genetically determined insulin resistance in lower model organisms. Therefore, ongoing studies focus on the elucidation of the molecular basis of how genetically determined partial insulin resistance protects from age-related impairment of glucose homeostasis in mice. Such information could then be usefully translated into new approaches to combating diabetes in the elderly.

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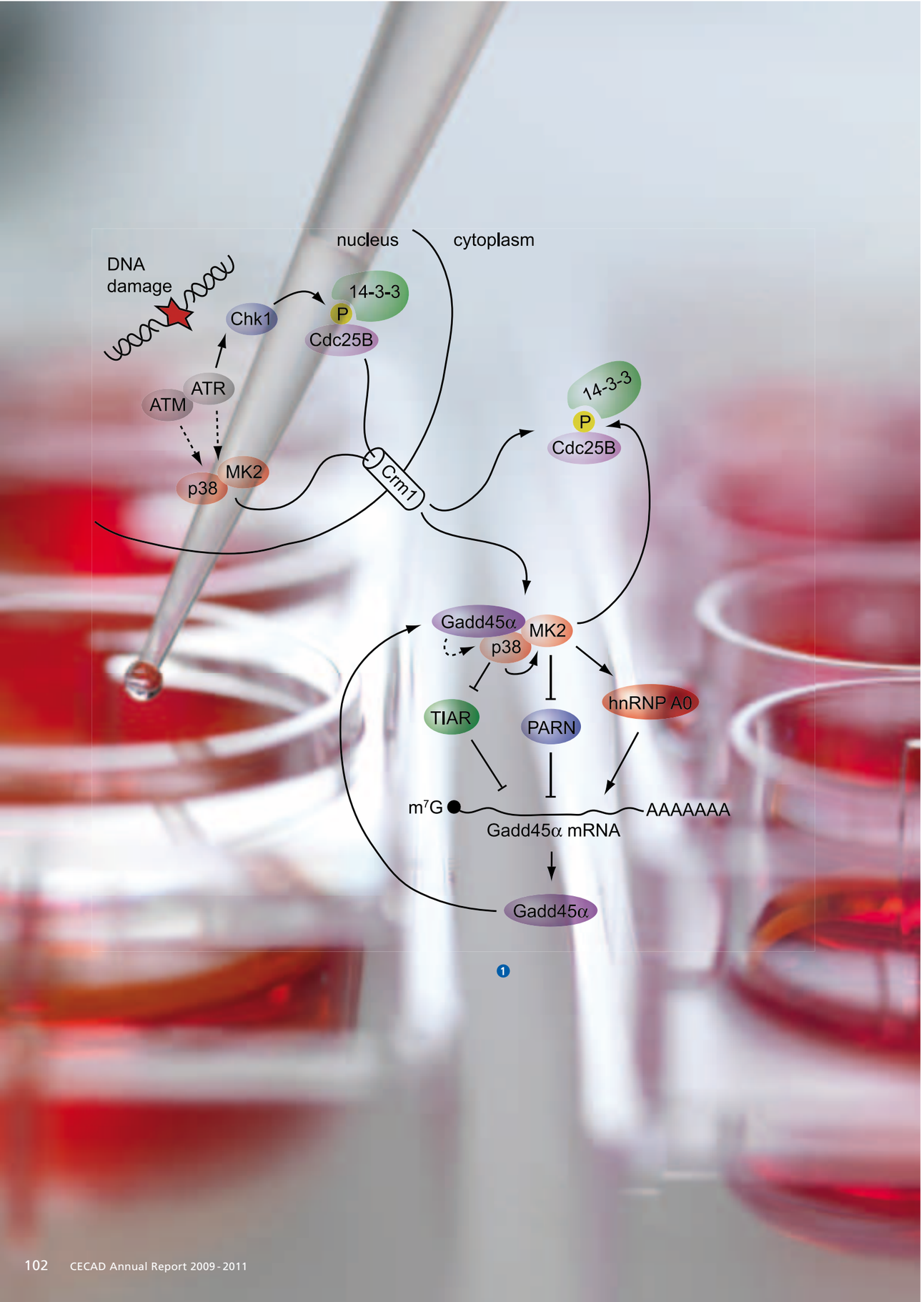

1

Dr. Christian Reinhardt

Principal Investigator
Department of Internal Medicine I

1 A simplified model depicting molecular details of the cell cycle checkpoint pathways activated in response to DNA damage. Recent work from our group elucidated a early, Chk1-dependent nuclear checkpoint and the late MK2-dependent cytoplasmic checkpoint. Dashed arrows between ATM/ATR and p38/MK2 indicate intermediate steps that are not well characterized. The MK2-mediated cytoplasmic checkpoint is sustained through a positive feedback loop. Following nuclear activation, the p38/MK2-signaling complex re-localizes to the cytoplasm through a Crm1 dependent transport mechanism. MK2-mediated hnRNP A0 and PARN phosphorylation, as well as p38-dependent TIAR phosphorylation are required to stabilize Gadd45α mRNA, resulting in increased Gadd45α protein levels. Gadd45α itself is then required to maintain MK2 activity in the cytoplasm.

Our laboratory's research is focused on the analysis of signaling pathways that are activated in response to DNA damage. These signaling cascades serve to maintain genomic integrity and genes involved in the DNA damage response are among the most commonly mutated genes in human cancers. In addition to their causal role in cancer susceptibility, genes involved in genome integrity and maintenance have been linked to a variety of premature aging syndromes. While these disabling mutations within the DNA damage response network clearly promote tumorigenesis, they are also commonly associated with vulnerabilities that are specific to these genetic lesions. For example, cancer cells that have lost the prominent tumor suppressor p53 rely on genes such as ATM, Chk2 or MK2 to survive chemotherapy-induced DNA damage. In our research we use mouse models and primary cells from humans and mice to characterize these genetic interactions, our ultimate goal being to develop tailored therapies that will target the specific vulnerabilities of tumor cells. We are currently investigating DNA-PKcs as a drug target for the treatment of human tumors that carry mutations in the DNA damage response gene ATM. We have shown that ATM-deficient tumors rely on the protein kinase DNA-PKcs for their survival after exposure to DNA-damaging chemotherapy. Intriguingly, ATM appears to be mutated in almost 20% of all human carcinomas. Thus, exploiting a vulnerability that is specific to these tumors holds great promise for future cancer therapy.

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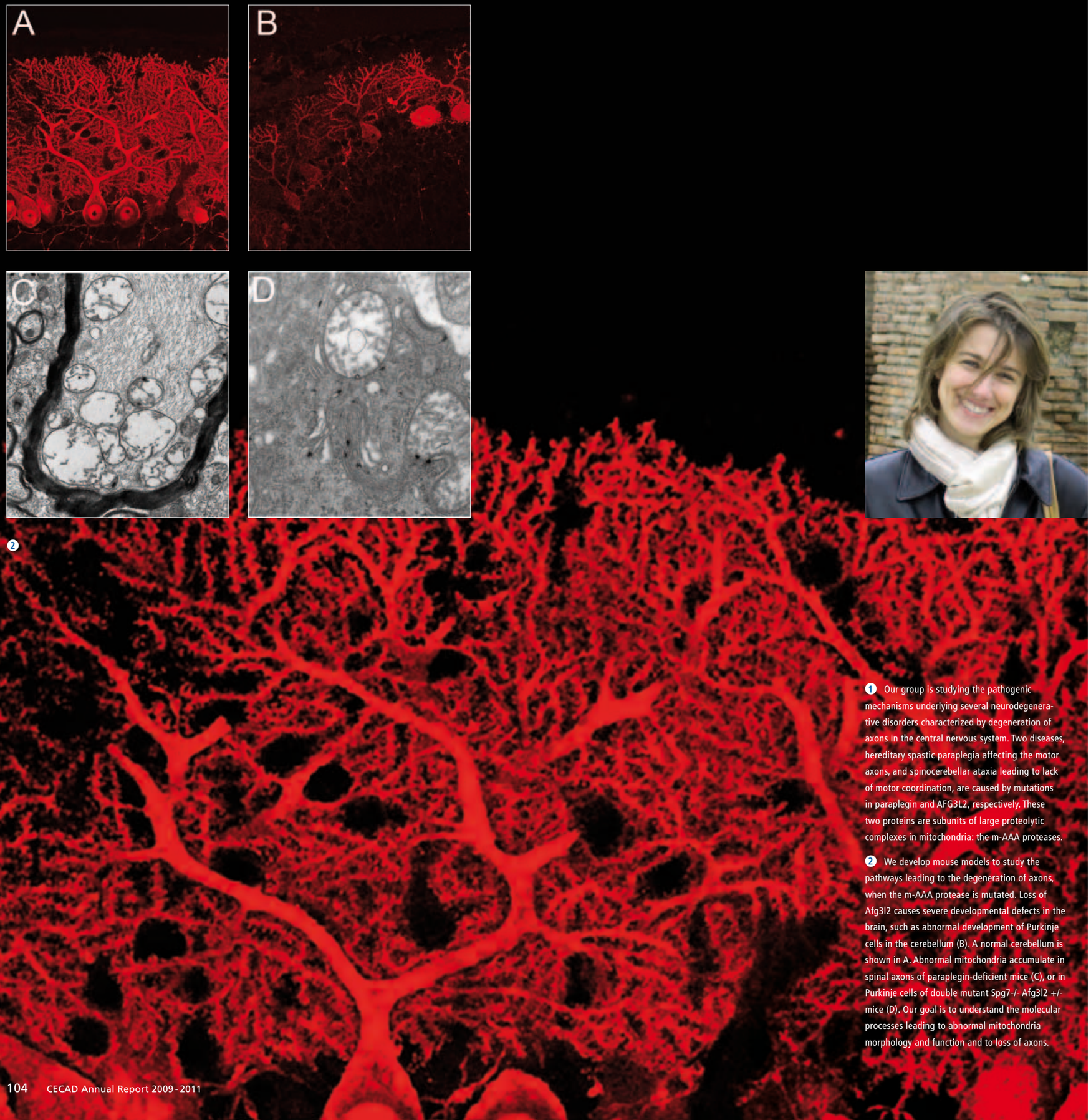


2

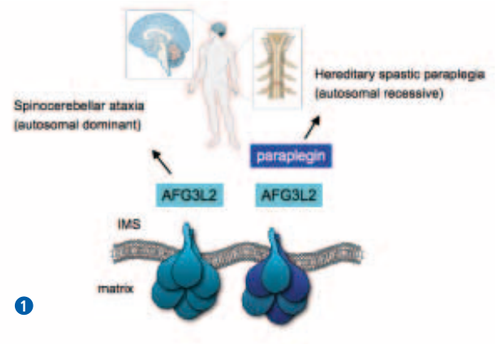
1 Our group is studying the pathogenic mechanisms underlying several neurodegenerative disorders characterized by degeneration of axons in the central nervous system. Two diseases, hereditary spastic paraplegia affecting the motor axons, and spinocerebellar ataxia leading to lack of motor coordination, are caused by mutations in paraplegin and AFG3L2, respectively. These two proteins are subunits of large proteolytic complexes in mitochondria: the m-AAA proteases.

2 We develop mouse models to study the pathways leading to the degeneration of axons, when the m-AAA protease is mutated. Loss of Afg3l2 causes severe developmental defects in the brain, such as abnormal development of Purkinje cells in the cerebellum (B). A normal cerebellum is shown in A. Abnormal mitochondria accumulate in spinal axons of paraplegin-deficient mice (C), or in Purkinje cells of double mutant Spg7-/- Afg3l2 +/- mice (D). Our goal is to understand the molecular processes leading to abnormal mitochondria morphology and function and to loss of axons.

Prof. Elena Rugarli

Principal Investigator
Cologne Biocenter

Axonal degeneration may follow a traumatic, toxic, metabolic, or genetic insult to axons. Chronic processes of degeneration in axons play an important role in several common neurodegenerative diseases, occurring well before the death of the neuronal cell bodies and often accounting for the first symptoms in patients. The mechanisms that lead to a loss of axons are still poorly understood. Research in our laboratory focuses on the pathogenic mechanisms underlying hereditary spastic paraplegia (HSP), a model disease for the study of axonal degeneration. HSP is an adult-onset disorder, characterized by progressive weakness and spasticity of the lower limbs and caused by retrograde degeneration of the corticospinal axons. HSP is genetically heterogeneous, and in recent years enormous progress has been made in mapping and cloning several of the genes involved. The goal of our research is to establish why ubiquitously expressed genes cause selective degeneration of a subset of axons in the body, whether any of the pathogenic steps are reversible, and what interventions can be devised to block or slow down progression of the phenotype.



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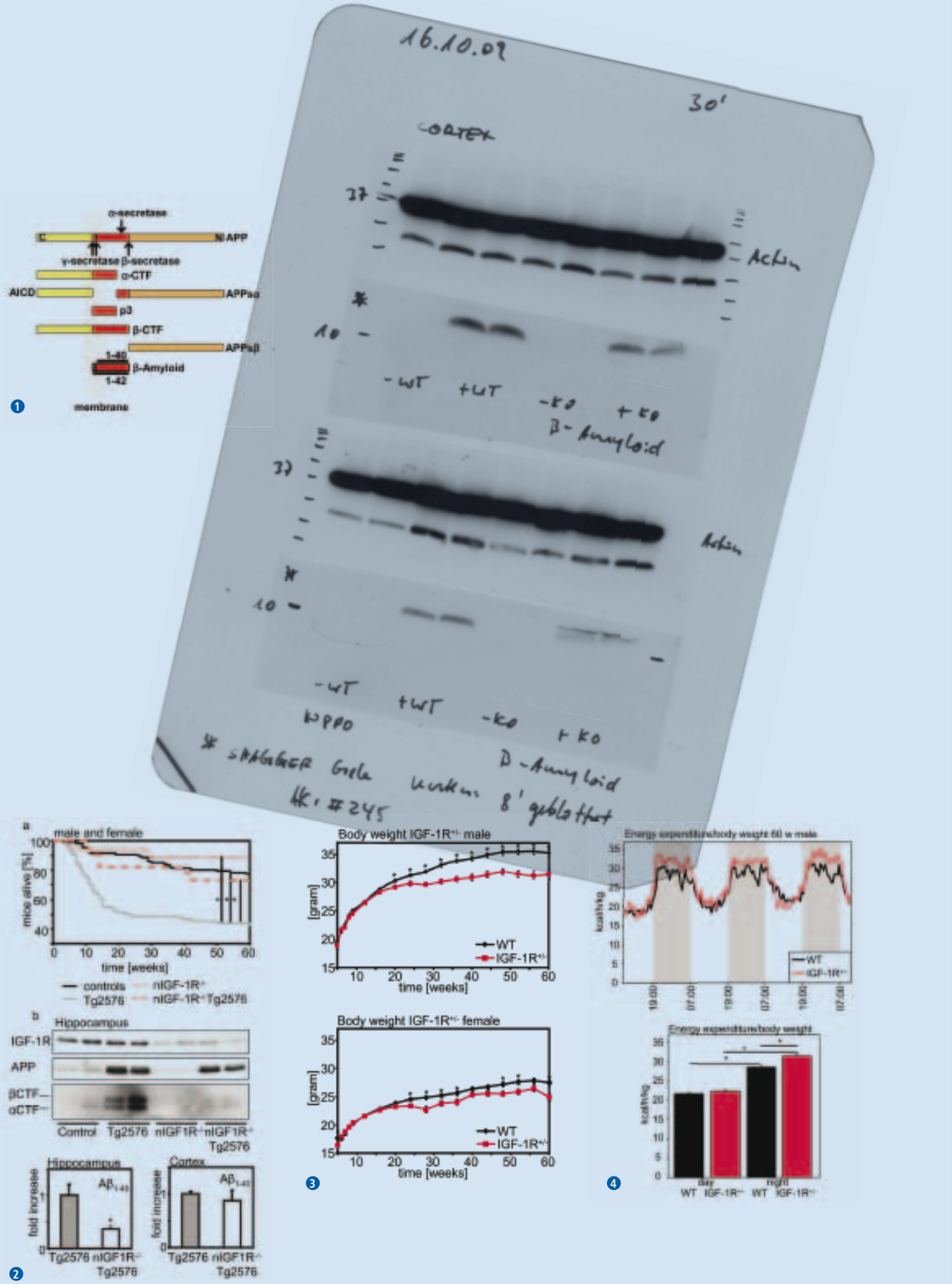

Dr. Markus Schubert

Principal Investigator
Department of Internal Medicine II

Patients suffering from type 2 diabetes (T2DM) or midlife obesity have a two- to three-fold increased risk for Alzheimer's disease (AD). This might be explained by vascular complications of T2DM leading to neurodegeneration. Alternatively, neuronal resistance for insulin/insulin-like growth factor-1 (IGF-1) might represent a molecular link between T2DM, obesity and AD. In line with this hypothesis, insulin receptor (IR) and IGF-1 receptor (IGF-1R) signaling (IIS) is markedly disturbed in the central nervous system of AD patients. Similar changes in the IIS have been reported in animals fed a high-fat diet and in human patients with T2DM, suggesting that decreased IR/IGF-1R signaling might be the common molecular basis of T2DM and AD. Our present work reveals that neuron-specific inactivation of the IGF-1R rescues premature mortality and reduces the β-amyloid burden in a mouse model for AD via decreased amyloid precursor protein processing. Furthermore, deletion of one copy of the hippocampal IGF-1R in neurons reduced age-associated weight gain, independent of food intake. Indirect calorimetry revealed increased energy expenditure in mice heterozygous for the IGF-1R, predominantly in the hippocampus. We conclude that IGF-1 mediated signals in the hippocampus influence mortality and β-amyloid accumulation in AD and also play a role in age-associated weight gain. The next step will be to identify the molecular mechanisms involved.

1 Schematic drawing of APP cleavage by the, α-, β-, γ-secretases. β-amyloid peptides are released from the amyloid precursor protein (APP) via simultaneous cleavage by the β- and γ-secretases. APPs: soluble APP; CTF: c-terminal fragment; AICD: APP intracellular domain.

2 Neuron-specific IGF-1R deletion rescues premature mortality and reduces β-amyloid burden in a mouse model for Alzheimer's disease (Tg2576 mice). a) Kaplan-Meier analysis of Tg2576, wild-type, hippocampal nIGF-1R-/- as well as mice nIGF-1R-/-/Tg2576 mice. b) APP processing and Aβ1-40-concentration in brains of the different genotypes.
APP: Amyloid precursor protein, CTF: c-terminal fragments of APP

3 Postnatal growth of mice heterozygous for the IGF-1R predominantly in the hippocampus.

4 Indirect calorimetry of mice heterozygous for the IGF-1R predominantly in the hippocampus.

Stöhr O, Hahn J, Moll L, Leeser U, Freude S, Bernard C, Schilbach K, Markl A, Udelhoven M, Krone W, Schubert M (2011) Insulin receptor substrate-1 and -2 mediate resistance to glucose-induced caspase-3 activation in human neuroblastoma cells. Biochim Biophys Acta. May;1812(5):573-80

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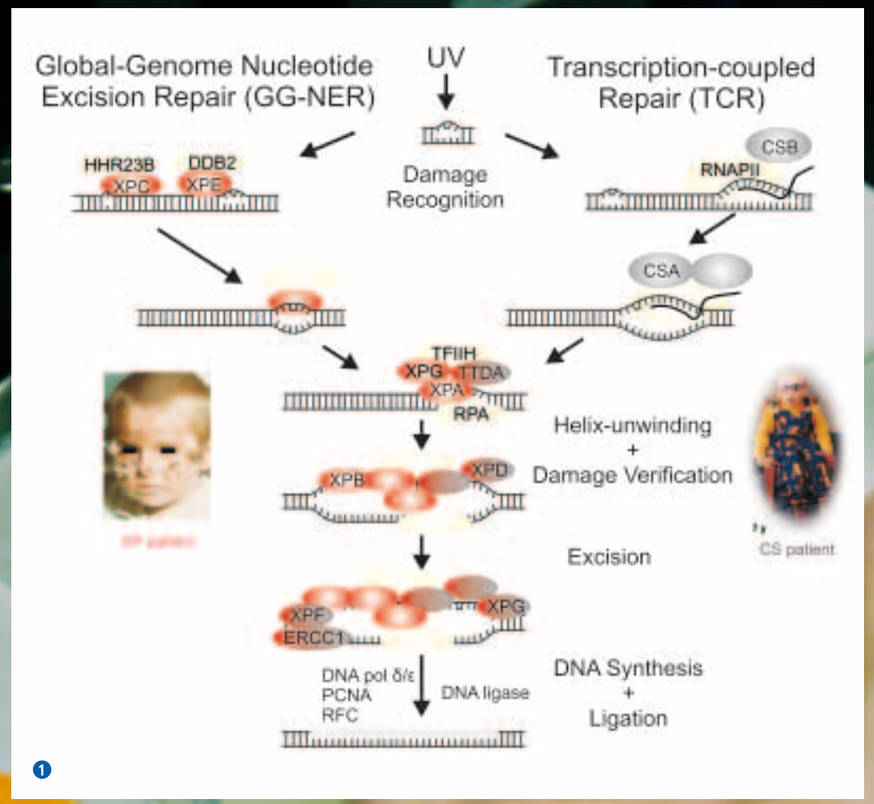

1 Excision repair in cancer and aging. UV lesions and helix-distorting chemical adducts are recognized and repaired by a multi-protein nucleotide excision repair (NER) complex comprising two pathways: global genome (GG) NER and transcription-coupled excision repair (TCR). Patients with a defective GG-NER pathway are highly susceptible to skin cancer, whereas defects in TCR lead to progeroid syndromes. Reproduced from Schumacher, Bioessays 2009.

Dr. Björn Schumacher

Principal Investigator
CECAD Cologne at the Institute for Genetics

Aging is strongly correlated with a host of human pathologies, most prominently cancer and neurodegenerative diseases such as Alzheimer's and Parkinson's disease, but also general functional decline. It is therefore of matter of importance to further our understanding of the mechanisms underlying human aging. DNA damage has been shown to play a central role in cancer and, more recently, in premature aging. The causal role of DNA damage in cancer and aging is particularly apparent in human patients with inborn deficiencies in nucleotide excision repair (NER). There are two distinct branches of initial damage recognition: global genome (GG) NER scans the entire genome for helix-distorting DNA lesions, while transcription-coupled repair (TCR) detects lesions in actively transcribed genes. Strikingly, GG-NER defects lead to skin cancer prone Xeroderma pigmentosum (XP) whereas defective TCR gives rise to the premature aging (progeroid) syndromes Cockayne syndrome (CS) and trichothiodystrophy (TTD). Our research group is using the genetic model organism Caenorhabditis elegans as well as mammalian disease models in studies designed to unravel the molecular mechanisms through which DNA damage contributes to aging.

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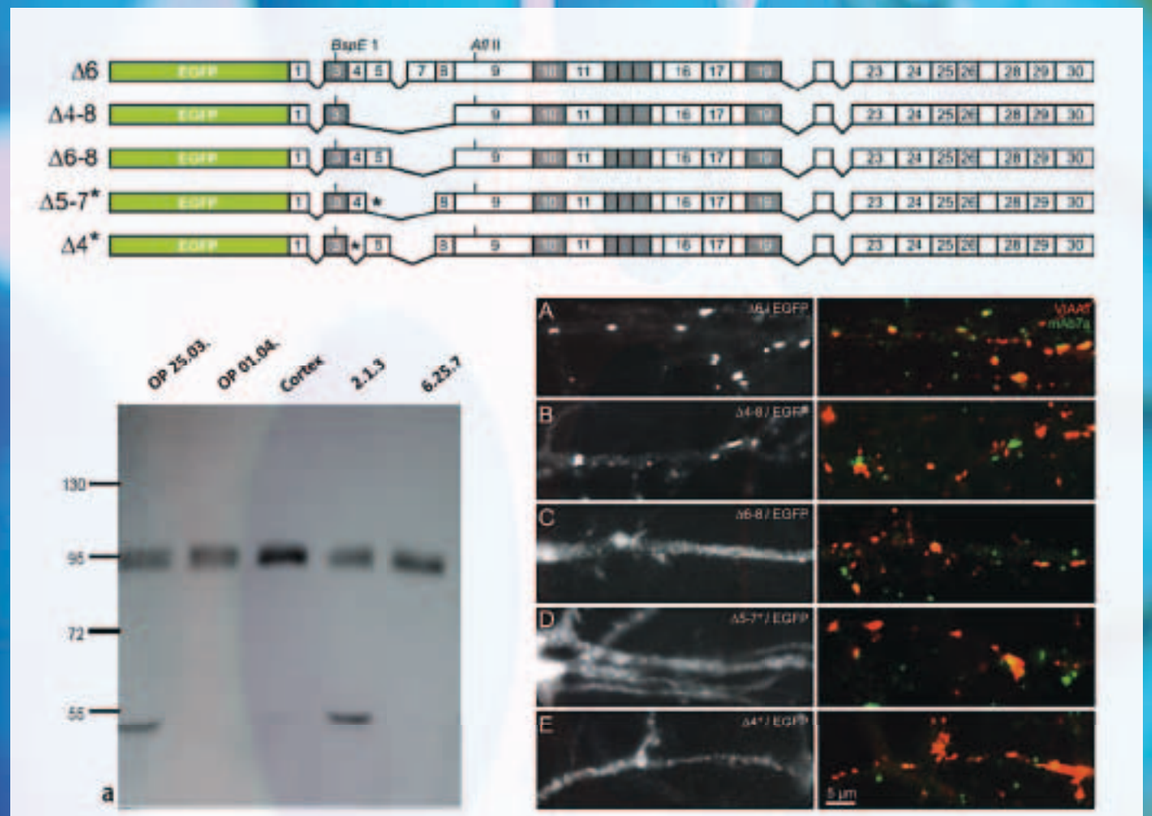

1

Prof. Günter Schwarz

Principal Investigator
Institute for Biochemistry

1 Gephyrin is crucial for the transport, clustering and normal dynamics of inhibitory glycine and GABA type A receptors. Recently, reduced gephyrin immunoreactivity has been reported in the hippocampus of patients with temporal lobe epilepsy (TLE). We have investigated gephyrin expression in the hippocampus of patients with intractable TLE and found irregular gephyrin expression in the cornu ammonis with four abnormally spliced gephyrin variants (Fig. 1, upper panel). All TLE gephyrins so far identified have oligomerisation deficits and show increased degradation (Fig. 1, left panel). They also curtail hippocampal postsynaptic gephyrin and GABA receptor 2 subunits while interacting with regularly spliced gephyrins (Fig. 1, panel A-E; expression of TLE variants in hippocampal neurons with co-localisation of VIAAT and gephyrin (colored yellow)). The observation that cellular stress can trigger irregular splicing of gephyrin could lead to a breakthrough in our understanding of the molecular mechanisms underlying age-associated neuronal disorders such as TLE. Förstera et al. 2010, Brain 133: 3778.

Anchoring and clustering of neuroreceptors is vital for correct signal transmission in the central nervous system. The protein gephyrin plays a critical role in the organization of postsynaptic structures at glycinergic and GABAergic synapses. We have determined the structures of both the N- and C-terminal domains of gephyrin, identified the binding site of the glycine receptor and described key motifs for gephyrin clustering. The functional diversity and specificity of gephyrin is believed to depend on a number of splice-variants that are expressed in a tissue-specific manner and are most complex in the brain. Our investigations of gephyrin expression in the hippocampus of patients with intractable TLE revealed irregular gephyrin expression in the cornu ammonis with four abnormally spliced gephyrin variants. All TLE gephyrins identified have oligomerization deficits, and curtail hippocampal postsynaptic gephyrin and GABA receptor subunits while interacting with regularly spliced gephyrins. We aim to identify the pathomechanism that leads to the formation of mis-spliced gephyrins and uncover the mode of dominant negative interaction between native and TLC-gephyrins. Targeting of these pathological protein-protein interactions could form a basis for novel treatments of TLE and other epilepsies associated with gephyrin-mediated receptor dysfunction in the developing and aging brain.

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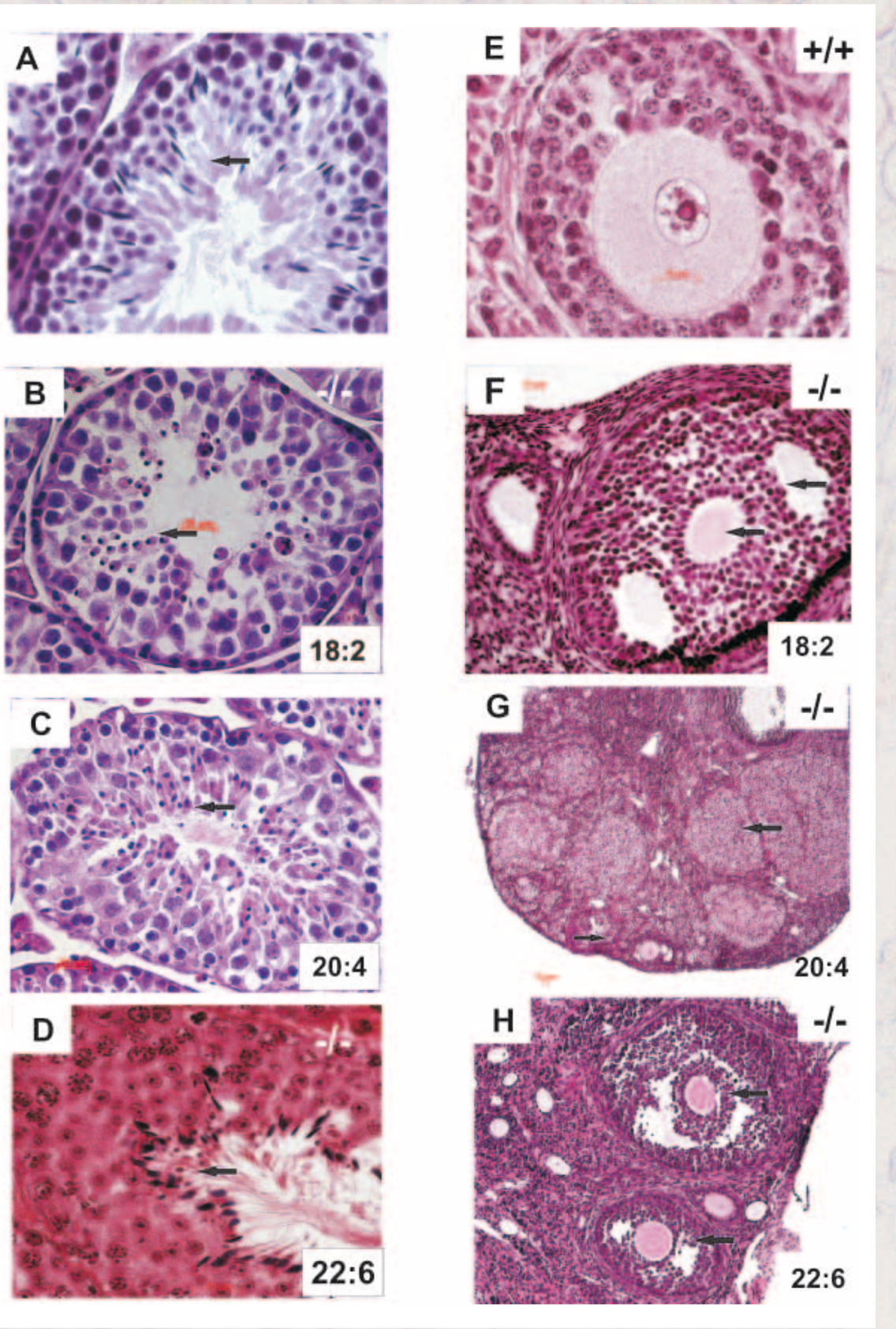

1 HE stained cross section of A wild type seminiferous tubulus and E ovary; of adult male and female fads2-/- mmice, supplemented B and F with linoleic adid (18:2): no rescue; C and G arachidonic acid (20:4): no rescue, and D and H: docosahexaenoic acid 22:6 (DHA): complete rescue of male and female fertility.

Arrows point to : mature spermatozoa in A and D, round immature spermatocytes in B and C; to mature oocytes and all stages of oogenesis E and H, degenerated follicles in F and G.

Comment:
Male and female fads2null mice are infertile due to loss of cell polarity in testis and ovary. This genetically induced membrane defect and infertility of both genders can be overcome by the dietary supply of one specific polyenoic fatty acid: docosahexaenoic acid (DHA), which is essential in the phospholipid-bilayer for ordered arrangement of integral membrane proteins of tight, adherens and gap junction in specialized tissues such as gonads and central nervous tissue. Our results challenge the fluid membrane structure dogma, in which polyenoic fatty acids are simply "membrane liquidizers", but indicate specific functions of DHA not only for reproduction and species survival, as shown here, but also for brain development and function, e.g. visual system, which is another aspect of our project.

1

Prof. Wilhelm Stoffel

Principal Investigator
Laboratory of Molecular Neuroscience

Plasma membranes and membranes of subcellular compartments of all mammalian cells are assembled from proteins attached or integrated into a lipid bilayer. Rapid enzymatic modifications of the polar head groups of the lipids and their fatty acyl-substituents render the lipid bilayer highly adaptable and optimize lipid-protein interactions. Advances in lipidomics applied to genetic models in which defined lipid structures are modified have now revealed functional correlations between specific lipid molecules and membrane protein functions accompanying adaptive changes in gene expression during development, aging or dysregulation of cellular homeostasis.

Our laboratory is researching the systemic and/or cell specific role of phospholipids substituted with mono- and polyunsaturated fatty acid (PUFAs) in cell membrane organization (cell polarity) and function, chiefly in the membrane stacks of photoreceptor outer segments of retina. ω3- and ω6-PUFAs are highly vulnerable to autoxidation and are therefore key targets of "oxidative stress". They are closely involved in the pathogenesis of atherosclerosis, brain development, age-related macula degeneration (AMD) and skin diseases. AMD is the main cause of vision impairment and blindness in the elderly. It has been proposed that AMD and retinitis pigmentosa are linked to 22:6 deficiency and/or their photo-autoxydation. Our Δ6-fatty acid deficient and auxotrophic mouse mutant (fads2) will allow us to address these and other phenotypic traits of the mutant.

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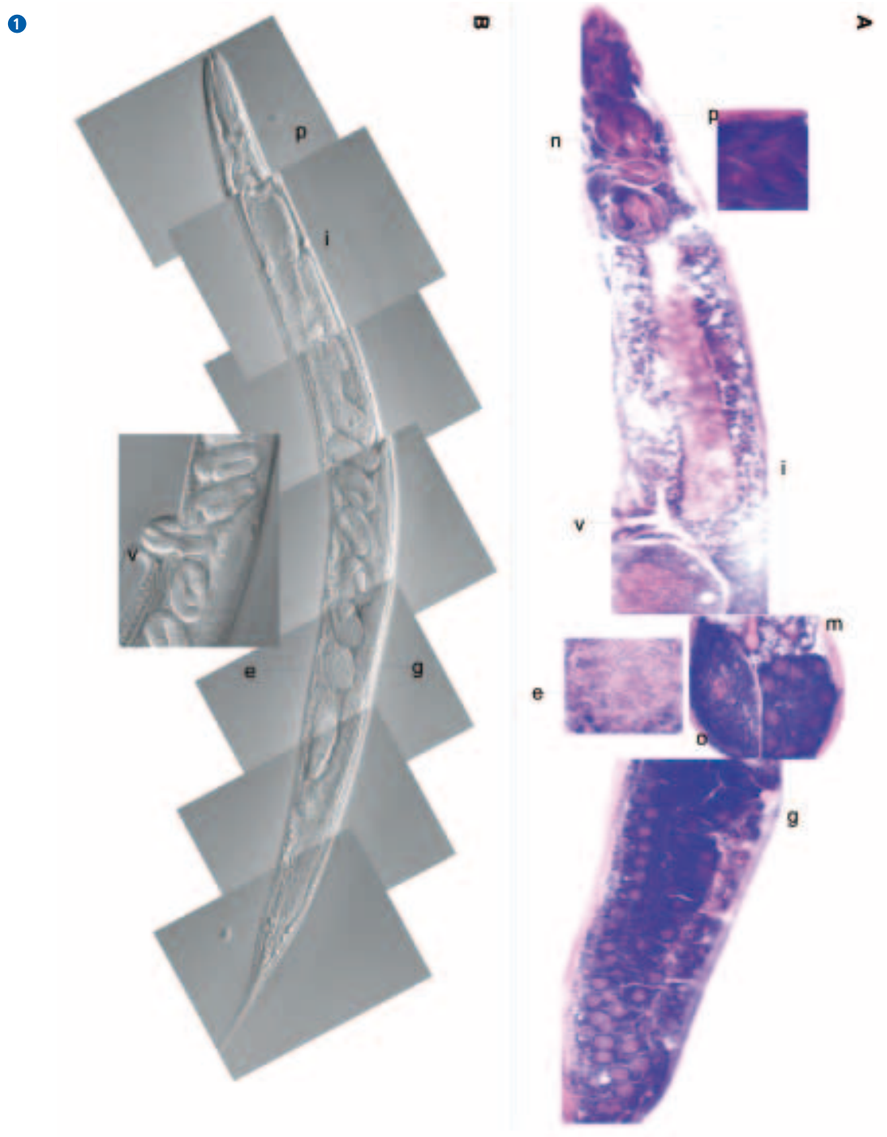

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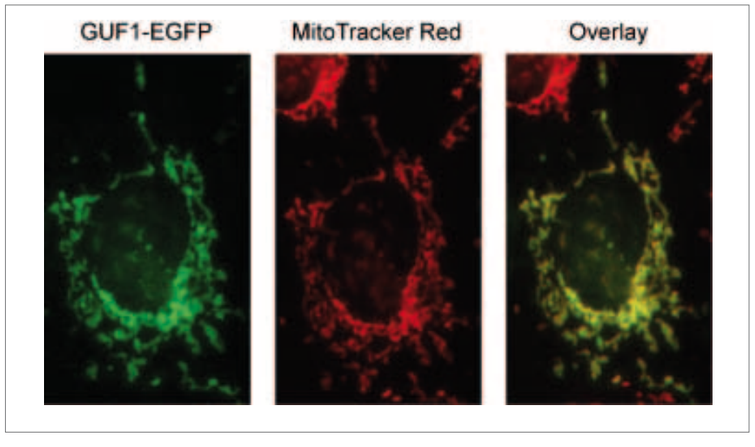

3

Dr. Aleksandra Trifunovic

Principal Investigator
Institute for Genetics

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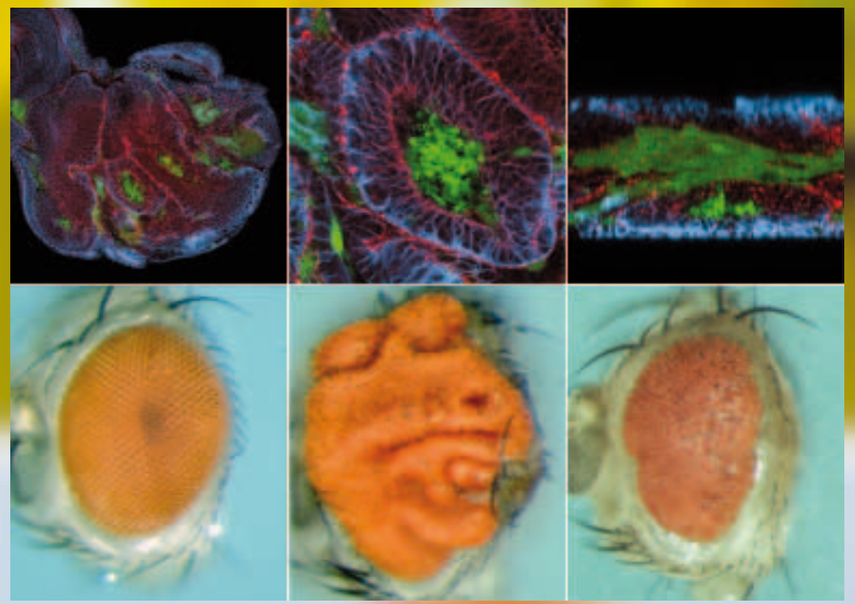
Mitochondrial dysfunction has been linked to the pathogenesis of many aging-associated diseases such as heart failure, diabetes and Parkinson's disease. Recently, we provided the first direct evidence that an accelerating mtDNA mutation rate can result in premature aging. However, little is known about the molecular mechanisms connecting an increased incidence of mtDNA mutations to the development of premature aging phenotypes. In particular, there is limited information available on the key steps that link mitochondrial dysfunction with the global control of nuclear gene expression. Using the roundworm Caenorhabditis elegans as well as transgenic and conditional knockout mice as model systems, our group is studying the role of mitochondrial dysfunction in determining life-span. Specifically, our studies focus on: (i) molecular mechanisms of aging driven by increased mtDNA mutation load; (ii) regulation of mitochondrial protein synthesis and quality control during aging; (iii) signaling pathways that determine longevity and are triggered by mitochondrial dysfunction.

1 In order to study the role of mitochondrial (dys)function in lifespan determination in roundworm C. elegans, we have developed a diagnostic toolbox that gives a more holistic picture of the metabolic state and energy storage simultaneously at the level of the organism and of the tissue. As a start-up point we have compared C. elegans morphology visualized by H&E staining (A) and DIC images (B) of adult wild-type worms at Day 1 of adulthood. p-pharynx, n-nucleus, v-vulva, e-embryo, g-germline, m–body wall muscle, o-oocyte, i-intestine.

2 The creation of mtDNA-mutator mice has provided the first direct evidence that accelerating mtDNA mutation rate can result in premature aging, in line with the view that loss of mitochondrial function is a major causal factor in aging (Trifunovic et al., 2004). Our latest results strongly argue that the observed phenotypes are a direct consequence of the accumulation of mtDNA point mutations leading to the synthesis of respiratory chain subunits with amino acid substitutions that impair complex stability in mtDNA mutator mice (Edgar et al., 2009).

3 Our results strongly argue that even though mtDNA mutator mice randomly accumulate point mutations, these mutations would have a deleterious impact primarily on the protein-coding genes. We want to test this hypothesis further by creating a mouse model with increased numbers of amino acid substitutions in mtDNA protein coding genes but no additional effects on mtDNA maintenance or integrity and no effect on mtDNA-encoded tRNA and rRNA genes. For this, we will use a recently described mitochondrial translation factor GUF1 with the unique function of a fidelity factor for mitochondrial protein synthesis. Moreover, this is the first knock-out model for a mitochondrial translational factor and will therefore broaden our understanding of this fundamental process. In our initial analysis we have performed experiments in order to elucidate cellular localization of the GUF1 protein in mammalian cells. Chimeric GUF1-EGFP protein shows a clear pattern of mitochondrial localization which overlaps perfectly with the mitochondria-specific staining of MitoTracker Red CMXRos.



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1 Upper row: Confocal micrographs of *Drosophila* eye imaginal disc epithelium (left and middle: xy sections, right: xz cross-section) carrying GFP-marked clonal tumors (green). Cell outlines are visualized with antibodies against Fasciclin III (blue) and DE-cadherin (red). Clonal activation of the Jun-N-terminal kinase (JNK) signaling pathway induces apoptosis and extrusion of dying cells from the epithelial surface. Surviving cells lose polarity and become motile.
Bottom row: Bright-field images of adult *Drosophila* eyes in which wild-type (left) or mutant clones were induced using the MARCM technique. JNK activation causes either tissue overgrowth (middle) or apoptosis (right) depending on the context of cooperating oncogenic mutations.

2 Upper row: Formation of the adult fly abdomen requires replacement of larval epidermal cells (large polyploid cells, left) with imaginal cells called histoblasts (right) that proliferate and migrate from nests (middle) during metamorphosis. Bottom row: Dorsal views of adult *Drosophila* abdomens. Abnormal Atf3 function in larval epidermal cells interferes with the epidermal cell replacement, resulting in abdominal cleft (right).

Dr. Mirka Uhlirova

Principal Investigator
CECAD Cologne at the Institute for Genetics

A highly complex regulatory network of signaling pathways has evolved in multicellular organisms to preserve cellular functions during development and under changing environmental conditions. Defects in these pathways cause abnormal cell behavior including uncontrolled growth and cancer.

Our lab is interested in understanding how signaling pathways cooperate to maintain cell and tissue homeostasis during normal development and under stress conditions, and how their function can be derailed during tumor formation. We study how signaling specificity is achieved and translated into proper cellular responses via changes in target gene expression. Our aim is to elucidate the role of stress signaling pathways and bZIP transcription factors in regulation of growth and cell migration. While both processes are elaborately controlled, both spatially and temporarily, during development, aberrant growth and cell motility are hallmarks of malignant tumors. The fruit fly *Drosophila melanogaster* offers an excellent in vivo animal model system for the study of developmental and tumor processes. We utilize the wide array of genetic and research tools available in *Drosophil*a in combination with molecular and cell biology techniques, and biochemical and genomic approaches, to gain new insights into molecular mechanisms of growth and motility.

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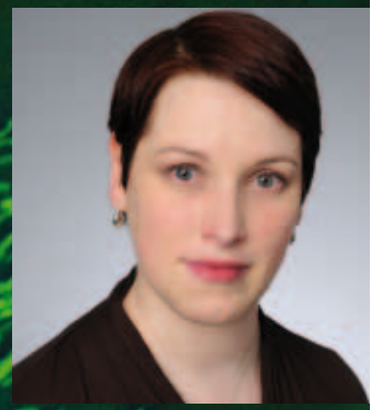

Distrubtion of mitochondria (green) and nucleus (blue) in HeLa cells

Dr. Tina Wenz

Principal Investigator
Institute for Genetics

Mitochondria supply the majority of cellular ATP through oxidative phosphorylation and are hence key players in cellular homeostasis. Most of the known mitochondrial disorders result in impaired ATP synthesis and affect high-energy demand tissues. Typical clinical manifestations include myopathy, seizures, encephalopathy and cardiomyopathy. Mitochondrial dysfunction is associated with disorders such as Parkinson's and Alzheimer's diseases, obesity, type 2 diabetes and the aging process. However, the role of mitochondria in the onset and progression of these disorders remains unclear.

We are studying mouse models with systemic or tissue-specific mitochondrial dysfunction to answer the following questions: What are the cellular responses to the mitochondrial dysfunction and how do these responses contribute to the pathology? How can mitochondrial dysfunction and its effects be prevented or reversed in different diseases? Does preserved mitochondrial function prevent the onset and/or progression of neurodegenerative or aging-associated diseases?

Studies on the newly established mouse strains will be complemented by analysis of cell lines from patients with diagnosed mitochondrial disease. The ultimate goal of such research is to develop new strategies to circumvent or prevent age-related mitochondrial dysfunction.

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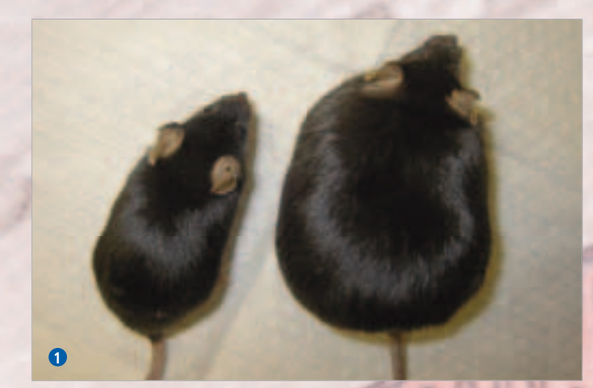

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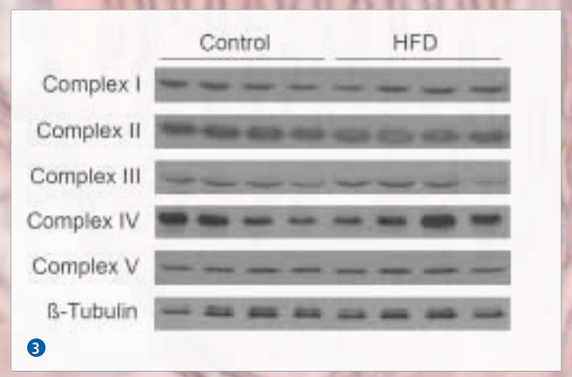

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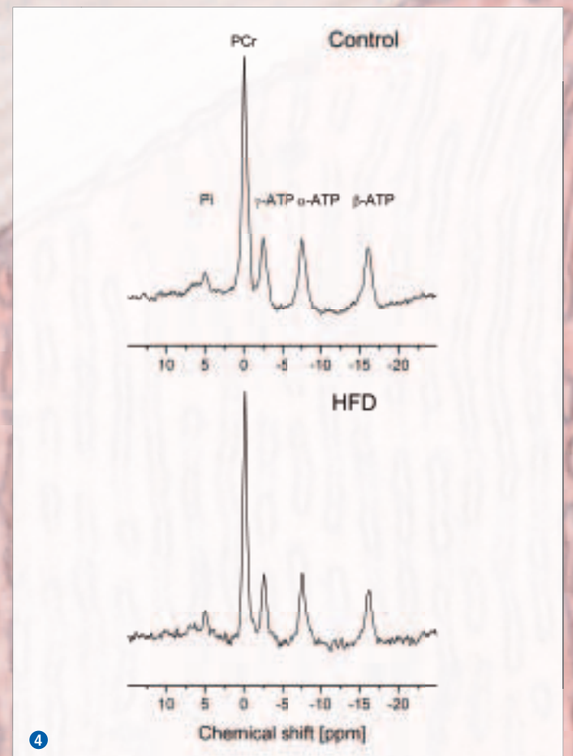

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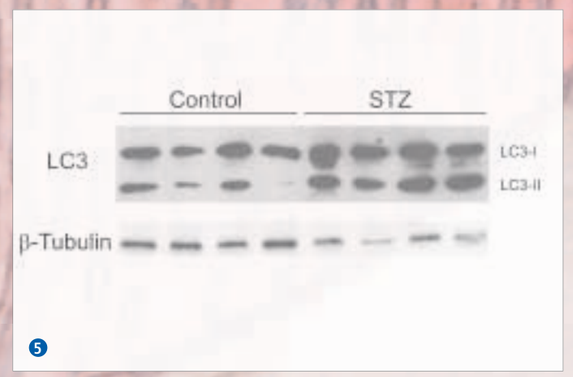

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1 Mice with a genetic defect (right) become obese and develop type 2 diabetes.

2 Intracellular lipids (Triacylglycerols; TG) are high in muscle of type 2 diabetic mice after a high-fat diet (HFD).

3 However, levels of the five mitochondrial respiratory chain complexes are unchanged in type 2 diabetic mice.

4 Also, ^{31}P-NMR spectroscopy of mouse muscle shows identical levels of the energy rich phosphates PCr and γ-ATP, thus there is no indication of mitochondrial dysfunction in type 2 diabetic mice also in vivo.

5 Increased autophagy, as indicated by the high levels of the autophagosome protein LC3-II, in muscle of type 1 diabetic mice after treatment with a ß-cell toxin (STZ).

Prof. Rudolf J. Wiesner

Principal Investigator
Institute for Vegetative Physiology

Despite intensive research, the pathways causing insulin resistance in muscle and liver and leading to aging-associated type 2 diabetes (Fig. 1) have not yet been established. Ectopic lipids accumulate in these tissues (Fig. 2) and are thought to cause alterations in the phosphorylation state of proteins involved in insulin receptor signaling. It has been postulated that mitochondrial dysfunction observed in muscle of diabetic patients impairs fatty acid oxidation, leading to accumulation of such toxic lipid metabolites and hence insulin resistance. To investigate this further, we looked at mitochondrial performance in muscle and liver of mouse models displaying distinct alterations in circulating factors or lacking components of the insulin-signaling pathway. Our results show that mitochondrial dysfunction in muscle and liver is neither the cause nor the consequence of obesity-associated insulin resistance (Figs. 3 & 4), either under normoglycemic or under hyperglycemic conditions. Furthermore, accumulation of intramyocellular lipid metabolites is not associated with impaired mitochondrial function. However, mitochondrial dysfunction, partly caused by increased autophagy in muscle (Fig. 5), is caused by very low insulin levels and hyperglycemia in type 1 diabetic mice and also by complete absence of the InsR, thus demonstrating a clear and previously undescribed link between insulin signaling and mitochondrial performance.

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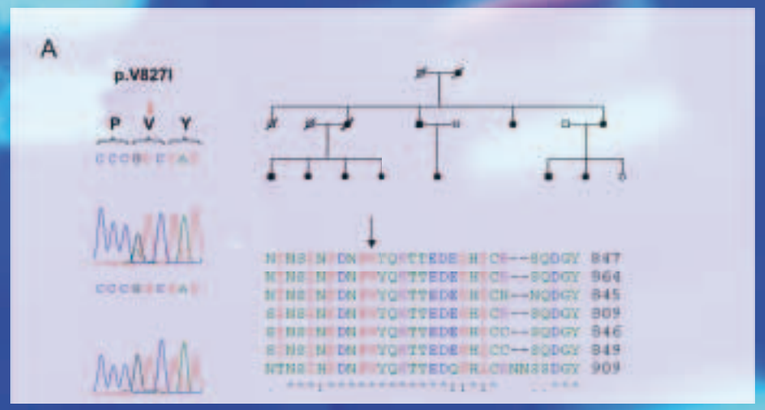

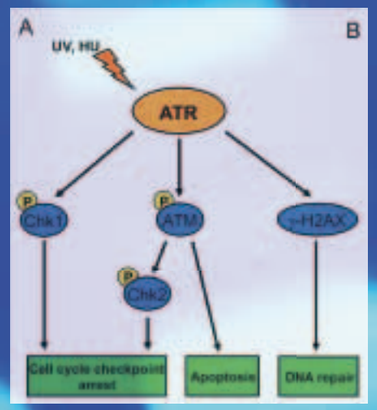

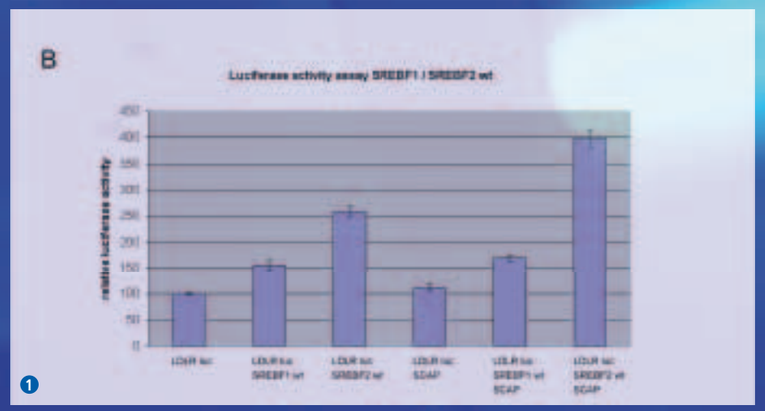

Dr. Bernd Wollnik

Principal Investigator
Center for Molecular Medicine Cologne (CMMC)

1 A. LDLR mutation screening identified novel mutations and mechanisms in familial and sporadic forms of hypercholesterolemia. B. Transcriptional effect of SREBF1 and SREBF2 on LDLR. HEK293 cells were transiently co-transfected with the LDLR promotor-luc reporter gene and SREBF1 or SREBF2 expression vectors, either in the absence or presence of expression vector for SCAP.

2 A. Simplified schematic overview of DNA damage response. B. Increased DNA damage response in Seckel fibroblasts. H2AX phophorylation of wildtype and Seckel primary fibroblasts after treatment with HU for 24 h.

Both aging and certain metabolic disorders are risk factors for a variety of common disorders of the elderly. Our aim is to identify novel genetic factors and distinct biological pathways contributing to hypercholesterolemia and raising the risk of coronary artery disease. We initiated a molecular study of 200 cases from the German LIANCO cohort and were able to show that LDLR mutations are frequently present in the LIANCO cohort. Moreover, our data indicate that transcriptional activation of LDLR is essential for maintenance of normal cholesterol levels and that mutations in the LDLR promoter as well as the transcriptional regulators SREBF1 and SREBF2 underlie hypercholesterolemia.

In addition, we have set up a study to investigate molecular mechanisms underlying Seckel syndrome, a congenital disorder belonging to the group of progeroid phenotypes. We have identified a novel centrosomal protein, regulating genomic integrity and cellular responses to DNA damage. Using homozygosity mapping and exome sequencing we have found mutations in this gene in Seckel syndrome and shown that impaired function leads to accumulation of genomic defects resulting from replicative stress. In future we will introduce and use further novel technologies such as next-generation sequencing for gene identification.

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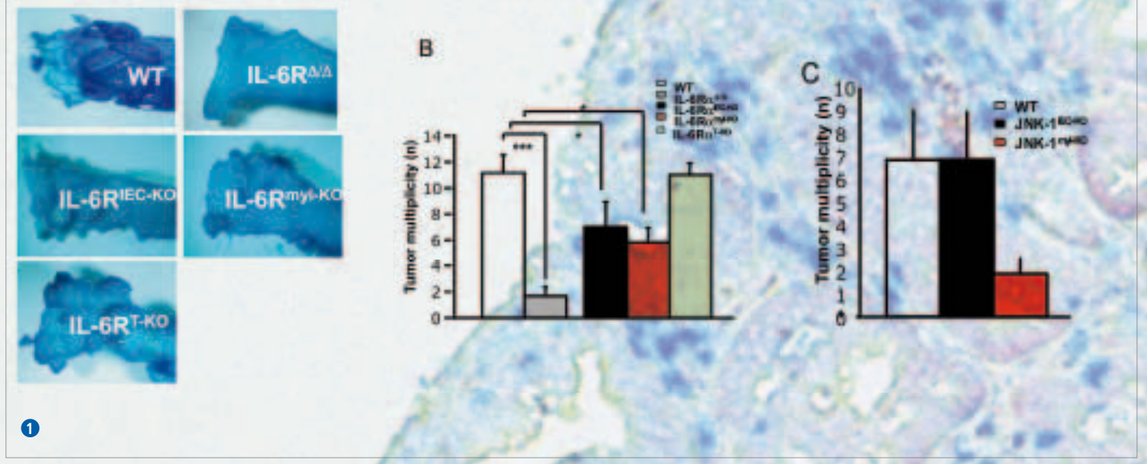
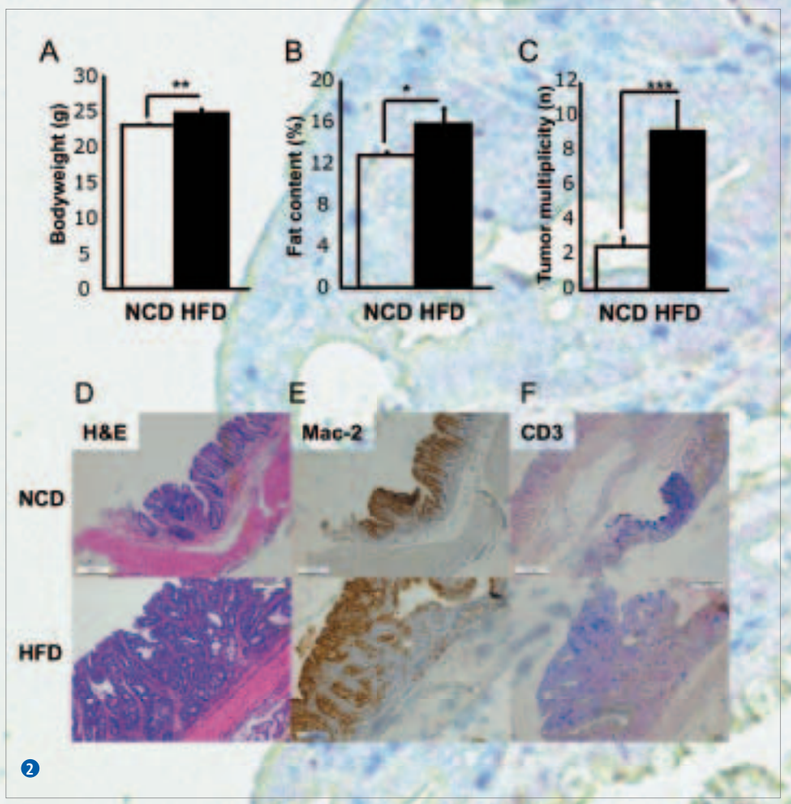


1 IL-6R- and JNK-1-deficiency in myeloid lineage cells protects mice from development of inflammation-driven colorectal cancer. 8-week-old mouse mutants were i.p. injected with AOM to induce CRC. Subsequently, 1.5% DSS was added to their drinking water for 5 days to promote inflammation and CRC development. Mice were sacrificed 60 days after AOM injection and investigated for tumor formation.
A) Representative distal colons of mouse mutants displaying cell type specific disruption of the IL-6R chain after subjection to the above treatment protocol. B) Quantification of inflammation-driven CRC development in IL-6R mouse mutants (n=10-15). (WT, white bar) wildtype, knock out of the IL-6R in the whole body (IL-6RΔ/Δ, gray bar), intestinal epithelial cells (IL-6RIEC-KO, black bar), myeloid lineage cells (IL-6Rmyl-KO, red bar) and mature T lymphocytes (IL-6RT-KO, green bar). C) Quantification of inflammation-driven CRC development in JNK-1 mouse mutants (n=10). (WT; white bar) wildtype, knock out of JNK-1 in intestinal epithelial cells (JNK-1IEC-KO, black bar) and myeloid lineage cells (JNK-1myl-KO, red bar).



2 Obesity increases CRC development. 8-week-old C57/BL6 mice, fed on either a normal chow diet (NCD; white bars) or a high fat diet (HFD; black bars), were i.p. injected with AOM to induce CRC and were further exposed to the respective diet. Five days later, 1.5% DSS was added to their drinking water for 5 days to promote inflammation and CRC development. Mice were sacrificed 60 days after AOM injection and investigated for tumor formation. A) Body weight and B) fat content of NCD and HFD fed mice after the CRC protocol (n=10). C) Quantitation of CRC development upon NCD and HFD feeding. Representative colon sections stained with D) H&E E) mac-2 and F) CD3 antibodies.

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Aging is accompanied by accumulation of a variety of genetic and epigenetic alterations in the genome, some of which may alter the expression of genes related to carcinogenesis. Moreover, the prevalence of obesity increases with age, along with associated diseases. Obesity elevates the incidence of cancers such as colorectal cancer (CRC) but the molecular and cellular mechanisms involved are poorly understood. Our aim is to elucidate the mechanisms underlying aging-associated CRC using mouse models in which certain inflammatory signaling pathways are inactivated. While knock out of IL-6R signaling throughout the body conferred almost complete protection to CRC development, we also observed reduced tumor multiplicity in IEC KO mice. However, interestingly, even inactivation of IL-6R signaling in myeloid lineage cells reduced CRC development while inactivation of TNF-induced JNK-1 in myeloid lineage cell types also conferred relative protection to CRC development. Thus, IL-6 and TNF signaling in myeloid lineage cells appear to contribute to the development of aging-associated CRC. Moreover, we found that diet-induced obesity increases CRC multiplicity and macrophage infiltration into the lesions when compared to normal chow-fed mice in a slightly modified inflammation-driven CRC approach. Thus, it is tempting to speculate that obesity-induced macrophage infiltration is a major cause of aging-associated CRC.

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Imprint

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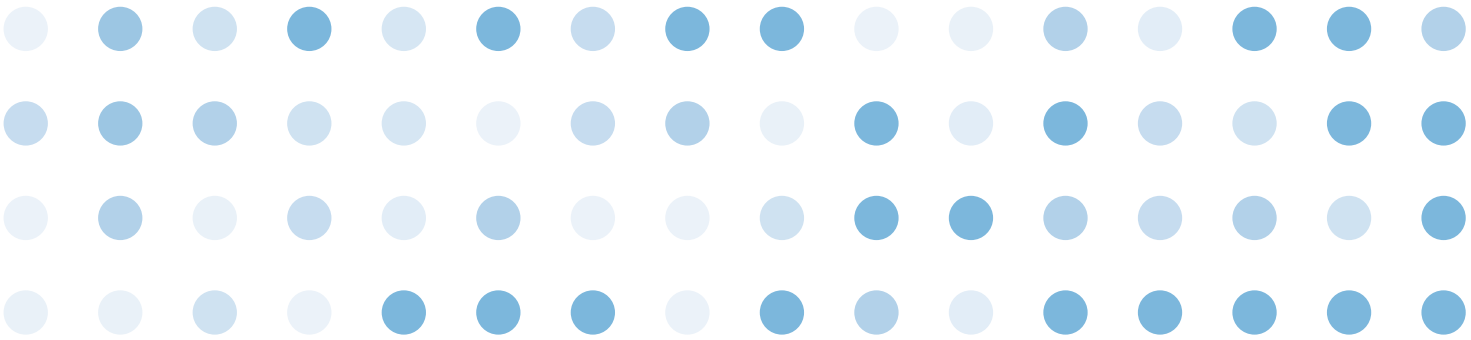
Design
FKK .design GmbH, Wuppertal

Printed by
Köllen-Druck, Bonn

Cologne, July 2011



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