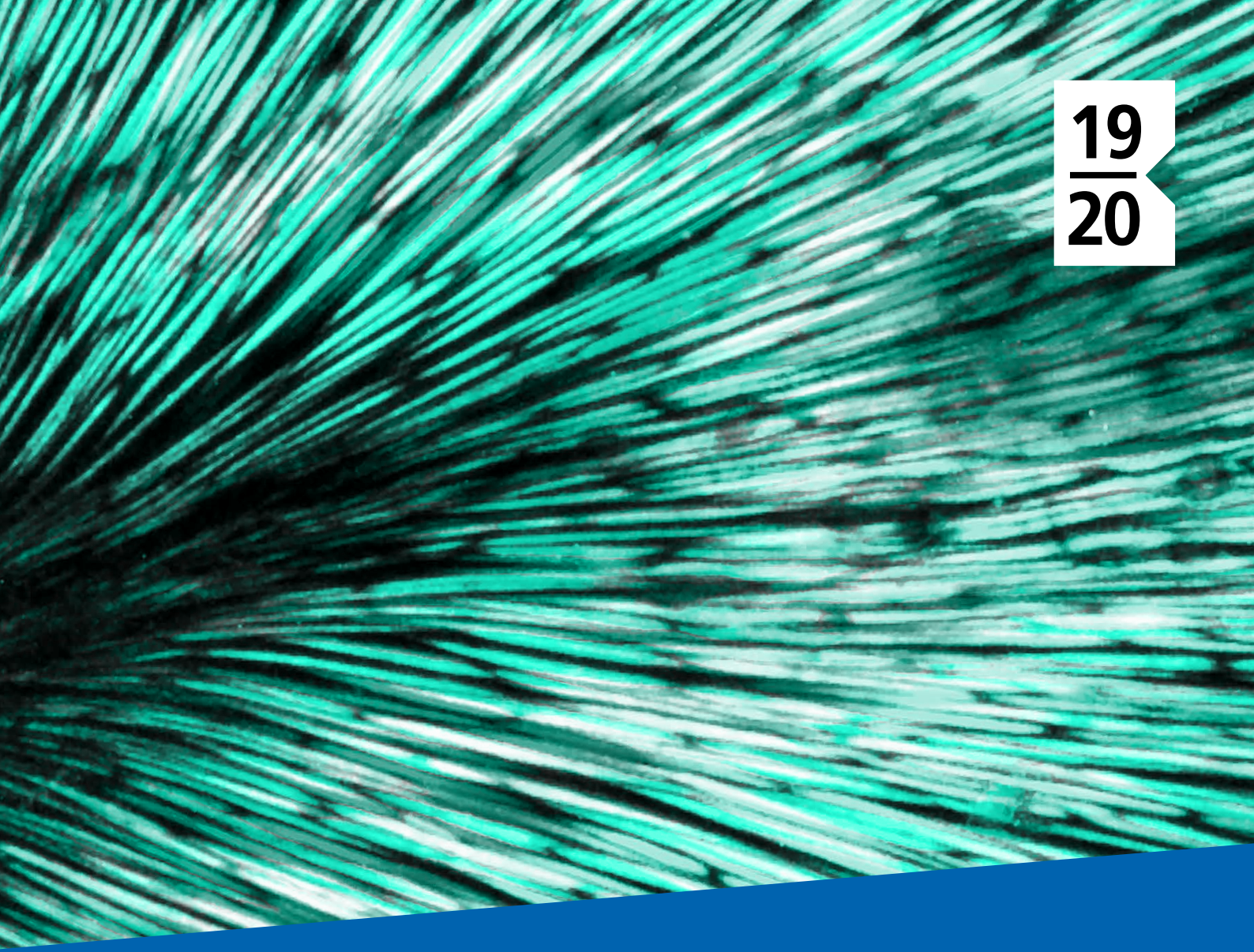


19/20

ANNUAL REPORT

CECAD CLUSTER OF EXCELLENCE

Cellular Stress Response in
Aging-Associated Diseases

CECAD
COLOGNE

“

To obtain a fundamental understanding of aging biology and cure disease requires a multidisciplinary approach accelerated by creating an international, open and diverse research environment that attracts the best people from all over the world.

Together for Healthy Aging



Carien Niessen
Scientific Coordinator

It is my honor to present the CECAD 2019-2021 report highlighting its outstanding and diverse scientific community and its achievements that empower CECAD to fulfill its mission: obtaining a fundamental understanding of the molecular, cellular, tissue and organismal processes that underlie the biology of aging to enable the identification of unifying translational targets for age-related diseases.

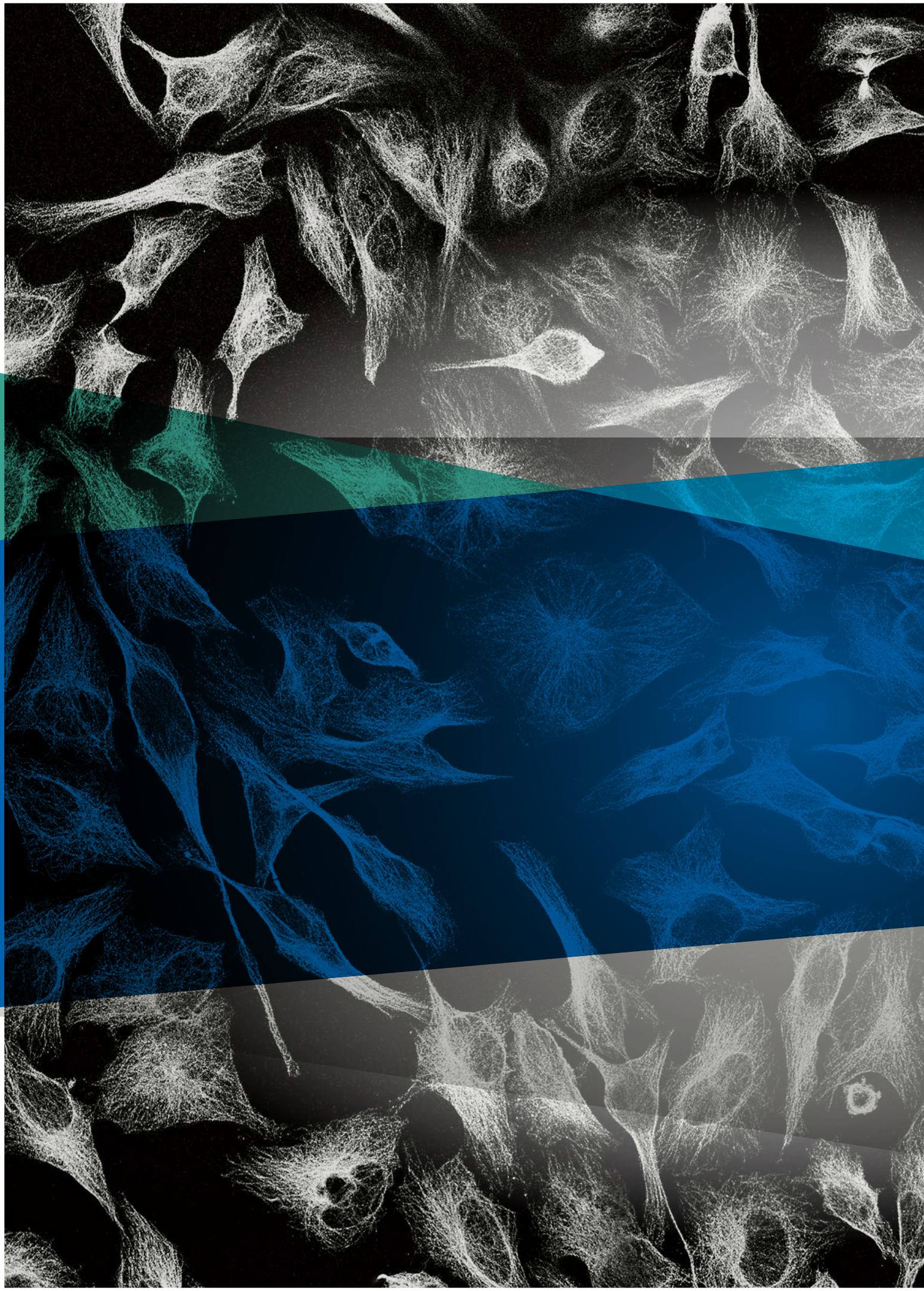
CECAD was established in 2007 through the DFG-organized German Excellence Initiative, carried by strong and highly supportive partners: the University of Cologne (UoC) and its University Hospital, the Max Planck Institutes (MPI) for Biology of Ageing and for Metabolism Research, and the Helmholtz' German Center for Neurodegenerative Diseases (DZNE). Through new professorships, the Graduate School for Aging Research (CGA), career & diversity programs, and state-of-the-art facilities, CECAD established a highly interactive and multidisciplinary research hub in the heart of Europe that attracts scientists from across the world and that is focused on aging and aging-associated diseases. The close vicinity of one of the leading teaching hospitals and implementation of new translational structures also empower CECAD to explore how its new discoveries will benefit humans and promote healthy aging.

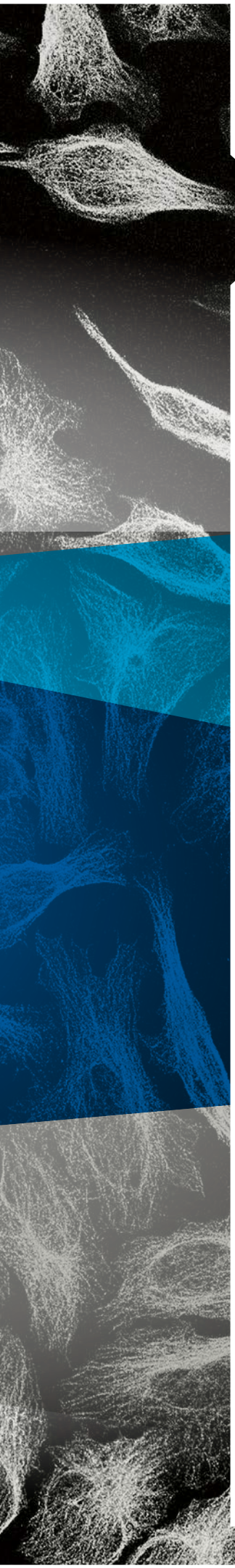
The last 10 years revolutionized our understanding of the biology of aging, in part driven through findings of CECAD principal investigators. This led to the realization that interactions between tissues and with the organism's environment provide essential cues that either delay or advance the aging process and thus disease. Capitalizing on these findings, CECAD established two new research areas on interorgan communication and on organism-environmental interactions in addition to the existing one on cell-autonomous aging mechanisms. This expanded CECAD research profile was successful in obtaining cluster funding through the 2018 German Excellence Strategy.

The last two years were dedicated to strategic recruitments to strengthen these new areas. CECAD attracted two very talented early career group leaders, Jane Reznick (injury and metabolic reprogramming) and Gilles Storelli (lipids, tissue barriers and inflammation). Moreover, two newly established UoC professorships enabled CECAD to recruit Filipe Cabreiro, an internationally renowned expert in microbiome-host-drug interactions in aging and health, and, with support of the Alexander-von-Humboldt foundation, Christian Frezza, a world leading expert in metabolomics in cancer and aging. These new CECAD Principal Investigators provide exciting new opportunities and synergies in aging research on the Cologne campus.

Demographic change leads to an increasingly aged population also beyond western societies and poses enormous socio-economic challenges. A fundamentally better understanding of the aging process and its contribution to disease thus remains of utmost societal urgency in order to promote healthy aging. We belief that CECAD's investments and achievements as reflected in this report will bear fruit towards new solutions. I wish you a pleasant and inspiring read.

Carien Niessen





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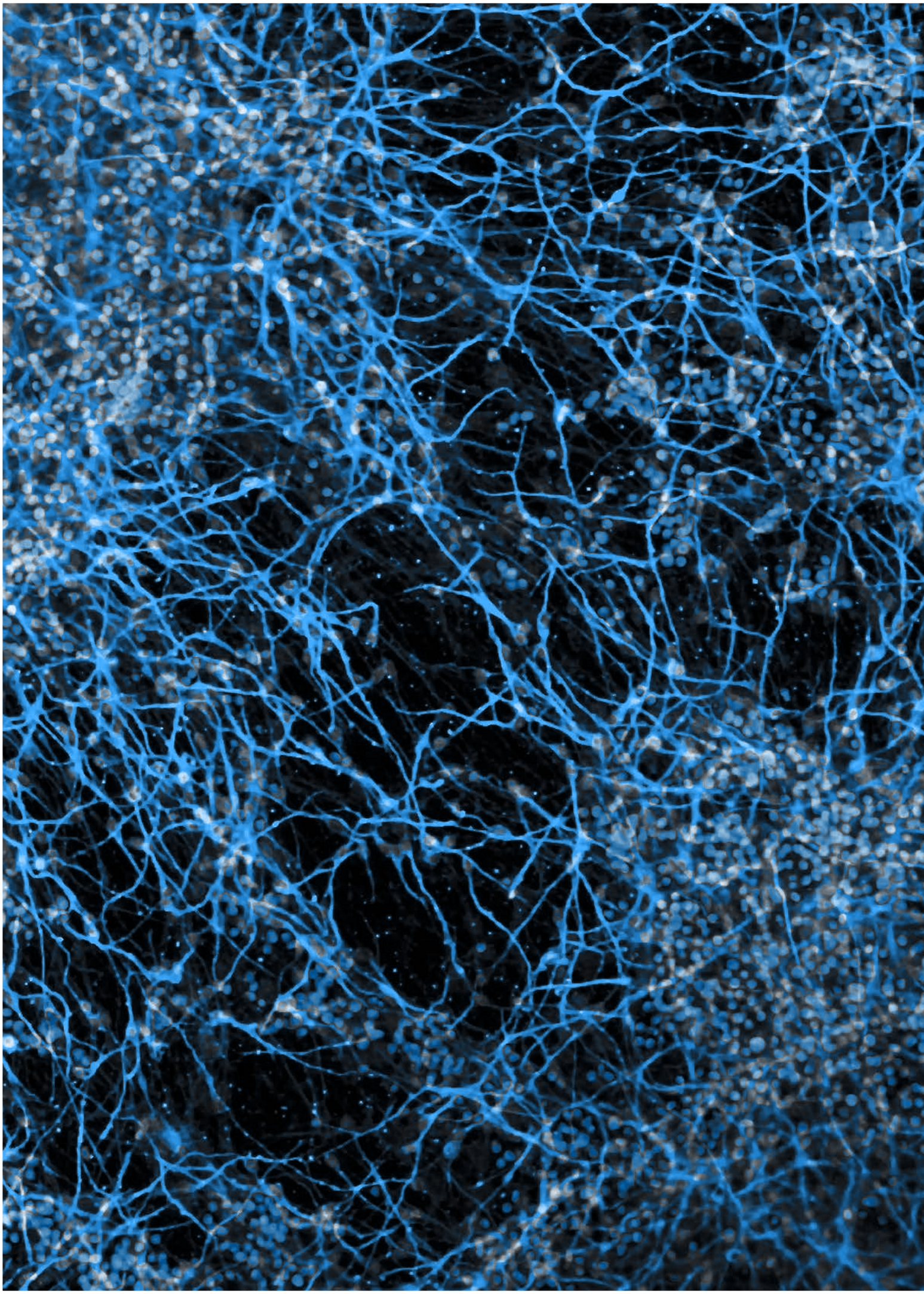
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/1 ABOUT CECAD



ABOUT CECAD

CECAD's vision – Uncover the aging process to promote healthy aging

With every hour, minute, and second we age. Aging thus affects everyone and presents society with major challenges as aging poses an increased disease burden. For society, the expected burden on the domestic economy for rising healthcare costs associated with aging is immense. The CECAD excellence cluster at the University of Cologne investigates the causes that both underlie aging and that trigger a wide range of age-associated disorders.

CECAD's mission

It is CECAD's mission to provide fundamental knowledge of the biology of aging and aging-associated diseases. CECAD's work includes elucidating the molecular and cellular mechanisms of aging in order to define new approaches for prevention, diagnosis and treatment of age-associated diseases including metabolic diseases, diabetes, cardiovascular disease, renal failure, cancer and neuro- and other degenerative disorders. To achieve its mission, CECAD unites the efforts of basic scientists with clinician scientists from the University of Cologne, the University Hospital Cologne, the Max Planck Institutes for Biology of Aging and for Metabolism Research, and the German Center for Neurodegenerative Diseases (DZNE) to foster a multidisciplinary approach using state-of-the-art technology and translational platforms.

Over the past decade, CECAD has developed into a globally visible, unique center for aging and aging-associated disease research that has made important inroads in understanding the biology of aging and how aging drives disease. CECAD is focused on the cellular mechanisms and how these are affected by interorgan and organism-environmental communication, with a special focus on translating results into new therapeutic approaches in the clinic. Conversely, clinical observations also create the basis for new research questions.

Demographic changes are continuing to show growth in the number and proportion of the elderly population, creating an urgent need for a better understanding of the biology of aging. The goal of CECAD is to better understand how to maintain health during aging while providing the foundation for a healthy aging society.

CECAD Organization and Management

CECAD is supported by lean and effective executive and management structures: The CECAD Executive Board steers the strategic and financial decisions while the CECAD Central Office runs the managerial and administrative operations of the cluster.

The Partners

CECAD is formed as a partnership between the University of Cologne (UoC), its University Hospital, the Max Planck Institute (MPI) for Biology of Ageing and the MPI for Metabolism Research, and the Helmholtz' German Center for Neurodegenerative Diseases (DZNE). To ensure its long-term scientific and organizational autonomy, CECAD is legally and organizationally positioned under the UoC Rectorate as an interfaculty institute between the Faculty of Mathematics and Natural Sciences, and the Faculty of Medicine. The partners are essential for carrying the long-term scientific direction and recruitment strategies of the excellence cluster.

The CECAD Executive Board

Headed by the Scientific Coordinator, the Executive Board is the most important instrument for the strategic leadership of the Cluster. The Executive Board decides about the budget, personnel and scientifically relevant issues as well as engages the partners in long-term strategic directions and decisions.

The CECAD Central Office

The Central Office is headed by the Administrative Coordinator and supports the Scientific Coordinator, the Executive Board, and external advisory board. The office provides essential support to the scientific community of CECAD, coordinating and executing all management, financial and administrative tasks of the cluster. Notably, the office is essential for communication, coordination and alignment of CECAD with the UoC management, the two faculties and its non-university partners while operating the activities of the Career Development and Diversity (p.132), and Public Relation and Marketing (p.136) platform.

MEMBERS OF THE CECAD EXECUTIVE BOARD

Prof. Dr. Carien Niessen
(Scientific Coordinator, Head)

Prof. Dr. Thomas Benzing / Prof. Dr. Thorsten Hoppe (Deputies)

Prof. Dr Thomas Langer

Prof. Dr. Manolis Pasperakis

Dr. Jane Reznick

Prof. Dr. Elena Rugarli

Prof. Dr. Björn Schumacher

Prof. Dr. Aleksandra Trifunovic

Permanent Guests:
Prof. Dr. Jens C. Brüning, Deans of the Medical and Natural Science Faculties

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CECAD IT



KIM OPGENOORTH

CECAD IT Manager

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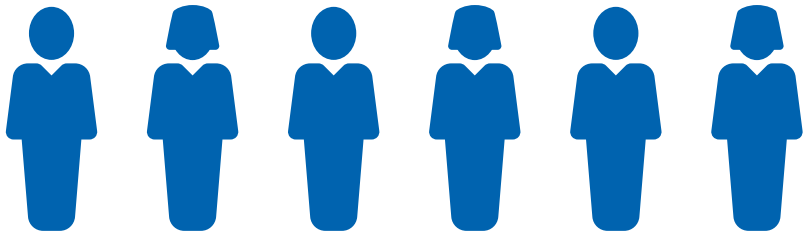
EIT HEALTH



DR. SARAH DENZEL

Project Manager of EIT Health

sarah.denzel@uk-koeln.de



>650 RESEARCHERS



73 PRINCIPAL INVESTIGATORS

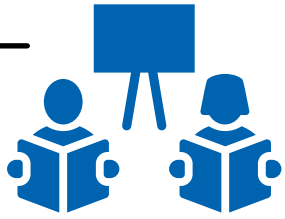
29 RESEARCH GROUP LEADERS

44 PROFESSORS



196 POSTDOCS

233 PHD STUDENTS



53 MEMBERS

20 ASSOCIATED MEMBERS



54 NATIONALITIES

>100  NON-SCIEN-TIFIC STAFF

>50%  FEMALE SCIENTISTS

6 HIGH-TECH FACILITIES

- BIOINFORMATICS
- IN VIVO
- IMAGING
- SYSTEMS NEUROSCIENCE
- LIPIDOMICS/METABOLOMICS
- PROTEOMICS

BUNDLED EXPERTISE

1 LOCATION

6 MAIN ORGANISMS

>750 PUBLICATIONS IN 2019/20

44 IF>30 HIGH IMPACT

>170 COOPERATIVE PAPERS

NETWORK

PARTNER:

UNIVERSITY OF COLOGNE

FACULTY OF MEDICINE

CECAD COLOGNE

FACULTY OF MATHEMATICS AND NATURAL SCIENCE

UNIVERSITY HOSPITAL COLOGNE

DZNE
GERMAN CENTER FOR NEURODEGENERATIVE DISEASES

MPI FOR BIOLOGY OF AGEING

MPI FOR METABOLISM RESEARCH

PROJECTS:

CRC 829*
MOLECULAR MECHANISM REGULATING SKIN HOMEOSTASIS

CRC 1218*
MITOCHONDRIAL REGULATION OF CELLULAR FUNCTION

CRC 1310
PREDICTABILITY IN EVOLUTION

CRC 1399
MECHANISMS OF DRUG SENSITIVITY AND RESISTANCE IN SMALL CELL LUNG CANCER

CRC 1403*
CELL DEATH IN IMMUNITY, INFLAMMATION AND DISEASE

CRC 1451
KEY MECHANISMS OF MOTOR CONTROL IN HEALTH AND DISEASE

CRU 329*
DISEASE PATHWAYS IN PODOCYTE INJURY – FROM MOLECULAR MECHANISMS TO INDIVIDUALIZED TREATMENT OPTIONS

RU 2240
(LYMPH) ANGIOGENESIS AND CELLULAR IMMUNITY IN INFLAMMATORY DISEASES OF THE EYE

RU 2743
MECHANICAL STRESS PROTECTION

ITN ADDRESS
CHROMATIN DYNAMICS & THE DNA DAMAGE RESPONSE

ITN HEALTHAGE
LIFESPAN REGULATION MECHANISMS IN HEALTH AN DISEASE

RTG 2407
INFLAMMATORY AND CELLULAR STRESS SIGNALING: SWITCHES TO VASCULAR DYSFUNCTION

RTG 2550
DYNAMIC REGULATION OF CELLULAR PROTEIN LOCALIZATION (RELOC)

TRR 259
AORTIC DISEASE

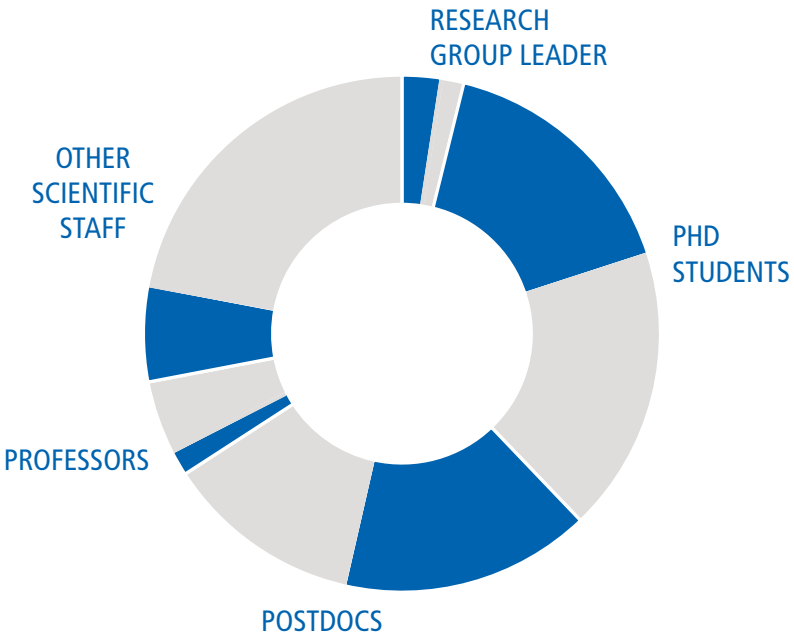
MPI: Max Planck Institute | **CRC:** Collaborative Research Center | **CRU:** Clinical Research Unit | **RU:** Research Unit | **ITN:** Innovative Training Network | **RTG:** Research Training Group | **TRR:** Transregio | ***coordinated by CECAD PI

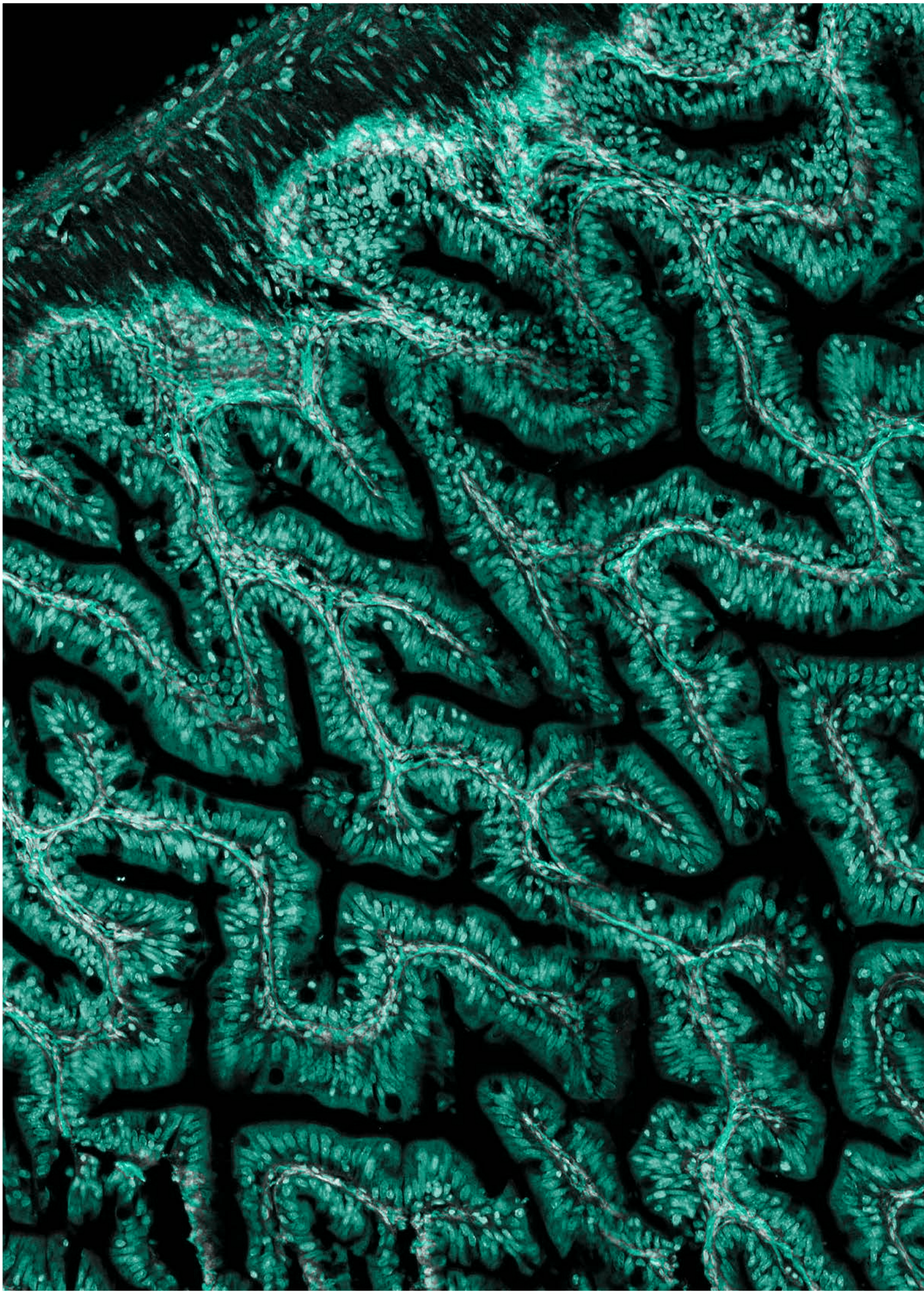
NATIONALITIES



The CECAD community is diverse and international at all levels, thus providing a vibrant, dynamic and stimulating environment for talent from all over the world.

43%
INTERNATIONALS







/2
CECAD RESEARCH

The Research Areas at CECAD

CECAD aims to reveal the mechanisms that underlie the aging process and its associated diseases. Aging affects a large variety of physiological processes ranging from molecular and cellular signaling mechanisms to systemic adaptations of the aging organism.

The overarching long-term scientific mission of CECAD is to develop effective, evidence-based prevention strategies for major age-associated diseases. The aim: extending lifespan while maintaining quality of life.

Based on breakthrough discoveries of CECAD scientists in the previous funding periods, CECAD has expanded its scope in its third funding period beyond the analysis of cell-autonomous stress signaling pathways to the investigation of the role of inter-organ communication and the integration of internal signals and external environmental cues in the aging process. Now, CECAD scientists are exploring the key mechanisms of aging in three defined research areas:

RA-1: THE CELLULAR LEVEL

Cell autonomous control of homeostatic mechanisms and cellular stress responses in aging and age-associated diseases

RA-2: THE ORGANISMAL LEVEL

Stress response mechanisms of tissue-related and interorgan communication in aging and age-associated diseases

RA-3: THE ENVIRONMENTAL LEVEL

Environment/organism interactions in aging and age-associated diseases

Supporting these three research areas, CECAD has successfully established three research platforms.

- Technology and technology development
- Translational research
- Education and Career Development, Diversity, Gender Equality and Family Programs, and Public Outreach and Visibility

The technology platform comprises the CECAD facilities that implement the state-of-the-art methodologies to support the investigators' research projects (page 108-119 Facilities).



The translational platform facilitates the clinical implementation of the new insights that CECAD scientists are acquiring (page 120 Translational research).

Education and career development are a top priority at CECAD, and one that offers training and support to young researchers. Additionally, CECAD supports gender equality and a family-friendly working environment (page 132 Career Development and Diversity).

CECAD further strives to engage the general public in research through outreach and engaging in dialogue (page 136 Outreach).

Research Area 1

Cell autonomous control of homeostatic mechanisms and cellular stress responses in aging and age-associated diseases

The decline of physiological integrity at the cellular, tissue and organismal level with age culminates in functional defects and increased risk of age-associated disease. CECAD groups in Research Area 1 study cell autonomous mechanisms contributing to the decline of cellular function during aging, with the goal of obtaining fundamental molecular insight and identifying novel targets for intervention. Several processes that are known for playing a role in determining a healthy lifespan are the focus of research, such as nutrient sensing, cellular responses to DNA damage, mitochondrial function or proteostasis surveillance mechanisms. Research groups examine the crosstalk between different cell autonomous processes during aging and how their disturbance causes age-associated diseases such as neurodegeneration, cardiomyopathies and cancer. Highlights from RA-1 include the finding of the Valenzano group that relaxation of purifying selection prominently shapes genomes and is a prime candidate force molding the evolution of lifespan and the distribution of genetic variants associated with late-onset diseases in different species (Cui R *et al.*, Cell. 2019). The Partridge group identified novel longevity promoting signal in the form of specific circular RNAs (circRNAs), circSfl that is regulated by the insulin signaling and sufficient to extent the lifespan (Weigelt CM *et al.*, Mol Cell. 2020). The results from the Trifunovic group underlined the importance of the xenobiotic detoxification in the mitohormetic, longevity assurance pathway and identify KLF-1 as a central factor in orchestrating this response (Herholz M *et al.*, Nat Commun. 2019). Several groups including the Rugarli group investigated the role of autophagy – the process of cellular self-recycling, and its regulator mTOR, in different physiological conditions. The Rugarli group showed the role of metabolic adaptation of liver mitochondria to nutrient availability that depends on a compartmentalized RNA-binding protein CLUH that controls both mTORC1 and G3BP signalling and ensures survival cell and organismal survival (Pla-Martín D *et al.*, EMBO J, 2020). Several outcomes of CECAD groups highlighted the central role of mitochondria for the age-associated decline of cells and unraveled novel lipid signaling cascades preserving mitochondrial functions. The Antebi group found that lipid pools coordinate lysosomal and mitochondrial functions and preserve healthy aging in C. elegans (Tharyan *et al.*, Nat Metab. 2020). The Brüning group demonstrated that the sphingolipid metabolism regulates mitochondrial fission and the fragmentation of the mitochondrial network as observed in aged cells (Hammerschmidt *et al.*, Cell. 2019). The Langer group found that a phospholipid signaling cascade, regulated by nutrient signaling, triggers reshaping of the mitochondrial proteome by proteolysis and metabolically reprograms mitochondria facilitating tumor growth (MacVicar *et al.*, Nature. 2019). The Trifunovic group, further focusing on mitochondria, found that the respiratory function of mitochondria depend on a novel salvage pathway ensuring the selective proteolysis of damaged parts of respiratory complex I and limiting deleterious production of reactive oxygen species (Szczepanowska *et al.*, Nat Commun. 2020).

HEAD PRINCIPAL INVESTIGATORS

Prof. Dr. Aleksandra Trifunovic

Prof. Dr. Thomas Langer

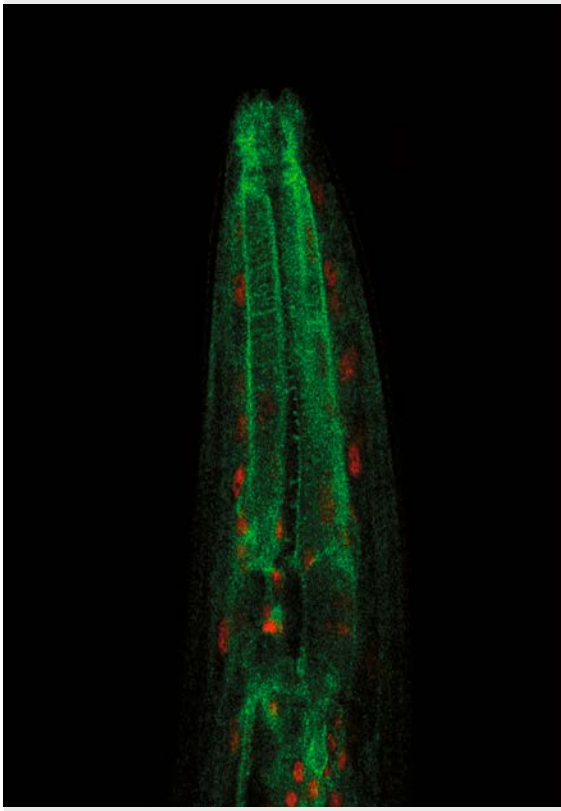


Fig. 2



VIDEO

DETAILED INFORMATION

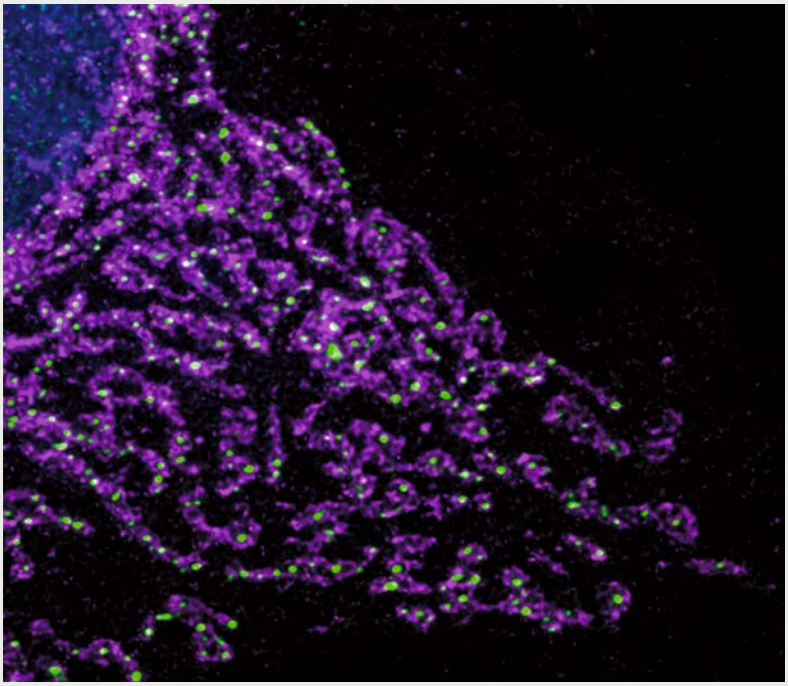


Fig. 1

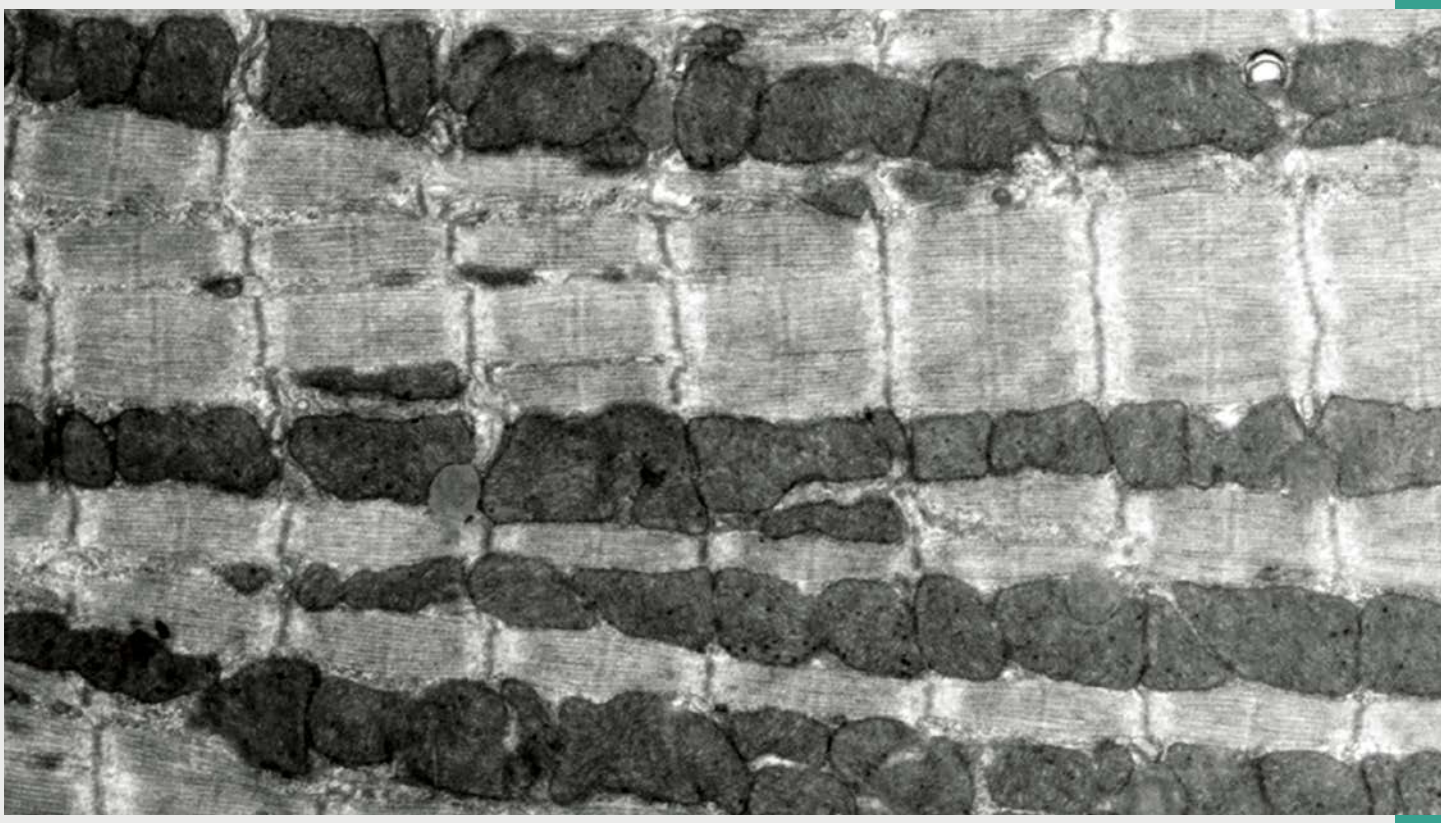


Fig. 3

Fig. 1: MacVicar *et al.*, 2019; Mitochondria (pink) form large networks in the cell. When cells lack oxygen this network is fragmented, mitochondria become fewer and are reprogrammed. Cell nucleus is stained blue and mitochondrial DNA green.

Fig. 2: Tharyan *et al.*, 2020; Microscopy image of C. elegans. Red marks the nucleus, where NFYB-1 is present, and green marks lysosomes

Fig. 3 Szczepanowska *et al.*, 2020; Ultra-thin transmission electron micrography of mouse wild type heart. Mitochondria (dark gray) occupy about 40% of the cardiomyocytes volume as heart has one of the highest needs for the energy production in the body. Therefore, quality control of the mitochondrial respiratory chain, the main ATP producer in the cell is essential for survival

Research Area 2

Stress response mechanisms of tissue-related and inter-organ communication in aging and age-associated diseases

During the aging process, different stress response pathways are tightly coordinated, thereby ensuring physiological integrity especially upon metabolic changes. Recent studies have identified cell non-autonomous regulation of cellular stress responses, suggesting interorgan communication mechanisms that are intricately balanced for integrity and maintenance of the entire organism.

At Research Area 2, scientists aim to unravel the interplay between homeostasis pathways at the molecular, cellular, and organismal level, as well as to define adaptation mechanisms in response to aging or inherited, disease-associated mutations. Highlights from RA-2 include the findings of the Partridge, Leptin and Eming groups on the roles of TOR complexes in epidermal morphogenesis and regeneration in flies, mice and humans (Kakanj *et al.*, Nat Protoc. 2020). The Eming group dissected how the TORC2 complex controls the skin barrier function (Ding *et al.*, JACI. 2020) and, together with the Wickström group, identified TORC2 as critical regulator of metabolism and longevity of hair follicle stems cells (Kim *et al.*, Cell Metab. 2020). Metabolism is strongly influenced by food intake, which requires adjustments of the cellular proteostasis machineries. The Hoppe group uncovered an unexpected microRNA-mediated mechanism through which food perception impacts the organism's proteostasis (Finger *et al.*, Nat Metab. 2020). In mammals, astrocytes respond to alterations in the nutritional intake. The Brüning group uncovered that this glial cell type regulates an adaptive stress response that improves systemic glucose homeostasis and memory formation (Timper *et al.*, Cell Metab. 2020). The memory effect of nutrition intake can actually trigger lifelong effects on longevity and metabolic remodeling as demonstrated by the Partridge group (Hahn *et al.*, Nat Metab. 2019). Environmental factors such as UV or mechanical stress can lead to genome damage. Collaborating with the Niessen team, the Wickström group demonstrated how the chromatin protects itself through epigenetic mechanisms from the impact of mechanical stress (Nava *et al.*, Cell. 2020). Epigentic regulators are not only important for modifying the consequence of environmental stress on the genome but were shown by the Schumacher group to also mediate the recovery of protein biosynthesis and homeostasis that is required for animals to survive the consequences of DNA damage (Wang *et al.*, Nat Struct Mol Biol. 2020). The Uhlirova group showed further that response mechanisms to oxidative stress regulate the renewal capacities of intestinal stem cells that are essential for maintaining the organism's homeostasis (Mundorf et al., Cell Rep. 2019). Stem cells of the germline are also impacted by niche signaling as the Schumacher group revealed in the p53-mediated DNA damage response (Ou *et al.*, Dev Cell. 2019). The Vilchez group showed that germ stem cells respond to reduced temperature and then impact the lifespan of animals (Ju Lee *et al.*, Nat Metab. 2019). On the organ level, the Schermer and Benzing groups identified a new molecular mechanism that links age-dependent morphological changes to chronic kidney disease (Butt *et al.* Nat Metab. 2020).

HEAD PRINCIPAL INVESTIGATORS

Prof. Dr. Sabine Eming

Prof. Dr. Björn Schumacher

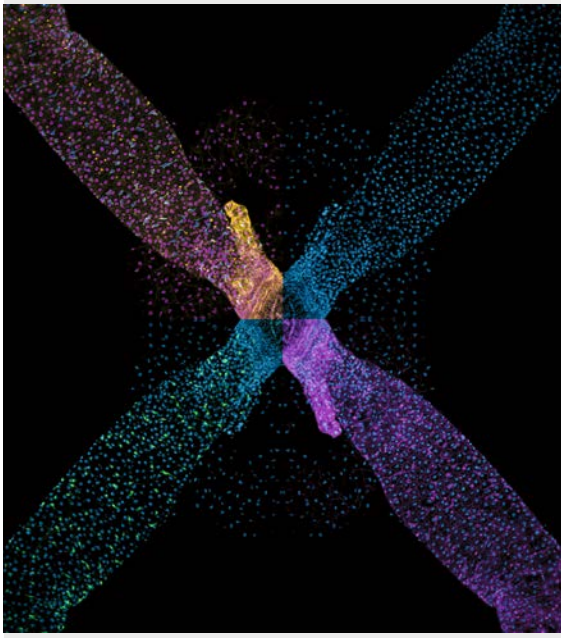


Fig. 3



VIDEO

DETAILED INFORMATION

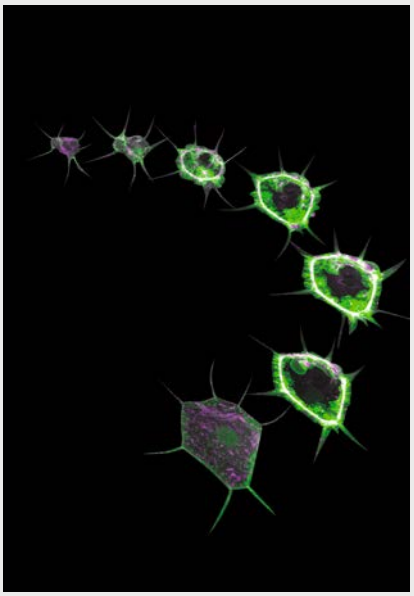


Fig. 1

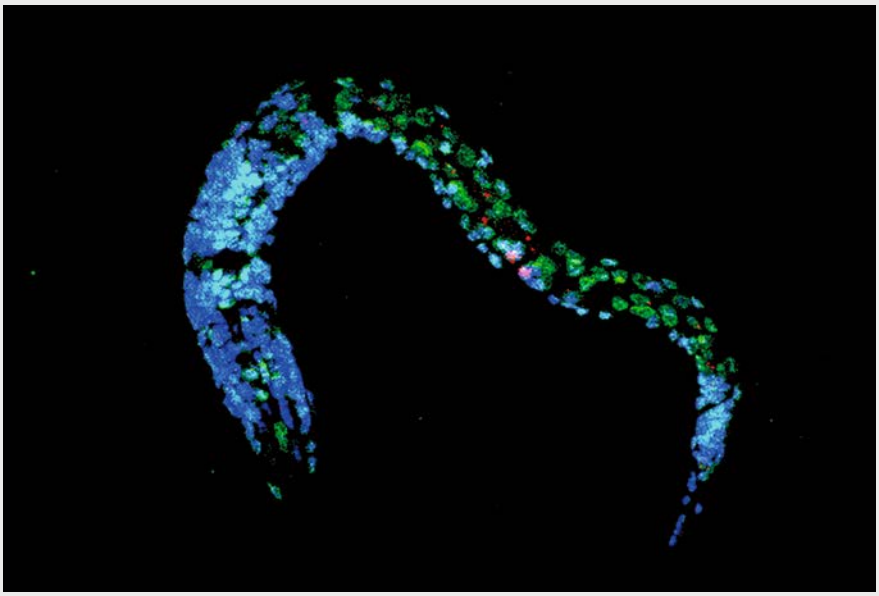


Fig. 2

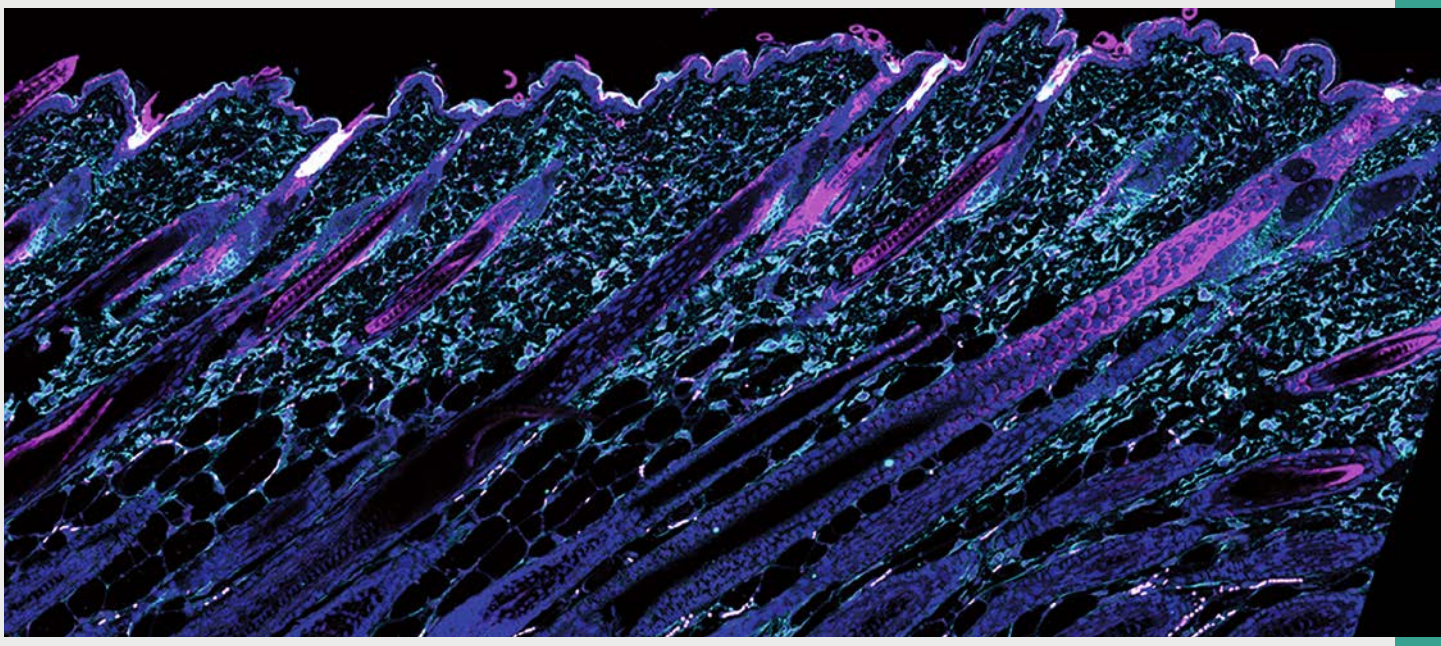


Fig. 4

Fig. 1: Kakanj *et al.*, 2020; Composition of snapshots from a timelapse video of a closing wound in the epidermis of a Drosophila larva. The cells express two fluorescently labelled markers: a PIP3 sensor (green) and the myosin light chain (magenta).

Fig. 2: Wang *et al.*, 2020; Confocal microscopy of C. elegans after UV irradiation. There are increased double occupations of the histones: H3K4me2 in green. Triple occupancy (H3K4me3) are stained red and nuclei are marked blue.

Fig. 3: Mundorf *et al.*, 2019; Collage of the posterior midgut of a Drosophila adult intestine. Immunostaining was used to visualize the different cell types comprising the gut, including the stem cells and the differentiated absorptive enterocytes and hormone-producing enteroendocrine cells.

Fig. 4: Ding *et al.*, 2020; Cross-section of a skin biopsy showing hair follicles extending downwards from the skin surface. Low oxygen around the hair follicle stem cells activates Rictor signaling (phosphorylated Akt; in magenta) locally at this site. Cell nuclei are labeled in blue.

Fig. 5: Ju Lee *et al.*, 2019; Germline of C. elegans at cold temperature. Proliferating germline stem cells are stained red and cell nuclei blue. Low temperature maintains a proliferative pool of germline stem cells at old ages.

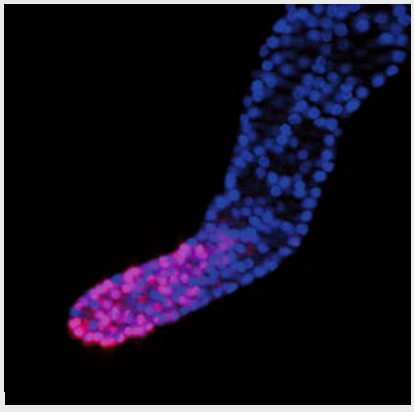


Fig. 5

Research Area 3

Environment/organism interactions in aging and age-associated diseases

The organism has constantly to integrate information about the internal state with external environmental stimuli. Adaptive brain and body interactions ensure the optimal physiological homeostasis, which critically determines lifespan. Research Area 3 focuses on studying the mechanisms regulating the interaction between organisms and the environment and how these affect health and disease, in particular, aging and aging-associated pathologies. Key neuronal networks in the hypothalamus provide a crucial integration point where neurons are specialized to sense hormones and nutrients as well as to respond to environmental stimuli and coordinate a broad spectrum of physiological responses. Impairments of these responses and processes can lead to the onset and development of major age-associated diseases. Highlights of RA-3 in 2019/2020 include the findings of the Bergami group that glial cells have a crucial function in enabling vascular remodeling following acute brain injury (Göbel *et al.*, Cell Metab. 2020) and discovery of a novel role for self-recycling process in the brain, important for neurodegeneration by the Kononenko group (Negrete-Hurtado *et al.*, Nat Commun. 2019). Further, RA-3 scientists developed a novel method to study temporal and local dynamics of dopaminergic transmission, crucial for reward signalling, in humans (Lippert *et al.*, Nat Commun. 2019). A collaboration of the Cornely, Brüning and Tittgemeyer groups characterized pathways enabling immediate orosensory and delayed post-ingestive reward system activation to promote food intake in humans (Thanarajah *et al.*, Cell Metab. 2019). Further, recent studies have linked metabolic and neurological conditions with the composition of microbiota, which represents a critical interface between the organism and its environment. The diversity of the gut microbiota appears to be linked with host immune, metabolic, as well as neurological conditions. The content and diversity of microbiota alters during aging and in response to dietary changes as well as some medical treatments. Deregulation of the host-microbiota crosstalk during aging results in an elevated inflammatory state often referred to as 'inflammaging', which is implicated in the pathogenesis of aging-associated diseases. The Pasparakis group shed light on the mechanisms by which impaired barrier function causes microbiota-driven cytokine responses and intestinal inflammation (Eftychi *et al.*, Immunity. 2019, Schwarzer *et al.*, Immunity. 2020). In addition, scientists of the Krönke, Pasparakis and Kashkar groups discovered novel mechanisms regulating cell death and inflammation. Caspase-8 was identified as a molecular switch controlling apoptosis, necroptosis and pyroptosis (Fritsch *et al.*, Nature. 2019), whereas macrophage necroptosis was shown to trigger inflammasome-dependent arthritis (Polykratis *et al.*, Nat Cell Biol. 2019). Moreover, sensing of endogenous Z-nucleic acids by ZBP1 was identified as a key mechanism driving cell death and chronic inflammatory responses in epithelial tissues (Jiao *et al.*, Nature. 2020).

HEAD PRINCIPAL INVESTIGATORS

Prof. Dr. Tatiana Korotkova

Prof. Dr. Manolis Pasparakis

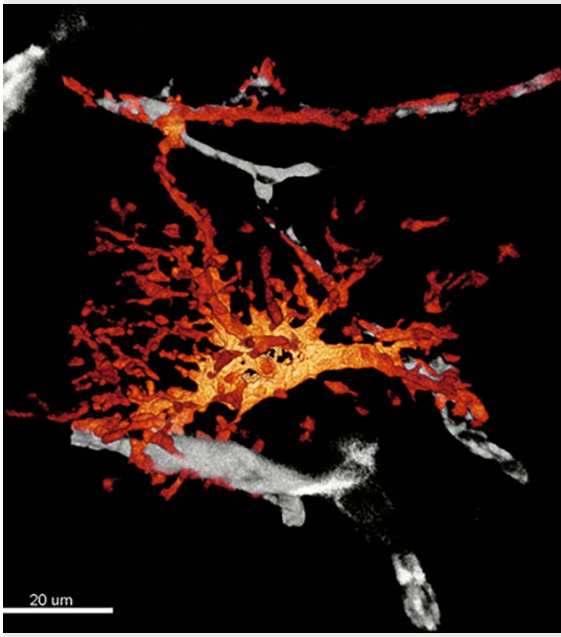


Fig. 2



VIDEO

DETAILED INFORMATION

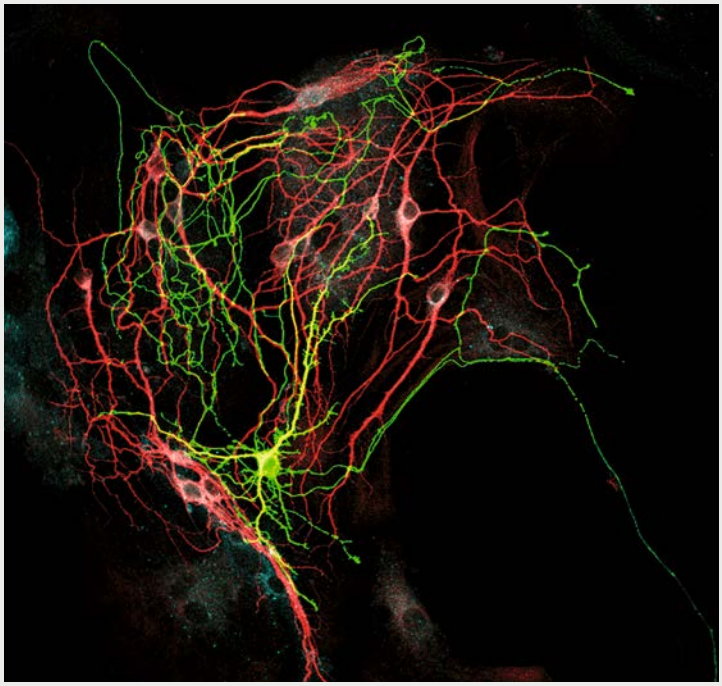


Fig. 1





Fig. 3

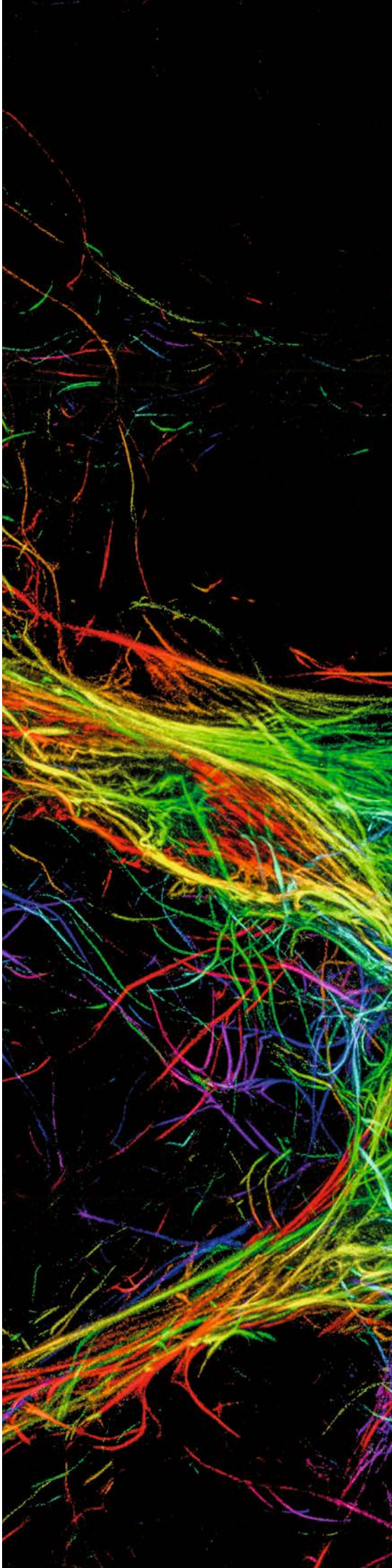
Fig. 1: Negrete-Hurtado *et al.*, 2020; GFP-labelled axons of wildtype cortical neurons in-vitro.

Fig. 2: Göbel *et al.*, 2020; Visualization of a single astrocyte expressing ER-GFP (in pseudocolors) in the mouse cerebral cortex, contacting the nearby microvasculature (grey).

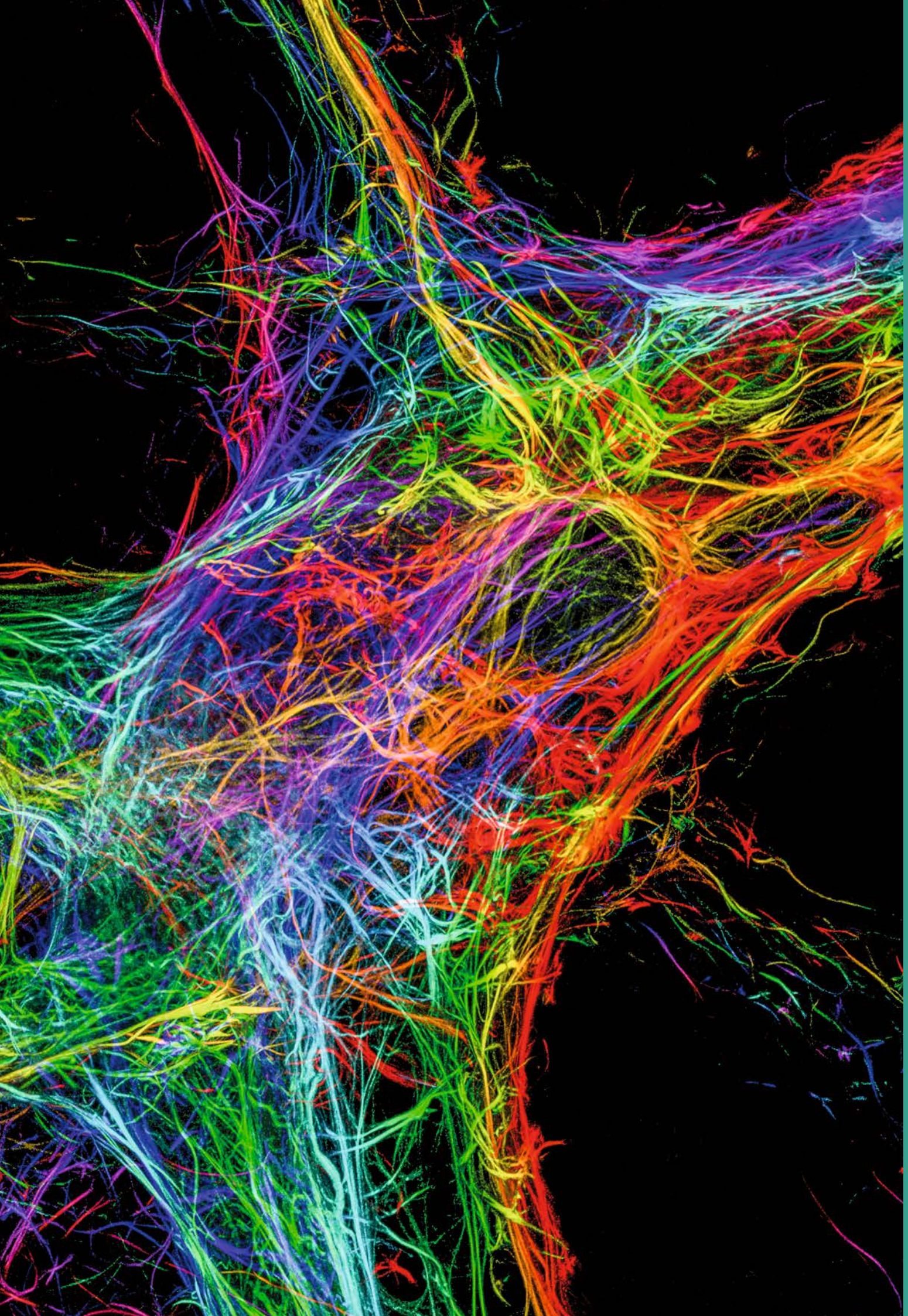
Fig. 3 Fritsch *et al.* 2019; Wild type embryo on the left and an embryo expressing inactive Caspase-8 causing cardiovascular destruction on the right.

Deep insights

In order to ensure the optimal nutrient supply of all organs, these are traversed by many blood vessels, which can become clogged with increasing age. The widely branched blood vessels are stabilized by an enveloping layer of collagen fibers, which are visualized here with the aid of a label-free microscopy technique. In order to be able to look inside the tissue, the murine kidney used here was optically cleared by chemical treatment before the image was acquired.



Picture: Dr. Christian Jüngst | Sample preparation: Julia Binz



Jun.-Prof. Dr. Dr. Miguel A. Alejandre Alcázar

Perinatal Injury and Cardiopulmonary Aging

Our research group investigates the premature activation of aging-associated processes after perinatal injury in order to define novel preventive and therapeutic strategies for neonatal chronic lung disease (CLD), promoting lung health early in life.



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>> RESEARCH FOCUS

The clinical significance of chronic lung disease (CLD) and the lack of preventive and curative strategies highlight the urgent need to unravel its early molecular origins in order to identify novel therapeutic targets. To this end, our research team has been investigating converging molecular mechanisms by which mechanical ventilation, oxygen, and obesity disrupt normal lung development, cause lung injury, and promote early cardiopulmonary aging.

> The purpose of our research is to identify converging perinatal pathways as well as mechanisms of neonatal chronic lung disease and aging, which will ultimately enable us to identify new therapeutic targets in order to preserve and promote lung health.

>> PROJECTS AND AIMS

Our research team has identified inflammatory processes, dysregulated expression of transcription factors (e.g. Klf4), increased DDR and matrix remodeling along with a loss of stemness as key mechanisms of neonatal CLD. These findings are closely related to the hallmarks of aging. Based on these findings, we now pursue three aims: first, we study an animal model of a prematurely aged mouse lung using a cell-specific deletion of DNA excision repair protein Ercc1. Second, we decipher converging signaling pathways of neonatal CLD, adult CLD, and naturally aged lungs. Finally, we target specific novel molecules and transcription factors to prevent premature aging and neonatal CLD. To this end, we employ a variety of techniques, ranging from in vitro and ex vivo models (precision cut lung slices) to genetically modified mice and neonatal lung models, along with state-of-the-art approaches in systems biology. Ultimately, our team envisions developing new strategies to promote lung health early on in life and preventing CLD.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Kuiper-Makris C, […], **Alejandre Alcazar MA.** Mendelian randomization and experimental IUGR reveal the adverse effect of low birth weight on lung structure and function. **Sci Rep.** 2020 ▮ Litzenburger T, […], **Alejandre Alcazar MA.** Maternal high-fat diet induces long-term obesity with sex-dependent metabolic programming of adipocyte differentiation, hypertrophy and dysfunction in the offspring. **Clin Sci. (Lond)** 2020. ▮ Polanyi L, Niessen CM, […], **Alejandre Alcazar MA.** Intrauterine growth restriction induces skin inflammation, increases TSLP and impairs epidermal barrier function. **J Mol Med.** (Berl) 2020. ▮ Will JP, […], **Alejandre Alcazar MA.** Strain-dependent effects on lung structure, matrix remodeling and Stat3/Smad2 signaling in C57BL/6N and C57BL/6J mice after neonatal hyperoxia. **Am J Physiol Regul Integr Comp Physiol.** 2019 ▮ Mohr J, […] **Alejandre Alcazar MA.** IL-6/Smad2 signaling mediates acute kidney injury and regeneration in a murine model of neonatal hyperoxia. **FASEB J.** 2019

Prof. Dr. Adam Antebi

Molecular Genetics of Aging

Our lab studies the regulatory processes that govern aging using the nematode *C.elegans*, the African turquoise killifish *Nothobranchius furzeri* and human cells, and combines traditional genetic approaches, systems biology and metabolomic profiling.

>> RESEARCH FOCUS

Aging is defined as a gradual decline of organismal homeostasis and of physiologic functions, and is associated with an increased risk of age-related disease. Our goal is to understand the regulatory pathways that control these processes, and to identify protective mechanisms that help prevent aging. Research over the last decades has identified multiple evolutionarily conserved signaling pathways that regulate longevity. Our lab has been instrumental in elucidating some of the key players at the nexus of these pathways, with our recent work focused on how the different pathways converge, to understand what lies at the heart of longevity and to identify clinical targets that could maintain health and extend lifespan.

>> PROJECTS AND AIMS

Our lab focuses on 5 main research topics:

1. We are dissecting how nutrient sensing pathways and metabolic signaling regulate lifespan. In particular, we study different states of long-lived quiescence (called diapause) to unravel how fasting/refeeding regimens promote rejuvenation and longevity.
2. We are examining how the interplay of organelles (nucleoli, mitochondria, lysosomes) regulates lifespan. We have identified the nucleolus as a central convergence point of lifespan regulation and discovered small nucleoli as an evolutionarily conserved hallmark of longevity. Unravelling how nucleolar outputs interact with other organelles and control longevity is a major research theme in our lab.
3. We identified a helix-loop-helix transcription factor network, consisting of MYC-MONDO, MAD-like and TFEB, which is required for life extension across different pathways, and are characterizing upstream inputs and downstream outputs of this regulatory cascade.
4. We seek to understand how naturally occurring metabolites regulate health and life span, and are using metabolomic approaches to identify molecules that impact longevity.
5. We are deciphering how innate immunity and inflammation impact aging, focusing especially on nucleic acid-triggered immune function.

> Observe and let nature speak.



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KEY PUBLICATIONS 2019/2020

Kew C, […], **Antebi A.** Evolutionarily conserved regulation of immunity by the splicing factor RNP-6/PUF60. **Elife**. 2020 ▮ Tharyan RG, [...], **Antebi A.** NFYB-1 regulates mitochondrial function and longevity via lysosomal prosaposin. **Nat Metab.** 2020 ▮ Gerisch B, […], **Antebi A.** HLH-30/TFEB is a master regulator of reproductive quiescence. **Dev Cell.** 2020 ▮ Dabrowski R, […], **Antebi A.** Optimization of mass spectrometry settings for steroidomic analysis in young and old killifish. **Anal Bioanal Chem.** 2020 ▮ Horn M, […], **Antebi A#**, Denzel MS#. Hexosamine pathway activation improves protein homeostasis through the integrated stress response. **iScience.** 2020 #joint last authorship

DETAILED INFORMATION

Dr. Hisham Bazzi

Cell Division Stem Cells

The precise monitoring of cell division is essential for the propagation and maintenance of stem cells. Our aim is to define how the spatio-temporal regulation of cell division impacts stem cell survival and fate choices in the mouse.



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>> RESEARCH FOCUS

Cell division is crucial for the continuity of every life form including multicellular organisms and their stem cells. During cell division, i.e. mitosis, the genetic material and the other cellular components are accurately segregated to the progeny. Thus, mitosis must be exquisitely regulated to prevent chromosome mis-segregation and genomic instability, a hallmark of cancer. Our lab is focused on elucidating how the duration of mitosis and its spatial regulation define the outcome of daughter cell fitness and fate.

>> PROJECTS AND AIMS

How cell division decides the fate of daughter cells is a fundamental open question in stem cell research. We have shown that prolonging mitosis activates a p53-dependent cell death pathway and that tuning cell division rates dictates stem cell dynamics and tissue architecture. Our goal is to dissect the mechanistic links between the spatio-temporal regulation of mitosis and the fate of stem cell progeny. To address this, we are using stem cells of the developing mouse and skin as model systems, where we combine cutting-edge methodologies such as single cell RNA sequencing (scRNA-Seq), CRISPR/Cas9-genome engineering, knock-in fluorescent reporters, time-lapse imaging, ultrastructural analysis, proximity-labeling, mass spectrometry and other biochemical and cell biological approaches. Our work will have profound implications for the identification of new druggable targets that regulate cell division in stem cells for the treatment of cancer and other aging-associated diseases.

> “To be, not to be or what to be is a question of how cell division is spatio-temporally regulated. If we understand how cell division is controlled, then we can steer cell survival and fate to our benefit.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Damen M, [...], **Bazzi H.** High proliferation and delamination during skin epidermal stratification. **Nat Commun.** 2020 Tamzalit F, […], **Bazzi H**, […], Huse M. Centrioles control the capacity, but not the specificity, of cytotoxic T cell killing. **PNAS**. 2020

Prof. Dr. Thomas Benzing

Aging-associated Kidney Disease

Kidney diseases are a major cause of morbidity in the elderly and a major risk factor for stroke, myocardial infarction or dementia. Benzing and his team study underlying molecular mechanisms to develop preventive and therapeutic strategies.

>> RESEARCH FOCUS

Kidney function depends on the bulk filtration of large volumes of water and small solutes to clear potential toxins derived from intracellular metabolism and gastrointestinal microbial metabolism and maintain salt and water and acid-base homeostasis. Although aging does not necessarily imply a loss of kidney function, many elderly patients develop a decline in renal filtration capacity which poses an enormous risk of cardiovascular and other complications. In the past decade, our team unravelled the molecular design and function of the kidney filtrations barrier using state-of-the-art imaging and omics technologies together with genetically engineered mouse models. Seminal studies of the lab have led to discovering novel genes involved in controlling the pathogenesis of various age-related kidney disorders.

> Renal filtration capacity declines with age affecting metabolism in the entire aging organism. A spectacular breakthrough by our team recently provided the first experimentally validated model of kidney ultrafiltration, which now allows new therapeutic approaches.



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>> PROJECTS AND AIMS

A central objective is to identify signalling pathways and protein complexes that control stress resistance, homeostasis, and intercellular communication in the mammalian kidney. The ultimate goal is to better understand disease-causing molecular mechanisms to develop new treatment options. In a highly interdisciplinary approach, we are investigating intracellular signalling networks in disease using a systems perspective and the alterations of these networks that occur with age. The tight connection of basic science with an internationally recognized clinical expertise provides the unique combination of translating new findings from bench to bedside.



KEY PUBLICATIONS 2019/2020

Butt L, […], **Benzing T.** A molecular mechanism explaining albuminuria in kidney disease. **Nature Metab**. 2020 ▮ Assady S, **Benzing T**, Kretzler M, Skorecki KL. Glomerular podocytes in kidney health and disease. **Lancet**. 2019

DETAILED INFORMATION

Prof. Dr. Matteo Bergami

Mechanisms of Neuronal and Glial Cell Plasticity

The adult brain maintains a significant degree of tissue remodelling that accommodates structural changes induced by experience or disease. However, how these important forms of plasticity are regulated at the cellular and tissue level is poorly understood.



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>> RESEARCH FOCUS

Our group is interested in the mechanisms underlying brain tissue plasticity in physiological and disease settings. Specifically, we aim at revealing the principles that govern the physiological generation and circuit incorporation of new neurons in the adult brain, and how experience may modify these processes. Our findings extend to models of injury and disease, in which we study how the activity of neuronal and glial networks can be manipulated to improve tissue repair.

> By utilizing state-of-the-art imaging and genetic approaches, our group is studying neuronal and glial cells to reveal key principles of brain plasticity regulated by experience and disease.

>> PROJECTS AND AIMS

We are currently pursuing two main research lines in the laboratory. First, we are investigating how neural stem cells and newly-generated neurons of the adult brain modify their behaviour in response to experience. For instance, we revealed that specific experiences trigger an important rewiring of adult-born neuron connectivity. Second, we are investigating mechanisms underlying brain tissue remodelling during injury, and in particular the role of astrocytes in these processes. We recently identified a new form of sub-cellular structural plasticity in reactive astrocytes with key implications for tissue repair.



DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Göbel J, […], Schauss A, […],Motori E#, **Bergami M#**. Mitochondria-endoplasmic reticulum contacts in reactive astrocytes promote vascular remodelling. **Cell Metab.** 2020 #joint last authorship ▮ Ren S, […], **Bergami M**, Shi SH. Precise long-range microcircuit-to-microcircuit communication connects the frontal and sensory cortices in the mammalian brain. **Neuron.** 2019 ▮ Sprenger HG, […], Rugarli EI, **Bergami M**, Langer T. Loss of the mitochondrial i-AAA protease YME1L leads to ocular dysfunction and spinal axonopathy. **EMBO Mol.** 2019

Prof. Dr. Andreas Beyer

Cellular Networks and Systems Biology

Modern biology creates enormous amounts of data. We are developing computational methods to turn this data into a mechanistic understanding of cell biology and disease processes.

>> RESEARCH FOCUS

A growing number of technologies allow for the genome-scale measurement of biological properties such as protein and mRNA concentrations or phenotypic changes (e.g. response to RNAi knock-downs). The genome-wide nature of the available data facilitates a systems perspective: it becomes possible to go beyond individual genes or pathways and to study regulatory processes of the entire system 'cell'. However, up to now, the potential is by far not being fully exploited. Our group has adopted a network perspective by studying relationships between proteins and other biomolecules (e.g. DNA, RNA) in silico to reveal the regulatory context of relevant genes. During the past years, we contributed new computational methods for large-scale data integration, network biology, and statistical genetics. A tight network of experimental collaborators facilitates the experimental validation of our computational analysis.

>> PROJECTS AND AIMS

Currently, we are investigating age-associated changes of RNA and protein production. We have discovered that the speed of RNA polymerase II changes with age, which has negative consequences for the quality of the produced RNA. Further, we have a great interest in the relationship between mRNA and protein amounts. Recently we started to also consider protein states, e.g. protein phosphorylation and protein structure, using high-throughput proteomics methods. In order to reveal causes of age-associated phenotypes, we have developed computational methods to quantify different types of somatic mutations and transcriptional mistakes from single cell data. All of this is geared towards better understanding molecular and cellular mechanisms of human diseases like cancer or chronic kidney disease.

> Molecular systems biology is much more than 'omics' data analysis. It aims to develop a mechanistic understanding of cellular changes at a systems level.



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KEY PUBLICATIONS 2019/2020

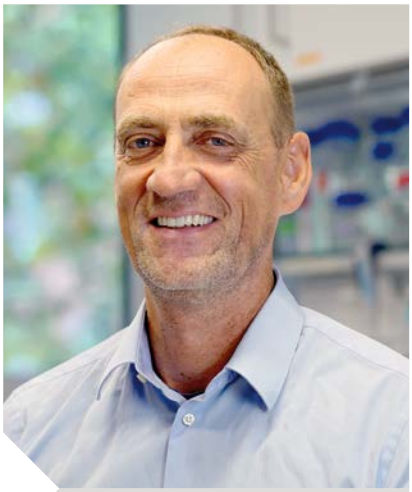
Charmpi K, [...], **Beyer A.** Convergent network effects along the axis of gene expression during prostate cancer progression. **Genome Biol.** 2020 ▮ Kamrad S, [...], **Beyer A**, [...], Bähler J. Pyruvate kinase variant of fission yeast tunes carbon metabolism, cell regulation, growth and stress resistance. **Mol Syst Biol.** 2020 ▮ Soste M, [...], **Beyer A**, Picotti P. Proteomics-Based monitoring of pathway activity reveals that blocking diacylglycerol biosynthesis rescues from alpha-synuclein toxicity. **Cell Syst.** 2019 ▮ Hahn O, [...], Langer T, [...], **Beyer A**, [...], Partridge L. Nutritional memory effect counteracts benefits of dietary restriction in old mice. **Nat Metab.** 2019 ▮ Späth MR, [....], **Beyer A**, [...], Benzing T, Schermer B, [...], Huesgen PF, Müller RU, Rinschen MM. The proteome microenvironment determines the protective effect of preconditioning in cisplatin-induced acute kidney injury. **Kidney Int.** 2019

DETAILED INFORMATION

Prof. Dr. Jens C. Brüning

Neuronal Control of Metabolism

Our research focusses on elucidating the CNS-dependent regulation and age-dependent dysregulation of energy and glucose metabolism.



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>> RESEARCH FOCUS

Our studies on CNS-dependent regulation of energy and glucose metabolism revealed a previously unappreciated role for insulin action in the CNS to control organismal glucose homeostasis and insulin sensitivity. We defined distinct Agouti-related peptide (AgRP)-expressing neurons in the hypothalamus as critical mediators of insulin's metabolic actions, revealed the molecular mechanisms of insulin action in these neurons as well as their alterations in obesity. We aim to precisely define the fundamental neuronal circuit mechanisms through which the CNS regulates peripheral metabolism and their dysregulation in old age.

> We aim to define the age- and obesity-associated regulation of the newly identified regulation of hepatic proteostasis through the sensory food perception-dependent regulation of melanocortin neurons.

>> PROJECTS AND AIMS

Contrary to the long-standing assumption that food intake and metabolism-regulating AgRP and POMC neurons are controlled by hormonal feedback signals that communicate the energy status of the organism – e.g., leptin, insulin - we have shown that sensory food perception already transiently regulates these neurons in exactly the same way as leptin and insulin do in the medium and long-term. We deciphered the physiological significance of the phenomenon and the molecular mechanisms involved. We also showed that the sensory food perception-dependent activation of POMC neurons stimulates the sympathetic innervation of the liver to activate the non-cell autonomous activation of an ER stress response in this organ. This leads to a priming of liver proteostasis and thus to the preparation of the liver for postprandial activation of protein synthesis and secretion. These findings lead to investigating the regulation of this mechanism and its relevance in obesity patients, healthy individuals, patients with type 2 diabetes and during aging.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

▮ Engström Ruud L, […], Fenselau H, **Brüning JC.** NPY mediates the rapid feeding and glucose metabolism regulatory functions of AgRP neurons. **Nat Commun.** 2020 ▮ Hammerschmidt P, […], Langer T, Krüger M, […], **Brüning JC.** CerS6-derived sphingolipids interact with Mff and promote mitochondrial fragmentation in obesity. **Cell.** 2019 ▮ Jais A, […], Korotkova T, […], Fenselau H, Wunderlich FT, Kloppenburg P, **Brüning JC.** PNOCARC neurons promote hyperphagia and obesity upon high-fat-diet feeding. **Neuron.** 2020 ▮ Jiang H, […], **Brüning JC.** MCH neurons regulate permeability of the median eminence barrier. **Neuron.** 2020 ▮ Lippert RN, […], Kloppenburg P, **Brüning JC.** Maternal high-fat diet during lactation reprograms the dopaminergic circuitry in mice. **J Clin Invest.** 2020

Prof. Dr. Oliver A. Cornely

Translating Research into Clinical Application

The purpose of our research is to systematically search for promising scientific findings and translate them into clinical practice. We serve as a catalyst for collaborations between basic researchers and clinicians.

>> RESEARCH FOCUS

Our research focuses on the following topics:

- Aging and aging-associated diseases
- Clinical trial design and support
- Infectious diseases
- Invasive fungal infections
- Vaccines

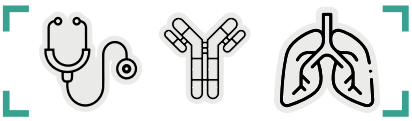
>> PROJECTS AND AIMS

Our aim is to identify promising research results and subsequently translate them into projects that are expected to have a high clinical impact. We therefore act as a catalyst between basic researchers and clinicians to define novel scientific approaches and solutions for aging-associated diseases within CECAD. Also, we design the remote training program »The Translational Scientist in Aging Research« (TSAR) to provide practical knowledge on clinical trial development for clinicians and life science researchers, to further enhance their expertise. In the light of the COVID-19 pandemic, the VACCELERATE vaccine research network was founded, comprising 26 partner institutions from 21 European countries. This consortium, led by our team and Prof. Cornely, has created a platform to address the vast demand for vaccine trials by planning, connecting and conducting an increasing number of trials. In addition, we assume a central role in the coordination of guidelines on invasive fungal infections. Prof. Cornely is in international collaboration with microbiologists and mycologists from over 80 countries for the elaboration of management guidelines for health care settings throughout the world.

> The next logical step in aging research is inevitably a close interaction between basic research and clinic. For this crucial interaction, our platform represents a central hub, providing the essential support to proceed to the next stage of testing research hypotheses.



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KEY PUBLICATIONS 2019/2020

Schommers P, […], **Cornely OA**, […], Klein F. Restriction of HIV-1 escape by a highly broad and potent neutralizing antibody. **Cell.** 2020 ▮ Bacher P, **Cornely OA**, […], Scheffold A. Human anti-fungal Th17 immunity and pathology rely on cross-reactivity against Candida albicans. **Cell.** 2019 ▮ Bacher P, **Cornely OA**, […], Scheffold A. Low-avidity CD4+ T cell responses to SARS-CoV-2 in unexposed individuals and humans with severe COVID-19. **Immunity.** 2020 ▮ Koehler P, […], **Cornely OA.** Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. **Lancet Infect Dis.** 2020 ▮ **Cornely OA**, […], Mucormycosis ECMM Global Guideline Writing Group. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. **Lancet Infect Dis.** 2019

DETAILED INFORMATION

Dr. Joris Deelen

Genetics and Biomarkers

Advancing age is the major risk factor for many chronic diseases. Instead of tackling each of these diseases one by one, we should focus on the identification of shared mechanisms that compress multimorbidity and thereby contribute to healthy aging.



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>> RESEARCH FOCUS

In our group, we use two different approaches to find out why some people age more healthily than others. The first approach is identification of the genetic mechanisms underlying healthy aging and extended lifespan in humans. The second approach is the identification of biomarkers of aging that can subsequently be used as surrogate endpoints in clinical trials or intervention studies that are aimed at improving general health.

>> PROJECTS AND AIMS

One of our main aims is to study the functional effect of common genetic variants (identified using large-scale genetic association studies of healthy aging) and rare protein-altering genetic variants (identified using sequencing data of long-lived individuals). To this end, we make use of the CRISPR/Cas9 system to generate transgenic cell lines and animals harboring the identified variants. We subsequently measure the in vitro (mouse embryonic stem cells) and in vivo (mice and fruit flies) effects of the genetic variants on the functioning of the genes. Another main aim is to establish novel human aging studies in Cologne to determine the efficacy of previously identified biomarkers of aging in clinical studies. The main focus is on biomarkers that have been identified in large-scale international collaborations of human studies using omics-based approaches, such as metabolomics. In addition, we include biomarkers originating from studies in model organisms to determine their translatability.

> The overarching aim of our research is to identify biomarkers that provide information about the molecular mechanisms underlying aging and can be introduced in the clinic to identify vulnerable people in the population that are at high risk for developing multimorbidity.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

▮ Timmers PRHJ, [...], **Deelen J.** Multivariate genomic scan implicates novel loci and haem metabolism in human ageing. **Nat Commun.** 2020 ▮ **Deelen J,** [...], Slagboom PE. A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals. **Nat Commun.** 2019 ▮ **Deelen J,** [...], Slagboom PE, Murabito JM. A meta-analysis of genome-wide association studies identifies multiple longevity genes. **Nat Commun.** 2019 ▮ Pisanti S, **Deelen J**, [...], Martinelli R. Correlation of the two most frequent HLA haplotypes in the Italian population to the differential regional incidence of Covid-19. **J Transl Med.** 2020

Dr. Constantinos Demetriades

Nutrient Sensing and Metabolism

The TSC/mTOR signaling pathway regulates cellular homeostasis in response to nutrient availability and to various stress stimuli. Its activity is commonly dysregulated in cancer, metabolic disease, neurological disorders, and during aging.

>> RESEARCH FOCUS

Because nutrients are the building blocks for cells to grow and proliferate, nutrient sensing mechanisms ensure that cells only grow when all necessary nutrients are available. Our group aims to understand the key molecular mechanisms that govern cellular growth upon starvation and stress and how their malfunction is implicated in aging and disease. We work on multiple research projects, focusing largely on the regulation of the TSC/mTOR signaling axis and its role in disease etiology.

>> PROJECTS AND AIMS

Our work investigates the intricate interplay between Nutrient Sensing, Lysosomal function and Signaling, Metabolism, Protein Secretion, and the Extracellular Proteome, focusing primarily on the TSC/mTOR signaling hub. Our research often identifies novel players in these pathways, and reveals previously unidentified mechanisms of mTOR regulation in cells.

> We aim to uncover new mechanisms and principles of mTOR activation, thus expanding our view on how nutrients and stresses control mTOR activity and cell growth. Our work also identifies novel mTOR regulators, as putative targets for drug development against mTOR-related diseases.



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We combine high-throughput omics (functional genomics, proteomics, metabolomics) with state-of-the-art molecular biology, biochemistry, cell biology and high-resolution microscopy techniques, in mammalian cell lines and mouse models, to identify evolutionarily conserved processes. Our vision is to understand: 1. how cells sense the availability of nutrients in their environment to adjust their growth and metabolism accordingly; 2. how the dysregulation of these cellular mechanisms contributes to the development of human diseases and the aging process; and 3. how we can intervene pharmacologically to target these mTOR-related conditions.



KEY PUBLICATIONS 2019/2020

Please scan the QR-Code for a list of recent publications.

DETAILED INFORMATION

Dr. Martin S. Denzel

Metabolism and Genetics in Aging

We combine genetic screens in *C. elegans* and in mammalian cells with structural biology to discover the basic principles of stress signaling, protein homeostasis and aging.



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>> RESEARCH FOCUS

Gains in human life expectancy are a major achievement but also lead to age-related diseases. The protein homeostasis network contributes to organismal resilience and its failure occurs early during aging, increasing disease risk. The guiding vision of our research is to use functional genomics to understand fundamental principles of protein homeostasis and aging. Our focus is on the cross-talk of stress signaling pathways, protein biosynthesis, and metabolism in aging.

> Basic geroscience makes it possible to discover the fundamental principles of biology while working in a highly relevant field for medicine and society. We use high-resolution genetic screens in various organisms to learn more about protein homeostasis and metabolism.

>> PROJECTS AND AIMS

We investigate regulators of protein homeostasis and metabolism that control organismal resilience and longevity.

1. We identified the metabolic hexosamine pathway as a regulator of protein homeostasis and longevity in *C. elegans*. In mammalian cells, the proteoprotective effect is conserved and mediated by the integrated stress response, which modulates mRNA translation and adaptation to stress.
2. In a forward genetic approach, we found a role of the key methyl donor S-adenosine methionine that directly affects ribosomal function. Ribosomal stress engages a signaling response that extends lifespan, providing a mechanistic explanation for longevity under dietary or methionine restriction.
3. In a genetic *C. elegans* screen for longevity, we have identified key regulators of mRNA translation that potently extend lifespan by reprogramming protein biosynthesis.
4. We have developed a new genetic screening platform in haploid embryonic stem cells that we use to study regulators of mRNA translation as well as clinically relevant therapy resistance mechanisms.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

▮ Ruegenberg S*, Horn M*, […], **Denzel MS.** Loss of GFAT-1 feedback regulation activates the hexosamine pathway that modulates protein homeostasis. **Nat Commun**. 2020 *shared first authorship ▮ Allmeroth K, […], Müller RU, **Denzel MS.** Bortezomib resistance mutations in PSMB5 determine response to second-generation proteasome inhibitors in multiple myeloma. **Leukemia.** 2020 ▮ Bonekamp NA, […], **Denzel MS**, […], Larsson NG. Small-molecule inhibitors of human mitochondrial DNA transcription. **Nature.** 2020 ▮ Kim CS, [..], **Denzel MS**, Eming SA, Wickström SA. A mTORC2-dependent switch to glutamine metabolism controls stem cell fate reversibility and long-term maintenance in the hair follicle. **Cell Metab.** 2020 ▮ Horn M*, Denzel SI*, […], Antebi A, **Denzel MS.** Hexosamine pathway activation improves protein homeostasis through the integrated stress response. **iScience.** 2020 *shared first authorship

Prof. Dr. Alexander Dilthey

Bioinformatics in Aging Research

We develop and apply methods for the generation and analysis of high-throughput sequencing data.

>> RESEARCH FOCUS

In our research group, we work on large-scale immunogenetics, the development of DNA-based diagnostics, bioinformatics methods development, and SARS-CoV-2 genomic epidemiology. In 2020, I was also appointed as head of the CECAD Bioinformatics Core Facility, which was restructured under my guidance to develop scalable and reproducible bioinformatics pipelines that support CECAD PIs with respect to the analysis of bulk or single-cell RNA sequencing data or multi-omic data analyses approaches.

>> PROJECTS AND AIMS

The Dilthey group focusses on

1. the elucidation of the genetic basis of autoimmune diseases like asthma, employing population immunogenetics to large case and control cohorts;
2. the development of diagnostics assays based on cell-free DNA, combining bioinformatics approaches for reliable pathogen detection and well as real-time Nanopore sequencing approaches;
3. the development of a national infrastructure for pathogen genomic surveillance, supported by the Netzwerk Universitätsmedizin, as well as the development of genomics-enabled contact tracing systems at local public health authorities. The overall goal of the Dilthey Group is to translate the expanding capabilities of high-throughput sequencing technologies into biological and medical knowledge and tools, employing an array of genomic and bioinformatics approaches. In 2021 Alexander has left CECAD to take up the W3 professorship in Genomic Microbiology and Immunity at the Heinrich Heine University Düsseldorf.

> In future pandemics, genomic epidemiology approaches will enable us to build faster and more effective systems for contact tracing.



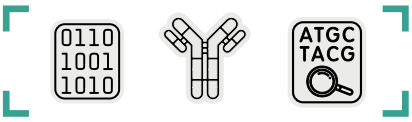
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KEY PUBLICATIONS 2019/2020

Walker A, […], **Dilthey AT.** Genetic structure of SARS-CoV-2 reflects clonal superspreading and multiple independent introduction events, North-Rhine Westphalia, Germany, February and March 2020. **Euro Surveill.** 2020 **Dilthey AT**, Meyer SA and Kaasch AJ. Ultraplexing: increasing the efficiency of long-read sequencing for hybrid assembly with k-mer-based multiplexing. **Genome Biol.** 2020 Henrich B, […], **Dilthey AT.** Characterisation of mobile genetic elements in *Mycoplasma hominis* with the description of ICEHo-II, a variant mycoplasma integrative and conjugative element. **Mob DNA.** 2020 **Dilthey AT**, […], Phillippy AM. HLA*LA - HLA typing from linearly projected graph alignments. **Bioinformatics.** 2019 **Dilthey AT**, Jain C, Koren S and Phillippy AM. Strain-level metagenomic assignment and compositional estimation for long reads with MetaMaps. **Nat Commun.** 2019.

DETAILED INFORMATION

Prof. Dr. Sabine A. Eming

Research into Healthy Skin Aging

Our group investigates the molecular basis of age-related skin pathologies and how this knowledge can be exploited for the treatment of disease.



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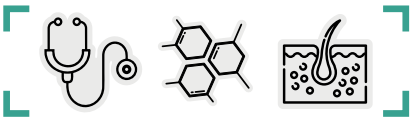
>> RESEARCH FOCUS

The skin provides a life-sustaining structural and immunological barrier of the organism. To ensure maintenance of proper structure and function, removal of damaged material and its replacement by regenerative processes needs to be tightly co-ordinated. Mechanisms driving this remarkable regenerative capacity throughout life are still only understood at a rudimentary level. Our group's aim is to identify regulators and effectors by which the skin orchestrates balanced defense while promoting regenerative responses to maintain skin barrier integrity and function during life.

> Awareness of the morbidity caused by age-related skin frailty is still underrepresented in today's medical practice. Clinicians and patients need to be made aware that healthy aging of the entire organism requires healthy skin.

>> CURRENT PROJECTS AND AIM

Our group is pursuing research in inter-connected areas to understand metabolic control of tissue degeneration and regeneration including TOR signaling, immunometabolism and regulation of cell death. A combination of in vitro and in vivo analyses using animal models and patient material allows us to assess how these molecular mechanisms regulate regenerative responses in the aging skin. Targeting the nutrient-sensing pathway TOR is seen as one of the most promising approaches for delaying aging-related pathologies, but severe side effects also raise concerns whether blocking TOR activity ultimately will be beneficial in humans.



Together with collaborating partners at CECAD, we are analyzing the mechanisms by which TOR signaling acts in skin maintenance during life. Our findings will potentially open up an area of therapeutic innovation to prevent aging-associated skin frailty and to facilitate healing of injured and aging tissues.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

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- Kim CS*, Ding X*, […], Denzel MS, **Eming SA**#, Wickström SA#. Glutamine metabolism controls stem cell fate reversibility and long-term maintenance in the hair follicle. **Cell Metab.** 2020 *shared first authorship; #joint last authorship
- Schiffmann LM, […], Brodesser S, […], Pasparakis M, Krönke M, **Eming SA**, […], Kashkar H. Mitochondrial respiration controls neoangiogenesis during wound healing and tumor growth. **Nat Commun.** 2020
- Kakanj P, **Eming SA**, Partridge L, Leptin M. Long-term in vivo imaging of *Drosophila* larvae. **Nat Protoc.** 2020
- Knipper JA, Ding X, **Eming SA.** Diabetes impedes the epigenetic switch of macrophages into repair mode. **Immunity.** 2019

Dr. Mafalda Escobar-Henriques

Mito-Dynamics and Ubiquitin

Cellular performance is strongly dependent on morphological changes of mitochondria. This plasticity requires mitofusin proteins, age-related disease gatekeepers that mediate fusion events via ubiquitin.

>> RESEARCH FOCUS

We focus on studying the mechanisms allowing tailored and coordinated adaptations of mitochondrial dynamics and mitofusins. Mitofusin defects cause the peripheral neuropathy Charcot-Marie-Tooth Type 2A (CMT2A) and affect the pathogenesis of many common age-related diseases, such as non-alcoholic fatty liver disease (NAFLD). Moreover, we investigate how novel forms of ubiquitin, present at the mitochondrial surface, regulate stress responses and impact cellular survival, in concert with the ubiquitin proteasome system (UPS) and the autophagic machinery.

> Understanding how ubiquin and mitofusins actively control mitochondrial morphology is at the heart of our research. We wish to transform their known relevance for quality control and aging processes into therapeutic options, for neurodegenerative and obesity-linked diseases.

>> PROJECTS AND AIMS

We exploit the yeast Saccharomyces cerevisiae and several cell culture models, aiming at:

- Unveiling the molecular mechanisms allowing ubiquitin to either promote mitochondrial fusion or drive mitochondrial fragmentation, in response to proteotoxic stress or metabolic changes.
- Elucidating the pathways accounting for the disease gatekeeper role of mitofusins, by investigating how mitofusin ubiquitylation ensures a proper communication between mitochondria and its cellular environment.
- Understanding how novel forms of ubiquitin that we just unraveled control protein homeostasis, stress resistance and cellular viability, by identifying the molecular targets and ubiquitin ligases involved.
- Exploring networks between deubiquitylases, the endocytic machinery and proteasomal degradation, to resist ribosomal defects, conferring stress resilience.
- Identifying biomarkers and exploring therapeutic strategies for neurodegenerative and liver diseases.



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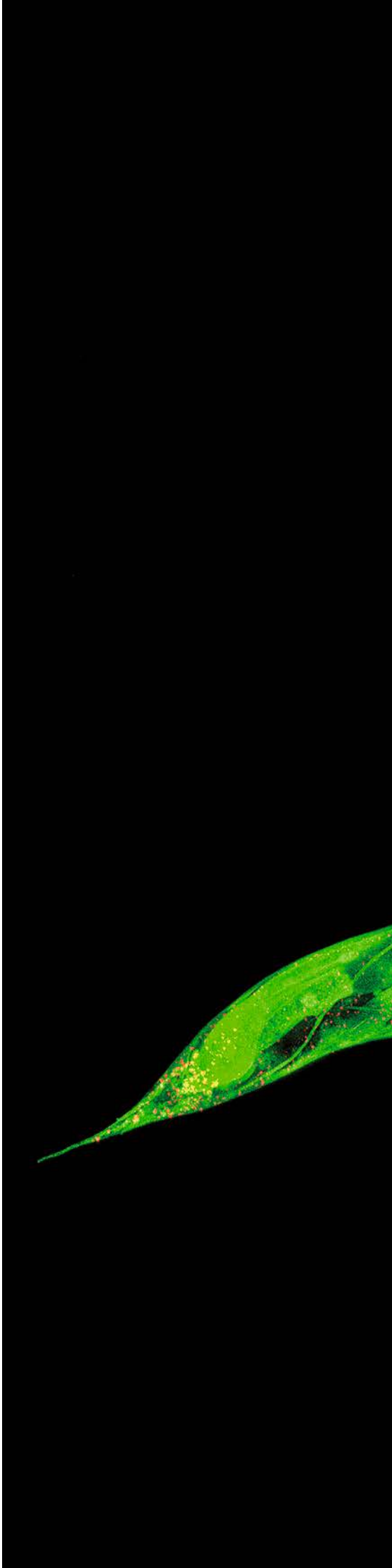
KEY PUBLICATIONS 2019/2020

Joaquim M, and **Escobar-Henriques M.** Role of mitofusins and mitophagy in life or death decisions, **Front Cell Dev Biol.**, eCollection, 2020 ▮ **Escobar-Henriques M.** and Anton V. Mitochondrial surveillance by Cdc48/p97: MAD vs membrane fusion. **Int J Mol Sci.** 2020 ▮ Schuster R, Anton V, […] **Escobar-Henrique M.** Dual role of a GTPase conformational switch for membrane fusion by mitofusin ubiquitylation **Life Sci Alliance.** 2020 ▮ Anton V, […], Riemer J, Schauss AC, **Escobar-Henriques M.** Plasticity in salt-bridge allows fusion-competent ubiquitylation of mitofusins and Cdc48 recognition. **Life Sci Alliance.** 2019 ▮ **Escobar-Henriques M.** and Joaquim M. Mitofusins: Disease gatekeepers and hubs in mitochondrial quality control by E3 ligases. **Front Physiol.,** eCollection 2019

DETAILED INFORMATION

A stressed Worm

The picture shows a fluorescent image of a *Caenorhabditis elegans*, a nematode that is commonly used to study aging and to model age-related diseases. Two proteins are fluorescently labeled: The major protein synthesis factor eIF4E (green) and the mRNA stability factor DCAP-1 (red). Both factors play a central role in cellular protein production, stress response pathways and the aging process. Visualizing these proteins in a living animal is of high relevance for understanding the molecular basis of illnesses, like Alzheimer's disease or Parkinson's disease.



Picture: Dr. Astrid Schauss | Sample preparation: Dr. Matthias Riecker



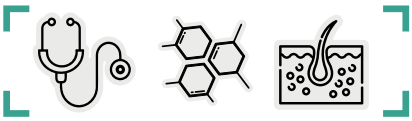
Dr. Henning Fenselau

Circuits and Plasticity

An organism's ability to tightly coordinate energy and glucose homeostasis is critical for survival. Such coordination is achieved by distinct neural circuits that adaptively control metabolic responses and behavior according to energy state.



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>> RESEARCH FOCUS

Our lab investigates synapse physiology and synaptic plasticity – such as long-term potentiation – at defined synapses of neuronal circuits that regulate energy and glucose homeostasis. The overarching goal of our research is to link synaptic transmission and plasticity in defined neural circuits with specific metabolic responses and behavior.

>> PROJECTS AND AIMS

We are currently addressing the following three key fundamental research questions:

1. How do sensory neuronal circuits contribute to gut-brain communication?
2. What is the role of energy-state-dependent synaptic plasticity in hypothalamic circuits?
3. How do POMC-derived neuropeptides regulate feeding neurocircuits?

> Our lab focuses on advancing our current understanding of synaptic transmission and synaptic plasticity in neural circuits that regulate energy and glucose homeostasis.

To this end, we employ a wide range of diverse, but complementary methodologies, including brain slice electrophysiology, recombinase-expressing mice, AAV viral approaches, optogenetics, chemogenetics, and in vivo imaging techniques. The powerful combination of these approaches allows us to study synaptic physiology in defined neuronal circuits that have a clear metabolic function. Further, these approaches enable us to study how synaptic transmission and synaptic plasticity within neural circuits could become dysregulated and how this relates to pathological conditions such as obesity or diabetes.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Reinoß P, [...], Kloppenburg P, **Fenselau H**, Hammerschmidt M. Hypothalamic POMC neurons innervate the spinal cord and modulate the excitability of premotor circuits. **Curr Biol.** 2020 ▮ Jais A, [...], Korotkova T, [...], **Fenselau H**, Wunderlich FT, Kloppenburg P, Brüning JC. PNOC^{ARC} Neurons promote hyperphagia and obesity upon high-fat-diet feeding. **Neuron.** 2020

Dr. Lukas Frenzel

Targeting resistance mechanisms in CLL

Tremendous changes may be seen in current treatment of CLL. However, novel therapeutic options require understanding of resistance towards these compounds. We are carrying out research into these central mechanisms of resistance in CLL.

>> RESEARCH FOCUS

Treatment of chronic lymphocytic leukemia (CLL) and other B-cell lymphoma is about to change. Inhibitors against BCL2 (and BTK) replaced classical chemotherapy regimens from first-line settings in CLL. While resistance towards classical chemotherapy was explored over the last decades, resistance mechanisms against novel, non-genotoxic compounds are not understood.

> One day, making leukemia a 100 % curable disease for everyone and in every case.
>
> – Jose Carreras

>> PROJECTS AND AIMS

Our overarching aims are to

- identify mechanisms of resistance towards BCL2 inhibitors and
- explore mechanisms that drive disease progression of B- cell lymphoma.

We identified that resistance towards the BCL2i venetoclax (VEN) in most patients is independent of mutations in the drug target but might be mediated by mutations in BTG1. While BTG1 is an inhibitor of the cell cycle and controls mRNA stability, our preliminary data show that it is involved in expression of BCL2. Our central hypotheses are that the functional loss of BTG1 acts as common molecular determinant of disease progression and (VEN) therapy resistance and affects the pathophysiological BCL2 protein complexes. We identified a deregulation of BCL2 family members such as MCL1, BAX and PUMA. These data point to a complex regulation of resistance mechanisms towards VEN, which raises questions on whether these changes occur at the same time in the same clone, or if each of the changes is sufficient to drive resistance on its own. Therefore, we aim to examine the hierarchy and evolution of intra-tumor events dependent on these changes.



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KEY PUBLICATIONS 2019/2020

Al-Sawaf O, […] Hallek M, **Frenzel LP.** Venetoclax plus rituximab or obinutuzumab after allogeneic hematopoietic stem cell transplantation in chronic lymphocytic leukemia. **Haematologica.** 2019 Kohlhaas V, […] **Frenzel LP**, Reinhardt HC, Brüning JC, Hallek M, Peifer M, […], Wunderlich FT. Active Akt signaling triggers CLL towards Richter transformation via overactivation of Notch1. **Blood.** 2020 Riabinska A, […] Jachimowicz RD, […], **Frenzel LP**, […],Krüger M, […], Reinhardt HC. ATM activity in T cells is critical for immune surveillance of lymphoma in vivo. **Leukemia.** 2020 Weiss J, […] **Frenzel LP**, Hallek M. Acquisition of the recurrent Gly101Val mutation in BCL2 confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia. **Haematologica.** 2019

DETAILED INFORMATION

Prof. Dr. Ana J. García-Sáez

Membrane Biophysics

We study the biophysics of dynamic membrane processes with a special interest in mitochondrial membrane alterations during regulated cell death and the proteins involved in these processes.



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>> RESEARCH FOCUS

We study dynamic membrane processes from a quantitative point of view with a special interest in the changes in cellular membranes during regulated cell death. One main line of research is the mitochondrial membrane alterations during apoptosis and the mechanism of action of Bcl-2 protein family members. We extended our research to other forms of cell death like necroptosis and ferroptosis. We apply membrane biophysics, advanced microscopy, including fluorescence correlation spectroscopy and atomic force microscopy, as well as single particle tracking.

> We are what we think.
> All that we are arises
> with our thoughts.
> With our thoughts,
> we make the world.
>
> – Buddha

>> PROJECTS AND AIMS

Molecular mechanisms of Bcl-2 proteins: The Bcl-2 family of pro- and anti-apoptotic and BH3-only proteins regulates apoptosis by controlling permeabilization of the mitochondrial outer membrane. We study the role of the membrane, of specific lipids and the interaction network between Bcl-2 members that are involved in the life-or-death decision-making process.

Membrane permeabilization in cell death: Disruption of the membrane barrier has emerged as a common theme in the execution of many cell death pathways, yet their molecular mechanisms remain poorly understood. We study the molecular machineries and biophysical alterations involved in the decisive step of membrane permeabilization in cell death signaling.

Model membranes and optical microscopy: To investigate dynamic processes in biological membranes we use model systems for experiments involving time-lapse microscopy, FRAP, FRET, FCS, AFM and other advanced microscopy techniques. We are implementing novel methods to quantify the stoichiometry and molecular architecture of macromolecular complexes based on single molecule imaging and super-resolution microscopy.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Pedrera L, […], von Karstedt S, **García-Sáez AJ.** Ferroptotic pores induce Ca^{2+} fluxes and ESCRT-III activation to modulate cell death kinetics. **Cell Death Differ.** 2020 ▮ Peña-Blanco A, [...], **García-Sáez AJ.** Drp1 modulates mitochondrial stress responses to mitotic arrest. **Cell Death Differ.** 2020 ▮ Hertlein V, […], **García-Sáez AJ.** MERLIN: a novel BRET-based proximity biosensor for studying mitochondria-ER contact sites. **Life Sci Alliance.** 2019 ▮ Danial JSH, **García-Sáez AJ.** Quantitative analysis of super-resolved structures using ASAP. **Nat Methods**. 2019 ▮ Murad F, **García-Sáez AJ.** Quantification of the interactions between BCL-2 proteins by fluorescence correlation spectroscopy. **Methods Mol Biol.** 2019

Dr. Martin Graef

Autophagy and Cellular Aging

Our research focuses on the intracellular process of autophagy (»self-eating«), which allows cells to degrade or remove parts of themselves in response to nutrient scarcity or other stresses to maintain their own functionality and homeostasis.

>> RESEARCH FOCUS

During autophagy, cells form small membrane cisternae that massively expand their membranes within minutes to close around cellular cargo into large transient double-membrane organelles, termed autophagosomes. Cells have to integrate complex metabolic and functional information in order to elicit stress-adapted autophagy responses in terms of number, size and substrate scope of autophagosomes or their physiological output in order to maintain cellular and organismal health and to counteract premature aging and disease.

>> PROJECTS AND AIMS

Our research aims at understanding the molecular mechanisms underlying the extraordinary membrane assembly required for autophagosome biogenesis. Specifically, we are characterizing mechanisms of localized biosynthesis, transfer, and scrambling of lipids at contact sites of the forming autophagosome with the endoplasmic reticulum and the resulting membrane properties of autophagosomes.

> For a cell, a certain amount of self-destructive behavior is rather healthy.

In addition, we aim to uncover how cells determine where and how many autophagosomes to form and how to recognize their cargoes. To understand the physiological role of autophagy, we focus on the multilayered interplay between autophagy and mitochondria. In particular, we are interested in the questions related to metabolic homeostasis, genome maintenance, organelle scaling, and quality control of mitochondria by autophagy.

Together, comprehensive insights into these processes will be foundational for our understanding of the defects in autophagy associated with the development of common human diseases including cancer and neurodegeneration.



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KEY PUBLICATIONS 2019/2020

Schütter M, Giavalisco P, Brodesser S, and **Graef M.** Local fatty acid channeling into phospholipid synthesis drives phagophore expansion during autophagy. **Cell.** 2020 ▮ Gross A, **Graef M.** Mechanisms of autophagy in metabolic stress response. **J Mol Biol.** 2020

DETAILED INFORMATION

Prof. Dr. Michael Hallek

Cure Chronic Lymphocytic Leukemia

Advances in understanding the pathogenesis of chronic lymphocytic leukemia and a clear commitment to the rapid implementation of this knowledge in the clinics have dramatically changed management of CLL and improved clinical outcome for patients.



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>> RESEARCH FOCUS

Our laboratory has a long-term interest in studying oncogenic signaling events in CLL and investigating the mechanisms that trigger leukemic development through their interaction with the cancer microenvironment. Moreover, our group benefits from a strong clinical trial portfolio of the German CLL Study Group as headed by Michael Hallek that facilitates the translation of novel ideas and concepts into therapeutic reality.

> The overall goal of our research is to substantially increase the cure rate of chronic lymphocytic leukemia by a holistic approach that elaborates a comprehensive inventory of the clonal dynamics of this leukemia in patients and in laboratory models.

>> PROJECTS AND AIMS

CLL is at the forefront of research efforts in this present innovative era in cancer medicine that is currently providing many new cancer drugs with promising efficacy. The advent of several, targeted therapies for CLL and the availability of novel analytical tools such as next generation sequencing has provided major ingredients for the creation of targeted anti-leukemic therapies. These advances allow testing of a probabilistic approach, which navigates the cancer patient through molecularly targeted therapies, thus preventing the onset of resistance by using a comprehensive array of cutting-edge technologies. The discoveries made by this approach will be used in a systematic and rapid translation of discoveries into clinical application. Our specific research aims include: (1) Understanding the heterogeneity, clonal evolution and mechanisms resistance of CLL at the cellular and molecular levels. (2) Creating a mechanistic understanding of key factors driving the co-evolution of the tumor microenvironment with CLL cells. (3) Conducting informed clinical trials for CLL (translation into clinical practice) to prevent clonal evolution towards development of resistance.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

▮ Condoluci A, [...], **Hallek M**, Rossi D. International prognostic score for asymptomatic early-stage chronic lymphocytic leukemia. **Blood.** 2020 ▮ Al-Sawaf O, [...], **Hallek M**, Fischer K. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. **Lancet Oncol.** 2020 ▮ Kurtz DM, [...], Hallek M, [...], Alizadeh AA. Dynamic risk profiling using serial tumor biomarkers for personalized outcome prediction. **Cell.** 2019 ▮ Fischer K, [...], **Hallek M.** Venetoclax and Obinutuzumab in patients with CLL and coexisting conditions. **N Engl J Med.** 2019 ▮ Nguyen PH, Niesen E, **Hallek M.** New roles for B cell receptor associated kinases: when the B cell is not the target. **Leukemia.** 2019

Dr. Robert Hänsel-Hertsch

(Epi)Genome Biology

Epigenetic alterations and genome instability are hallmarks of aging and cancer. Our lab explores the existence and significance of age and cancer-related epigenome structural alterations and its interconnection with genome instability.

>> RESEARCH FOCUS

The genomic structure may significantly change with age, which for mammals may create a predisposition to disease development. We discovered substantial guanine quadruplex DNA secondary structure (G4) formation in regulatory regions of cancer genomes, marking amplified genes that are also highly expressed. We are now addressing the physiological causes and consequences of G4-linked genome instability, as well as its diagnostic and therapeutic potential.

> Epigenetic mechanisms regulate gene transcription but how these fundamental processes are linked to genome instability and together inflict aging-related diseases constitute the underlying basis of our research.

>> PROJECTS AND AIMS

Our lab aims to address conceptual questions: are epigenome structural alterations passengers or drivers of mammalian aging and disease? Are defined epigenome states of diagnostic and therapeutic value?

1. Existence of epigenome structural alterations that promote genomic instability during normal and rapid tissue aging. We are investigating age-related epigenome alterations in tissues of different but closely-related rodents, extremely long-lived rodents and human stem-cell models.
2. Epigenome structural alterations predisposing to cancer development and/or drug resistance. Precision medicine aims to characterise tumour heterogeneity and identify cancer-specific molecular vulnerabilities. Our lab aims to uncover epigenome alterations that critically drive cancer and resistance mechanisms using quantitative bulk and single-cell genomics to better stratify patients, reflecting on personalised genome architecture, transcription factor regulation and activity, as well as cancer subtypes suitable for drug treatment.



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KEY PUBLICATIONS 2019/2020

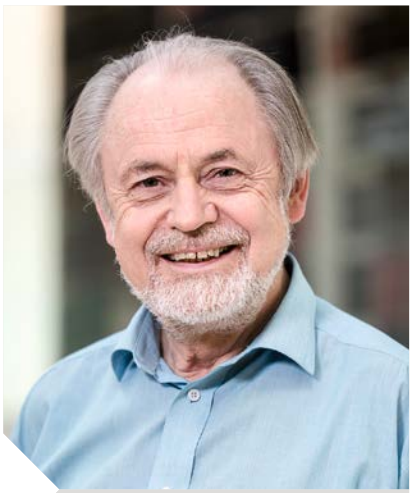
Hänsel-Hertsch R, Simeone A, Shea A, Hui WWI, Zyner KG, Marsico G, Rueda OM, Bruna A, Martin A, Zhang X, Adhikari S, Tannahill D, Caldas C, Balasubramanian S, Landscape of G-quadruplex DNA structural regions in breast cancer. **Nat Genet.** 2020

DETAILED INFORMATION

Prof. Dr. Jan H. J. Hoeijmakers

DNA Damage in Skin Aging

We aim to understand the role of DNA damage and repair in (skin) aging focusing on stress-induced stem cell differentiation, cell death and cellular senescence with the goal to develop strategies to delay or revert aging-associated pathology.



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>> RESEARCH FOCUS

Previously, we generated DNA-repair-deficient mouse mutants, which closely resemble severe human repair syndromes, and found that they exhibit prominent features of accelerated but genuine aging. We discovered in the skin of these mice increased senescence as well as associated secretion of pro-inflammatory and other factors, which may trigger apoptosis of neighbouring cells and early stem cell depletion, i.e. all hallmarks of aging, these findings thus establishing the importance of DNA repair in skin aging.

>> PROJECTS AND AIMS

We also found that during aging transcription in mouse liver progressively declines, whereas RNA polymerases concomitantly increase in gene bodies. We show that transcription is directly, randomly blocked by endogenous DNA lesions that accumulate with age. This age-related 'transcription stress' leads to a reduced and skewed transcriptional output, affecting preferentially large genes, is broadly present across species and (post-mitotic) tissues, and is a significant upstream factor in establishing transcriptomes in aging. It specifically affects pathways of aging such as nutrient sensing, proteostasis, energy metabolism and the immune system. Because transcription stress appears as a general aging phenotype across distant species, deregulates hallmark pathways of aging and provides pro- and anti-aging signals, we propose that transcription stress is a novel important aging factor. We intend to further delineate the consequences of this key intermediate from DNA damage to systemic aging.

> Our research has established the key role of DNA damage and genome integrity in the process of aging and the impact of nutrition and metabolism on aging-related diseases. This important novel insight opens perspectives to delay/prevent aging pathologies and promote healthy aging.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Kim DE, […], **Hoeijmakers JHJ**, […], Campisi J. Deficiency in the DNA repair protein ERCC1 triggers a link between senescence and apoptosis in human fibroblasts and mouse skin. **Aging Cell.** 2019 ▮ Milanese C, […], **Hoeijmakers JHJ**, Mastroberardino PG. DNA damage and transcription stress cause ATP-mediated redesign of metabolism and potentiation of anti-oxidant buffering. **Nat Commun.** 2019 ▮ Lans H, **Hoeijmakers JHJ**, Vermeulen W, Marteijn JA. The DNA damage response to transcription stress. **Nat Rev Mol Cell Biol.** 2019 ▮ Theil AF, […], **Hoeijmakers JHJ**, Vermeulen W, Orioli D. Bi-allelic TARS mutations are associated with brittle hair phenotype. **Am J Hum Genet.** 2019 ▮ Alyodawi K, […], **Hoeijmakers JHJ**, Patel K. Compression of morbidity in a progeroid mouse model through the attenuation of myostatin/activin signalling. **J Cachexia Sarcopenia Muscle.** 2019

Prof. Dr. Thorsten Hoppe

Proteostasis in Development and Aging

Our team studies the molecular bases of protein quality control and age-associated diseases using *C. elegans* as multicellular model. Combining genetic and biochemical approaches, we pioneered organismal proteostasis mechanisms regulated by ubiquitin.

>> RESEARCH FOCUS

The maintenance of proteostasis in every cell-type involves repair and degradation of defective proteins, which is essential for organismal physiology and longevity. The key interest of our laboratory is to understand how protein quality control systems are mechanistically regulated to overcome age-associated protein damage. Our recent work identified conserved disease mechanisms related to mitochondrial pathologies, diabetes, obesity, progressive myopathy, and neurodegenerative diseases.

>> PROJECTS AND AIMS

Current projects address physiological aspects of protein turnover in the context of aging-associated processes, such as muscle development and regeneration, genome stability, mitochondrial metabolism, and protein aggregation. Therefore, we combine innovative in vitro and in vivo protein degradation assays, microscopical, optogenetic, and chemosensory methods, which allow the identification and characterization of conserved proteostasis mechanisms. In addition to intracellular proteostasis networks we address cell-nonautonomous proteostasis pathways regulated by paracrine signals. Our most recent work unraveled how the smell of food sensed via a single pair of olfactory neurons affects physiology and aging. We aim to understand the functional role of protein degradation in the context of aging-associated diseases. Our long-term goal is to define the crosstalk between stress-induced proteostasis networks and aging, which will help to identify conserved disease mechanisms.

> We study protein degradation mechanisms with the ultimate goal of delaying the aging process and the aggregation of misfolded proteins for therapeutic interventions against degenerative disorders, such as Alzheimer's, Huntington's, and Parkinson's disease.



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KEY PUBLICATIONS 2019/2020

Donkervoort S, […], **Hoppe T**#, Bönnemann CG#. Pathogenic variants in the myosin chaperone UNC-45B cause progressive myopathy with eccentric cores. **Am J Hum Genet.** 2020 #shared last authorship ▮ Albert MC, […], Krönke M, **Hoppe T**#, Kashkar H#. CHIP ubiquitylates NOXA and induces its lysosomal degradation in response to DNA damage. **Cell Death Dis.** 2020 #shared last authorship ▮ Herzog LK, […], **Hoppe T**, Dantuma N.P. The Machado-Joseph disease deubiquitylase ataxin-3 interacts with LC3C/GABARAP and promotes autophagy. **Aging Cell.** 2020 ▮ Kumsta C, […], **Hoppe T**, Vilchez D, Hansen M. The autophagy receptor p62/SQST-1 promotes proteostasis and longevity in *C. elegans* by inducing autophagy. **Nat Commun.** 2019 ▮ Finger F, […], **Hoppe T.** Olfaction regulates organismal proteostasis and longevity via microRNA-dependent signaling. **Nat Metab.** 2019

DETAILED INFORMATION

Prof. Dr. Tamas Horvath

Brain Control of Health-Span

We study the signaling flow and regulatory relationship within and between brain cells that support physiological and pathological homeostatic conditions with particular emphasis on metabolic disorders, reproduction, neurodegeneration, aging and higher brain functions.



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>> RESEARCH FOCUS

Guided by the notion that late onset chronic diseases are the consequence of prolonged overworking of various tissues that have genetic and epigenetic vulnerabilities, we assert that it is the cellular energy metabolism of the different tissues that determines their health and longevity and consequently that of the entire organism. Based on our previous and ongoing work,our central theme is that a small set of neurons in the hypothalamus, which produce Agouti-related protein (AgRP), acts as the master regulator of energy utilization by all tissues, and hence, these hypothalamic neurons determine healthy tissue function and longevity.

>> PROJECTS AND AIMS

1. Hypothalamus-driven anti-aging processes impact murine models of Alzheimer's Disease: the goal of these studies is to determine a functional link between ASgRP neurons in the etiology of AD using animal models.
2. Hypocretinergic control of cocaine abuse: the long-term goal of this proposal is to bridge the gap between clinical studies and basic research on the role of the hypocretin system in cocaine addiction-related behaviors.
3. AgRP neurons promote the effects of calorie restriction on lifespan: the goal is to determine the role of the hypothalamic hunger-promoting neurons in aging.
4. The role of mitochondrial dynamics in diet-induced regulation of food intake and adiposity: the goal of this project to determine the relationship between mitochondrial dynamics in hypothalamic AgRP neurons and in adipocytes.



DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Timper K, […], Trifunovic A, **Horvath TL**, Kloppenburg, […], Brüning JC. GLP-1 receptor signaling in astrocytes regulates fatty acid oxidation, mitochondrial integrity, and function. **Cell Metab.** 2020 ▮ Hosier H, […], **Horvath TL**, […], Lipkind H. SARS-CoV-2 infection of the placenta. **J Clin Invest.** 2020 ▮ Taylor-Giorlando M, […], **Horvath TL.** Prefrontal cortical and behavioral adaptations to surgical delivery mediated by metabolic principles. **Cerebral Cortex.** 2019 ▮ Stutz B, […], **Horvath TL.** Dopamine neuronal protection in the mouse Substantia nigra by GHSR is independent of electric activity. **Mole Metab.** 2019 ▮ Mancini G, […], **Horvath TL.** Mitofusin 2 in mature adipocytes controls adiposity and body weight. **Cell Rep.** 2019

Prof. Dr. Pitter Huesgen

Regulatory Proteolysis

Proteolytic enzymes regulate numerous biological processes. Deregulation of their activity is involved in many severe human diseases. We develop mass spectrometry-based degradomics methods to trace proteolytic cleavage in complex samples.

>> RESEARCH FOCUS

How are proteases regulating various biological processes? Which protease cleaves which substrates, where and under which conditions? What is the functional consequence for the substrate, and what is the fate and function of the cleaved products? To address these questions, we develop mass spectrometry-based degradomics methods that enable identification and quantification of protein termini, and thereby proteolytic processing events, on a proteome-wide scale.

>> PROJECTS AND AIMS

We established a new method that enables sensitive detection of protein N termini even in microscale samples. We established new proteases complementary to trypsin as tools to increase proteome sequence coverage, including protein termini. Now, we are working towards further improving robustness and increasing throughput to enable analysis of clinical cohorts. We aim to correlate processing events with other post-translational modifications and changes in protein-protein interactions. We apply our method in collaborative research efforts: As part of the new collaborative research center SFB1403, we study proteolytic regulation of cell death in both mammalian and plant systems in response to specific triggers aiming to determine the signals to the surrounding tissue. In the collaborative research unit FOR 2743, we study the fate of mechanosensitive proteins after exposure to mechanical stress. In addition, we are interested in proteolytic protein maturation and proteostasis in endosymbiont-derived organelles.

> Proteases are fascinating enzymes that have an impact on almost all biological processes. We develop new methods to determine their substrates and function. This will allow us to develop new diagnostic tools and validate targets for therapeutic intervention.



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KEY PUBLICATIONS 2019/2020

▮ Hofsetz E, […], Trifunovic A#, **Huesgen PF#**. The mouse heart mitochondria N terminome provides insights into ClpXP-mediated proteolysis. **Mol Cell Proteomics.** 2020 #joint last authorship ▮ Soh WT*, Demir F*, […], **Huesgen PF.** ExteNDing proteome coverage with legumain as highly specific digestion protease. **Anal Chem.** 2020 *shared first authorship ▮ Weng SSH*, Demir F*, […], **Huesgen PF#**, Lange T#. Sensitive determination of proteolytic proteoforms in limited microscale proteome samples. **Mol Cell Proteomics.** 2019 *shared first authorship #joint last authorship ▮ Misas-Villamil J, […], **Huesgen PF**, Doehlemann G. The fungal effector Pit2 acts as molecular mimicry to suppress plant immunity via an inter-kingdom conserved motif. **Nat Commun.** 2019 ▮ Späth MR, […], Brodesser S, […], Benzing T, Schermer B, […], **Huesgen PF**, Müller RU, Rinschen MM. The proteome microenvironment determines the protective effect of preconditioning in cisplatin-induced acute kidney injury. **Kidney Int.** 2019

DETAILED INFORMATION

Prof. Dr. Sandra Iden

Cell Polarity and Cancer

We use mouse models and primary cell systems to study how changes in cell shape and intercellular communication are coordinated in self-renewing tissues like the skin epidermis in health and disease.



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>> RESEARCH FOCUS

Our ongoing research aims at understanding how different cell types, or cells of different fate, communicate, synergize or compete with each other at tissue scale, how polarity networks impinge on these dynamic interactions, and how these processes fail in the disease context. These studies should help identify basic principles of development and tissue homeostasis as well as pathophysiological mechanisms linked to disturbed cell polarity.

>> PROJECTS AND AIMS

We combine mouse genetics and animal disease models with cell and molecular biology, biophysics, imaging technologies and protein biochemistry to acquire new knowledge about mechanisms that drive cell and tissue polarization, from subcellular details towards the tissue and organismal context. This way, we aim to understand how polarity, cell adhesion, growth and mechanical signaling are coordinated to ensure proper tissue function. We further develop and improve simple and complex in vitro (co) culture systems to complement the in vivo models used. Together with our clinical collaborators we combine these with analyses of human (patient) datasets and specimen to test the significance of our findings for human disease and to explore translational directions for disease prevention and control. In 2020, the Iden laboratory relocated to Saarland University, Medical Faculty.

> Our in vivo research and various collaborations at CECAD have laid an important foundation for our current and future scientific paths at Saarland University.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Dias Gomes M*, Letzian S*, [….], **Iden S.** Polarity signaling ensures epidermal homeostasis by coupling cellular mechanics and genomic integrity. **Nat Commun.** 2019 *shared first authorship ▮ Li M, [..], **Iden S.** Mechanisms of melanocyte polarity and differentiation: What can we learn from other neuroectoderm-derived lineages? **Curr Opin Cell Biol.** 2020

Dr. Ron D. Jachimowicz

Mechanisms of DNA Repair

We dissect defects in DNA repair pathways in patients with genome instability syndromes and in patients suffering from mantle cell lymphoma, providing a rich opportunity to uncover the relationship between genome maintenance, aging, and cancer.

>> RESEARCH FOCUS

The overarching goal of our research program is to understand disease mechanisms in patients with an underlying genome instability syndrome and DNA repair-deficient mantle cell lymphoma. We strive to identify novel therapeutic approaches based on DNA repair. Associated molecular liabilities discovered in this research program thus contribute to a deepened functional understanding of genome maintenance and DNA repair in the context of aging and cancer.

> We utilize tools involving biochemistry, cell biology, and computational biology, and transfer these findings to modern mouse genetics, that will ultimately lead to genetically-informed therapies for patients suffering from cancer and ageing associated diseases.

>> PROJECTS AND AIMS

1. How defective DNA repair rewires aging- and cancer pathways The occurrence of premature aging and DNA repair defects in human genome instability syndromes creates a unique opportunity to identify and investigate novel components of DNA repair pathways. Furthering our understanding of the mechanisms underlying novel genome instability syndromes allows us to examine their crucial role in aging, aging-associated diseases, and cancer.
2. How DNA repair defects expose genotype-specific vulnerabilities in mantle cell lymphoma Somatic mutations in ATM are observed in approximately 50% of mantle cell lymphoma cases, but no targeted treatment options exist to date for this major genetic subtype. Innovative treatments are hence urgently needed, especially for the growing population of older mantle cell lymphoma patients who are not eligible for intensified therapies.



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KEY PUBLICATIONS 2019/2020

Jachimowicz RD, […], Krüger M, Schumacher B, […], Reinhard HC, […], Shilon Y. UBQLN4 represses homologous recombination and is overexpressed in aggressive tumors. **Cell.** 2019 **Jachimowicz RD**, Goergens J. and Reinhardt HC. DNA double-strand break repair pathway choice - from basic biology to clinical exploitation. **Cell Cycle.** 2019 Riabinska A, […], **Jachimowicz RD**, […], Frenzel LP, […], Krüger M, […], Wunderlich TF, […], Reinhardt HC. ATM activity in T cells is critical for immune surveillance of lymphoma in vivo. **Leukemia.** 2020 Brockelmann PJ, de Jong MRW, and **Jachimowicz RD.** Targeting DNA repair, cell cycle, and tumor microenvironment in B cell lymphoma. **Cells.** 2000

DETAILED INFORMATION

Prof. Dr. Frank Jessen

Alzheimer Disease Research

The work of our group addresses clinical research questions in the area of Alzheimer disease (AD) and late life depression (LLD) with the aim of improving early diagnosis, treatment and prevention of both conditions.



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>> RESEARCH FOCUS

The focus of our research group is the conceptual and empirical delineation of the earliest manifestation of Alzheimer Disease (AD) making use of clinical, neuropsychological, brain imaging and biomarker technologies. We also study the link of AD with late life depression (LLD). For both, early AD and LLD we aim at developing early treatment and approaches of prevention.

>> PROJECTS AND AIMS

The backbone of our work are 1. the Cologne Center for Memory Disorders, 2. the Cologne Alzheimer Prevention Center and 3. the Late Life Depression outpatient clinic. Based on these structures, we work in local and multisite projects on the development of early disease markers and disease course prediction in AD (DELCODE study, DZNE), individual AD risk profiling (INSPIRATION) and the molecular and functional link between early AD and LLD (ADIPA). We further explore effects of early AD diagnosis on mental health and quality of life (PreDadQual, PreTAD). In LLD, we are coordinating a national multicenter psychotherapy trial (CBTlate) and study motor control within the CRC 1451 together with the MPI for metabolism research. Our projects interact with the Section of Molecular Neuropsychiatry of the Department of Psychiatry at the University of Cologne and are embedded in several local, national and international collaborations and networks. Our overall aim is to create new approaches for early intervention and prevention of brain and mental disorders in late life with focus on AD and depression.

> “The integration of several disciplines and technologies in patient-related research opens new avenues to understand, successfully treat and prevent complex brain disease at a greater age with major impact on individuals and society.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

▮ **Jessen F**, […], Wagner M. Prediction of dementia of Alzheimer type by different types of subjective cognitive decline. **Alzheimers Dement.** 2020 ▮ Maier F, […], **Jessen F.** Bupropion for the treatment of apathy in alzheimer disease: a randomized clinical trial. **JAMA Netw Open.** 2020 ▮ **Jessen F**, […], Wagner M. The characterisation of subjective cognitive decline. **Lancet Neurol.** 2020 ▮ **Jessen F.** Refining the understanding of typical Alzheimer disease. **Nat Rev Neurol.** 2019 ▮ Hu X, […], **Jessen F.** Smaller medial temporal lobe volumes in individuals with subjective cognitive decline and biomarker evidence of Alzheimer's disease-Data from three memory clinic studies. **Alzheimers Dement.** 2019

Prof. Dr. Hamid Kashkar

Cell Death and Immunity

Our lab investigates how cell death impacts on tissue surveillance mechanisms and controls immunity. We aim to explore how alteration of cell death contributes to pathogenesis of human diseases and will exploit this knowledge in therapeutic interventions.

>> RESEARCH FOCUS

Cell death represents a central component of the immune system and its alteration has been intimately associated with human diseases. Whereas initial studies considered cell death as a quantitative counterbalance of mitosis, it is increasingly evident that dying cells efficiently coordinate the fade of the surrounding tissue by emitting different factors. Different modes of cellular death process have been identified that involve distinct cellular death machineries and release a battery of different mediators ultimately leading to beneficial or detrimental tissue outcomes.

> The plasticity of cell death pathways safeguards the efficient removal of »unwanted cells« but can provoke diverse tissue reactions. Cell death can thereby be beneficial or detrimental for the affected tissues during the course of disease pathogenesis or therapy.

>> PROJECTS AND AIMS

Although different cellular death pathways are executed with molecularly distinct death machineries, recent evidence including our own results indicated that these pathways are molecularly interlinked and provide a dynamic plasticity in cellular death and inflammatory responses. The molecular link between different cellular death modalities and inflammation represents the central objective of our research group. We are, in particular, investigating the role of caspases, inhibitor of apoptosis proteins (IAPS) and mitochondria as signalling components that mediate cell death and inflammation. By modelling human diseases in appropriate in vivo model-systems, we will discover the physiological roles of theses processes in tissue homeostasis and their contribution to pathophysiology of human diseases. The molecular knowledge obtained will be exploited to design novel therapeutic protocols for human diseases by targeting cellular death pathways.



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KEY PUBLICATIONS 2019/2020

Fritsch M, […], Krönke M, Pasparakis M, **Kashkar H.** Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. **Nature.** 2019 Günther SD, […], Krönke M, […], **Kashkar H.** Cytosolic Gram-negative bacteria prevent apoptosis by inhibition of effector caspases through lipopolysaccharide. **Nat Microbiol.** 2020 Schiffmann LM, […], Brodesser S, […], Pasparakis M, Krönke M, Eming SA, [….], **Kashkar H.** Mitochondrial respiration controls neoangiogenesis during wound healing and tumour growth. **Nat Commun.** 2020 Albert MC, [...], Krönke M, Hoppe T#, **Kashkar H#**. Dynamic ubiquitylation of NOXA regulates MCL-1 antagonization and controls cellular stress response. **Cell Death Dis.** 2020 #joint last authorship Mayer CT, […], **Kashkar H**, Nussenzweig MC. An apoptosis-dependent checkpoint for autoimmunity in memory B and plasma cells. **PNAS.** 2020

DETAILED INFORMATION

Prof. Dr. Peter Kloppenburg

Modulation of Neurocircuits

Understanding the neural circuits that regulate the organism's physiological state and how this circuitry changes during aging and disease promotes the identification of therapeutic strategies against metabolic disorders and their comorbidities.



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>> RESEARCH FOCUS

Homeostasis of vital physiological parameters, including energy, is tightly controlled by specialized, highly adaptive neural circuits in the central nervous system. These neurocircuits acquire and integrate information about the internal milieu and the external environment. Based on this integrated information, they adjust their regulatory output to ensure optimal physiological homeostasis. Aging, extreme diets, and diseases can impair these homeostasis-regulating neuronal systems. These impairments drive the development of metabolic disorders such as obesity, type 2 diabetes, and associated comorbidities, including neurodegenerative diseases. By defining the physiological properties of these networks and their age and diet-related changes, our group aims to understand the molecular and cellular mechanisms that mediate the development of metabolic disorders.

>> PROJECTS AND AIMS

One of our main goals is to define the biophysical parameters and cellular mechanisms that cause age and diet-dependent changes in the neuronal circuits that regulate physiological homeostasis. The research aims to understand how the modulation of intrinsic and synaptic properties of individual neurons (or groups of neurons) ultimately controls homeostatic pathways. In this context, it is of particular interest how multiple intra- and intercellular signaling pathways are processed and integrated at the level of individual neurons. The intracellular signaling pathways for many neuromodulators have been explored from the receptor to the ion channel. However, the interplay of the various intracellular signaling pathways and how they act together on intrinsic electrophysiological properties is not known in detail.

> In order to understand things such as reading, memory or consciousness, or anything of this nature, it's important to understand it is all based on neurons, on nerve cells.
>
> - Christophe Koch

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Jais A, […], Korotkova T, […], Wunderlich FT, **Kloppenburg P**, Brüning JC. PNOCARC Neurons promote hyperphagia and obesity upon high-fat-diet feeding. **Neuron.** 2020 ▮ Benkert J, […], **Kloppenburg P**, Liss B. Cav2.3 channels contribute to dopaminergic neuron loss in a model of Parkinson's disease. **Nat Commun.** 2019

Prof. Dr. Natalia Kononenko

Mechanisms of Neurodegeneration

Our lab integrates molecular, genetic and cell biology approaches with live cell imaging and in vivo neuroanatomy techniques to understand the role of membrane trafficking and autophagy in the pathogenesis of age-dependent neurodegenerative diseases.

>> RESEARCH FOCUS

The dysfunction of autophagy in the brain is accompanied by the accumulation of insoluble protein inclusions, but the prevention of inclusion formation does not suppress neurodegeneration in autophagy-deficient mice. This challenges the doctrine of protein aggregate removal as a sole function of neuronal autophagy and raises the question: »What is the precise physiological role of autophagy in the brain«? Our lab is uniquely positioned to explore this question by integrating state-of-the-art genetic and cell biology approaches with live-cell imaging and neuroanatomy. Using this multidisciplinary approach, we discovered that autophagy functions in the brain to regulate axonal microtubule dynamics independently of its role in protein degradation. We found that autophagy proteins, which are crucial for autophagosome expansion, also mediate the intracellular cargo transport in neurons and are important regulators of neuronal-activity dependent gene expression. How autophagy proteins switch from their canonical function in protein degradation to cargo transport regulation is currently unknown. We believe that our studies could revolutionize our understanding of molecular mechanisms of neurodegeneration.

>> PROJECTS AND AIMS

Key research questions are:

1. Do autophagy and endocytosis regulate neuronal survival independently of their known functions in protein (and organelle) homeostasis?
2. Neuronal cell type-specific functions of autophagy and their role in animal physiology across the life span. Major research projects: 1. Role of membrane trafficking in selective brain vulnerability and their relevance for AD and ALS. 2. Role of autophagy in pathophysiology of epileptic seizures.
3. Regulation of neuronal proliferation by non-canonical function of endocytic machinery.

> The reward of the scientist is the emotional thrill of being the first person in the history of the world to see some-thing or to understand something. Nothing can compare with that experience.
>
> – Cecilia Payne-Gaposchkin



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KEY PUBLICATIONS 2019/2020

▮ Overhoff M, De Bruyckere E, **Kononenko NL.** Mechanisms of neuronal survival safeguarded by endocytosis and autophagy. **J Neurochem.** 2020 ▮ Bera S, […], **Kononenko NL.** AP-2 reduces amyloidogenesis by promoting BACE1 trafficking and degradaiton in neurons. **EMBO Rep.** 2020 ▮ Negrete A, […], **Kononenko NL.** Autophagy lipidation machinery regulates axonal microtubule dynamics but is dispensable for survival of mammalian neurons. **Nat Commun.** 2020 ▮ Torres-Benito L, […], **Kononenko NL**, […], Wirth B. NCALD antisense oligonucleotide-based therapy additionally to low-dose Nusinersen further ameliorates spinal muscular atrophy in mice. **AJHG.** 2019

DETAILED INFORMATION

Prof. Dr. Tatiana Korotkova

Neuronal Circuits and Behavior

Our lab studies neuronal circuits regulating different aspects of innate behaviors, including feeding behaviors. Our aim is to reveal and decode functions of various hypothalamic neuronal circuits in these behaviors in health, disease, and aging.



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>> RESEARCH FOCUS

The Neuronal Circuits and Behavior group studies neuronal circuits regulating different aspects of innate behaviors, including feeding-related behaviors. The overall goal of our group is to unravel functions of hypothalamic neuronal circuits related to health, disease and healthy aging. We focus on decoding neuronal mechanisms of neuropsychiatric disorders, associated with dysfunctions of hypothalamus, including eating disorders. To reveal and decode the influence of various neuronal groups and their inputs on innate behaviors, we combine state-of-the-art technologies, including multisite high-density neuronal recordings in transgenic behaving mice; optogenetics; chemogenetics; and novel computational and engineering approaches.

> We aim to identify the neuronal circuits underlying metabolic and behavioral changes in health, during healthy aging, and in the context of disease. Our goals is that this knowledge be used in the identification of novel therapeutic targets.

>> PROJECTS AND AIMS

We aim to understand the changes in neuronal activity in the lateral hypothalamus during aging, and how these changes underlie metabolic and sleep disorders that represent major health problems in the elderly population. We further seek to investigate changes of neuronal circuitries involved in the regulation of innate behaviors in aging, to identify the neuronal groups and neural dynamics that underlie these changes, and to study consequences of optogenetically restored physiological signaling within hypothalamic groups. Further, we are investigating a role of neural circuits in the translation of cognitive- and reward-related information to the hypothalamus during innate behaviors, and analyzing how this translation changes in the context of disease as well as during healthy aging.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

▮ Jais A, […], **Korotkova T**, […], Fenselau H, Wunderlich FT, Kloppenburg P, Brüning JC. PNOC-ARC neurons promote hyperphagia and obesity upon high-fat-diet feeding. **Neuron.** 2020 ▮ Heikenfeld C, […], **Korotkova T**, Schnitzler A, Ponomarenko A. Prefrontal - subthalamic pathway supports action selection in a spatial working memory task. **Sci Rep.** 2020 ▮ Ruud J, […], Krüger M, […], **Korotkova T**, […], Brüning JC. The fat mass and obesity-associated protein (FTO) regulates locomotor responses to novelty via D2R medium spiny neurons. **Cell Rep.** 2019

Prof. Dr. Thomas Krieg

Translational Matrix Biology

A tightly controlled balance of ECM synthesis and degradation is crucial for guaranteeing the homeostasis of the skin and other connective tissue containing organs. We aim to unravel mechanisms leading to fibrotic and aging associated skin diseases.

>> RESEARCH FOCUS

Our group aims at investigating the mechanisms underlying the control of connective synthesis and the role of cell-matrix interactions. Fibroblasts represent a heterogeneous group of cells that derive from different cellular origins and they are the key cells orchestrating the formation of connective tissues following any type of injury. Their phenotype and function are regulated by interactions with the surrounding extracellular matrix (ECM), mediated by specific receptors and by the activity of growth factors and cytokines through complex paracrine and autocrine regulatory loops. As a model we use fibroblasts obtained from patients with scleroderma, an autoimmune-driven chronic fibrotic disease that involves the skin but can also affect many other organs. We have identified the key role of TGFβand force transduction for ECM production and translate the results from in vitro and mouse experiments to well characterized patient cohorts.

> We have assigned unique and overlapping functions to different receptors that interact with collagens and uncovered the role of integrin-mediated mechanotransduction for regulating fibrotic reactions, the stromal response in tumors and skin homeostasis in aging.



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>> PROJECTS AND AIMS

Our aim is to better understand the molecular and cellular mechanisms controlling activation of fibroblasts and to unravel how skin homeostasis depends on fibroblast communication with the surrounding ECM. We characterize fibroblast subpopulations and identify them in their spatial context. Our in vitro findings together with mouse models are expected to lead to a better understanding of the molecular basis of diseases associated with excessive fibroblast activation and to design targeted therapies.



KEY PUBLICATIONS 2019/2020

▮ Üstün Y, […], **Krieg T.** Dual role of laminin 511 in regulating melanocyte migration and differentiation. **Matrix Biol.** 2019 ▮ Chaigne B, […], **Krieg T**, […], Mouthon L. Proteomic analysis of human scleroderma fibroblasts response to transforming growth factor-ß. **Proteomics Clin Appl.** 2019 ▮ Schönborn K, […], Eming SA, […], **Krieg T.** Role of collagen XII in skin homeostasis and repair. **Matrix Biol.** 2020 ▮ Moinzadeh P, […], **Krieg T**. Whole blood gene expression profiling distinguishes systemic sclerosis-overlap syndromes from other subsets. **J Eur Acad Dermatol Venereol.** 2020 ▮ Moinzadeh P, […], **Krieg T**, Hunzelmann N. Registry of the German Network for Systemic Scleroderma. Older age onset of systemic sclerosis - accelerated disease progression in all disease subsets. **Rheumatology (Oxford)**. 2020

DETAILED INFORMATION

Prof. Dr. Martin Krönke

Staphylococcus Aureus Vaccine

The development of a vaccine against *Staphylococcus aureus* remains an important unmet clinical need, especially for the elderly. Unfortunately, classical attempts targeting *S. aureus* failed. We developed an iterative concept of epitope-based optimization of vaccine design.



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>> RESEARCH FOCUS

Multiple vaccine candidates for *S. aureus* infections have shown promise through preclinical development in a range of animal models. However, those that have reached late-stage clinical testing have failed to demonstrate efficacy in human trials and occasionally aggravated the course of disease. Further progress in the design of vaccines against *S. aureus* with greater precision and efficacy is needed and can be expected from increasing structural and functional characterisation of protective *S. aureus* antigens and the delineation of protective and non-protective epitopes.

>> PROJECTS AND AIMS

> If you want to develop an efficient Staphylococcus aureus vaccine you have to target different antigens or target antigens differently.

We here target two non-redundant S. aureus housekeeping proteins, coproporphyrinogen III oxidase (CgoX) and triose phosphate isomerase (TPI), which are essential for heme synthesis and glycolysis, respectively. Monoclonal antibodies (mAb) were raised to identify protective epitopes. One protective mAb CgoX-D3 bound to a linear epitope spanning 12 amino acids. Active immunization with the CgoX-D3 epitope elicited excellent immunoprotection in a murine model of S. aureus bacteremia. Together, the data provide a preclinical proof-of-principle for an epitope-based development of a S. aureus vaccine with greater efficacy and better safety profile. The protective action of a S. aureus antigen-derived epitope is unique among the wealth of other S. aureus vaccine candidates so far tested in clinical trials. We, therefore, will address the mode of immunoprotective action of the CgoX D3 epitope. In this respect, we aim to

1. delineate the molecular mechanism by which CgoX exerts virulence activity in the host;
2. specifically define the function of the D3 epitope within this mode of action; and
3. characterize the mode of protective action of the mAb anti-CgoX D3.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Klimka A, […], **Krönke M.** Epitope-specific Immunity against *Staphylococcus aureus* coproporphyrinogen III oxidase. **NPJ Vaccines.** 2020 ▮ Tosetti B, Brodesser S, […] **Krönke M.** A tissue-specific screen of ceramide expression in aged mice identifies ceramide synthases-1 and -5 as potential regulators of fiber size and strength in skeletal muscle. **Aging Cell.** 2020 ▮ Fritsch M, […] **Krönke M**, Pasparakis M, Kashkar H. Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. **Nature.** 2019 ▮ Günther SD, […], **Krönke M**, […], Kashkar H. Cytosolic Gram-negative bacteria prevent apoptosis by inhibition of effector caspases through lipopolysaccharide. **Nat Microbiol.** 2020 ▮ Utermöhlen O, […], **Krönke M.** Emergence of AnnexinVpos CD31neg CD42blow/neg extracellular vesicles in plasma of humans at extreme altitude. **PLoS One.** 2019

Prof. Dr. Marcus Krüger

Quantitative Proteomics

Our group addresses questions of cell signalling and the quantitative analysis of post-translational modifications (PTMs). The aim of the group is to characterize disease-relevant changes in signalling networks in different animal models.

>> RESEARCH FOCUS

The research focus of our group is the development and application of quantitative proteomics methods in various biological fields. The aim of our study is to analyze protein dynamics and post-translational modifications (PTMs) in cellular networks under regular and pathological conditions, such as type 2 diabetes mellitus, muscle weakness and neurodegenerative diseases. We are also interested in using stable isotope incorporation in living animals to study protein dynamics by mass spectrometry.

> We aim to characterize how signaling networks differentially modulate cellular responses when mediated by phosphorylation and other post-translational modifications.

>> PROJECTS AND AIMS

Skeletal muscle tissue is highly adaptable and able to respond rapidly to environmental changes by modulating the synthesis and degradation of proteins. We are using protein profiles determined by quantitative proteomics to distinguish skeletal muscle tissue in different states, such as healthy muscles versus muscles with a loss of neuronal innervation. We are also investigating the function and localization of mitochondria in skeletal muscle. Mitochondria located in specific cell regions have different morphological and biochemical properties. The presence of different mitochondrial subpopulations, in particular subsarcolemmal mitochondria and interfibrillar mitochondria, highlights this mitochondrial heterogeneity. However, it remains unclear whether these subpopulations are functionally distinct and how they respond to cellular changes. We therefore want to use genetic mouse models and quantitative proteomics to analyze these subpopulations in more detail in order to gain new insights into metabolic adaptations under physiological and pathological conditions.



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KEY PUBLICATIONS 2019/2020

▮ Tellkamp F, […], **Krüger M.** Proteomics of Galápagos marine iguanas links function of femoral gland proteins to the immune system. **Mol Cell Proteomics.** 2020 ▮ Kallabis S, […], **Krüger M.** High-throughput proteomics fiber typing (ProFiT) for comprehensive characterization of single skeletal muscle fibers. **Skeletal Muscle.** 2020 ▮ Pla-Martín D, […] **Krüger M**, Rugarli EI. CLUH granules coordinate translation of mitochondrial proteins with mTORC1 signaling and mitophagy. **EMBO J.** 2020 ▮ Hammerschmidt P, […], Langer T, **Krüger M**, […], Brüning JC. CerS6-derived sphingolipids interact with Mff and promote mitochondrial fragmentation in obesity. **Cell.** 2019 ▮ Lim R, […], **Krüger M**, […], Potente M. Deubiquitinase USP10 regulates Notch signaling in the endothelium. **Science.** 2019

DETAILED INFORMATION

Dr. Leo Kurian

Decoding the Genome

Our lab studies the fundamental principles by which information is accurately decoded from the genome to define cellular identity and function in humans. We use this knowledge to understand the molecular basis of congenital and age-associated diseases.



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>> RESEARCH FOCUS

All the information required to sustain life is coded on the genome. RNA is the universal language primarily used for communication from the genome. Apart from acting as an accurate template for the synthesis of proteins, RNA carries a compendium of embedded codes that instruct and control the forward communication of genetic information, ranging from its processing and splicing to how, when, and where mRNA is translated. According to current estimates > 95% of the RNA encoded by the genome do not template for protein synthesis but function as RNA molecules. These RNA codes are further instructed by ~2000 RNA binding proteins, thus constructing complex RNA centric regulatory networks or RNA regulons. We are only beginning to understand these RNA-based encryptions in the flow of genetic information that program cellular identity and function. Our laboratory is dedicated to understanding the RNA-centric regulatory rules that encode cellular identity, cellular physiology, and function and how these processes break down in the context of congenital disorders and aging. We study this in the milieu of human cardiac development and homeostasis.

>> PROJECTS AND AIMS

1. Long non-coding RNA mediated regulation of cell-fate decisions during development and homeostasis
2. Translational control over cell-fate decisions and homeostasis
3. Conserved metabolic mediators of tissue-specific aging
4. RNA-regulons mediating cell-fate decisions during cardiac regeneration

We address these questions using a holistic approach combining human pluripotent stem cell-based 2D and organoid models, mouse models, targeted genome engineering strategies, and systems biology-based approaches.

> Our long-term goal is to gain a systems-level understanding of the RNA-code that encrypt cellular identity and functional specialization in humans.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

▮ Frank S, […], Rada-Iglesias A, […], **Kurian L.** yylncT defines a class of divergently-transcribed lncRNAs and safeguards the T-mediated mesodermal commitment of human PSCs. **Cell Stem Cell.** 2019 ▮ Ahuja G, […], Trifunovic A, […], Valenzano DR, **Kurian L.** Loss of genomic integrity by lysosphingolipid imbalance drives ageing in the heart. **EMBO Rep.** 2019 ▮ Kuo CC, […], **Kurian L**, Costa IG. Detection of RNA–DNA binding sites in long noncoding RNAs. **Nucleic Acids Res.** 2019 ▮ Mitra S, […], **Kurian L**, […], Kanduri C. A p53 responsive lncRNA NBAT1 determines chemotherapeutic response in neuroblastoma through regulating p53 sub-cellular distribution. **Cancer Res.** 2020

Prof. Dr. Thomas Langer

Mitochondrial Plasticity in Aging and Disease

Aging and numerous age-related diseases are associated with defects in mitochondria, which serve as metabolic and cellular signaling hubs. Our group analyses molecular mechanisms determining the functional plasticity and dynamic behavior of mitochondria.

>> RESEARCH FOCUS

Mitochondria are essential cellular organelles that adapt their form and function to physiological demands. Loss of mitochondrial plasticity is associated with aging and numerous age-related diseases, including neurodegeneration, cardiomyopathies, and cancer. We examine molecular mechanisms determining the structural and functional plasticity of mitochondria focusing on mitochondrial proteases. Metabolic reprogramming of mitochondria by these proteases drives the progression of diverse cancers, while loss-of-function mutations in protease-encoding genes are associated with neurodegenerative disorders.

> Mitochondria are fascinating organelles, highly dynamic with multifaceted functions. Understanding the molecular mechanisms driving their functional plasticity holds the promise to find new paths to tackle aging and age-related diseases.

>> PROJECTS AND AIMS

The metabolic flexibility of mitochondria is provided by alterations in the mitochondrial proteome and lipidome and is tightly coupled to changes in the shape of mitochondria. Current projects examine molecular mechanisms as to how mitochondrial proteases drive mitochondrial plasticity in response to physiological stress, during aging, stem cell differentiation or neurodegeneration. We combine multi-omic approaches with genome editing and genetic screens to define substrate profiles of mitochondrial proteases and examine their (patho-) physiological relevance in mice. Recent studies identified YME1L as a key regulatory protease at the interface of mitochondrial metabolism, mitochondrial dynamics and inflammation. Tissue-specific loss of YME1L in mice causes heart failure and axonal degeneration, while YME1L supports growth of pancreatic ductal adenocarcinoma cells, highlighting the pathogenic significance of YME1L-mediated proteolysis.



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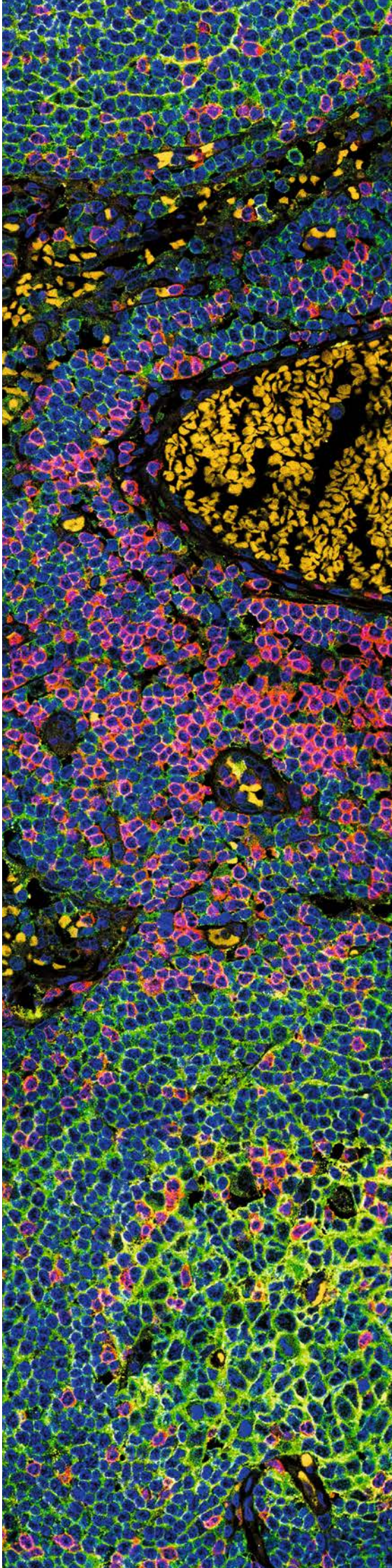
KEY PUBLICATIONS 2019/2020

▮ Deshwal S, Fiedler KU, **Langer T.** Mitochondrial proteases – multifaceted regulators of mitochondrial plasticity. **Ann Rev Biochem.** 2020 ▮ MacVicar T, […], Krüger M, […], Riemer J, […], Pasparakis M, […], Brüning JC, […], **Langer T.** Lipid signalling drives proteolytic rewiring of mitochondria by YME1L. **Nature.** 2019 ▮ Sprenger HS, […], Rugarli EI, Bergami M, **Langer T.** Loss of the mitochondrial i-AAA protease YME1L leads to ocular dysfunction and spinal axonopathy. **EMBO Mol Med.** 2019 ▮ Miliara X, […], **Langer T.** Structural determinants of lipid specificity within Ups/PRELI lipid transfer proteins. **Nat Commun.** 2019 ▮ Richter F, […], **Langer T**, Rehling P. ROMO1 is a constituent of the human presequence translocase required for YME1L protease import. **J Cell Biol.** 2019

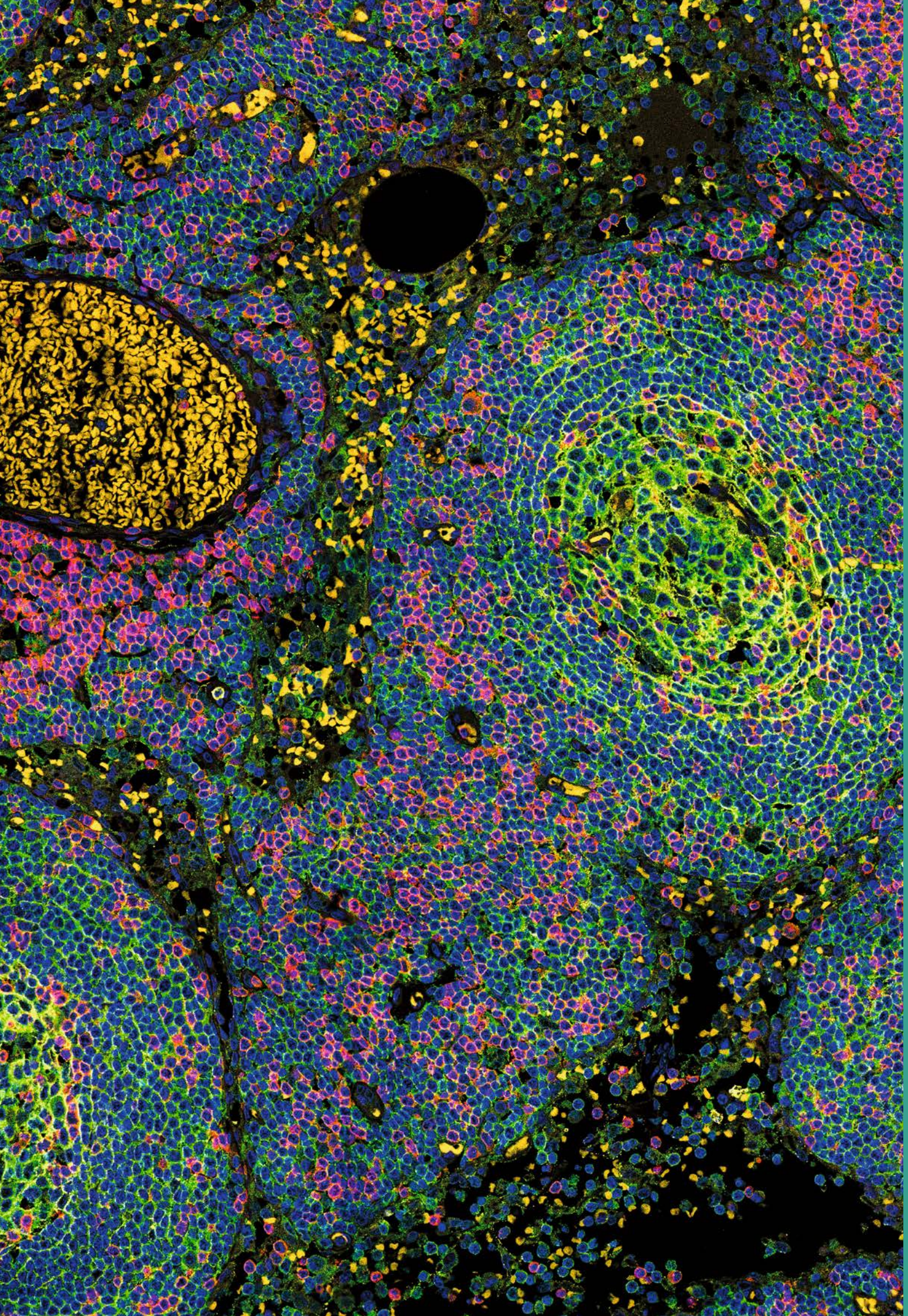
DETAILED INFORMATION

Hotspot of the Immune System

Lymph nodes do not only play a central role in the recognition of infections but also tumor diseases can be detected by the immune system. Lymphatic vessels span the whole body and are responsible for waste disposal of cell debris as well as intruded viruses, fungi or bacteria. Within the lymph nodes these particles are filtered out.
The node also serves as a meeting point for different immune cells where they work tightly packed on a successful immune defence.
The picture shows a section of a lymph node with an accumulation of differently stained immune cells.



Picture: Dr. Astrid Schauss | Sample preparation: M.Sc. Martin Thelen



Prof. Dr. Maria Leptin

Epidermal Homeostasis

TOR, a central element of a conserved nutrient signaling pathway, controls processes from energy homeostasis to stress responses, growth and aging. We use the *Drosophila* larva as model organism to study insulin and TOR function.



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>> RESEARCH FOCUS

We use long-term multi-dimensional live imaging of the normal and wounded epidermis in *Drosophila* larvae to understand the mechanisms governing maintenance and re-establishment of epithelial integrity. We found that loss of TORC1/insulin signaling reduces the healing rate, with TORC1 acting via S6K and insulin via FOXO, controlling the actomyosin network and proper cell shape changes during wound healing. They also help maintain cell shape and epithelial integrity in the healthy epidermis.

> “Observation of cells closing a wound, with organelles, membranes and the cytoskeleton changing their arrangements and organization to support wound healing or maintain epithelial integrity triggers new insights on the underlying molecular control of the processes.

>> PROJECTS AND AIMS

Autophagy is strongly upregulated, in wound healing while few autophagosomes are seen in the normal epidermis. At the same time, the cells around the wound form a multinucleate syncytium. We found that autophagy is necessary for the fusion of these cells and uncontrolled autophagy in the intact epidermis also triggers syncytium formation. This process is normally kept under control by TORC1. When loss of TORC1 releases autophagy, many cellular membrane systems are degraded. The lateral plasma membranes disappear, but the apical and basal plasma membranes remain intact. Most organelles – Golgi, ER, nuclei - are also affected, but mitochondria are not. We must now find out by which mechanism TORC1 and autophagy affect epidermal structure and homeostasis and what role syncytium formation during wound healing has. Recent detection of an interplay between autophagy and nuclear structure has opened a door for studying the role of autophagy in nuclear pathophysiology.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Kakanj P, Eming S, Partridge L, and **Leptin M.** Long-term in vivo imaging of *Drosophila* larvae. **Nat Protoc.** 2020 ▮ de Medeiros G, […], **Leptin M**, […], Hufnagel L. Cell and tissue manipulation with ultrashort infrared laser pulses in light-sheet microscopy. **Sci Rep.** 2020 ▮ Mathew R, […], **Leptin M.** Transcytosis via the late endocytic pathway as a cell morphogenetic mechanism. **EMBO J.** 2020 ▮ Suurväli J, […], **Leptin M**, Wiehe T. The Laboratory Domestication of Zebrafish: From Diverse Populations to Inbred. **Mol Biol Evol.** 2020 ▮ Ding X, […], **Leptin M**, Eming S. Regulation of the wound healing response during aging. **J Invest Dermatol.** 2020

Dr. Ivan Matic

Proteomics and ADP-Ribosylation Signaling

Protein ADP-ribosylation (ADPr) by PARP1 plays a key role in the maintenance of genome integrity and has received a great deal of attention due to its significant clinical relevance in cancer treatment.

>> RESEARCH FOCUS

ADPr by PARP1 acts as a first responder to DNA damage. Despite a wealth of evidence pointing to its biomedical importance - PARP1 inhibitors treat many thousands of cancer patients every year - a deeper understanding of this signaling pathway has been hampered by difficulties in establishing the underlying molecular mechanisms. Our overall aim is to understand the role of PARP1-mediated ADPr in the DNA damage response by conceiving and applying advanced proteomics and chemical biology approaches.

>> PROJECTS AND AIMS

Following our initial discovery of Ser-ADPr as a new type of histone mark (Nature Chem Bio 2016) we revealed HPF1/PARP1 as the 'writer' complex of this new PTM (Mol Cell 2017). These and our subsequent discoveries (eLife 2017, eLife 2018, Cell Reports 2018) have reversed 50 years of consensus understanding and are stimulating studies of how Ser-ADPr regulates DNA repair and chromatin dynamics. As these efforts have been hampered by a lack of tools, we have recently established a technology that draws upon biology to circumvent long-standing chemical challenges and uses chemistry to engineer an enzymatic reaction (Cell 2020). This new chemical biology approach has allowed us to elucidate the prevalence of mono-ADPr upon DNA damage and generate a range of innovative research tools that are already used in many laboratories worldwide. Our current aim is to deepen our understanding of Ser-ADPr signaling by addressing some of the key questions opened up by our seminal discoveries.

> The overarching aim of our interdisciplinary research program is to address fundamental questions in PARP1/DNA repair signaling by establishing and applying conceptually novel approaches at the intersection of chemical biology and proteomics.



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KEY PUBLICATIONS 2019/2020

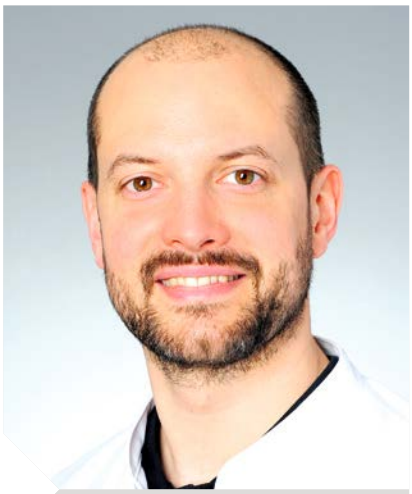
Bonfiglio JJ, [...], **Matic I.** An HPF1/PARP1-based chemical biology strategy for exploring ADP-ribosylation **Cell.** 2020

DETAILED INFORMATION

Prof. Dr. Roman-Ulrich Müller

Modulation of Metabolism in Kidney Disease

Aging is associated with profound changes in cellular metabolism and the decline in metabolic fitness results in aging-associated disease. We study metabolic interventions as strategies to prevent organ failure with a specific focus on kidney disease.



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>> RESEARCH FOCUS

The kidneys are central targets of aging-associated disease. On the one hand, aging is associated with a decline in kidney function and an increase susceptibility to acute kidney injury. On the other hand, kidney failure is accompanied by a pre-mature aging phenotype and strongly increases the burden of cardiovascular co-morbidities. Integrity of cellular metabolism in the kidney is a pre-requisite to organ integrity and is affected by aging. Interestingly, interventions that modulate cellular metabolism – e.g., activation of hypoxia signaling or dietary restriction – have shown an amazing potential in protection against kidney failure.

> I believe that the extension of human well-being and maintenance of health is a key purpose of research in the life sciences. Closing the gap between basic science and novel strategies in everyday patient care is a major challenge, but also a lot of fun to work on.

>> PROJECTS AND AIMS

We study interventions that increase fitness and resilience by modulation of cellular metabolism with the aim to prevent loss of kidney function and increase the human healthspan. Translational strategies are central to our research including experiments spanning the whole spectrum from the nematode to humans. Specifically, we use *C. elegans* to screen for interventions that extend lifespan, examine the identified interventions in mouse models of kidney injury and transfer the most potent approaches to clinical trials. Considering the major impact of RNA biology on cellular metabolism, RNA-binding proteins and non-coding RNAs are one of our central interests regarding the molecular mechanisms underlying organ protection.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Ignarski M, [...], Schermer B, Benzing T, [...], **Müller RU.** The RNA-protein interactome of differentiated kidney tubular epithelial cells. **J Am Soc Nephrol.** 2019 ▮ Kaiser RWL, [...], Schermer B, Benzing T, [...], **Müller RU#**, F. Fabretti#, A protein-RNA interaction atlas of the ribosome biogenesis factor AATF, **Sci Rep.** 2019 #joint last authorship ▮ Johnsen M, [...], Beyer, A., Benzing, T., [...], **Müller RU.** Integrated RNA landscape of renal preconditioning against ischemia-reperfusion injury. **J Am Soc Nephrol.** 2020 ▮ Braun F, [...], Lackmann JW, [...], Hallek M, Schermer B, Benzing T, [...], Beyer A, [...], **Müller RU.** The proteomic landscape of small urinary extracellular vesicles during kidney transplantation. **J Extracell Vesicles.** 2020 ▮ Grundmann F, **Müller RU**, [...], Benzing T, Burst V. Dietary restriction for prevention of contrast-induced acute kidney injury in patients undergoing percutaneous coronary angiography: a randomized controlled trial. **Sci Rep.** 2020

Prof. Dr. Carien M. Niessen

Cell and Tissue Architecture in Health and Disease

The purpose of our research is to understand how cell shape controls the formation and (dys)function of barrier-forming epithelia like the skin epidermis. Aging reduces skin barrier function and alters the mechanics and architecture of the epidermis.

>> RESEARCH FOCUS

The multilayered skin epidermis protects organisms from dehydration and against external challenges, such as mechanical insults, sun damage and microbes. To guarantee life-long barrier function, basal proliferation is balanced with tightly controlled suprabasal differentiation and cell shape change programs. Using a combination of genetics, high resolution imaging, proteomics, genomics and biophysical approaches, we address how adhesion, mechanics and signaling coordinate shape, fate and position of cells to make and regenerate a functional barrier. We also ask how uncoupling of these processes affect aging and cause inflammatory skin diseases or cancer.

>> PROJECTS AND AIMS

We aim to understand how the epidermis makes and maintains spatially distinct fate compartments, how single cells overcome these fate boundaries to regenerate a functional barrier, and why these are ignored in disease. We ask how cell adhesion and mechanics control these boundaries. We have shown that local dynamics in adhesion mechanics control cell shape changes necessary to functionally make and renew the barrier while also protecting it from mechanical stress. We also explore how biochemical signals cooperate with adhesion to coordinate stem cell renewal with differentiation, identifying key roles for lipid homeostasis in barrier maintenance to counteract inflammatory disease. Altered tissue architecture is also a hallmark of cancer. We thus investigate how biomechanical signals affect carcinogenesis. Our work shows that known oncogenes/tumor suppressors synergize with regulators of mechanics to either drive or inhibit skin cancer linked to inflammation. We are now exploring the role of cell shape and fate in inflammation and cancer.

> “Understanding how aging reshapes tissue architecture to promote disease may open up novel therapeutic opportunities for age-associated diseases.



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KEY PUBLICATIONS 2019/2020

Peters F*, Tellkamp F*, Brodesser S, […] Krönke M, **Niessen CM.** Murine epidermal Ceramide Synthase 4 is a key regulator of skin barrier homeostasis. **J Investig Derm.** 2020 *shared first authorship ▮ Nava MM, […] **Niessen CM**, Dahl KN, Wickström SA. Heterochromatin-driven nuclear softening protects the genome against mechanical stress-induced damage. **Cell.** 2020 ▮ Sahu P, […], **Niessen CM**, Marchetti MC, Manning ML, Schwarz JM. Small-scale demixing in confluent biological tissues. **Soft Matter.** 2020 ▮ Rübsam M. and **Niessen CM**. Stretch exercises for stem cells expand the skin. **Nature.** 2020 ▮ Persa OD, **Niessen CM.** Epithelial polarity limits EMT. **Nat Cell Biol.** 2019

DETAILED INFORMATION

Dr. Stephanie Panier

DNA Damage and Aging

Cells respond to DNA damage and protect their genomic integrity by activating specialized DNA damage response pathways. These pathways not only coordinate DNA repair, but they also impinge on numerous aspects of cell metabolism and cell homeostasis.



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>> RESEARCH FOCUS

Our research program focuses on understanding how cellular DNA damage response pathways safeguard genomic integrity in the face of genotoxic stress. It has important implications for understanding the etiology of many genome instability- and age-associated diseases, including cancer and neurodegeneration.

>> PROJECTS AND AIMS

While many RNA-binding proteins have well-characterized roles in adjusting gene expression in response to genotoxic stress, it is becoming increasingly clear that these proteins also have non-canonical functions in the DNA damage response that go well beyond transcription, splicing and mRNA processing. Using cell biological and biochemical approaches, we currently aim to identify and characterize such non-canonical RNA-binding protein functions, particularly in the response to DNA double-strand breaks. In addition, the DNA damage response does not consist of insulated signaling and repair pathways whose activities are restricted solely to the nucleus and to DNA damage sites. Instead, these pathways affect and are affected by very many other aspects of cell biology inside and outside of the nucleus, in particular cell metabolism. By combining genomic, metabolomic and cell biological approaches, we aim to understand how DNA damage response pathways, such as the response to DNA double-strand breaks, cross-talk with cell metabolic pathways and also how they respond to changing microenvironmental cues.

> “Genotoxic stress plays a central role in aging. As such, the detailed knowledge of how cells respond to DNA damage, and how DNA damage response pathways are integrated into the wider metabolic landscape, is essential for understanding the molecular basis of the aging process.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Panier S, […], Boulton, SJ. SLX4IP antagonizes promiscuous BLM activity during ALT maintenance. **Mol Cell**. 2019

Prof. Dr. Linda Partridge

Biological Mechanisms of Aging

We are working on the biology of aging. Our research is directed to understanding the mechanisms by which a healthy lifespan can be extended in laboratory model organisms and humans.

>> RESEARCH FOCUS

My work focuses in particular on the role of nutrient-sensing pathways and diet, and my primary interest is in geroprotective drugs. We investigate dietary, genetic and pharmacological interventions that improve health and function during aging. To this end, we use *Drosophila*, mice and human tissue culture, together with in silico analysis of public data. The goal is to discover broad spectrum preventative interventions for diseases of human aging.

>> PROJECTS AND AIMS

Dietary restriction (DR) can extend healthy lifespan in diverse animal species. DR regimes also improve human health, but are difficult to maintain. We investigate mechanisms mediating the health benefits of DR, by identifying nutrients that induce DR, how they are sensed, physiological responses, and the mechanisms involved in memory of diet. Lowered activity of the insulin/insulin-like growth factor/target of rapamycin signaling (ITT) network can extend lifespan and improve health during aging in laboratory animals and possibly in humans. The network senses nutrient and stress status, and modulates processes such as growth, reproduction, and metabolism in response. We unravel the mechanisms by which reduced ITT improves health, and develop pharmacological methods of manipulating it. Age is a major risk factor for neurodegeneration. We use fly models of Alzheimer's disease and amyotrophic lateral sclerosis/frontotemporal dementia, to understand pathogenesis, and to discover mechanisms that can prevent pathology.

> We won't be able to do away with death, but we can certainly reduce illness and infirmity in old age.



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KEY PUBLICATIONS 2019/2020

Weigelt CM, […], Grönke S and **Partridge L.** Insulin-sensitive circular RNA that regulates lifespan in *Drosophila*. **Mol Cell.** 2020 ▮ Partridge L, Fuentealba M and Kennedy BK. The quest to slow ageing through drug discovery. **Nat Rev Drug Discov.** 2020 ▮ Juricic P, Grönke S and **Partridge L.** Branched-chain amino acids have equivalent effects to other essential amino acids on lifespan and ageing-related traits in *Drosophila*. **J Gerontol A Biol Sci Med Sci.** 2019 ▮ Morón-Oset J, […], **Partridge L.** Glycine-alanine dipeptide repeats spread rapidly in a repeat length- and age-dependent manner in the fly brain. **Acta Neuropathol Commun.** 2019 ▮ Hahn O,[…], Langer T, […], Beyer A, […], **Partridge L.** A nutritional memory effect counteracts benefits of dietary restriction in old mice. **Nat Metab.** 2019

DETAILED INFORMATION

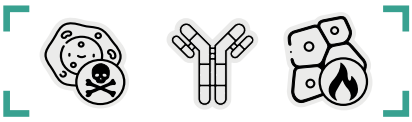
Prof. Dr. Manolis Pasparakis

Cell Death and Inflammation

Our aim is to understand the mechanisms that regulate inflammation and contribute to the pathogenesis of aging-associated diseases, focusing particularly on the role of inflammatory types of cell death, such as necroptosis.



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>> RESEARCH FOCUS

Inflammation is a reaction of the immune system that is essential for host-defense against pathogens and for efficient tissue regeneration after injury. However, excessive or prolonged inflammatory responses often cause tissue damage and contribute to the pathogenesis of many diseases. Our research aims to understand the mechanisms that trigger and perpetuate pathogenic inflammatory responses causing acute and chronic immune-related diseases, focusing particularly on NF-κB signaling and regulated cell death pathways such as necroptosis.

> “Elucidating the mechanisms that regulate cell death and inflammation and understanding how these contribute to the pathogenesis of aging-associated diseases will be important to identify new therapeutic approaches.

>> PROJECTS AND AIMS

A main aim of our research is to understand how dying cells trigger immune responses in the tissue context causing inflammatory diseases. Using genetic mouse models, we have established the important role of necroptosis in causing inflammation. Our current research aims to identify the signals released by cells undergoing different types of cell death that are sensed by bystander cells causing inflammation, with a specific focus on damage-associated molecular patterns (DAMPs). Another research topic in our lab aims to understand the role of Z-DNA and Z-RNA, nucleic acids with a left-handed double helix structure, in inflammation and disease, focusing particularly on ZBP1, a protein that senses Z-nucleic acids and triggers inflammatory cell death. A further focus of our research is to understand the mechanisms that regulate the activation of the kinase RIPK1 inducing apoptosis and necroptosis resulting in the pathogenesis of inflammatory diseases.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

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Dr. Nieves Peltzer

Cell Death and Inflammation in Disease

We investigate how distinct types of programmed cell death affect inflammatory responses and disrupt tissue homeostasis. Currently, we focus on understanding how cell death processes affect metabolic syndromes linked to obesity.

>> RESEARCH FOCUS

Cell death is important for many pathophysiological processes. However, uncontrolled cell death can lead to chronic inflammation and autoimmunity. Cell death-induced inflammation is also associated with cancer. Different cell death programs release specific factors that impact on immune responses and tumorigenesis in a distinctive manner. Our goal is to study the impact of different forms of programmed cell death on disease pathogenesis and to exploit this therapeutically by controlling the levels of cell death and by rewiring cell death programs to the hosts advantage.

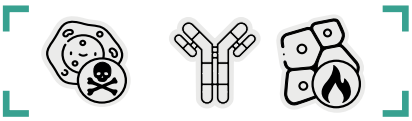
>> PROJECTS AND AIMS

TNFR1 activation, the best characterized immune receptor, results in downstream events that cause: inflammation/survival via NF-kB/MAPK, apoptosis, or pyroptosis, via FADD/RIPK1/Casp-8, or necroptosis via RIPK1/RIPK3 and MLKL. In normal physiology, TNFR1-signalling output is skewed towards inflammation/survival; however, in pathological conditions this balance is shifted towards cell death induction. We study how different modes of inflammatory cell death impact autoimmunity, chronic inflammation and tumorigenesis. One aspect of our research plan focuses on the role of cell death in inducing or perpetuating autoimmunity in Type I Diabetes. We also study the role of cell death in obesity-induced inflammation and associated complications such as insulin resistance, Type 2 Diabetes (T2D) and lung cancer. Last, we aim to understand how tumor cells regulate cell death programs to their own advantage and identify tumor suppressors and vulnerabilities.

> Our goal is to study the impact of different forms of programmed cell death on disease pathogenesis and to exploit this therapeutically by controlling the levels of cell death and by rewiring cell death programs to the host's advantage.



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KEY PUBLICATIONS 2019/2020

Peltzer N, Walczak H. Cell death and inflammation - a vital but dangerous liaison. **Trends Immunol.** 2019

DETAILED INFORMATION

Dr. Lena Pernas

Metabolism of Infection

We study how metabolism and organellar function are rewired to execute cellular defense against microbes. A parallel, but important chapter of research in the lab, is on the role of mitochondria in the regulation of cholesterol and steroid hormone synthesis.



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>> RESEARCH FOCUS

We are developing a novel dimension to the field of immunometabolism. We are studying how an infected cell actively rewires metabolic processes and organellar function to defend against—and adapt to—the challenge of microbial infection (rather than how immune cells adapt their metabolism to enable their effector functions). We then seek to understand whether the mechanisms we uncover also regulate cellular metabolic homeostasis independently of infection.

> The prevailing perception of the host-pathogen interaction is that the host cytosol is an exploitable 'growth medium' for microbes. We instead ask how a cell actively rewires its metabolism to defend against microbes.

>> PROJECTS AND AIMS

• How are mitochondrial membranes remodeled during stress?

We recently discovered large structures that we term SPOTs (structures positive for outer mitochondrial membrane proteins) that emerge from mitochondria during Toxoplasma infection. We seek to identify and structurally characterize the machinery required for SPOTs to emerge, and more broadly, understand their role in the remodeling of mitochondria during stress.

• Is the rewiring of mitochondrial metabolism an effector branch of innate immunity?

We are combining genetic, metabolomic, and proteomic approaches in both host and parasite to determine how changes in cellular metabolism modulate microbial growth.

• How do mitochondria regulate cholesterol and steroid synthesis?

The cell is an interconnected entity, yet the mechanisms that synchronize organellar function are little understood. We seek to define the crosstalk between mitochondria and the endoplasmic reticulum that regulates the synthesis of cholesterol and steroid hormones.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Machado TS, […] **Pernas L**, Seneda MM, Chiaratti MR. Mitofusin 1 is required for the oocyte-granulosa cell communication that regulates oogenesis. **FASEB J.** 2020

Prof. Dr. M. Cristina Polidori

Promotors of Robustness

Aging is a complex multifactorial process, physiologically occurring with increasing chronological age but varying intra- and inter-individually depending on biological age. Our goal is addressing this multifactoriality and disentangling resulting complexity.

>> RESEARCH FOCUS

Within the global efforts to shift from lifespan to healthspan, we focus on specific biomolecular-phenotypical-clinical profiles of frailty and robustness as well as their person-centered trajectories. We dedicate particular attention to renal frailty, cognitive frailty and the interaction of the two to identify biomolecular and lifestyle-related promotors of robustness.

>> PROJECTS AND AIMS

- MPI_Bio. We use the second largest cross-setting patient 65+ cohort worldwide evaluated by means of the frailty tool Multidimensional Prognostic Index (MPI) to identify biomolecular, including laboratory, signatures of organism- and disease-centered frailty, particularly frailty related to kidney disease.
- CogLife, NeuroExercise, BrainProtect Studies. Due to the central role of cognitive fitness to maintain robustness and activity during life, we explore the effects of lipophilic micronutrients and endothelial function as well as of cognitive training on mental performance and quality of life.
- In the framewok of Nutritional Cognitive Neuroscience of Aging and of Biomarkers of frailty, we aim at identifying profiles of lipophilic micronutrients preferentially associated with measures of cognitive and physical fitness as well as of overall robustness (MPI 0-0.33) independent of nutrition, chronological age and gender.

> “Chronos, cruel and ugly, represents quantity of time. Kairos is young and good-looking, embodies quality of time, the right moment. We concentrate our efforts on unveiling critical chronological age-independent factors for frailty prevention, robustness maintenance and quality of life.



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KEY PUBLICATIONS 2019/2020

Gerger P, […], **Polidori MC.** Associations of lipophilic micronutrients with physical and cognitive fitness in persons with mild cognitive impairment. **Nutrients.** 2019 ▮ Meyer AM, […], Benzing T, […], **Polidori MC.** The prognostic significance of geriatric syndromes and resources. **Aging Clin Exp Res.** 2020 ▮ Dias IHK, […], **Polidori MC**, […], Griffiths HR. Inflammation, lipid (per)oxidation, and redox regulation. **Antioxid Redox Signal.** 2020 ▮ Pilotto A, **Polidori MC**, […], Ferrucci L. A multidimensional approach to frailty in older people. **Ageing Res Rev.** 2020 ▮ Rarek MP, […], Benzing T, […], **Polidori MC.** The prognostic signature of health-related quality of life in older patients admitted to the emergency department: a 6-month follow-up study. **Aging Clin Exp Res.** 2020

DETAILED INFORMATION

Dr. Simon Pöpsel

Mechanisms of Chromatin Regulation

Chromatin modifying enzymes shape the genome biochemically, helping to control the levels at which genes are expressed, for example during cellular differentiation. We aim to understand how these crucial factors are regulated.



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>> RESEARCH FOCUS

Chromatin is the dynamic assembly of DNA and associated proteins and nucleic acids. We are interested in the mechanisms by which gene regulation is coordinated through regulatory factors within this complex biochemical environment. We particularly focus on chromatin modifying enzymes that deposit and remove chemical modifications of histone proteins that form the core of nucleosomes, the basic structural unit of chromatin.

>> PROJECTS AND AIMS

Our projects aim at unravelling regulatory mechanisms in the chromatin context by using structural biology and biochemistry. In particular, we employ cryo-electron microscopy (cryo-EM) to determine three-dimensional structures of large and dynamic protein complexes. Thereby, we aim for a better understanding of how gene activity is controlled through their localized activity. Despite their central roles in gene regulation, the topologies and detailed structures of many chromatin regulators are still unknown. Since changes in the chromatin state are associated with aging and their de-regulation as contributing to diseases such as cancer, a mechanistic understanding of chromatin modifiers is of utmost importance. We are currently focusing on human histone methyltransferase and demethylase complexes that are key players in coordinating transcriptional patterns during development, differentiation and disease. We put a particular emphasis on the interactions within and between multi-protein assemblies on chromatin that help to target their activities within the cell.

> “Understanding how regulatory enzymes are guided to their targets within the genome, how they interact and are locally activated, is of key importance to understanding gene regulation in health and disease. Guided by structural biology, we aim to uncover these mechanisms.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Finogenova K, [...], **Poepsel S**, [...], Müller J. Structural basis for PRC2 decoding of active histone methylation marks H3K36me2/3. **eLife.** 2020 Kasinath V*, **Poepsel S***, and Nogales E. Recent structural insights into polycomb repressive complex 2 regulation and substrate binding (REVIEW). **Biochemistry.** 2019 *shared first authorship

Dr. Jane Reznick

From Naked Mole-Rats to Mice

At ages far beyond their expected lifespan, naked mole-rats fail to exhibit any standard sign of physiological decline achieving lifespans of >35 years. Hence, this mammal provides a proof-of-concept that age-related health decline can be avoided.

>> RESEARCH FOCUS

As a subterranean mammal, the naked mole-rat faces a particularly challenging environment characterised by patchily available food, low O2 and high CO2 levels. In response to these pressures naked mole-rats have evolved a suite of molecular and physiological adaptations. These environmental challenges closely parallel the cellular milieu encountered in diseased states. As such, we believe that the adaptations evolved in the naked mole-rat as a response to its environmental stresses offer this animal pleiotropic protection against age-dependent decline.

> Naked mole-rats give us unique insights into molecular strategies that evolution utilizes to deal with environmental stress. Our challenge now is to discover, understand and harness these for human health.

>> PROJECTS AND AIMS

We are investigating the means by which the naked mole-rat remodels its metabolism to counteract environmental challenges like hypoxia. Since many human diseases are defined by metabolic abnormalities, we want to understand the nuances of metabolic plasticity leading to either dysfunctional disease- or adaptive health-promoting states. We have identified several examples of metabolic rewiring in response to hypoxia in the naked mole-rat including a switch to fructose metabolism and retention of neonatal-like traits into adult life. Now we want to understand how this rewiring is achieved by interrogating the epigenetic and post-translational regulation across different environmental challenges. We ask whether neonatal-like features retained in adult naked mole-rat hearts facilitate faster repair and promote regeneration. Further, by generating transgenic mouse models harboring naked mole-rat-like traits, we will verify whether these are also beneficial in mice under different environmental and pathological contexts.



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KEY PUBLICATIONS 2019/2020

Eigenbrod O*, Debus KY*, **Reznick J**, […], Lewin GR. Rapid molecular evolution of pain insensitivity in multiple African rodents. **Science.** 2019 *shared first authorship
Small L, […] **Reznick J**, […] Cooney GJ. Reduced insulin action in muscle of high fat diet rats over the diurnal cycle is not associated with defective insulin signaling. **Mol Metab.** 2019

DETAILED INFORMATION

Prof. Dr. Jan Riemer

Mitochondrial Redoxbiology

Mitochondria are tightly integrated into cellular signalling networks. Major signalling processes are thereby driven by redox molecules. We analyze redox processes and their impact on signalling and on mitochondrial biogenesis.



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>> RESEARCH FOCUS

Redox reactions are at the center of most cellular processes: they are the mechanistic basis of metabolic pathways, they contribute to proteostasis, e.g. by the introduction and removal of disulphide bonds, and they drive the production of reactive oxygen species (ROS), which - with their Janus-faced character of being on the one hand toxic and on the other essential for signalling - impact heavily on cellular physiology. A number of diseases have been directly linked with dysregulated redox homeostasis, including cancer, neurological disorders, cardiovascular diseases, obesity and metabolic diseases, as well as aging.

> Redox reactions are at the core of most cellular processes and we aim to understand their contribution to the regulation and flawless functionality of these processes.

>> PROJECTS AND AIMS

We aim to understand in molecular detail how redox homeostasis is maintained in the different compartments of a cell, how mitochondria as major ROS generators are integrated into cellular signalling networks, how redox processes drive mitochondrial biogenesis, and how organellar proteome plasticity is driven by metabolic and redox changes, e.g. during cell differentiation. We employ a combination of biochemical and cell biological methods ranging from in vitro reconstitution experiments of whole enzymatic cascades, via different proteomics approaches to tackle specific redox changes and complex assembly processes, genetic screens using CRISPR-Cas technology, to the application of genetically encoded sensors and engineering tools. As model systems, we rely on mammalian cell culture, on mice and baker's yeast.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Murschall L, […], Langer T, **Riemer J.** The conserved negatively charged C-terminal region of human MIA40 stabilizes the precursor in the cytosol during slow posttranslational mitochondrial import. **BMC Biology.** 2020
Finger Y, […], **Riemer J.** Proteasomal degradation induced by DPP9-mediated processing competes with mitochondrial protein import. **EMBO J.** 2020
Calabrese G, […], **Riemer J.** Hyperoxidation of mitochondrial peroxiredoxin limits H_2O_2-induced cell death in yeast. **EMBO J.** 2019
Habich M, […], Kashkar H, […], **Riemer J.** Vectorial import via a metastable disulfide-linked complex allows for a quality control step and import by the mitochondrial disulfide relay **Cell Rep.** 2019

Prof. Dr. Elena I. Rugarli

Mitochondria and Neurodegeneration

In our brain, axons transmit information over long distances, and are susceptible to degenerate during aging and in pathological conditions. We study how axons are preserved during life and how mitochondrial integrity power axonal function.

>> RESEARCH FOCUS

We are interested in understanding how axons maintain their function during a lifetime. Human axons can reach the length of 1 m, and contain up to 99% of the cytoplasm. Axonal function and survival depend on efficient trafficking mechanisms to deliver proteins, lipids, and cellular organelles, including mitochondria, to their distal regions. Neuronal survival critically depends on the integrity and functionality of mitochondria. We aim to understand which cellular pathways are implicated in axonal degeneration. Moreover, we investigate how the quality and the function of mitochondria is regulated and maintained in axons during life.

>> PROJECTS AND AIMS

We aim to:

1. Shed light on the pathogenesis of hereditary spastic paraplegia (HSP), and identify common disrupted pathways amenable to therapy. HSP is a genetic disorder, characterized by progressive weakness and spasticity of the lower limbs owing to the retrograde degeneration of the central motor axons, which are responsible for voluntary movements. We investigate the basic function of different HSP genes using cell biology approaches and murine model systems.
2. Identify mechanisms that maintain the quality of axonal distal mitochondria. We investigate the physiological role of intra-mitochondrial proteases that perform quality control of the mitochondrial proteome and regulate the activity of specific mitochondrial proteins. In addition, we are interested in how cytosolic RNA-binding proteins control the fate of mRNAs encoding mitochondrial proteins.

> “Axons are like long and narrow roads connecting a main factory to outposts located far away. Avoiding traffic accidents and maintaining the efficiency of the outposts is essential during our lifetime. Understanding how this is achieved is at the core of our research.



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KEY PUBLICATIONS 2019/2020

▮ Pla-Martín D, […], Krüger M, **Rugarli EI.** CLUH granules coordinate translation of mitochondrial proteins with mTORC1 signaling and mitophagy. **EMBO J.** 2020 ▮ Tadepalle N, […], Brodesser S, […], Schauss A, […], **Rugarli EI**. Microtubule-dependent and independent roles of spastin in lipid droplet dispersion and biogenesis. **Life Sci Alliance.** 2020 ▮ Schatton D, and **Rugarli EI.** A concert of RNA-binding proteins coordinates mitochondrial function. **Crit Rev Biochem Mol Biol.** 2019 ▮ Murru S, […], Brodesser S, Langer T, Kloppenburg P, **Rugarli EI.** Astrocyte-specific deletion of the mitochondrial m-AAA protease reveals glial contribution to neurodegeneration. **Glia.** 2019 ▮ Sprenger HG, […], **Rugarli EI,** Bergami M, Langer, T. Loss of the mitochondrial i-AAA protease YME1L leads to ocular dysfunction and spinal axonopathy. **EMBO Mol Med.** 2019

DETAILED INFORMATION

Prof. Dr. Björn Schumacher

Genome Stability in Aging

DNA damage is a causal driver of the aging process. A complex set of genome maintenance mechanisms is essential for human health. We are exploring how the aging organism responds to and maintains its health amid the accumulation of DNA damage during life.



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>> RESEARCH FOCUS

DNA repair is essential for removing a plethora of lesions in the genome. During the aging process, DNA damage accumulates, increasing cancer risk and driving the functional deterioration of cells and tissues. The DNA damage response impinges on virtually all physiological alterations occurring during aging. The complexity of the DNA damage response prompted us to investigate these mechanisms in the nematode *C. elegans* to explore the cellular and organismal consequences of genome instability.

> We are increasingly gaining a more complete picture of the complex regulatory networks with which organisms respond to the invariable build-up of genome damage during aging.

>> PROJECTS AND AIMS

Similar to humans, the nematode model shows that DNA damage triggers functional deterioration including progressive neurodegeneration with aging. We are investigating the systemic response mechanisms to genome instability. Somatic tissues increasingly deteriorate with aging, while germ cells indefinitely perpetuate the genetic information. We uncovered regulatory inputs from the soma that regulate the DNA damage response in germ cells and thus the maintenance of heritable genomes. We have also shown that microRNAs regulate the decision whether germ cells are eliminated through apoptosis. The DNA damage response impinges on a wide range of physiological mechanisms during aging. We have shown that epigenetic remodeling factors regulate the recovery of the cellular homeostasis following repair. Specific histone modifications regulate the restoration protein biosynthesis and profoundly impact the organism's development and aging process amid DNA damage. The understanding of how tissues, particularly the mortal soma and the immortal germline, interact with each other will provide new conceptual advances into the fundamental mechanisms of aging and also provide new intervention targets to promote healthy aging.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

▮ Wang S, Meyer DH, **Schumacher B.** H3K4me2 regulates the recovery of protein biosynthesis and homeostasis following DNA damage. **Nat Struct Mol Biol.** 2020 ▮ Lopes AFC, […], Trifunovic A, Rieckher M#, **Schumacher B#**. A *C. elegans* model for neurodegeneration in Cockayne syndrome. **Nucleic Acids Res.** 2020 #joint last authorship ▮ Ou HL, […], Wickström SA, **Schumacher B.** Somatic niche cells regulate the CEP-1/p53-mediated DNA damage response in primordial germ cells. **Dev Cell.** 2019 ▮ Doll MA, Soltanmohammadi N, **Schumacher B.** ALG-2/AGO-dependent mir-35 family regulates DNA damage-induced apoptosis through MPK-1/ERK MAPK signaling downstream of the core apoptotic machinery in *Caenorhabditis elegans*. **Genetics.** 2019

Prof. Dr. P. Eline Slagboom

Biology and Epidemiology of Human Aging

We perform genetic/genomic studies into the etiology and heterogeneity of human aging, exceptional longevity, biomarker studies to predict vulnerability and biological age, and intervention studies (lifestyle, clinical) for those at risk.

>> RESEARCH FOCUS

Using multi-omics and clinical data we integrate Epidemiology, Medical Sciences and Molecular Biology. We link clinical studies to biobanking and biology to understand the mechanisms determining heterogeneity in the rate of aging, the increasing susceptibility to disease and factors that promote healthy aging. In the Leiden Longevity Study (LLS), we focus on features of immune and metabolic health in longevity families; in large scale metabolomics studies, we generate novel biomarkers of overall health and of the response of older adults to lifestyle (GOTO study) and clinical interventions.

> The aging process and divergence of human physiology throughout the life course means that health treatment and recommendation schedules require maximum insight into personal risks and capacities, and understanding of the biology of extremes.



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>> PROJECTS AND AIMS

Current projects include identification of and genetic studies into multi-generational longevity families by whole genome sequencing data analysis at LUMC, and functional follow up of variants in cell systems and animal models by an MPI Fellowship in collaboration with MPI colleagues aimed at identifying target mechanisms of human longevity. In large, multi-cohort projects, such as BBMRI and public private project VOILA, we explore omics markers and determinants of biological age. Proteomics studies in particular are being performed in collaboration with CECAD colleagues. These studies are aimed at early recognition of physiological vulnerability among the elderly in the general population and clinical populations. Studies include exploring marker profiles in intervention studies and challenge tests to identify personal responses to interventions. Proteomics studies for these aims in collaboration with CECAD include the study of LLS and GOTO participants.



KEY PUBLICATIONS 2019/2020

▮ Deelen J, […], **Slagboom PE.** A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals. **Nat Commun.** 2019 ▮ van den Berg N, […], **Slagboom PE.** Longevity defined as top 10% survivors and beyond Is transmitted as a quantitative genetic trait. **Nat Commun.** 2019 ▮ Deelen J, [...], **Slagboom PE#**, Murabito JM#. A meta-analysis of genome-wide association studies identifies multiple longevity genes. **Nat Commun.** 2019 #joint last authourship ▮ van den Berg N, [...], **Slagboom PE.** Longevity Relatives Count score identifies heritable longevity carriers and suggests case improvement in genetic studies. **Aging Cell.** 2020 ▮ Beekman M, [...], Deelen J, [...], **Slagboom PE.** Lifestyle-intervention-induced reduction of abdominal fat is reflected by a decreased circulating glycerol level and an increased HDL diameter. **Mol Nutr Food Res.** 2020

DETAILED INFORMATION

Dr. Sophie Steculorum

Sensory Regulation of Metabolism

Sensory food detection has recently emerged as a pivotal regulator of key feeding neurons and peripheral metabolism. Our research aims at further defining the regulatory principles of sensory food detection in health and aging-associated diseases.



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>> RESEARCH FOCUS

Our understanding of how our brain governs food intake and metabolism has recently been revolutionized by the discovery that key hypothalamic hunger neurons are inhibited within a few seconds upon food sensory detection, i.e. sight and smell. Cumulative evidence further demonstrated the critical importance of sensory regulation in the control of whole-body metabolism. Relatedly, aging, obesity, and type 2 diabetes are associated with sensory deficits such as olfactory dysfunctions and taste loss. However, the exact causal relationship between the onset of aging-associated diseases and sensory impairments remains elusive.

>> PROJECTS AND AIMS

While our understanding of the central control feeding and metabolism was recently challenged and revisited through the groundbreaking discovery of the fundamental importance of sensory perception, our knowledge of the neural mechanisms of how food-sensory perception alters hypothalamic neurocircuits, metabolism and behavioral outcomes is scarce. Thus, one key research focus of our research group is to decipher the regulatory principles of food sensory perception in health and diseases by addressing two fundamental aims: (1) deciphering the neurocircuits mediating the sensory-regulation of feeding-regulatory neurocircuits; and (2) determining the contributory role of the sensory-dependent control of metabolism in the etiology of obesity and type 2 diabetes.

> Our group ultimately intends on furthering our understanding of the pathophysiology of aging-associated diseases by providing novel insights into the molecular underpinnings of sensory dysfunctions associated with obesity and type 2 diabetes.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Please scan the QR-Code for a list of recent publications.

Prof. Dr. Philipp Steven

Investigating Eye Disease

Diseases of the ocular surface such as dry-eye affect millions of patients world-wide. Severe forms as Graft-versus-Host Disease may lead to blindness, but treatment options are limited. Translational research develops new diagnosis and treatment forms.

>> RESEARCH FOCUS

We aim to understand and treat severe dry-eye and ocular Graft-versus-Host Disease (GVHD). Using model systems and integrating patient data, we unravel pathomechanisms and develop highly effective new diagnostics and treatments. Here, we focus on GVHD immunopathology, risk-factor influence and prevention. We identify new therapeutic targets and work with academic and industrial partners on drug-formulation. We also use non-invasive imaging techniques and deep-learning algorithms to implement novel software for identifying new optical disease biomarkers that allow precise diagnosis and monitoring of therapy.

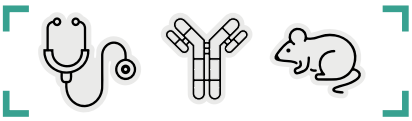
> Translational research by an interdisciplinary group with competent local and supra-regional partners provides direct benefits for patients with dry-eye or ocular GVHD.

>> PROJECTS AND AIMS

We use disease models for dry-eye and ocular GVHD with advanced imaging in our experimental eye imaging facility. Within the DFG research unit FOR2240, we focus on angiogenesis as a target for treating ocular GVHD. Within the EU consortium IT-DED3 we identify therapeutic targets in the endocannabinoid system to develop a new topical multifunctional therapy to treat inflammation, tissue damage and pain simultaneously. Promising pre-clinical data resulted in the formulation of candidate substances as topical eyedrops that will be tested soon in a first clinical trial. Using data from clinically established optical coherence tomography, we generate AI/deep-learning algorithms for automatized data analysis of large data sets. Hereby, we aim at identifying new optical biomarkers to better diagnose disease and quantify disease activity. Close collaboration with regional or international academic and industrial partners in pharmacy and medical-technology underline our translational approach.



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KEY PUBLICATIONS 2019/2020

Steven P, [...], Gehlsen U. Disease-specific expression of conjunctiva associated lymphoid tissue (CALT) in mouse models of dry eye disease and ocular allergy. **Int J Mol Sci.** 2020 **Steven P**, [...], Gehlsen U. Adverse environmental conditions are a risk factor for ocular GvHD after allogeneic hematopoietic stem cell transplantation. **Bone Marrow Transplant.** 2020 Eberwein P, [...], **Steven P.** Semifluorinated alkane eye drops in chronic ocular-graft-versus-host disease: a prospective, multicenter, noninterventional study. **Ophthalmic Res.** 2020

DETAILED INFORMATION

Dr. Gilles Storelli

Stress and Metabolism

We use the invertebrate *Drosophila* to study how cells and tissues adjust their metabolism according to environmental conditions, and how defects in this regulation can cause certain pathologies or contribute to systemic aging.



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>> RESEARCH FOCUS

Our research group is interested in a basic, but fundamental question: how do organisms maintain homeostasis, despite facing constant internal and environmental perturbations? In particular, we wish to understand how cellular metabolism is adjusted to support physiology and survival when animals face different challenges. We also wish to describe the limits of these adaptations, to understand how chronic metabolic dysfunction can impair tissue function and contribute to disease and aging.

>> PROJECTS AND AIMS

Our current projects use the invertebrate model *Drosophila melanogaster*, and are centered around the roles for metabolism in intestinal health and disease.

1. We wish to describe how metabolism is adjusted during intestinal stress, to support tissue physiology and epithelial regeneration. In particular, we are interested in how the intestine switches its metabolism in response to dysbiosis and to pathogenic infection.
2. We wish to understand how chronic metabolic dysregulation provokes disease. We recently discovered that altering select pathways of lipid metabolism in enterocytes recapitulate major hallmarks of inflammatory bowel diseases and induce a sedentary behavior in *Drosophila*. We currently investigate these connections between cellular lipid metabolism, inflammatory signaling, and the gut/brain axis.

> Understanding how metabolism is adjusted to maintain tissue and systemic homeostasis not only expands our knowledge of physiology, but can deliver key insights into the deleterious effects of aging, a complex biological process characterized by chronic metabolic dysfunction.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Storelli G, […], Thummel CS. *Drosophila* HNF4 directs a switch in lipid metabolism that supports the transition to adulthood. **Dev Cell.** 2019

Dr. Peter Tessarz

Chromatin and Aging

We are interested in understanding how chromatin architecture regulates transcription. We study this on a mechanistic level, but are increasingly fascinated on how physiological alterations such as metabolic changes and/or aging impinge on chromatin.

>> RESEARCH FOCUS

Our group is interested in how the local architecture of chromatin regulates gene expression. In particular, we are interested in how the interplay between chromatin and transcription is directly impacted by changes in cellular metabolism, as the metabolism-epigenetics axis has emerged as an important contributor to influence cellular state decisions.

> We believe that a better understanding of epigenetics and its reversible nature hold great promise for therapeutic intervention in aging and age-associated diseases.

>> PROJECTS AND AIMS

Using bone-marrow derived mesenchymal stem cells, we could show that aging redirects the flow of a central metabolite – acetyl-CoA – away from acetylation. This leads to reduced plasticity in stem cell chromatin and a loss of differentiation into bone and cartilage, which increases the risk for aged individuals to develop osteoporosis. Importantly, restoring acetyl-CoA flow not only reverted chromatin back to a »young« state, but also led to an increase in differentiation into bone and cartilage, demonstrating a tight connection between metabolism, epigenetics and cellular differentiation. In a second line of research, we addressed the increase in cellular heterogeneity with age using single-cell (epi-) genomic approaches to understand how epigenome, transcriptome and metabolism are linked on a single-cell level in the aging liver. Here, we showed that age-dependent chromatin alterations in specific regions in the liver underlie the previously observed accumulation of fat storage in these locations. Intriguingly, many of the epigenetic and metabolic changes are maintained in an in vitro model system of the aging liver (organoids). We will expand on these cellular systems to further our understanding of the metabolism-epigenetics crosstalk and to identify possibilities for epigenetic rejuvenation.



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KEY PUBLICATIONS 2019/2020

Mylonas C, **Tessarz P.** NET-prism enables RNA polymerase-dedicated transcriptional interrogation at nucleotide resolution. **RNA Biology.** 2019 ▮ Nikopoulou C, […], **Tessarz P.** Ageing and sources of transcriptional heterogeneity. **Biol Chem.** 2019

DETAILED INFORMATION

Dr. Marc Tittgemeyer

Translational Neurocircuitry

Regarding the neural circuits in support of adaptive physiological and homeostatic functions, we extend the basic research being pursued at CECAD on metabolic processes with studies on human physiology, clinical diseases and pertaining states.



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>> RESEARCH FOCUS

We investigate how the human brain represents, integrates and prioritizes internal physiological and external environmental signals to initiate adequate behavioural responses with a special focus on circuit-level models, metabolic mechanisms and aging. Thereby, our main research focus concerns the physiological pathways by which peripheral signals are communicated to the brain to interact with reward processing and motivated behaviour.

> With the aim to understand the biological pathways mediating individual differences in behavior and risk for (psycho-) pathology implicated in controlling energy homeostasis, we explore the role of reward processing and motivated behavior in obesity and aging-associated diseases.

>> PROJECTS AND AIMS

To investigate how bodily signals act on motivated behaviour requires that we link the physiology of neural circuits and peripheral sensory signals to associated expressions of behaviour. Accordingly, we apply computational modelling techniques to human neuroimaging and behavioural data with the goal to obtain quantitative in vivo markers to predict potential individual expressions of behavioural outcome. These models combine recent advances in generative modelling of human neuroimaging and behavioural data with genetic, metabolic, endocrine and immunological analyses during novel experimental perturbations of homeostasis and reward processing; hence, our aim is to provide a mechanistically interpretable prediction of individual outcome. Currently, we investigate how peripheral peptidergic modulators may bias neuronal activity in the midbrain affecting reward learning, incentivised motivation and motor control, or how individual variability in different behavioral domains could arise from individual differences in neuromodulatory mechanisms.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Edwin Thanarajah S, […], Cornely OA, […], Brüning JC, **Tittgemeyer M.** Food intake recruits orosensory andp ost-ingestive dopaminergic circuits to affect eating desire in humans. **Cell Metab.** 2019 ▮ Edwin Thanarajah S, […], Brüning JC, **Tittgemeyer M.** Modulation of midbrain neurocircuitry by intranasal insulin. **NeuroImage.** 2019 ▮ Edwin Thanarajah S, [...], Brüning JC, **Tittgemeyer M.** The role of insulin sensitivity and intranasally applied insulin on olfactory perception. **Sci Rep.** 2019 ▮ Kostic D, […], **Tittgemeyer M.** Unifying the essential concepts of biological networks: biological insights and philosophical foundations. **Phil Trans Royal Soc B.** 2020 ▮ Pelzer EA, [...], **Tittgemeyer M.** Axonal degeneration in Parkinson's disease - Basal ganglia circuitry and D2 receptor availability. **Neuroimage Clin.** 2019

Dr. Débora B. Trentini Schmidt

Protein Quality Control and Stress Response

Our research group is interested in understanding how the ribosome is used as a platform for protein quality control and stress signaling.

>> RESEARCH FOCUS

Sustaining proteome balance is a challenging task in the face of many external and endogenous stresses that accumulate during ageing. This task is carried out by a large number of intricate cellular pathways promoting correct protein folding and the elimination of defective protein species. Most protein quality control systems act post-translationally, thereby allowing new proteins to engage with the protein folding machinery prior to decisions about degradation. A notable exception is the ribosome-associated quality control (RQC) pathway, which functions in removing partially synthesized protein products from ribosomes that have stalled during translation. In recent years, it became evident that the stalled ribosome serves as a signal for multiple processes, including protein quality control, mRNA silencing and degradation, and stress signaling. Our aim is to elucidate the physiologically relevant causes of ribosome stalling, and how RQC failure is connected to loss of proteome homeostasis and neurodegeneration.

> Our aim is to elucidate the physiologically relevant causes of ribosome stalling, and how RQC failure is connected to loss of proteome homeostasis and neurodegeneration.

>> PROJECTS AND AIMS

We have previously characterized the endogenous targets of RQC-mediated degradation in human cells using advanced mass spectrometry analysis. We discovered that large multipass transmembrane proteins are particularly susceptible to RQC-mediated degradation, suggesting that problems in co-translational membrane insertion could represent a trigger for ribosome stalling. We are currently investigating the causes of ribosome stalling and RQC recruitment during the synthesis of complex transmembrane proteins at the ER. Since mutated transmembrane proteins are the cause of prominent genetic disorders, we will also study the impact of disease-associated mutations on co-translational quality control processes, thereby exploring new potential venues for therapy.



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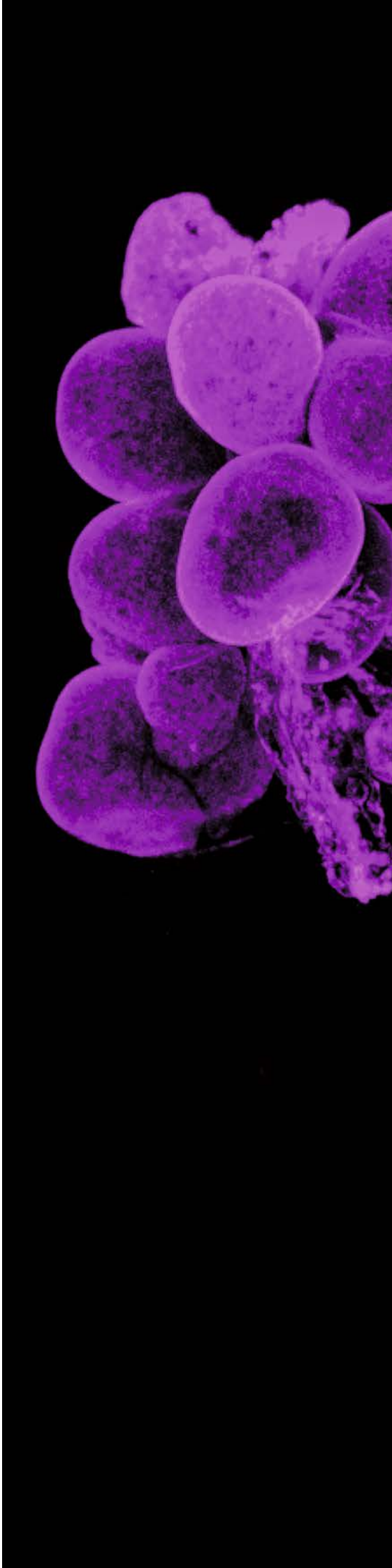
KEY PUBLICATIONS 2019/2020

Trentini DB, […], Hartl FU. Role for ribosome-associated quality control in sampling proteins for MHC class I-mediated antigen presentation. **PNAS.** 2020

DETAILED INFORMATION

Well Filtered

The human kidney is indispensable for the excretion of metabolic waste products and toxins as well as for a balanced water and acid-base balance. As part of the natural aging process, the filtration performance of the kidneys, which is primarily ensured by specialized kidney cells (podocytes), decreases continuously. In order to understand the molecular mechanisms of the filtration process, model organisms such as the fruit fly *Drosophila melanogaster* are used. *Drosophila* has podocyte-like cells, the nephrocytes, which were stained here.



Picture: Johanna Odenthal | Sample preparation: Johanna Odenthal



Prof. Dr. Achim Tresch

RNA Metabolism, Statistical and Machine Learning

The Computational Biology group has its biological focus on gene regulation, mRNA metabolism, and epigenomics. We perform integrative analyses of high dimensional biomedical omics data.



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>> RESEARCH FOCUS

1. RNA metabolism RNA and protein homeostasis are essential components of cellular integrity that deteriorate with age. Using RNA labelling techniques, we measure RNA synthesis-, export- and degradation rates at a genome-wide scale.
2. Image analysis The analysis of multifluorescent microscopic images by neural networks allows high-resolution mapping of cell interactions in cancer. 3. Spatio-temporal single cell analyses Single cell technologies quantify cellular heterogeneity within tissues. To discover cell type-specific regulatory processes, we develop statistical methods for sparse, high dimensional data with substantial measurement noise.

> Our goal is to identify RNA regulatory processes that are active in development, aging, stress response and disease. We develop statistical and machine learning methods and implement efficient algorithms for their training.

>> PROJECTS AND AIMS

3. Co-embedding of single cell ATAC and single cell RNA data in liver organoids. Single cell RNA-Seq and single cell ATAC-Seq technologies were developed to measure gene regulatory respectively chromatin accessibility in individual cells. We develop computational methods for matching scRNA-Seq data with scATAC-Seq data from cells of the same kind in silico.
4. Characterization of tumor microenvironment using multi-fluorescent microscopic imaging and neural networks Cancer immunotherapy has led to significant therapeutic progress in the treatment of formerly untreatable tumors. We aim to identify biomarkers that help to select those patients that will benefit the most from immunotherapy. This is done by investigating the tumor microenvironment, i.e. the interplay between different cell types like immune cells, stromal cells and malignant cells.
5. Quantification of RNA export in human cells
6. Evolution of Alu element transcriptio.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

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Prof. Dr. Aleksandra Trifunovic

Mitochondrial Signalling

Mitochondria not only harbour a number of essential metabolic pathways, including majority of energy production, they have also emerged as a major signalling hub for processes determining the fate of the cell under stress conditions.

>> RESEARCH FOCUS

When mitochondria experience stress or when dysfunction occurs, the organelle sends signals to the nucleus, which launches different types of adaptive responses. We aim to further understand these largely unknown mechanisms that play a central role in determining the extent of the specific defect arising from the respiratory chain deficiency.

>> PROJECTS AND AIMS

In response to disturbed mitochondrial gene expression and protein synthesis, an adaptive transcriptional response sharing a signature of the integrated stress response is activated. However, the mechanisms for regulation of the mitochondrial stress response in mammals remains elusive. We mainly focus on further understanding the intricate interplay between transcription factors regulating the mitochondrial stress response.

To ensure correct function, mitochondria have developed several mechanisms of protein quality control that mainly rely on chaperones and proteases to maintain proper folding and removal of damaged proteins. Besides quality control, mitochondrial proteases modulate and regulate many other essential functions. Our group primary focuses on the role of mitochondrial matrix protease LON and ClpXP in the regulation of proteostasis, but also in controlled proteolysis, especially in mtDNA gene expression and the maintenances of OXPHOS complexes. Notably, we identified CLPP protease as a promising target in the large group of mitochondrial diseases characterized by complex I instability.

> The primary focus of our research is to decipher the precise signalling cascade of the pathogenic mechanisms leading to mitochondrial diseases and aging, with the ultimate goal of identifying new therapeutic targets and possible treatment strategies.



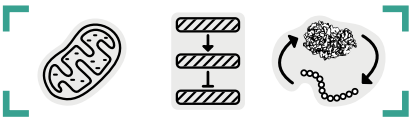
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KEY PUBLICATIONS 2019/2020

Szczepanowska K, […], Müller S, […], Riemer J, **Trifunovic A**. A salvage pathway maintains highly functional respiratory complex I. **Nat Commun.** 2020 ▮ Rumyantseva A, Motori E, **Trifunovic A.** DARS2 is indispensable for Purkinje cell survival and protects against cerebellar ataxia. **Hum Mol Genet.** 2020 ▮ Hofsetz E, […],**Trifunovic A#**, Huesgen PF#. The mouse heart mitochondria N terminome provides insights into ClpXP-mediated proteolysis. **Mol Cell Proteomics.** 2020 #joint last authorship ▮ Nemeth CL, […], **Trifunovic A**, Fatemi A. Neuronal ablation of mt-AspRS in mice induces immune pathway activation prior to severe and progressive cortical and behavioral disruption. **Exp Neurol.** 2020 ▮ Herholz M, […], **Trifunovic A.** KLF-1 orchestrates a xenobiotic detoxification program essential for longevity of mitochondrial mutants. **Nat Commun.** 2019

DETAILED INFORMATION

Prof. Dr. Mirka Uhlirova

Signaling and Gene Expression

To maintain tissue homeostasis and function in multicellular organisms, cells need to continuously respond to various cues and adjust their behaviors. They do so through tight regulation of signaling pathways activities that govern gene expression.



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>> RESEARCH FOCUS

Our lab investigates the pleiotropic functions of the stress-inducible signaling pathways and downstream mechanisms orchestrating gene expression in the context of epithelial tissues and innate immune cells. We study how diverse stress signals modulate transcription factor and spliceosome activities during development and physiology and how malfunction of transcription and splicing machinery affect epithelial and immune cell behaviors and the interactions between the two systems during aging and disease. We focus on the mechanisms that determine the cell type- and life stage-specific splicing patterns and that underlie the differential cell and transcript sensitivity to spliceosome dysfunction.

> The ability of cells to sense and interpret various stress signals to generate meaningful biological responses by coordinating transcription and pre-mRNA splicing is pivotal to the development, maintenance, and healthspan of multicellular organisms.

>> PROJECTS AND AIMS

Combining functional genetics using *Drosophila* and mouse modes with cell and molecular biology, imaging, biochemistry, and omic approaches our current projects investigate:

- The mechanisms governing the assembly and the functional plasticity of the spliceosome and the link between pre-mRNA splicing and the maintenance of the transcriptome and genome integrity.
- The stress signaling network triggered by spliceosome deregulation and how its activity contributes to loss of cell and tissue homeostasis.
- The crosstalk between epithelial tumors and innate immune cells and the roles of transcription and splicing machinery in driving malignancy.
- The cellular and molecular mechanisms governing the formation of multinucleated giant cells of macrophage origin in response to developmental and inflammatory signals.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

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Dr. Dario Riccardo Valenzano

Aging Evolution

Our lab explores the evolutionary roots of aging across species in nature and investigates how host-microbiota interactions predict and causally dictate aging dynamics.

>> RESEARCH FOCUS

The research focus of our lab is to develop a multidisciplinary approach to the study of biology of aging, which includes theoretical and computational approaches, as well as novel experimental interventions aimed at extending lifespan and delaying aging. We explore how evolution has molded genomes in long vs. short-lived species in nature and we focus on microbiome-host interactions as a new window into the biology of aging.

> We study aging from the perspective of ecologists or evolutionary biologists. We ask how the complex interactions between hosts and their microbiota unfold during the time scale of host life and we device strategies to effectively modulate the aging process.

>> PROJECTS AND AIMS

We currently study the role of effective population size, past population bottlenecks, demography and ecological constraints into shaping life history trajectories in species, with a special focus on naturally short-lived African killifishes, which we contributed to develop as an experimental model organism for aging research. We further explore genome evolution in killifish, including the events that led to genome size expansion in short-lived annual species, as well as the genetics/genomics of sexual coloration, neurodegeneration and spontaneous neoplasias. We use killifish as a model taxon to study the evolution of the IgH locus and the T cell receptor locus, as a basis to study aging of the adaptive immune system in vertebrates. Furthermore, we explore the role of the gut microbiome during aging in killifish and mice. We study the microbiome both as a predictor for host lifespan and aging, as well as a tool for targeted, individualized anti-aging interventions.



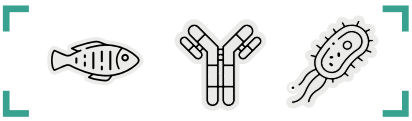
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KEY PUBLICATIONS 2019/2020

Willemsen D, Cui R, Reichard M, **Valenzano DR.** Intra-species differences in population size shape life history and genome evolution. **eLife.** 2020 ▮ Bradshaw WJ, **Valenzano DR.** Extreme genomic volatility characterises the evolution of the immunoglobulin heavy chain locus in cyprinodontiform fishes. **Pro Biol Sci.** 2020 ▮ Cui R, […], Graef M, […] **Valenzano DR.** Relaxed selection limits lifespan by increasing mutation load.. **Cell.** 2019 ▮ Ahuja G, […], Brodesser S, […], Trifunovic A, […], **Valenzano DR#**, Kurian L#. Loss of genomic integrity induced by lysosphingolipid imbalance drives ageing in the heart. **EMBO Rep.** 2019 #joint last authorship

DETAILED INFORMATION

Dr. David Vilchez

Proteostasis of Aging and Stem Cells

The aging process is only beginning to be understood. To define novel approaches that can improve the quality of life at older ages, we study immortality of pluripotent stem cells and how the communication between tissues regulates longevity.



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>> RESEARCH FOCUS

We seek to understand how protein homeostasis (proteostasis), epigenetic alterations, post-transcriptional modifications and cell non-autonomous responses modulate stem cell function, cell-fate decisions, organismal aging, and the onset of age-related diseases to uncover mechanisms of regeneration and healthspan extension. To address this ambitious task, we use an innovative approach that combines state-of-the-art proteomics, human stem cell research, iPSC-disease modelling and genetics in the model organism *C. elegans*.

> Our research has many potential outcomes and our findings can have a big impact in several fields such as proteostasis, stem cell research, cell reprogramming, cell therapy, aging and age-related diseases.

>> PROJECTS AND AIMS

In our lab, we aim to probe the requirements of proteostasis in stem cells, healthspan and regenerative potential by addressing the following questions:

1. What are the mechanisms of super-vigilant protein quality control in pluripotent stem cells?
2. Can sustained increased proteasome activity ameliorate age-associated neural stem cell exhaustion?
3. Can post-translational ubiquitin modifications extend longevity?
4. How post-transcriptionally regulatory mechanisms impinge upon cell fate decisions and organismal longevity?

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Fatima A, […], Hoppe T, Rada-Iglesias A, **Vilchez D.** The ubiquitin-conjugating enzyme UBE2K determines neurogenic potential through histone H3 in human embryonic stem cells. **Commun Biol.** 2020 ▮ Lee HJ, […], Trifunovic A, **Vilchez D.** Prostaglandin signals from adult germline stem cells delay somatic ageing of *Caenorhabditis elegans*. **Nat Metab.** 2019 ▮ Saez I, […], Denzel M, […], **Vilchez D.** The E3 ubiquitin ligase UBR5 interacts with the H/ACA ribonucleoprotein complex and regulates ribosomal RNA biogenesis in embryonic stem cells. **FEBS Letters.** 2019 ▮ Kumsta C, […], Hoppe T, **Vilchez D**, Hansen M. The autophagy receptor p62/SQST-1 promotes proteostasis and longevity in *C. elegans* by inducing autophagy. **Nat Commun.** 2019 ▮ Llamas E, […], **Vilchez D.** The intrinsic proteostasis network of stem cells. **Curr Opin Cell Biol.** 2020

Prof. Dr. Johannes Vogt

Synaptic Lipids in Brain Aging

Bioactive lipid levels underlie metabolic influences but also regulate glutamatergic transmission in the cortex. Our data suggest that synaptic lipids are drivers of cortical network hyperexcitability, a typical finding in the aging brain.

>> RESEARCH FOCUS

Cortical network excitability shifts to higher levels in the aging brain and involves synaptic lipid signaling. Already middle-aged brains display increased cortical network excitability, which was reduced to juvenile levels in animals with disrupted synaptic lipid signaling. Hyperexcitability of neuronal networks is a characteristic of premature brain aging. Our research focus is on the maladaptive role of synaptic lipid signaling and its modulation by metabolic changes in the aging and in the prematurely aging brain.

> Our aim is to assess the role of synaptic lipid signaling and its role in cortical hyperexcitability in the aging brain. It will offer greater understanding on how reduction of cortical excitability preserves brain function while its continuous increase leads to premature brain aging.

>> PROJECTS AND AIMS

Middle-aged mice (>50 weeks) display increased synaptic lipid-related cortical excitability, however, it is not known whether these changes in middle-aged brains are part of a prodromal stage or represent a transient increase in cortical excitability, which may lay the ground for other mechanisms leading to pathophysiological age-related disorders. To substantiate our findings, we will perform longitudinal studies under different metabolic conditions using transgenic mouse lines, where deletion of single elements of synaptic lipid signaling lead to either increased cortical excitability or to protection from it. Hereby, we will be able to understand effects of synaptic lipid-related cortical excitability and its metabolic modulation in the aging brain on a molecular, electrophysiological and behavioral level, and to assess genetic and pharmacological interventions, which modulate this signaling aiming to reduce age-related cortical excitability and behavioral deficits.



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KEY PUBLICATIONS 2019/2020

Fischer C, […], **Vogt J#**, Tegeder I#. Prevention of age-associated neuronal hyperexcitability with improved learning and attention upon knockout or antagonism of LPAR2. **Cell Mol Life Sci.** 2020 #joint last authorship

DETAILED INFORMATION

Dr. Silvia von Karstedt

Cell Death and Cancer

The evolution of tumors is shaped by cell divisions and cell death. Our group is exploring the mechanisms underlying constitutive cancer cell death, in particular ferroptosis - a novel type of regulated necrosis.



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>> RESEARCH FOCUS

Cancers undergo »Darwinian« selection throughout their existence which may be triggered cell intrinsically, by immune surveillance or through therapy. Recently, several cancers were described to be sensitive to ferroptosis - an oxidative type of cell death. Our lab studies mechanisms of ferroptosis execution in cancer in order to unravel basic mechanisms, immunological consequences and potential therapeutic applications in human disease.

>> PROJECTS AND AIMS

Our lab's overarching aim is to understand which cell death pathways are selected against by the immune system during cancer development. By unravelling mechanisms of selection-of-the-fittest cellular clone, we anticipate a better understanding of what these cells are selected for and thereby identify new treatment opportunities for cancer. To this end, our lab makes use of several genetically engineered mouse model systems including small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDAC). Recently, the group identified that the ferroptosis pathway remains available to kill the non-neuroendocrine (NE) subtype of SCLC while the NE SCLC subtype was selectively vulnerable to inhibition of the thioredoxin anti-oxidant pathway. In ongoing projects, our lab investigates the role of caspase 8 in selection-of-the-fittest in SCLC, NSCLC and PDAC, as well as inflammatory functions of ferroptosis in cancer.

> “Although its key pathway players are well conserved throughout phylogeny, ferroptosis has only been discovered in 2012. It seems we know the least about some of the most primitive types of cell death. But primitive is good, as it means cancers will be vulnerable to these mechanisms.

DETAILED INFORMATION

KEY PUBLICATIONS 2019/2020

Pedrera L, [...], **von Karstedt S**, García-Sáez AJ. Ferroptotic pores induce Ca 2+ fluxes and ESCRT-III activation to modulate cell death kinetics. **Cell Death and Differ.** 2020 ▮ Clemente LP, [...], **von Karstedt S.** Dynasore blocks ferroptosis through combined modulation of iron uptake and inhibition of mitochondrial respiration. **Cells.** 2020 ▮ Bebber CM, [...], **von Karstedt S.** Ferroptosis in cancer cell biology. **Cancers.** 2020 ▮ Lim JKM, [...], von **Karstedt S**, [...], Sorensen PH. Cystine/glutamate antiporter xCT (SLC7A11) facilitates oncogenic RAS transformation by preserving intracellular redox balance. **PNAS.** 2019

Prof. Dr. Henning Walczak

Cell Death and Inflammation

Cell death and inflammation are closely intertwined in the development of cancer and auto-immune diseases. Our group aims to uncover the molecular mechanisms that underlie the functional interplay between cell death and inflammation.

>> RESEARCH FOCUS

Our group has laboratories at both the University of Cologne and University College London. Research in our group focuses on the study of the functional interplay between cell death and inflammation in cancer, immunity, autoimmune and infectious diseases. A specific focus is placed on the roles played by their functional interaction in the biology and immunology of cancer and how we can best harness the newly gained knowledge on these functional interactions therapeutically.

> The aim of our research is to combine fundamental, preclinical and translational research to gain a deep understanding of the development of severe diseases such as cancer and auto-immunity with the ultimate goal of developing highly effective therapies for such diseases.

>> PROJECTS AND AIMS

The lab is particularly interested in unraveling the mechanisms on how different death receptor-ligand systems such as the TNF, Fas (CD95) and TRAIL systems are regulated and how they impact cell survival, inflammation and immunity in health and disease. Our research aims are to develop novel therapies by specifically inducing or preventing cell death and/or inflammation. A specific means to achieve this is by therapeutically directing the type of death induced to convert cancer-related inflammation from being immune-regulatory to enabling the immune system to recognize and kill cancer cells. Based on a scientific rationale recently developed by Professor Walczak, a biotherapeutic inhibitor of the apoptosis-inducing ligand FasL (CD95L) is currently in phase II clinical testing as a potential novel drug for the treatment of severe COVID-19.



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KEY PUBLICATIONS 2019/2020

▮ von Karstedt S, **Walczak H.** An unexpected turn of fortune: targeting TRAIL-Rs in KRAS-driven cancer. **Cell Death Discov.** 2020. ▮ Annibaldi A, **Walczak H.** Death Receptors and Their Ligands in Inflammatory Disease and Cancer. **Cold Spring Harb Perspect Biol.** 2020 ▮ Müller I, […], **Walczak H**, […], Kulms D. Cancer cells employ nuclear caspase-8 to overcome the p53-dependent G2/M checkpoint through cleavage of USP28. **Molecular Cell.** 2020 ▮ Peltzer N, **Walczak H.** Cell death and inflammation - a vital but dangerous liaison-**Trends Immunol.** 2019 ▮ Krishna-Subramanian S, […], **Walczak H**, […], Pasparakis M, Kondylis V. RIPK1 and death receptor signaling drive biliary damage and early liver tumorigenesis in mice with chronic hepatobiliary injury. **Cell Death Differ.** 2019

DETAILED INFORMATION

Prof. Dr. Sara A. Wickström

Stem Cell Dynamics and Aging

We study how epithelial tissues are formed, maintained, and regenerated through mechanisms of stem cell self-organization and how these processes are compromised during aging.



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>> RESEARCH FOCUS

We address a set of fundamental questions in the fields of aging and regeneration: what determines stemness within tissues? How can this phenotype be dynamically adapted to the changing need of an organ/organism? How are stem cell properties harnessed by malignant transformation and compromised during aging? To answer these questions, we study how single cell states are established and maintained by mechanochemical signals and how single cell dynamics are coupled to tissue-scale dynamics and architecture. Uncovering these regulatory principles will facilitate development of stem cell therapies and effective treatments against cancers.

> We use a combination of biology, physics and engineering to understand how epithelial tissues are generated and maintained through coordinated actions of stem cells and their tissue environment.

>> PROJECTS AND AIMS

As self-renewing organs maintained by distinct stem populations and with clinically challenging cancers, stratified epithelia of the skin and oral cavities, and the simple epithelium of the intestine, represent outstanding, clinically relevant paradigms to address the fundamental questions of stem cell fate regulation, tissue dynamics, aging and cancer. Our current research focuses **on three main research areas that bridge scales from tissue- to molecule-level processes: 1. mechanisms of epithelial morphogenesis and maintenance; 2. universal and cell state-specific principles of mechanochemical regulation of cell fate and reprogramming; and 3. mechanical regulation of genome architecture, transcription, and genome integrity.** These areas are pursued by a highly interdisciplinary research strategy that builds on mouse genetics but also human patient material, combining scale-bridging tools of bioengineering and biophysics, machine learning-based quantitative imaging, genome-wide analyses, and computational modeling.

DETAILED INFORMATION

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Kim CS, […], Denzel M, Eming SA, **Wickström SA.** Glutamine metabolism controls stem cell fate reversibility and long-term maintenance in the hair follicle. **Cell Metab.** 2020 ▮ Nava MM, […], Niessen CM, […], **Wickström SA**. Heterochromatin-driven nuclear softening protects the genome against mechanical stress-induced damage. **Cell.** 2020 ▮ Dekoninck C, […], **Wickström SA**, […], Blanpain C. Defining the design principles of skin epidermis postnatal growth. **Cell.** 2020 ▮ Punovuori K, **Wickström SA.** How cancer invasion takes shape. **Nature.** 2020 ▮ Ou HL, […], **Wickström SA**, Schumacher B. Somatic niche cells regulate the CEP-1/p53-mediated DNA damage response in primordial germ cells. **Dev Cell.** 2019

Prof. Dr. Rudolf J. Wiesner

mtDNA Mutations in Aging

All cells contain thousands of copies of mitochondrial DNA (mtDNA). Mutations of mtDNA accumulate during aging and contribute significantly to aging-related diseases in the heart, muscle, skin and brain.

>> RESEARCH FOCUS

In order to understand how mtDNA mutations cause aging-related diseases and how cells attempt to prevent an extensive accumulation, we have developed a conditional transgenic mouse model showing an accelerated mutation load in any cell type of our choice. In the past, we found that very few cardiomyocytes with mitochondrial dysfunction embedded in normal tissue are sufficient to cause severe cardiac arrhythmia. On the other hand, a similar mosaic in muscle neither leads to motor impairment nor to sarcopenia (aging-related muscle loss), while mtDNA mutations in muscle stem cells severely impair the capacity for muscle regeneration. Surprisingly, dopaminergic neurons, which degenerate in Parkinson`s disease, show a striking capacity to counteract the accumulation of mtDNA mutations.

> Mutations of the small mitochondrial genome accumulate during aging and cause aging-related diseases.
> We try to understand how cellular quality control mechanisms counterbalance the accumulation of these mutations to keep cells healthy.



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>> PROJECTS AND AIMS

Our current projects aim to understand the molecular mechanisms which enable cells to avoid an extensive burden of mtDNA mutations. We manipulate mitochondrial dynamics, i.e. fusion and fission of the network, in the heart of mice with enhanced mutagenesis in order to further accelerate or slow down the development of cardiac arrhythmia, respectively. We also are currently looking at the question of how tissue stem cells, focusing on muscle satellite cells and epidermal stem cells, respectively, control the accumulation of such mutations in order to remain functional throughout the duration of a lifetime. Finally, we aim to decipher new specific pathways removing mutated mtDNA from the mitochondrial network without affecting the total mitochondrial pool.



KEY PUBLICATIONS 2019/2020

Ricke KM, [...], Schauss A, [...], Bergami M, **Wiesner RJ.** Mitochondrial dysfunction combined with high calcium load leads to impaired antioxidant defense underlying the selective loss of nigral dopaminergic neurons. **J Neurosci.** 2020 Haumann S, [...], Kashkar H, [...], **Wiesner RJ.** Mitochondrial DNA mutations induce mitochondrial biogenesis and increase the tumorigenic potential of Hodgkin and Reed-Sternberg cells. **Carcinogenesis.** 2020 Paß T, [...], **Wiesner RJ**, Ricke KM. The impact of mitochondrial dysfunction on dopaminergic neurons in the olfactory bulb and odor detection. **Mol Neurobiol.** 2020 Oexner RR, [...], Schauss A, [...], **Wiesner RJ.** Extraocular muscle reveals selective vulnerability of type IIB fibers to respiratory chain defects induced by mitochondrial DNA alterations. **Invest Ophthalmol Vis Sci.** 2020 Holzer T, [...], Kashkar H, [...], **Wiesner RJ**, Brachvogel B. Respiratory chain inactivation links cartilage-mediated growth retardation to mitochondrial diseases. **J Cell Biol.** 2019

DETAILED INFORMATION

Prof. Dr. Andreas Wodarz

Cell Polarity and Stem Cells

The general research interest in our group is to unravel the molecular mechanisms that control cell polarity in different cell types. In this context we study epithelial morphogenesis and the regulation of asymmetric division of stem cells.



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>> RESEARCH FOCUS

Cell polarity is a key feature of epithelia and stem cells. Morphogenesis of epithelial tissues requires cell polarity to allow cell shape changes driven by local activation of actomyosin contractility, for instance, apical constriction or junctional remodeling during convergent extension movements. Stem cells need to be polarized prior to asymmetric cell division, resulting in daughter cells with different fates. Our research is focused on the functional analysis of factors that control cell polarity and cell shape changes. We pursue our research in the model organism *Drosophila*, because it provides the most advanced toolkit for genetics, imaging and genomics.

> I am convinced that basic research in model organisms is extremely important to understand the normal function of our body. This in turn is crucial for understanding the cellular and molecular basis of diseases and what we can do to treat them.

>> PROJECTS AND AIMS

We study the regulation of actomyosin contractility in epithelia. The junction-associated protein Smash regulates junctional tension and interacts with the polarity regulator Baz/Par3 and with Rho kinase, the key activator of non-muscle myosin II. We investigate how Smash modulates Rho kinase activity and aim to unravel the Smash interactome. A second project deals with the Tip60 chromatin remodeling complex in the regulation of stem cell maintenance. We found that functional impairment of the Tip60 complex leads to premature differentiation of stem cells in the brain and the larval gut. We have mapped the target genes of the Tip60 complex by targeted DamID and are now pursuing the detailed analysis of the Tip60 knockdown phenotype by single cell RNAseq to identify the genes required for stem cell maintenance and proper differentiation of their progeny.

DETAILED INFORMATION

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- Linnemannstöns K, […], **Wodarz A**, Gross J C. Ykt6-dependent endosomal recycling is required for Wnt secretion in the *Drosophila* wing epithelium. **Development.** 2020
- Witte L, Linnemannstöns K, Schmidt K, Honemann-Capito M, Grawe F, **Wodarz A**, Gross JC. Kinesin motor Klp98A mediates apical to basal Wg transport. **Development.** 2020

PD Dr. F. Thomas Wunderlich

Obesity and cancer

Metabolic low-grade inflammation in obesity results in metabolic and oncogenic disorders. Our aim is to decipher the missing link between obesity-induced inflammation and cancer progression to ultimately develop strategies for therapeutic approaches.

>> RESEARCH FOCUS

Obesity is a current health burden in Western countries that creates a predisposition to numerous disorders such as T2DM and cancer. Our group aims to dissect the role of the obesity-associated low-grade inflammation in cancer, especially in hepatocellular and colorectal carcinoma. To this end, we are using self-generated sophisticated mouse models enabling restriction of transgene expression to a specific cell type or even to different organs. We have combined Cre/loxP with Dre/rox technologies to achieve these goals.

> We aim to dissect the link between obesity-induced inflammation and cancer by using sophisticated transgenic mice models.



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>> PROJECTS AND AIMS

IL-6 resistance and hepatocellular carcinoma One cytokine that is increased in obesity is IL-6. However, the elevated circulating IL-6 levels in obesity lead to acute hepatic IL-6 unresponsiveness due to basal increased SOCS3, the negative regulator of IL-6 signaling. Thus, we term this condition as hepatic IL-6 resistance. We have developed transgenic mouse models that mimic hepatic IL-6 resistance and are currently investigating those in different types of liver cancer. **Inflammatory signaling in the progression from NASH to HCC** Obesity leads to the ectopic accumulation of fat in the liver known as NAFLD that can progress to NASH and HCC upon inflammatory signaling. We are determining the cell type specific function of inflammatory mediators in metabolic NASH, fibrotic NASH and HCC models. **Gut leakiness and colorectal cancer** The obesity-induced inflammation may originate from a leaky gut that enables bacterial components to reach the liver to induce inflammation that in turn impacts on systemic insulin sensitivity. We are working on intestinal mechanisms that strengthen the intestinal barrier to circumvent leakage and obesity-associated disorders.



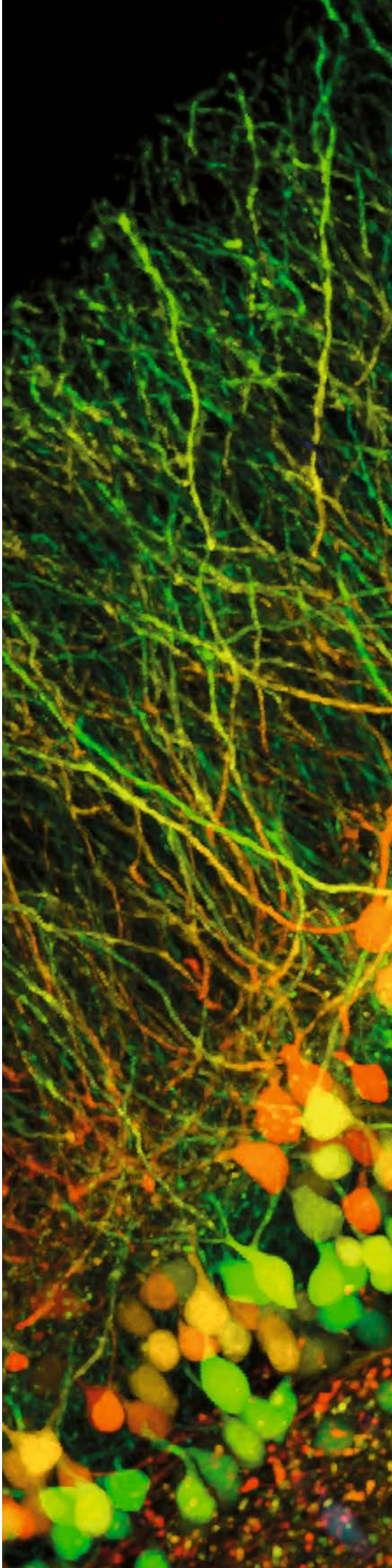
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DETAILED INFORMATION

Orderly Chaos

Many age-related diseases such as Alzheimer or Parkinson have their origin in the brain. The death of certain nerve cells leads to a disturbance of the complex neurophysiological processes and thus to neurodegenerative diseases. Genetically stained nerve cells, which are found billions of times in the brain, are shown here. Their interaction enables conscious control of the body and mental performance.



Picture: Dr. Christian Jüngst | Sample preparation: Bergami lab



International Faculty

The University of Cologne and CECAD are strongly committed to promote internationalization. The International Faculty Program is a cornerstone of the internationalization strategy of the University's four Key Profile Areas (KPA) including KPA1 on Aging-associated Diseases centered around CECAD.

International Faculty Program

The program aims at attracting academic leaders from around the globe who are closely collaborating with scientists at the University of Cologne. Through this program, each KPA can expand its international visibility and competitiveness. The program also contributes to the internationalization of teaching especially at the post-graduate level and is steered by the Prorector for Academic Career, Diversity and International Affairs in close collaboration with the KPAs.CECAD has attracted world leaders in the field of aging research as KPAI international faculty members that strengthen CECAD's collaborative networks in the field of mitochondria, metabolism, genome stability, skin aging and stem cell dynamics.



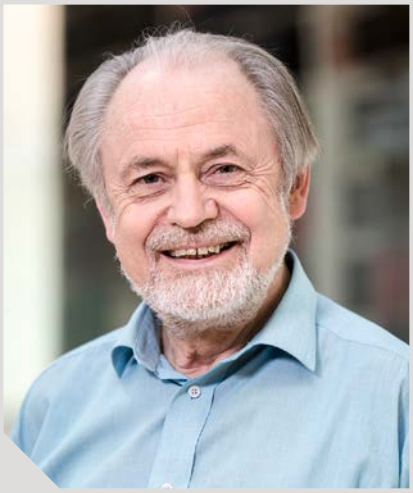


PROF. DR. TAMAS HORVATH

Full Member

International Faculty
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PROF. DR. JAN H.J. HOEIJMAKERS

Full Member

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PROF. DR. SARA A. WICKSTRÖM

Full Member

International Faculty
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KPA I International Faculty members:

Prof. Dr. Ulrich Brandt is a professor for Mitochondrial Molecular Medicine at the Radboud University Medical Center in Nijmegen. He also holds an adjunct professorship for Biochemistry at the Goethe University in Frankfurt am Main. He is actively involved in CRC1218 on mitochondrial regulation of cellular function.

Prof. Dr. Andrew Dillin holds a professorship for genetics and works at the Helen Wills Neuroscience Institute of the University of Berkeley. Dillin is an international leader in the genetics of aging and has generated strong synergy within CECAD on the role of neurological control of metabolism and aging.

Prof. Dr. Jan H. J. Hoeijmakers of the Erasmus University Rotterdam and the Princess Maxima Center for Pediatric Oncology Utrecht runs a lab at the CECAD research center since 2017. He is a full CECAD member and project leader in the CRC 829 on skin homeostasis. (p. 48) Hoeijmakers has been a world leader in the DNA repair field for over three decades and closely collaborates in Cologne on understanding how genome instability drives the aging process.

Prof. Dr. Sara Wickström is the newest International Faculty Member. After ten years of research on Stem Cell Dynamics and Aging (p. 98) in Cologne at MPI AGE, Sara took up a professorship of Cell and Developmental Biology at the Faculty of Medicine and Helsinki Institute for Life Science (HiLIFE) in Helsinki. Her seminal contributions on the role of mechanical stress in stem cell function were forged by a highly interactive research program at CECAD.

Prof. Dr. Tamas Horvarth, a renowned expert on neuronal network regulation of energy metabolism, neurodegeneration and reproduction, of Yale University School of Medicine served as an International Faculty Member and full CECAD PI from 2019 to 2020 (p. 50). He has long standing collaborations with CECAD groups at the MPI Metabolism on the role of the brain-body axis in metabolic syndrome and aging.

DETAILED INFORMATION

Recruitment

CECAD strives to constantly expand its high level of expertise in aging research through the recruitment of excellent, outstanding scientists for its research cluster. With the new funding period, two internationally recognized scientists were recruited for the Cologne campus.

As of the summer of 2021, Filipe Cabreiro will fill the W3 professorship for »Microbiota in Aging«, while Christian Frezza, Alexander von Humboldt Professorship awardee, will take up the W3 professorship »Metabolomics in Aging« in the fall of 2021.

Prof. Dr. Filipe Cabreiro - Awakening Drugs with Bugs

Filipe Cabreiro is a scientist of international recognition and one of the leading experts in the field of drugs and microbiota. For his important contributions to science, he has received a prestigious EMBO Young Investigator award and a Sir Henry Dale Fellowship from the Royal Society and Wellcome Trust. Filipe trained as a biochemist at Paris Diderot University (Paris VII) where he received his doctoral degree in 2008, on understanding the biological mechanisms underlying molecular stress protection, metabolism and aging. He then moved to the UK for his post-doctoral studies at the University College London. His seminal work led to a paradigm shift in the use of *C. elegans* for studying host-microbe-drug interactions in the context of aging. He set up his independent lab at University College London in 2013, taking up a Readership and MRC Investigator position in 2018 at Imperial College London.

> “Continuing my research at the outstanding CECAD Institute for Aging Research, our lab will aim at understanding the gut microbial action of drugs during aging in a wide range of model organisms, including mice. In the future, this will allow us to develop strategies targeting the microbiota and to treat metabolic disease during aging in humans.



PROF. DR. FILIPE CABREIRO
Institute for Genetics
Microbiota in Aging
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The Cabreiro lab developed a unique experimental pipeline with the potential to unravel drug-diet-microbe-host interactions. By combining classical and advanced microbial genetics, high-throughput genomic and chemical approaches, targeted metabolomics and computational approaches, the Cabreiro lab studies both host and microbial physiology in very fine mechanistic detail. Over the years, the Cabreiro lab has made fundamental contributions to this growing field, by identifying signaling and biochemical pathways in bacteria regulating metabolite availability with the capacity to regulate host physiology and aging.



Prof. Dr. Christian Frezza – The Metabolic Cues of Human Diseases

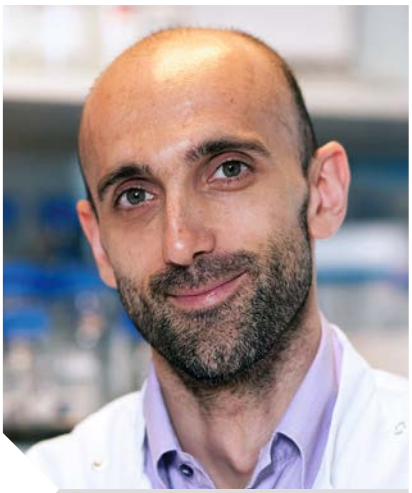
Christian Frezza is an internationally recognized scientist and leading expert in the field of cancer metabolism and metabolomics. He is the recipient of the 'Alexander von Humboldt Professorship – International Award for Research in Germany' award by the Medical Faculty and the Cluster of Excellence for Aging Research CECAD at the University of Cologne.

Christian started his scientific career in his home country Italy, receiving his doctorate in Padova in 2008. An EMBO long-term grant from the European Molecular Biology Organization brought him to the Cancer Research UK Beatson Institute for Cancer Research in Glasgow, Scotland. In 2012, he moved to Cambridge to conduct research as a program leader in the field of Cancer Metabolism at the MRC Cancer Unit.

> I am honored to have been selected as a recipient of the Alexander von Humboldt Professorship. This professorship will enable me to consolidate and expand our work on metabolism in a vibrant environment at CECAD and the University of Cologne, and to build new and exciting collaborations.

The Frezza lab investigates the role of dysregulated mitochondrial metabolism in cancer using a combination of computational, metabolomics, and biochemical approaches. Of note, the Frezza lab provided a comprehensive investigation of the metabolic changes that occur in cancer cells and the first functional link between metabolic changes and epigenetic reprogramming to drive epithelial-to-mesenchymal transition, an event critical for cancer initiation and metastasis. In addition, the Frezza lab contributed to the elucidation of the role of succinate in inflammation and ischaemia reperfusion injury.

The award of the Alexander von Humboldt Professorship to and appointment of Christian Frezza is a huge success for the CECAD Cologne campus. Christian Frezza is an outstanding scientist who is internationally renowned for harnessing metabolomics, i.e. the analyses of hundreds of small molecule metabolites in a cell, to discover novel mechanisms of disease of human pathologies, in particular in cancer and inflammation.



PROF. DR. CHRISTIAN FREZZA

Faculty of Medicine

Metabolomics in Aging

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@FrezzaLab

COMPREHENSIVE SUPPORT FOR STANDARD AND INDIVIDUALLY TAILORED ANALYSES

Bioinformatics Facility

We develop and deploy reproducible high-throughput analysis pipelines using modern software tools and best practices for analysis of common data types, as well as provide integrative analysis of diverse datasets to answer biological questions.

The facility is transitioning to the use of new pipeline management tools based on 'nextflow' in conjunction with our colleagues at the Regional Computing Center of the University of Cologne (RRZK) who support our hardware infrastructure. We will be making use of and participating in efforts such as 'nf-core' to provide high-quality reproducible bioinformatic pipelines for implementing best practices, thus allowing us to contribute back to the community and increase visibility to outside experts.

>> SERVICES

We provide consultation on the design of experiments which will generate large datasets. We also support the analysis of these datasets, whether as standard designs, such as RNA-seq comparing two groups, or a complex integrative multi-omic series of experiments.

We aim to support researchers at all levels of proficiency with bioinformatic methods, from the novice to the expert. We can provide consultation and support for complex, custom or interactive data visualisations, for publication or exploratory purposes. We provide similar support for the development and distribution of bioinformatic software tools based on new research to maximise the reach and impact of novel analytic methods.

Assisting researchers to frame their questions in the language of modern data analysis techniques, and letting them experiment with such techniques via interactive tools, will ultimately help towards supporting better use of the detailed and diverse datasets currently being generated.



PROF. DR. ALEXANDER DILTHEY

Head of Bioinformatics Facility (2020)

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1001
1010

DETAILED INFORMATION

We love helping bench scientists turn their data into biological understanding.



PROF. DR. ANDREAS BEYER

Acting Head of Bioinformatics Facility

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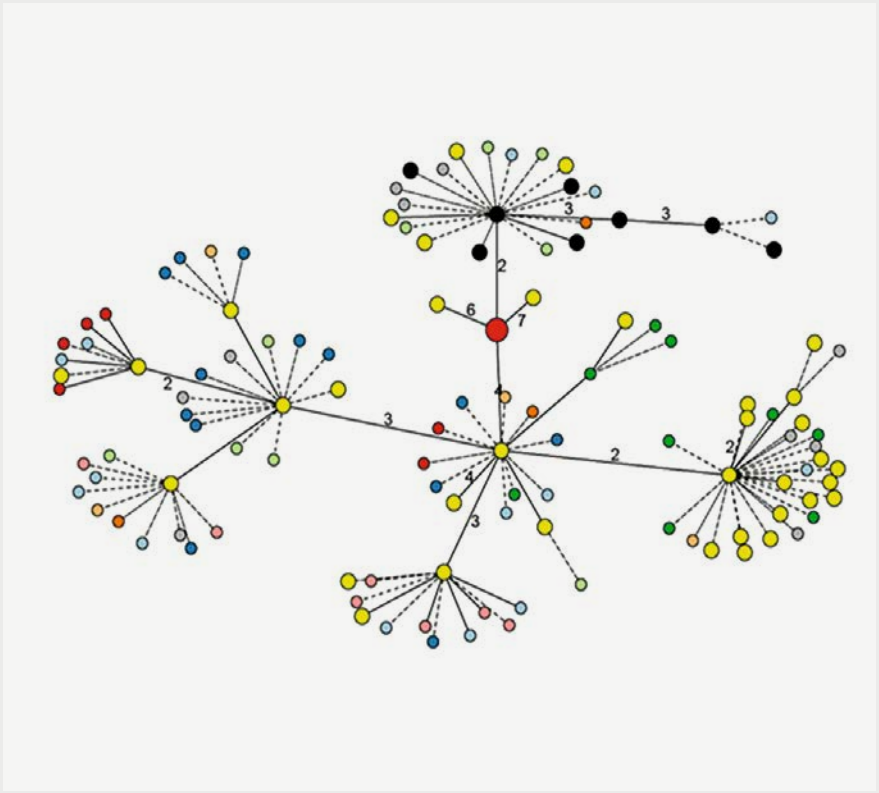


Fig. 1

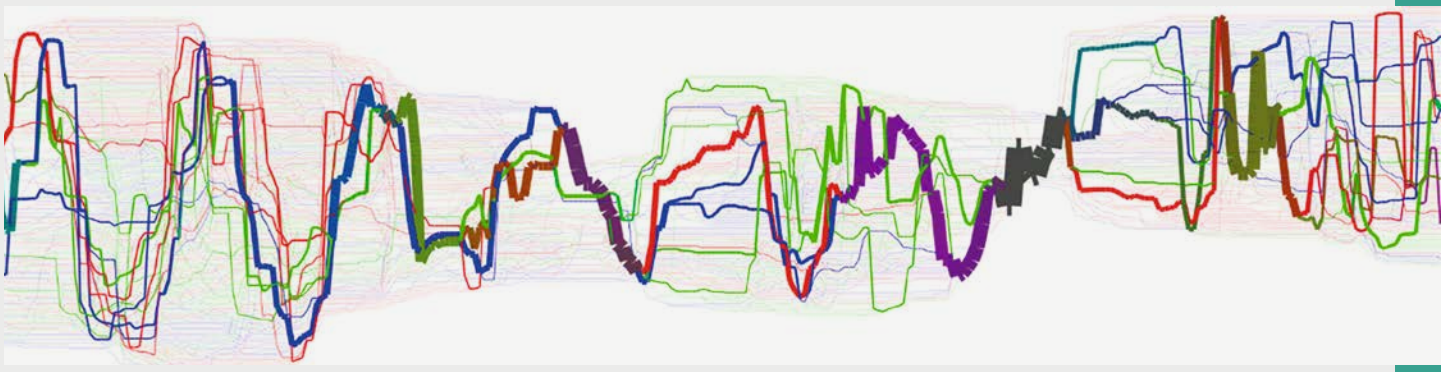


Fig. 2

Fig. 1: Minimum Spanning Tree visualization of the genetic structure of the 2020 SARS-CoV-2 superspreading outbreak in Heinsberg.

Fig. 2: Sequence homology and allele haplotype frequencies within the Human Leukocyte Antigen genes HLA-A, -B, and -C.

MAKE AGING VISIBLE AT ALL STAGES

CECAD Imaging Facility

Over the last two years, we have improved our techniques in superresolution and its live-cell compatibility in light microscopy. In electron microscopy, we achieved a better preservation of ultrastructure through high-pressure freezing.

We are supporting our researchers during the entire process of their light and electron microscopy projects, starting with a project discussion and experiment design. We also help our users in image analysis and set up OMERO as dedicated imaging data platform.

>> SERVICES

For light microscopy projects, users receive training on the respective microscopes followed by special imaging techniques. These techniques range from live cell to intravital imaging, second harmonic generation imaging, fluorescence lifetime imaging, different kinds of superresolution imaging, and more. At present, we are improving our superresolution approaches towards better live-cell compatibility (see Fig. 1).

In electron microscopy, we provide full-service options, including sample preparation and image acquisition, with the option of EM training for dedicated EM users. Within the last two years, we expanded our TEM acquisition towards tile-scanning and electron tomography by setting up the serialEM software and a post-processing workflow using IMOD. We also implemented high-pressure freezing into the sample preparation, allowing preservation of the specimen in a near to native state (see Fig. 2). Different CLEM (Correlative Light and Electron Microscopy) approaches, including pre-embedding techniques, can now be offered to the researchers. In the future, we will move towards volume EM by cutting and registering serial sections as well as serial tomograms.

In addition, our services include support in data analysis as well as training on data analysis software that is either open-source software or that can be used remotely on our data analysis station. Most recently, we upgraded our Imaris license with a cell module that allows the analysis and interconnections between organelles in 3D. With Omero (OME), we set up a data storage system dedicated to image data handling in close collaboration with the local computational center (RRZK). Omero was recently complemented by a new software purchase (Pathviewer, Glencoe) to improve the visualization and annotation of histology data. Our future goal is the implementation of a MetaDataEditor and DeepLearning algorithms.



DR. ASTRID SCHAUSS

Head of CECAD Imaging Facility

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DETAILED INFORMATION

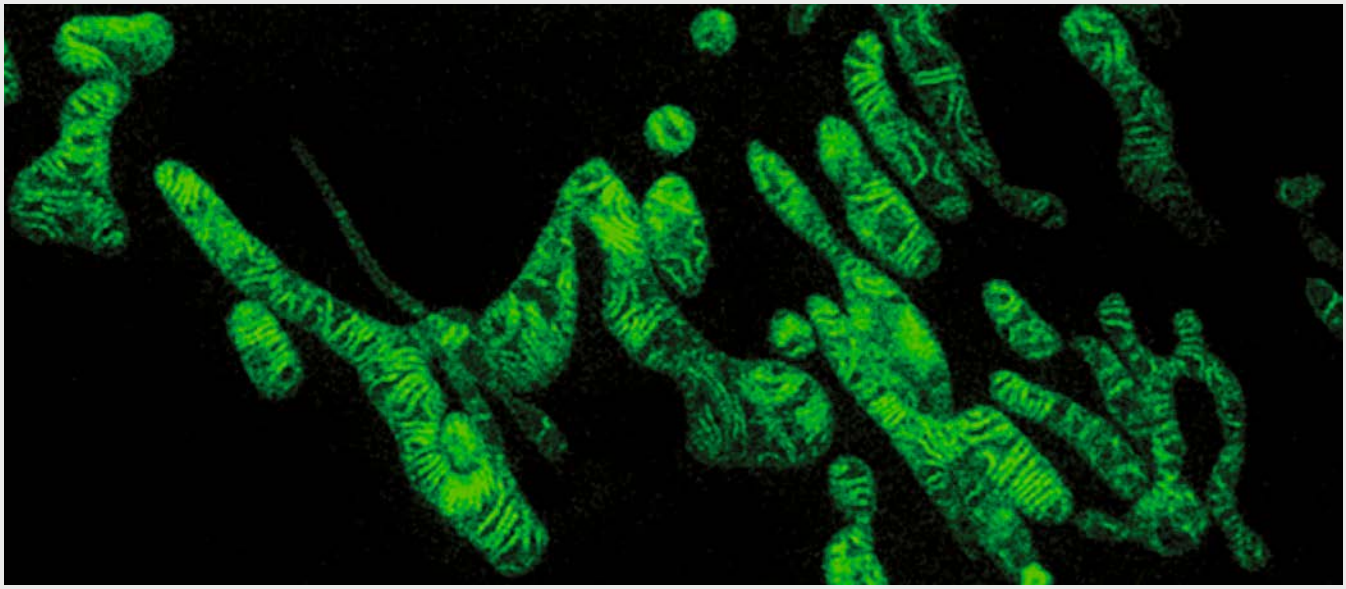


Fig. 1

>> THE CEAD IMAGING TEAM

Dr. Astrid Schauss	Head of CECAD Imaging	Light and Electron Microscopy, project support, administration, teaching
Dr. Christian Jüngst	Light Microscopist	LM introductions, big variety of LM techniques including superresolution, FLIM, intravital imaging, new techniques
Dr. Felix Babatz	Electron Microscopist	TEM, tomography, CLEM, HPF, new techniques
Peter Zentis	Image Analyst	FiJi, Omero, Cellprofiler, custom-tailored data analysis
Veronika Wulff	Lab organization, TA	LMD, Evos, Histoscanner, cell culture
Beatrix Martiny	EM-TA	TEM, standard sample preparation, immunogold
Janine Klask	EM-TA	TEM, standard sample preparation, tilescanning
Katrin Seidel	EM-TA (CRC1218)	TEM, serial section, CLEM, tomography

Fig. 1: To achieve live-cell compatible superresolution, the membrane-permeable dye silicon rhodamine (SiR) is used. Shown are HeLa cells, transfected with Cox8A-SiR, highlighting mitochondrial cristae in living cells.

Fig. 2: High-pressure freezing in combination with freeze substitution allows the fixation and embedding of EM samples in a close-to-native state without membrane distortions. Shown is a TEM image of *C.elegans*.

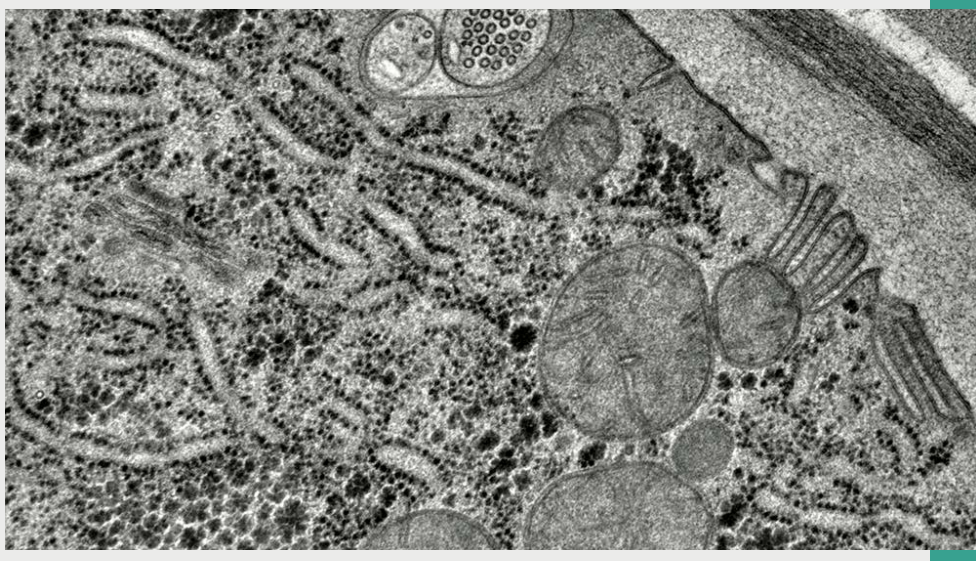


Fig. 2

APPLIED GENETICS – PROVIDING SERVICES FOR TRANSLATIONAL RESEARCH

in vivo Research Facility (ivRF)

CECAD's in vivo Research Facility (ivRF) is an animal facility with state-of-the-art technology, designed and operated in compliance with the latest scientific findings, legislation, ergonomics, and, especially, requirements on animal welfare.

Five separate, individually operated barriers allow maximum flexibility for the wide variety of demands made by the research groups. In addition, the ivRF offers an experimental platform for establishing new mouse models, as well as an efficient means of long-term cryopreservation. The ivRF meets all the legal requirements for the protection of animals used for scientific purposes and consistently adheres to the three Rs principle of animal welfare: reduction, refinement, and replacement.

>> SERVICES

The ivRF is built on two pillars. The first encompasses the Animal Facility, managed by Paul Friedemann Pohlig. This facility is a large superior centralized unit meeting the latest technical, ergonomic, scientific and animal welfare demands and requirements. Individual barriers are dedicated to specific experimental purposes, including needs for higher biosecurity and genetic engineering safety levels. Researchers are supported by scientific management consultation in areas such as colony management, experimental design, animal welfare issues and mouse genetics. Our team of highly educated Laboratory Animal Technicians provides a wide range of services. Quality is assured through continuous professional development. We adhere to the standards of the 3Rs principles of animal welfare: reduction, refinement, and replacement. In the near future, we will expand our portfolio by including facilities for gnotobiotic mouse holding and housing of naked mole-rats.

The second pillar of the ivRF is a Transgenic Core Unit (TCU) one of the leading of its kind in Germany, managed by Dr. Simon Tröder..

The TCU provides a transgenic platform for Assisted Reproduction Technologies and for establishing genetically engineered mouse models in accordance with the latest scientific knowledge, most importantly, CRISPR/Cas9-mediated genome editing. We have established a standardized workflow for cloning-free CRISPR/Cas9-mediated mouse mutagenesis, which enables us to routinely generate mouse models harboring the desired mutation on a chosen genetic background with high efficiency. On average, we are currently establishing two mutant mouse lines every week with frequencies of up to 65% for large knock-ins, up to 90% for specific point mutations, and up to 100% for knock-outs in the resulting animals. Consistent research ensures the constant improvement of efficiency and specificity of CRISPR/Cas9-mediated mutagenesis and the swift implementation of new techniques in this rapidly growing field.

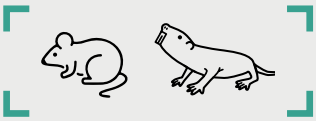


PROF. DR. BRANKO ZEVNIK

Head of ivRF

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(coming 2021)

DETAILED INFORMATION

Successful biological and biomedical research relies on the availability of suitable experimental and therapy related animal models.



DR. YLVA ILLING

Scientific Manager of ivRF

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CRISPR / CAS9 MODE OF ACTION

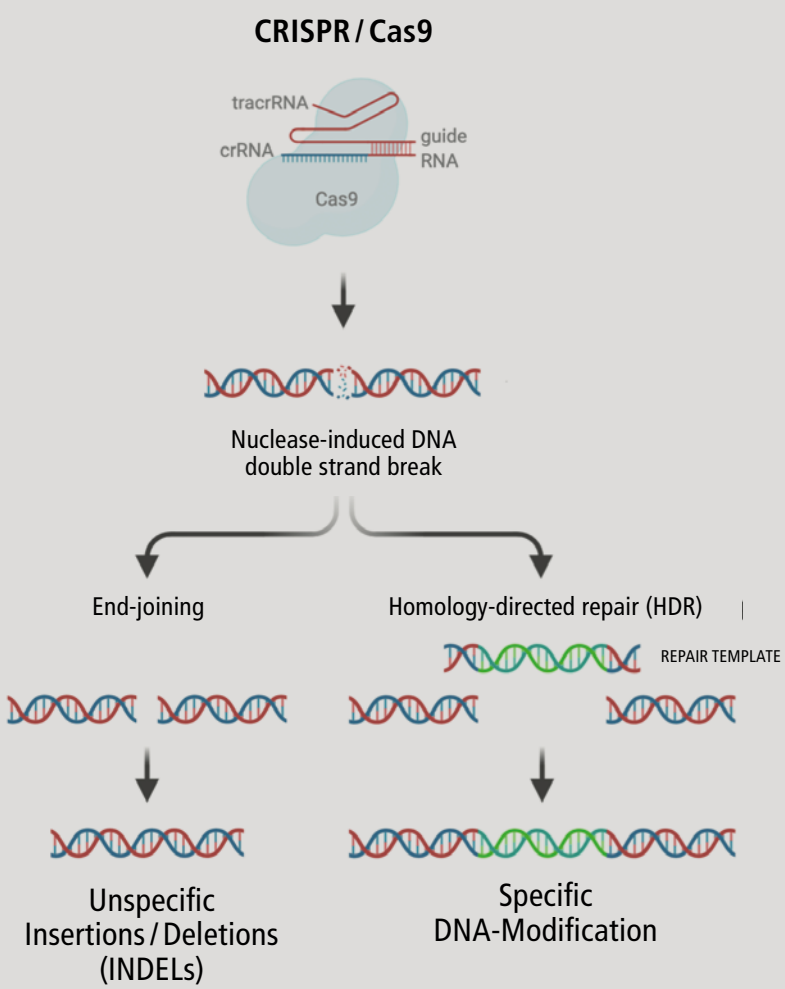




Fig. 1



Fig. 2

Fig. 1: Genetically engineered mouse models – C57BL/6 N coat color mutants

Fig. 2: Storage of cryopreserved embryos of genetically engineered mice

ON THE TRAIL OF METABOLISM

Lipidomics / Metabolomics Facility

The Lipidomics/Metabolomics Facility offers a comprehensive service for the analysis of lipids and polar/ionic metabolites in biological samples using state-of-the-art chromatographic and mass spectrometric (MS) techniques.

The service covers the entire workflow from sample preparation and MS measurement of the relevant metabolites to processing and analysis of the raw data obtained. Assistance with experimental design and data interpretation is also provided.

>> SERVICES

The CECAD Lipidomics/Metabolomics Facility houses three new-generation mass spectrometers (Q Exactive HF, QTRAP 6500, TripleTOF 6600), including different UHPLC systems and a chip-based infusion system for nano-electrospray ionization (TriVersa NanoMate). A comprehensive software package facilitates the processing and analysis of collected raw metabolomics data sets.

In recent years, the Facility has focused on targeted quantifications of pre-defined sets of metabolites. This has allowed the Facility to contribute to over 20 publications in 2019 and 2020. The Facility is experienced in analyzing small metabolites from various model organisms and is able to handle a wide range of sample matrices such as cells, tissues, and isolated cell organelles (e.g. mitochondria). The set of small biological molecules for which quantitative methods are available at the Facility includes all common lipid classes as well as polar metabolites, such as amino acids, acyl carnitines, nucleotides and metabolites of the central carbon metabolism.

The Facility plans to expand its service to unbiased non-targeted metabolomics approaches to get a global overview of the metabolome by detecting as many metabolites as possible in the sample, thereby covering a broad range of metabolites from multiple metabolic pathways. In addition, the Facility will establish isotope tracing workflows to gain insight into intracellular metabolic rates (fluxes) within specific metabolic pathways.

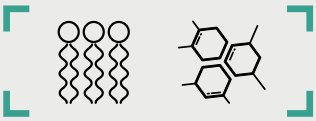


DR. SUSANNE BRODESSER

Head of Lipidomics / Metabolomics Facility

Specialized in mass spectrometric analysis of small molecules

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DETAILED INFORMATION

Metabolomics enables insight into physiological functions of metabolites and investigation of molecular mechanisms of health impairment. New analytical technologies allow the determination of even minor changes in metabolic pathways.

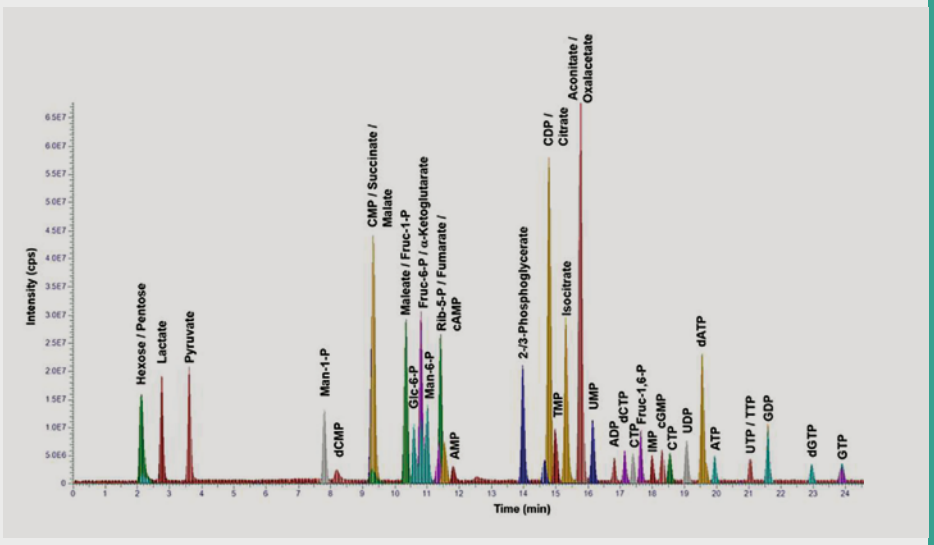


Fig. 1



Fig. 2



Fig. 3

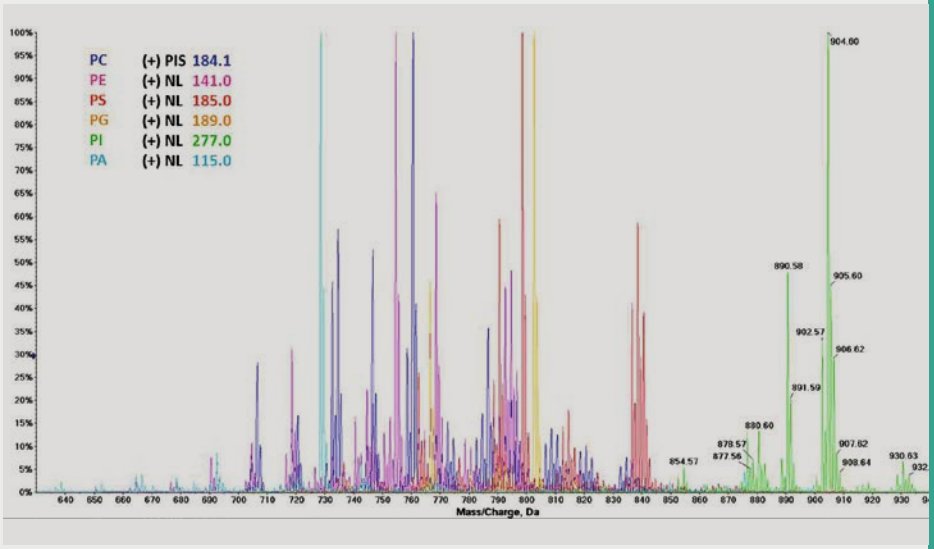


Fig. 4

Fig. 1: LC/MS separation of nucleotides and of intermediates of the central carbon metabolism: Metabolites are separated by Anion-Exchange Chromatography and detected using High-Resolution Mass Spectrometry (IC-HRMS).

Fig. 2: QTRAP 6500 (SCIEX) and TriVersa NanoMate System (Advion)

Fig. 3: TripleTOF 6600 System (SCIEX)

Fig. 4: Shotgun Lipidomics analysis of glycero-phospholipids (GPLs) from B lymphocytes: GPL subclasses are simultaneously detected by applying specific precursor ion and neutral loss scans for each subclass. Each peak in the mass spectrum represents GPL species with a distinct fatty acid composition.

GETTING THE PEPTIDES TO THE MASSES

Proteomics Facility

In 2015, two separate facilities affiliated to CECAD and the Center for Molecular Medicine Cologne (CMMC) have merged into the present Proteomics Facility which has developed into a modern and highly productive mass spectrometry (MS) platform located at CECAD.

The Proteomics Facility applies state of the art methods of mass spectrometry to measure protein expression profiles and changes in post-translational modifications (PTMs) of peptides with maximum sensitivity. Shotgun proteomics is performed by data-dependent (DDA) and data-independent acquisition (DIA) and applied to high-throughput analysis, in depth-PTM screening, complexome profiling and protein-protein interaction studies. In addition, parallel reaction monitoring (PRM) assays are applied to target selected proteins with the highest sensitivity and accuracy.

>> SERVICES

The proteomics facility offers state of the art proteomics at the Campus Cologne. Users submit projects online and deliver prepared samples to the facility.

Samples are analyzed based on specific needs of the clients as determined in preliminary discussions. After measurement, protein intensities are determined by powerful software tools and the facility performs basic statistical data evaluation as well as post-analysis consultation. Whether the client wants to target a few specific proteins of interest, analyze some IPs, several proteomes, or a clinical cohort, we offer solutions for all individual project and their needs. Over the years, the facility was involved in thousands of projects and many of them were delivered to high-impact journals. We are looking forward to many more fruitful undertakings in the future!

The facility is constantly involved in establishing new methods. Recently, we expanded our methods portfolio to data-independent analysis (DIA), which can now be routinely offered for all client projects. Clients can benefit from more protein IDs and more robust quantification at shorter run times. Furthermore, we now also offer chemical labeling of samples via TMT to enhance quantifications compared to label-free experiments. Of course, we also still offer our tried-and-true methods for all ongoing projects!

Going forward, we will keep up with the developments in the field of proteomics to deliver constant high-quality data for all projects. Currently we are establishing an automated sample preparation platform for fast and precise sample processing. In addition, we are improving our workflows for maximum sensitivity. A combination of optimized digestion and enrichment protocols and ultra-sensitive LC-MS methods will allow for phosphopeptide analysis from low microgrammm amounts, as well as whole proteome measurements starting with micro-dissected specimens or low numbers of sorted cells.



DR. STEFAN MÜLLER

Head of Proteomics Facility

Specialized in LC-MS-based proteomics, targeted analyses, method development

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DETAILED INFORMATION

The proteome is a highly dynamic entity and systematic protein profiling is important to study cellular processes under regular and diseased conditions.



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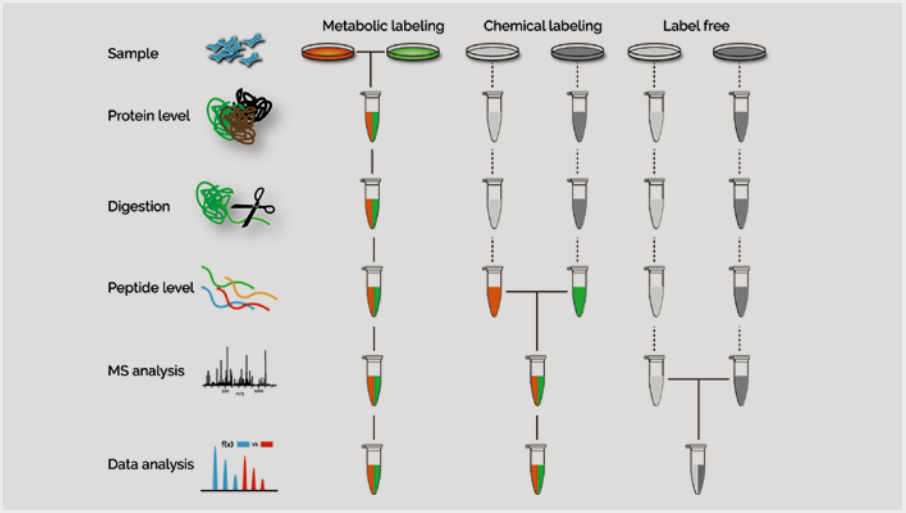


Fig. 1

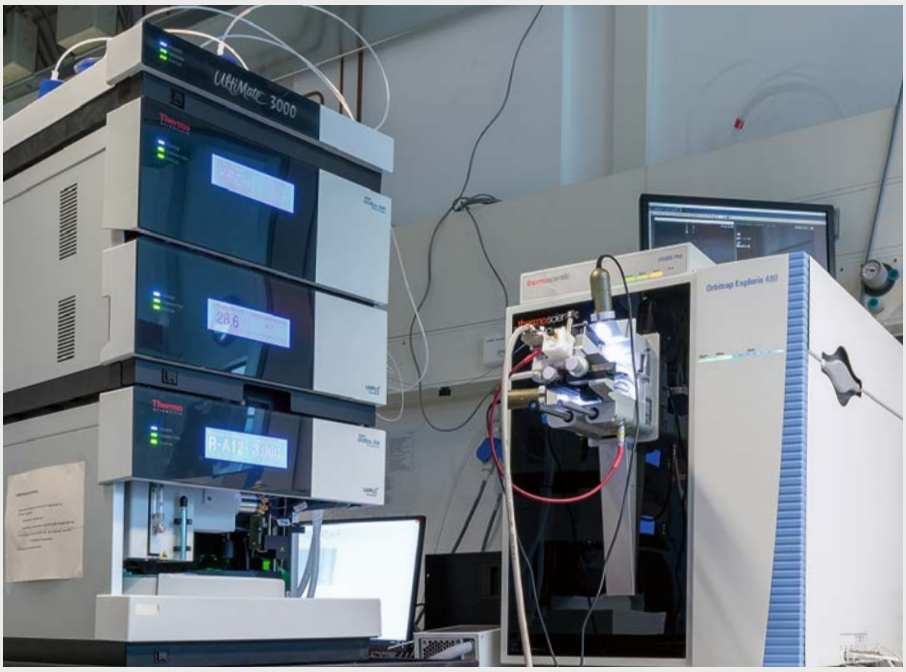


Fig. 2



Fig. 3

Fig. 1: Workflows offered by the facility. Besides label-free analyses, we also offer chemical (TMT) and metabolic (SILAC) labeling, all adjusted to scientific questions.

Fig. 2: Our new Orbitrap Eclipse is ready to handle TMT samples with enhanced quantification in MS3.

Fig. 3: Our Orbitrap Exploris 480 is dedicated to provide high proteome coverage on short gradients.

CONNECTING NEURONAL MECHANISM TO BEHAVIORAL AND METABOLIC CHANGES

Systems Neuroscience Facility

This newly established facility aims to achieve a circuit-level understanding of neuronal mechanisms that underlie behavioral and metabolic changes during aging.

Recordings of neuronal activity in hypothalamic circuits during metabolic and behavioral phenotyping will allow us to better decipher the functional role of specific cell groups and neuronal circuits in key processes involved in aging and the onset of age-associated diseases.

>> SERVICES

Analysis of collective and single-cell calcium activity dynamics of defined cell populations and their projections to other brain regions using deep-brain calcium imaging, as well as selective manipulations of defined cell populations and their projections with high temporal precision using optogenetics, will enable us to investigate and manipulate neuronal activity of defined neuronal types triggered during various behavioral states and during various pathological conditions.

To analyze these high-throughput data sets, we will set up the unified database and arrange an organized library of custom scripts for all experiments performed within the facility. This integrated data management approach will enable not only fast and unified data analysis, but also the coordination of custom analysis software coding when needed. This will enable CECAD PIs to gain new and profound insights into the causal role of defined cell populations, neuronal circuits, and neuronal dynamics in aging.



PROF. DR. TATIANA KOROTKOVA

Head of Systems Neuroscience

Specialized in *in vivo* electrophysiology and calcium imaging

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DETAILED INFORMATION

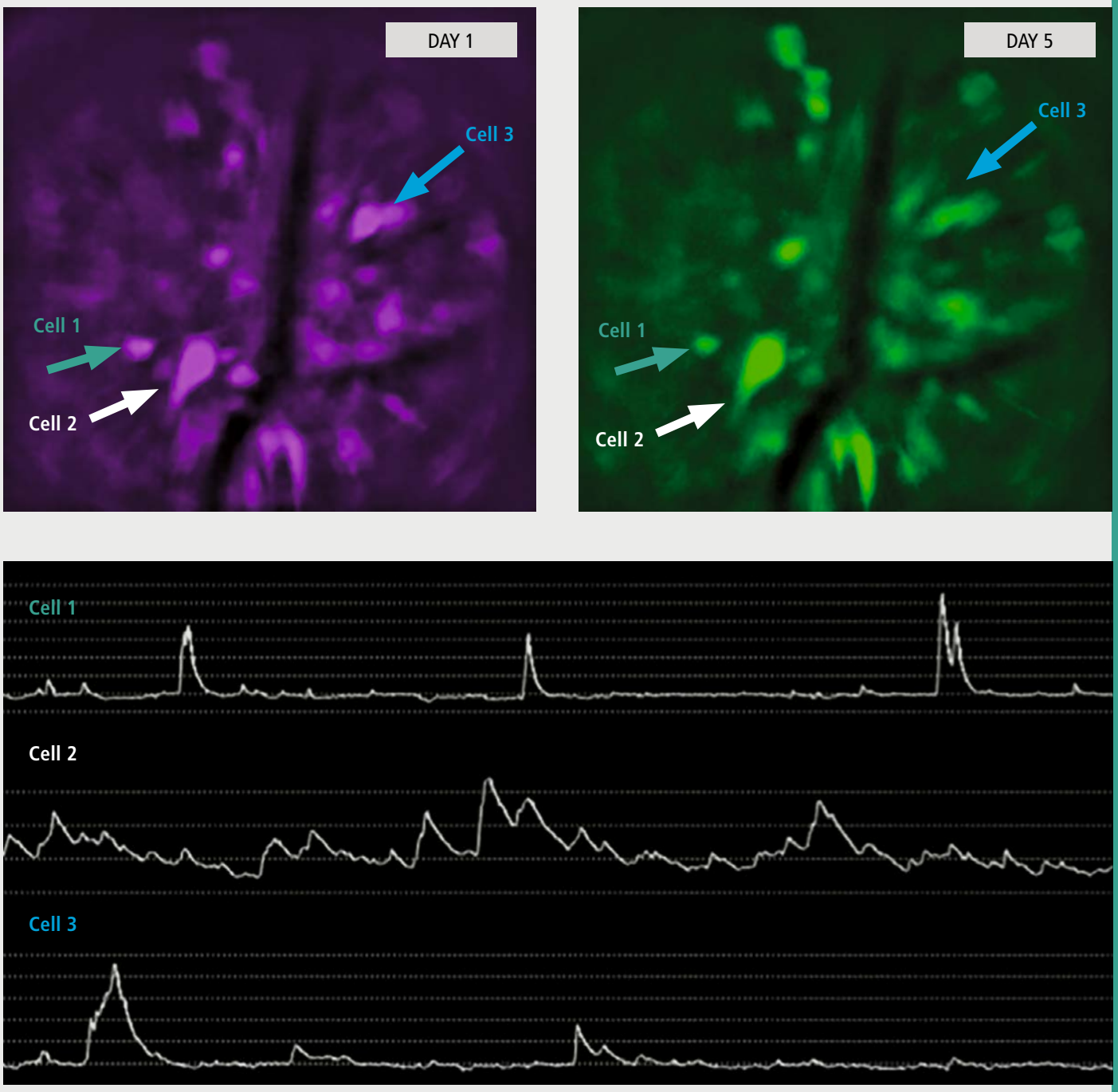


Fig. 1

Fig. 1: Deep-brain calcium imaging allows the analysis of the activity of multiple identified, neurochemically defined cells across different days during various states and behaviors.

SUPPORTING CLINICAL RESEARCH FOR AGING-ASSOCIATED DISEASES

Translational Research Platform

The Translational Platform provides CECAD researchers with specialized expertise on clinical trial and cohort design and supports transitioning findings from basic research into clinical projects.

The Platform's goal is to realize CECAD's vision of developing novel solutions for aging-associated diseases by adding the clinical perspective to hypotheses, results and compounds derived from laboratory-based research. The platform accelerates the path to clinical testing with tailored support and solutions, including but not limited to patenting, trial design, protocol development, budgeting, ethics and regulatory approval, as well as study conduct. The Platform team connects to potential collaborators on and off campus, from clinic and academia to research networks or industry partners. In addition, the Translational Platform strives to provide fundamental knowledge on clinical trial development to all CECAD researchers, from graduate students to PIs.

>> SERVICES

The Translational Platform connected four on-campus groups to translate phenotypical data from the unique ceres cohort of octogenarians+ into a clinical setting. The CECAD Executive Board supports the project with funding to secure collection of biosamples (stool, urine and blood) from volunteers ≥80 years. After a successful start and enrollment of 10 volunteers, the study was put on hold in light of the ongoing COVID-19 pandemic.

The ongoing collaboration with the Max-Planck-Institute for Metabolism Research currently spans 7 translational projects. The Platform contributes, among others, to concept design, funding applications, study document development, ethics submission, study coordination and conduct, data review and quality control.

Highlights from 2019 and 2020 include:

- »Physiological Effects of Uridine« received the Karl-Oberdisse-Preis 2019 from the Nordrhein-Westfälische Gesellschaft für Endokrinologie und Diabetologie e. V.
- Assessing neural activation and dopamine release in response to palatable food intake in humans combining fMRI and PET imaging methods highlighted the role of brain-peripheral interaction in reinforcing food intake
- Design, evaluation and publication of the interdisciplinary weight loss program »Change your Life!« for obese patients aiming for long-lasting lifestyle changes and weight reduction in collaboration with the PEDP

The platform supported set-up of Prof. Dr. med. M. Vehreschild's GMP-facility for fecal microbiota transfer at the campus of the University Hospital of Cologne. From 2021, the facility will produce oral capsules of viable gut microbiota extracted from donated stool samples of healthy individuals along GMP quality standards.



PROF. DR. OLIVER A. CORNELY

Head of Translational Research Platform

Specialized in internal medicine, infectious diseases, clinical mycology

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DETAILED INFORMATION

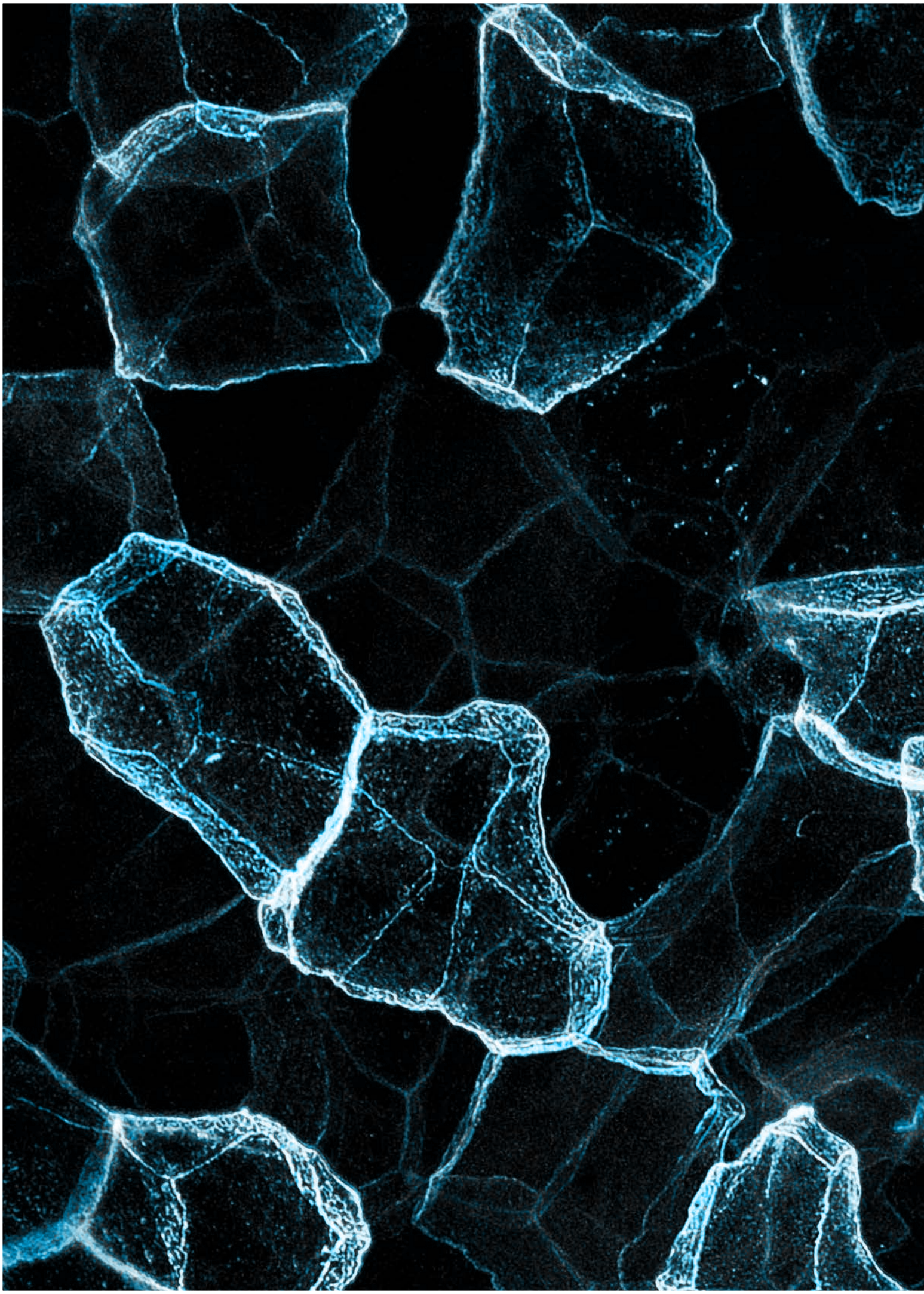
Our goal is to develop novel solutions for aging-associated diseases by adding the clinical perspective and supporting clinical testing.





The facility enables individualized treatment of patients with relapsing Clostridioides infections, an infectious disease of the gut prone to relapses and severe complications. Transfer of human fecal microbiota has shown to be a safe and effective treatment for recurring infection and restoring a healthy gut microbiome.

The translational approach to life science-based research has become prevalent during the past 10 years. However, providing practical knowledge on clinical trial development to researchers outside the medical field was often neglected. The Translational Platform is developing a remote training program targeted at life science researchers as well as clinicians at all levels of professional experience. The Translational Scientist in Aging Research (TSAR) will encompass eight modules enabling participants to successfully set up and conduct aging research-focused clinical trials and studies. Modules will cover evaluating clinical research questions and choosing the appropriate trial design to approach them, the steps and processes required to set up and successfully conduct a clinical trial, and utilization of trial results. A dedicated projected manager is currently working on delivering the first training module.





/3
CECAD LIFE

CECAD and Covid 19 – New Routes for Research

March 2020: The number of Sars-CoV-2 cases is increasing and safety measures were taken to avoid infections in the CECAD research center. Restricted in their own research CECAD Scientists looked outside the box and started new projects.



Research and experiments have been scaled down to a minimum. Only essential tasks were allowed and many experiments were interrupted. But scientist are always looking for a solution.

Translating basic science into innovative applications

The pictures from Italy were shocking and the fear of overcrowded emergency rooms also increased in Cologne. »We were really worried that at some point the situation would develop as it has already in the Lombardy, region of Italy,« said Prof. Dr. Bernhard Schermer, head of the nephrological research laboratory (Nephrolab) at CECAD. The Nephrolab used their expertise in molecular biology to develop an innovative rapid test to detect Sars-CoV-2 quickly, on site, and as accurately as a PCR-test. The test relies on the reverse transcription loop-mediated isothermal amplification method, or rtLAMP for short. The first positive results were available after just one to two weeks. »LAMP has been unjustly neglected until now,« said Schermer. One reason is that the end product of the LAMP reaction is a wild mixture of DNA structures that cannot easily be used in further analyses and experiments. However, since further processing is not important in a rapid Corona test, this is not a disadvantage. The Nephrolab founded the start-up Detechgene which will optimize the test and bring it to market. »The novel rapid test has potential and can also be extrapolate to determine pathogens of many other infections, including bacterial infections, in doctors' offices or hospitals more quickly, and thus being able to start targeted therapies earlier. Only the primers need to be modified and tested,« said Dr. Reza Esmaillie, co-founder of Detechgene.

> The novel rapid test has potential and can also be extrapolated to determine pathogens of many other infections, including bacterial infections, in doctors' offices or hospitals more quickly, and thus supports the start of targeted therapies earlier. Only the primers need to be modified and tested.
>
> - Dr. Reza Esmaillie



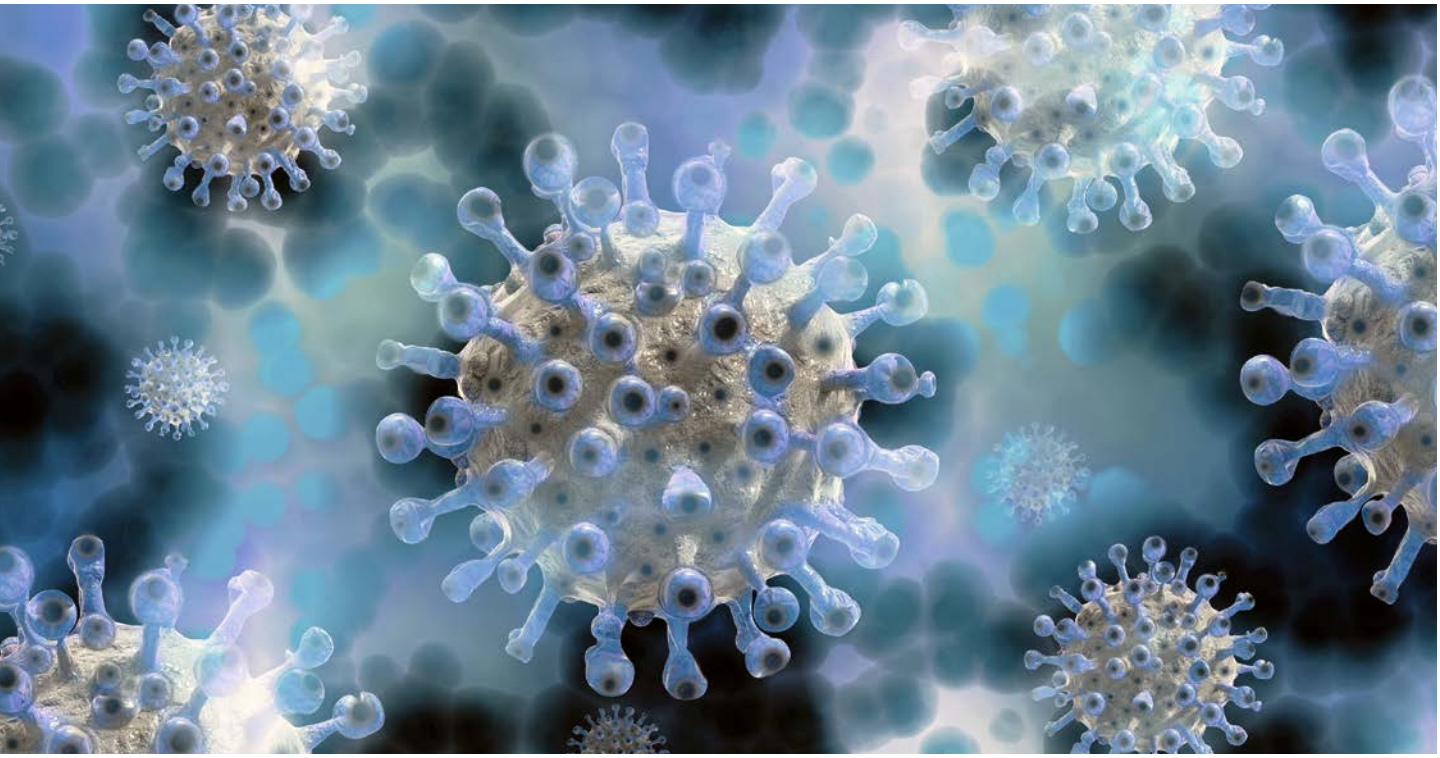
LAMP reactions in test tubes: yellow - SARS-CoV-2 positive, pink - SARS-CoV-2 negative

> We are currently in the process of standardizing SARS-CoV-2 sequencing protocols at all major sequencing centers in Germany in order to determine viral genomes in a wide variety of regions across the country.
>
> - Prof. Dr. Alexander Dilthey

Getting to the bone of Sars-Cov-2

To fight a pandemic, collaboration is indispensable. Therefore, national genome researchers have joined forces to form the German COVID-19 OMICS Initiative (DeCOI). The aim: accelerate research into the virus and understand why some people become severely ill and others only mildly ill. Scientists at more than 40 institutions are actively involved in DeCOI.

»We are currently in the process of standardizing SARS-CoV-2 sequencing protocols at all major sequencing centers in Germany in order to determine viral genomes in a wide variety of regions across the country,« said Prof. Dr. Alexander Dilthey, head of the CECAD Bioinformatics facility in May 2020. He is coordinating the viral genome research activities within the German COVID-19 OMICS Initiative (DeCOI). With the help of multi-omics analyses, it can be quickly and comprehensively determined which biological processes are triggered in the disease itself and how these can be positively influenced by drugs. DeCOI researchers are involved in large international consortia to determine, among other things, the distribution of receptors on the body's cells that are thought to be responsible for the entry of SARS-CoV-2. The aim is to find out which immune cells are involved in processes that occur particularly in patients with severe courses of the disease, in order to identify new therapeutic options for this.



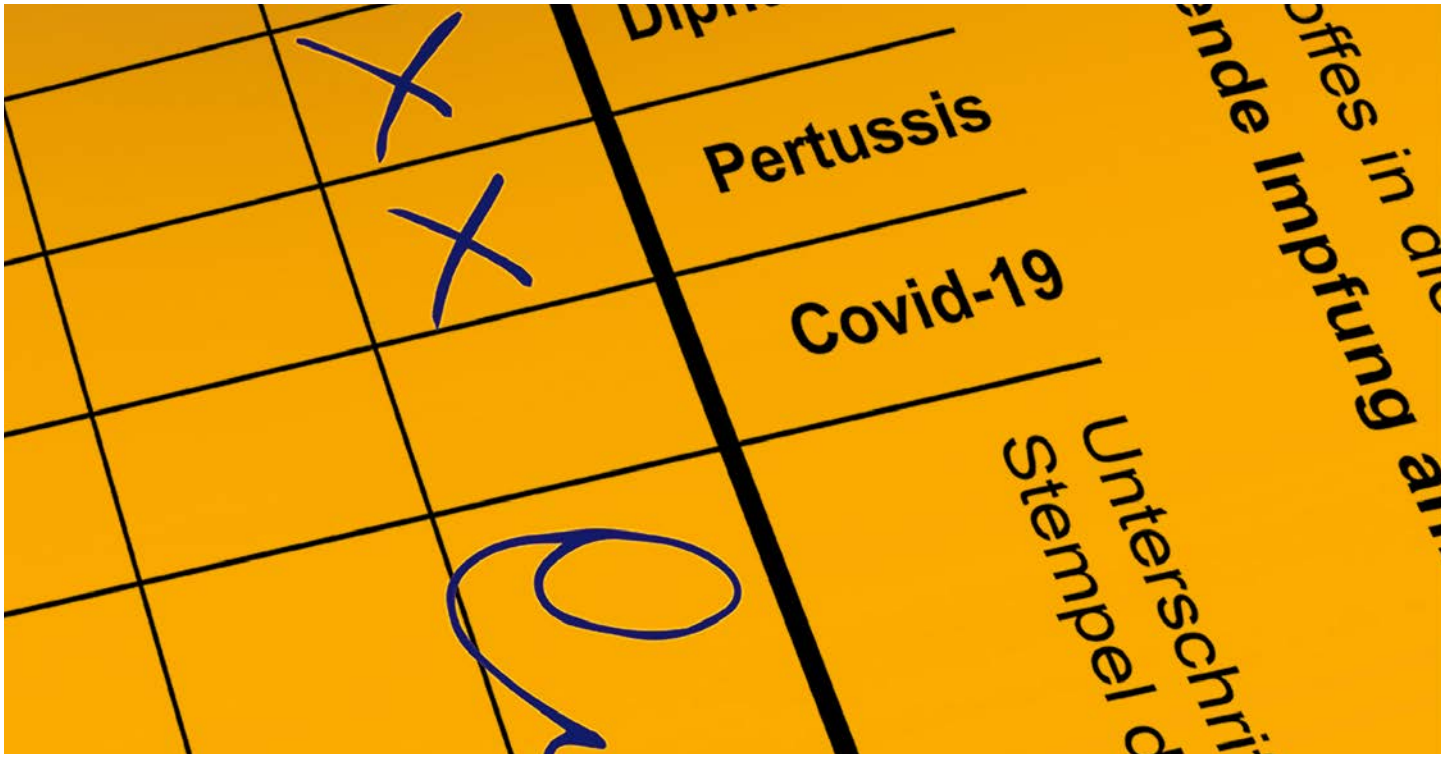


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Rethink, reuse, reduce

CECAD PI and Alexander von Humboldt Professor Henning Walczak started together with colleagues from the Medical University of Vienna and the biotech company Apogenix a phase II clinical trial with the immunotherapeutic agent Asunercept, a Fas ligand inhibitor. Originally, the Fas ligand inhibitor was developed for cancer therapy. In the framework of the »Austrian CoronaVirus Adaptive Clinical Trial (ACOVACT)« patients with severe to critical COVID-19 disease are being treated with the immunotherapeutic agent. ACOVACT is an open-label, MedUni Vienna sponsored, scientifically initiated, randomized, controlled, multi-centre clinical trial and compares different treatments for COVID-19. In conjunction with results published by other researchers, Walczak and colleagues concluded that tissue destruction and lung failure in patients with severe COVID-19 may actually be the result of the overactivity of so-called death ligands, rather than the virus infection itself. Death ligands are proteins that our own body cells normally produce in the course of immune defence. The immunotherapeutic agent intercepts the death ligand known as Fas ligand or CD95 ligand. »It appears that SARS-CoV-2 infection induces an overreaction of our immune system, resulting in overproduction of Fas ligand. This killer protein can then kill healthy, uninfected cells in the lungs of COVID-19 patients, thus causing lung damage,« Walczak explained. The concept of preventing cell death in the treatment of COVID-19 is innovative and the scientists are excited about the outcome of this clinical trial.

> It appears that SARS-CoV-2 infection induces an overreaction of our immune system, resulting in overproduction of Fas ligand. This killer protein can then kill healthy, uninfected cells in the lungs of COVID-19 patients, thus causing lung damage.



Accelerate research and vaccination – VACCELERATE

> We want to network facilities, pool expertise, and promote knowledge exchange among our currently 26 partners. Our goal is to plan and coordinate vaccine trials under one strategic scientific umbrella in all EU member states and other EU-associated countries.

Next to detecting and treating the virus the research for a vaccine towards protection, kept scientist all over the world busy. Prof. Dr. Oliver Cornely, head of the CECAD Translational Research Platform, created a new platform where people interested in participating in a clinical study for Sars-Cov-2 vaccines could register, at first only national at impfstudien-corona.de, then across the European Union and EU-associated countries. On 19 November the national German platform went live. Within the first three hours over 2.000 people registered in the platform. After setting the course at the national level, Cornely and his colleagues went international. »VACCELERATE is designed as a pan-European backbone for a coordinated approach to vaccine research. We want to network facilities, pool expertise, and promote knowledge exchange among our currently 26 partners. Our goal is to plan and coordinate vaccine trials under one strategic scientific umbrella in all EU member states and other EU-associated countries.« An important step in establishing the network is to map capacities for clinical trial sites and laboratory facilities to identify suitable sites for vaccine trials in Europe. Cornely added: »VACCELERATE will serve as the pandemic preparedness network, providing a structure beyond the current coronavirus pandemic to rapidly and effectively test vaccine candidates across Europe.«



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Challenges of CGA Students in 2020

The changing regulations that were implemented to control the COVID-19 pandemic in 2020 at the Campus in Cologne also had a strong impact on PhD Students at CGA. Two of them share their personal experiences – positive and negative.

Kept away from the bench – Inspiration from literature

Due to the COVID-19 Pandemic Saygin Bilican could not spend the entire first year of his PhD in the Vilchez Lab at CECAD performing experiments. But instead of becoming demotivated he found an alternative way to progress with his project in the area of Stem Cell Research: The inspiring analysis of scientific publications in this field.



SAYGIN BILICAN

PhD Student at CGA

CECAD – Vilchez Lab

Stem Cell Research

Saygin had already been working on his research project for eight months when the COVID-19 Pandemic broke out. He was well settled in the lab and had already generated the first data. COVID-19 halted the experiments. Scientists were only allowed to enter the building for essential tasks.

> It was nice to be able to read many scientific publications.

»I couldn't do experiments, but I had to keep my cells alive. That is, I had to go to the lab every 2 days, even if it was only for a short time,« the PhD student recalled. In general, work was done from home, which also had positive aspects: »It was nice to be able to read many scientific publications. Under normal circumstances, you often don't have enough time for that in addition to your lab work. I did a thorough literature search and got inspiration from other papers.«

CECAD transitioned to shift work after some time, so larger experiments were possible again and a sort of 'normality' has returned to Saygin at work. As an international student, Saygin regularly calls his family in Turkey. He doesn't want to risk a visit. »There are too many points of contact: at the airport, in the cab…,« said the biologist. »It's strange how you suddenly miss the simple breakfast in a café or going out to eat, even if you didn't do it before. The difference is that you had the opportunity! I don't like to be around too many people at the moment and I miss having a tea with friends.«



An unexpected end to a PhD – A mask to mask defence

Magdalena Kremer, took advantage of the working from home order to streamline writing up her thesis. She will always remember the day of her disputation in a special way. It was very different from what she expected during the years that she worked in synthetic biochemistry and bacterial genetics.



DR. MAGDALENA KREMER

CGA Alumni

Biochemistry – Lammers Lab

Synthetic and Structural Biochemistry

> Are you on the right or are you on the wrong track? I couldn't judge that very well.

Magdalena was about to complete her practical lab work for her PhD in mid-March when she switched to working from home due to the shutdown of the institute. The ideal time to look at all the data and form a rounded story. Some things weren't finished yet, but it was foreseeable nonetheless. »I traded the lab for the desk overnight and took my time putting everything together,« Magdalena said. After three or four weeks, it was possible to return to the lab with hygiene requirements and a plan.

»After consulting with my supervisor, I determined which experiments were still necessary and focused on them. I postponed further experiments until after my doctorate.« Work was then done in blocks with a few weeks in the lab and then several at the desk until submission in July. »It was very effective because I could completely focus on either the experiments or writing. Under normal circumstances, you'd be in the lab and you'd be doing this and that,« the biochemist said.

In September, she had to defend her thesis. Thanks to a certified examination room in the institute with sufficient distance and an air filter system, she was able to present and answer questions about her work in the presence of others. However, wearing mask was mandatory. »It was very difficult to read the facial expressions of the examiners during the question section. Are you on the right or are you on the wrong track? I couldn't judge that very well,« the doctor reports. »Still, I'm very glad I didn't have to defend online. I think it's more effective to getting into an exam mode than in front of a PC at home. I would have found it sad if the examiners said 'you passed' and then you click to leave the meeting.«

Starting a Research Group in 2020

Starting your own research group as a PI while moving countries is always a challenge, but doing so during a pandemic is unusual. Were the circumstances due to Covid-19 curse or blessing?



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In 2019 CECAD recruited two talented research group leaders, Dr. Gilles Storelli and Dr. Jane Reszick who both started their laboratories in 2020. Whereas Gilles Storelli strengthens CECAD's focus on tissue-environmental interactions, Dr. Jane Reznick examines metabolic regenerative processes using a unique aging model, the naked mole-rat, thus expanding CECAD's portfolio of model organisms.

Gilles Storelli started two weeks before the first lockdown in March 2020. While working remotely, he purchased equipment, and announced job opportunities with strong support of the CECAD central office. »I am often asked how hard it was to start a group during the pandemic. There were certainly difficulties, but I also realized the chance I had to already be in an independent PI position at that very time. How many fellow postdocs and PhD students had to stall their research, sometimes for months, while they were at a turning point in their career?«, Gilles said. »One negative aspect, however, was that we could not start experiments. Initially, it was even difficult to buy essentials like gloves and pipette tips for the lab. However, when you are starting your research group you are full of enthusiasm and energy. I managed to preserve that and applied it as soon as the restrictions loosened up.«

> I was excited to move to Cologne to study metabolism in disease and aging, in a dynamic and vibrant scientific community.





Jane Reznick arrived in the summer of 2020, when restrictions and regulations eased up a bit. »The first weeks were filled with adrenaline and excitement which gave me a unique energy to get things moving so that I didn't even mind doing work in a pandemic. Since it was summer and infection rates were very low, I even had coffee with a few colleagues and one or two mask-to-mask meetings,« said Jane. She made extra efforts to organize virtual meetings to meet as many colleagues as possible, even if that did not replace meeting colleagues in person during seminars or at the coffeebar. »The colleagues in CECAD and on campus are extremely welcoming and helpful. Many of my colleagues offered help. My neighbors, the lab of Marcus Krüger, invited me to join their weekly virtual lab meetings which I found extremely motivating and which allowed me to integrate directly into the CECAD scientific community,« Jane said.

> I wanted to be where the science was dynamic and my research interests were also the interests of many talented researchers around me. CECAD is an extremely attractive place for my scientific growth and development.

Gilles and Jane are two examples of the resilience of scientists in the 2020 pandemic year, even when moving to a new place under conditions that were subject to continuous change. »I think these lessons have probably equipped me to deal with future challenges that come with being a group leader,« Jane concluded.



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Career Development and Diversity

The ability to attract and retain top scientists is a key priority at CECAD. We are dedicated to recruiting the best researchers and thus aim to provide a diverse, family-friendly and international environment.

At CECAD, the areas of career development and diversity are integrated in one platform (RP-C). At the start of the CECAD Excellence strategy funding in 2019 RP-C has implemented a 'Career Development and Diversity Board' with a focus on developing effective strategies in supporting careers at all levels and creating an attractive, open, and family friendly work environment for a diverse group of scientists. The board consists of six elected representatives of PhD students, postdocs, group leaders and professors, as well as the two CECAD heads for career development (Elena Rugarli) and diversity (Carien Niessen), both of whom are also members of the CECAD Executive Board. The RP-C is managed by the full-time coordinator Julia Zielinski who coordinates the CGA together with Daniela Morick from the MPI AGE, organizes career development programs and hard- and soft-skill trainings and implements measures and activities of the Career Development and Diversity Board. She is assisted by Saskia Wilming.



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Promoting Young Scientists at CECAD



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In the competitive environment of top-level research, excellently trained young researchers are essential for CECAD's success. For this reason, CECAD is intensely engaged in the promotion of young scientists at all career stages through subject- and stage-specific training and mentoring ranging from master- and medical students, to PhD students, postdocs and early-stage independent PIs. Individual needs are regularly surveyed in order to guarantee that appropriate soft skill courses and career support measures are adjusted to the needs and demands of present-day science.

As part of the restructured Biology Master Program at the University of Cologne, CECAD implemented the Master Track »Mechanisms of Aging and Aging Associated Diseases« in 2020 to attract students at an early age and provide them with the fundaments to excel in aging research.

DETAILED INFORMATION



CGA Class of 2020

In order to support the leap into scientific independence, CECAD regularly awards 2-year postdoctoral grants that covers a technical assistant and consumables. The goal of this grant is to support projects that provide a foundation towards own lines of research to accelerate the transition into independence. Almost all former CECAD Postdoc Grant recipients successfully established their own laboratories, thus illustrating the success of this program.

In 2020, CECAD introduced, »Junior Tuesdays«, open-door meetings of (early stage) group leaders for postdocs interested in pursuing an academic career aimed at informally sharing experiences in setting up a laboratory, grant writing, networking etc, and to promote longer term mentor mentee relationships. This new measure is embedded in a CECAD postdoc program that includes team management courses, alternative careers seminar series and career and funding opportunities days.

> “Every being is a special creation of nature, so align with nature and let nature reveal why it created the enigma that is you. Follow your instincts fearlessly, work hard to stand up for your dreams, turn every challenge into opportunity, and don’t forget to celebrate your achievements, or stepping stones.



HARSHITA KAUL

PhD student, CGA class 2019



Cologne Graduate School of Aging Research

The Cologne Graduate School of Aging Research (CGA) was founded in 2013 as a result of the fusion between the CECAD Graduate School and the International Max Planck Research School AGE. The CGA offers young scientists of exceptional talent from across the world a structured PhD training in Aging research. Each year, an international class of students is recruited for a three-year program that involves excellent, state-of-the-art research conditions with intensive mentoring. Moreover, the school offers seminars and courses in aging research, writing and presentation workshops, as well as career development training opportunities. A graduate symposium, a festive event at which the PhD students give presentations on their PhD project, marks the end of the CGA program.



STEPHANIE DE ALCANTARA FERNANDES

PhD student, CGA class 2017

> As an international student from Brazil, the CGA coordination supported me in every way. Academically and personally, their assistance was essential in all matters, including visa and accommodation, so my PhD could start as smoothly as possible, allowing me to be fully dedicated to my studies.

Since 2019, the CGA additionally offers a Master Fellowship Program. This new program offers excellent, motivated students the chance to join a lab and become a mentee of a CGA faculty member while pursuing their studies in the Aging track of the UoC Biological Science Master Program. Master fellows are supported by a fellowship, actively engage in scientific and social activities of the mentor's lab and have regular advisory meetings with their mentor before they decide upon a Master's project in the field of aging research. Building on its growing alumni network, the CGA in 2020 started a new mentoring program. This program provides CGA students opportunities to get advice from former students on future career options and paths, thus enabling possible contacts with potential future employers.



Gender Equality, Diversity and Family Support

> We will know that we are doing things right when the term »gender equality« is no longer needed in science.

Promoting a diverse, inclusive and family friendly work environment is an essential prerequisite for people to thrive and successfully contribute to CECAD's mission. CECAD therefore invests in active recruitment strategies, training and measures that promote awareness of any prejudices that may influence recruitment decisions and lab management processes. To counteract the female »leaky career pipeline« CECAD has implemented a range of gender programs that provide career advice, mentoring and gender training. Since 2012, CECAD offers an increasing number of childcare spots for employees in the university child center and other collaborating child care facilities. CECAD also finances the usage of the university childcare backup service to cover overtime or closing times of the regular childcare facility. Since 2019, CECAD offers a flexible »family support grant« financing, e.g. a student assistant for employees who need to reduce working hours due to family obligations. Since 2014, CECAD installed a family room for CECAD employees who need to bring their child to work. In 2020, CECAD equipped both male and female toilet facilities with changing tables and will install a gender-neutral toilet facility in 2021.

Close collaborations with HR development for researchers of the University and their mentoring programs designed for female scientists and departments for gender equality and family support are key elements in promoting staff diversity in science.



VERONICA MARTINEZ OSORIO,
PhD student, CGA class 2020

Communicating Science for Everybody

Since aging affects each and every one of us, CECAD is motivated to talk to people of all ages using a multitude of available channels.



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Scientists usually communicate and disseminate their results and findings through scientific publication in expert scientific journals. Results are also discussed on specific national and international conferences and through seminar series. The advancement of science is fueled by holding conversations and engaging questions not only with experts in the field but also with other stakeholders, including the general public, policy makers and industry actors. For scientists, it is accordingly of great importance to inform, explain and engage in discussion with the public. Sometimes a small question can be the trigger for scientists to think outside the box or to look at their own research from a different perspective.

Highlights of 2019/2020

In 2019/2020 CECAD engaged with the public in various events. Examples of such events included discussing science and its progress with a beer (or a non-alcoholic beverage) in hand in a bar at »Pint of Science« 2019 and online from the couch in 2020; a combination of aging research and art was presented at the AGE-ART Event (Aging is in Our DNA: The Finite Thread of Life); and an exhibition of colorful microscope pictures was on display in the CECAD corridors (Challenge Aging). Furthermore, CECAD scientists have given various talks and were involved in public panel discussions such as the Cologne Townhall discussion public panel discussion »Altern und Regenerationsmedizin: Wohin geht die Reise?«, and a public workshop of the event series »Wissenschaft in Kölner Häusern« about



Vernissage of Challenge Aging - Microcosm of Aging Research in May 2019



»Successful aging: myth or reality?«. Additionally, CECAD, as a member of the »Kölner Wissenschaftsrunde«, also took part in a successful Science Show. CECAD is generating and distributing multimedia content on various channels. In addition to press releases on new findings, explanatory videos on aging and interviews were produced and social media channel communication was enhanced. Furthermore, CECAD is regularly featured in the university magazine of the University of Cologne with articles on CECAD scientists and research projects.

In addition to the above ongoing activities, in 2021 CECAD is aiming to further expand its communication outreach. Through Twitter, the scientific community will be extended, public will be reached via videos about latest science publications »Wissenschaftsnachrichtenvideos«. Moreover, CECAD, through its PR Officer Dr. Anna Euteneuer, is actively involved in shaping the planned podcast of all German excellence clusters called »Exzellent erklärt – Spitzenforschung für alle«. Similar to »Pint of Science«, CECAD also plans to take part in an outreach event to passers-by in Cologne, called Soapbox Science, which especially encourages women in science.

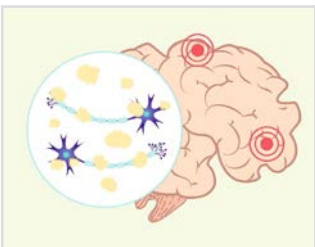


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VIDEOS DE **VIDEOS EN**

About EIT Health & EIT Health Germany

Excellent research and healthcare are based on strong collaborations and innovative solutions to challenges. These values are at the center of the CECAD – EIT Health partnership.

“

We are excited to have the Cologne University, CECAD and University Hospital as strong partners in our network. The Needs-Led Innovation Fellowship programme is a great example of how the involvement of leading institutions around Europe fosters innovation and promotes growth in the healthcare sector.

- Dr. Katharina Ladewig, Managing Director EIT Health Germany



As part of the European Institute of Innovation & Technology (EIT), EIT Health promotes innovation and entrepreneurship in the health sector across Europe. EIT Health is currently working with around 150 partners from 18 countries in a »public-private partnership« to determine and solve the major challenges European healthcare is presently facing.

EIT Health Germany is one of 7 Regional Innovation Hubs in Europe, and currently supports 35 partners from industry, research and education in Germany, Austria and Switzerland, as well as start-ups and SMEs in the development of ground-breaking innovations in the healthcare sector. Through funding, mentorship programmes, connections to key players and interdisciplinary discussion rounds, EIT Health Germany brings the network together to move towards a sustainable and competitive health system that fosters health and wellbeing for all Europeans.



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University of Cologne, CECAD & EIT Health – A fruitful partnership

As one of the leading German research institutes with a strong international focus, CECAD Cologne shares many mutual goals with EIT Health and has established itself as a valuable Associate Partner. Over the past years, various game-changing projects benefitted from the Cologne partners´ resources, like Innovation Days (i-Days) or AIProHealth, Practical Artificial Intelligence for Healthcare Professionals. By supporting the project PAPRIKA, Patient empowerment for major surgery preparation at home, the university works towards establishing a technologically enabled and personalised programme to prepare patients for elective surgery and provide follow-up to improve the outcomes of the operation. Another activity that deserves special attention are the Needs-Led Innovation Fellowships.



Needs-Led Innovation Fellowships at Cologne

Cologne became the first German partner of the prestigious EIT Health funded Needs-Led Innovation Fellowships Network. The newly founded StarMed Campus Köln will host fellows with diverse educational backgrounds and working experience. By adopting the BioDesign methodology, selected fellows will identify pressing, unmet clinical needs and develop a competitive business plan with the ultimate goal of funding a start-up enterprise. Forming small interdisciplinary teams, the fellows will undergo intense training, followed by a period of immersion into selected clinics, with need identification and development of their business idea under continuous expert mentorship.

DETAILED INFORMATION

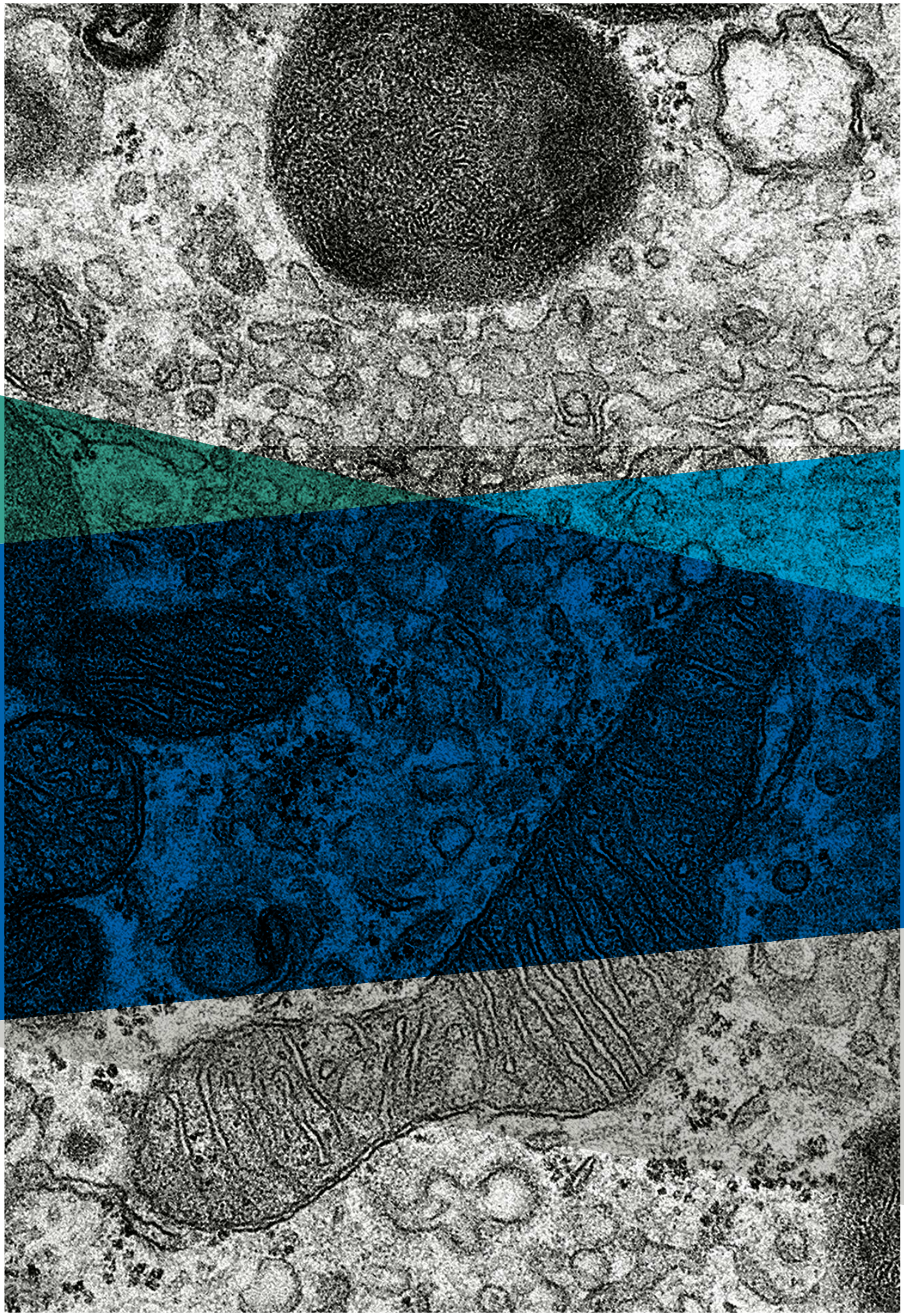
> The prestigious NLIF program will strengthen our institutions´ translation- and knowledge-transfer activities and will benefit immensely from the tight interconnection of medical care with clinical and basic research that is embedded in the innovation-strong Cologne region.



PROF. DR. PHILIPP STEVEN

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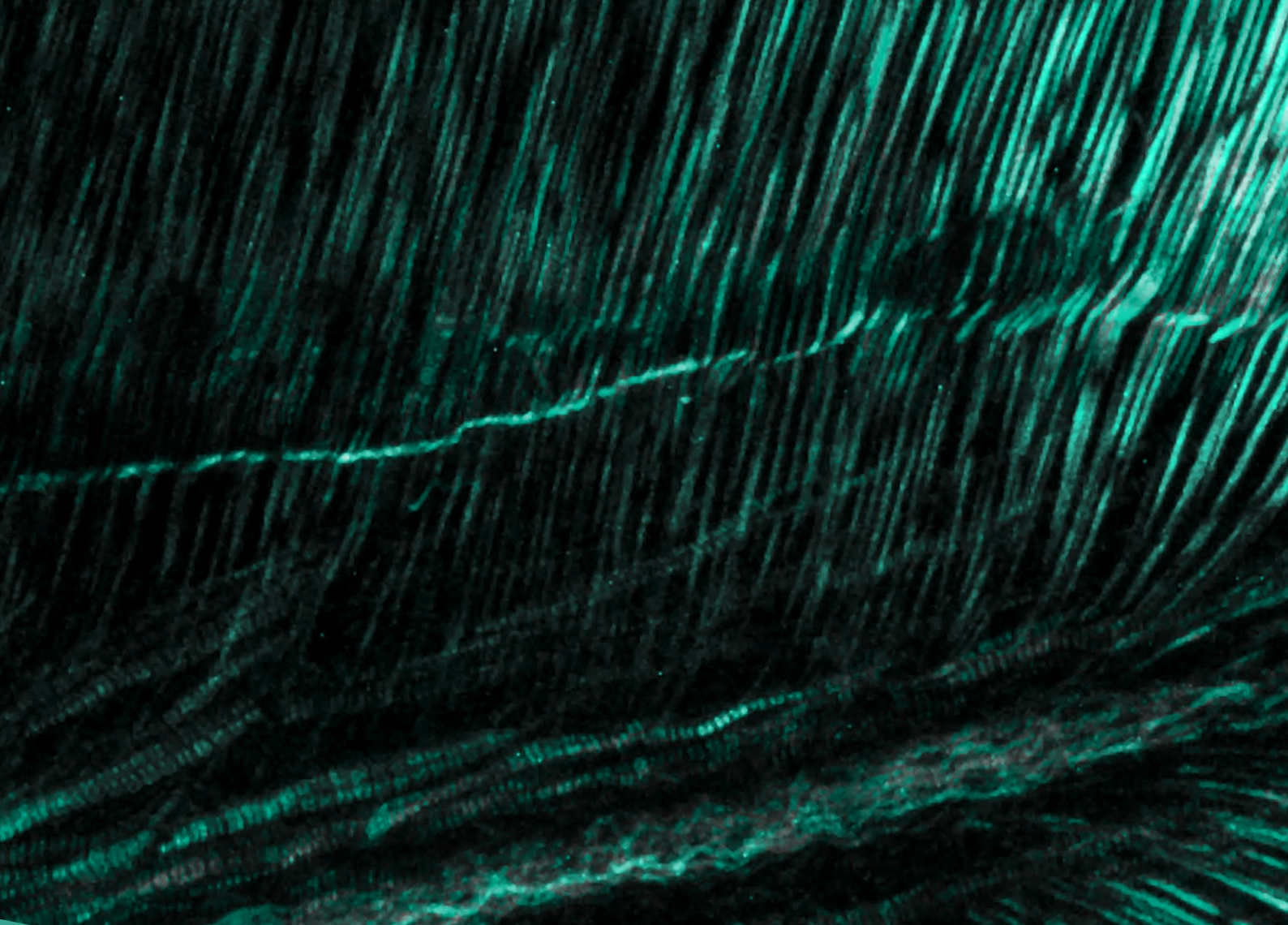
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