

CECAD
COLOGNE Excellent in Aging Research – Exzellent in Alternsforschung

CECAD Cluster of Excellence Report 2012 – 15

Exzellenzcluster CECAD Cologne Geschäftsbericht 2012 – 15

Universität zu Köln

DZNE Deutsches Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft

UNIKLINIK KÖLN

MAX PLANCK INSTITUTE FOR BIOLOGY OF AGEING

Max Planck Institute for Metabolism Research

CECAD Cluster of Excellence
Report 2012 – 15

Exzellenzcluster CECAD Cologne
Geschäftsbericht 2012 – 15

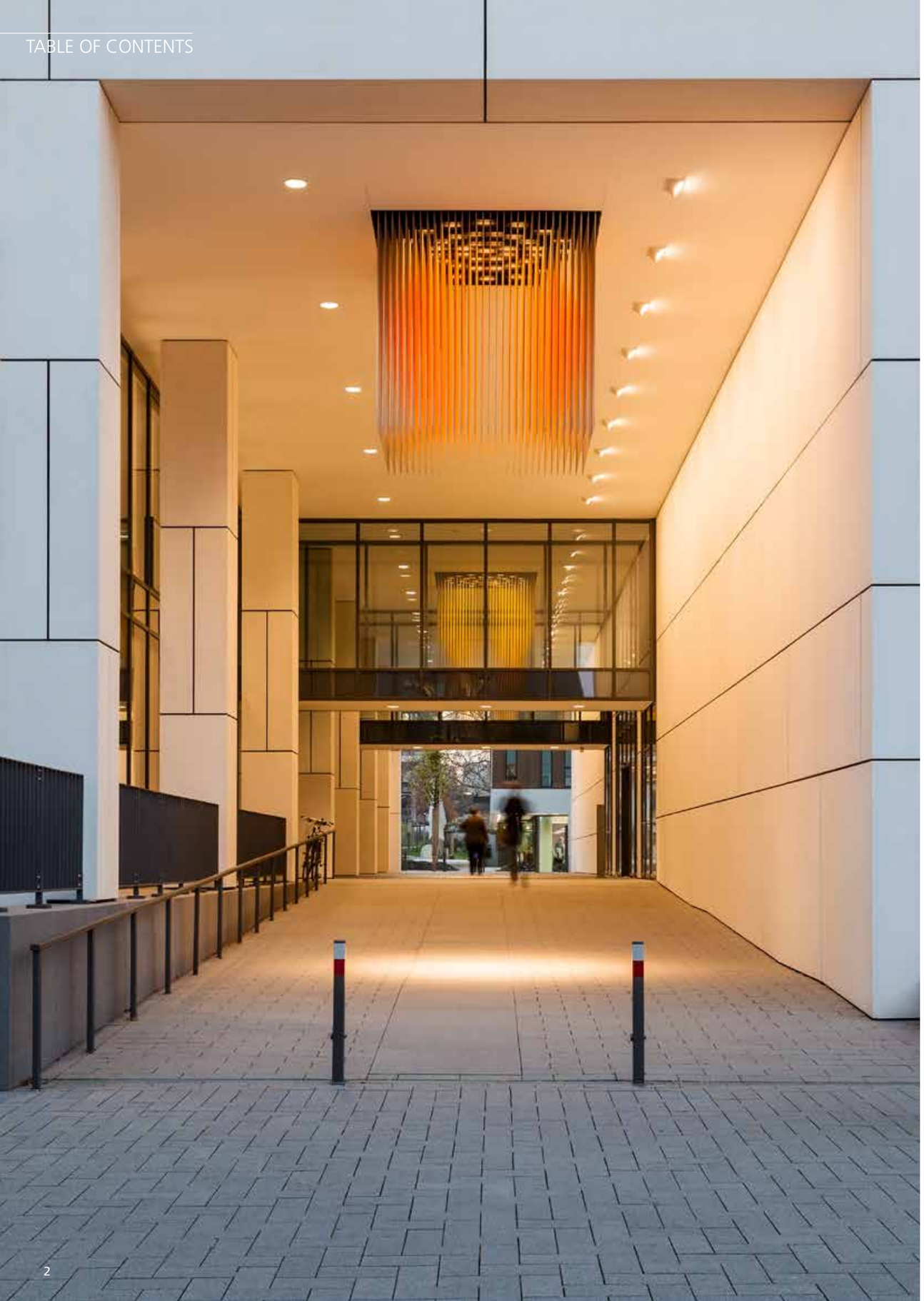


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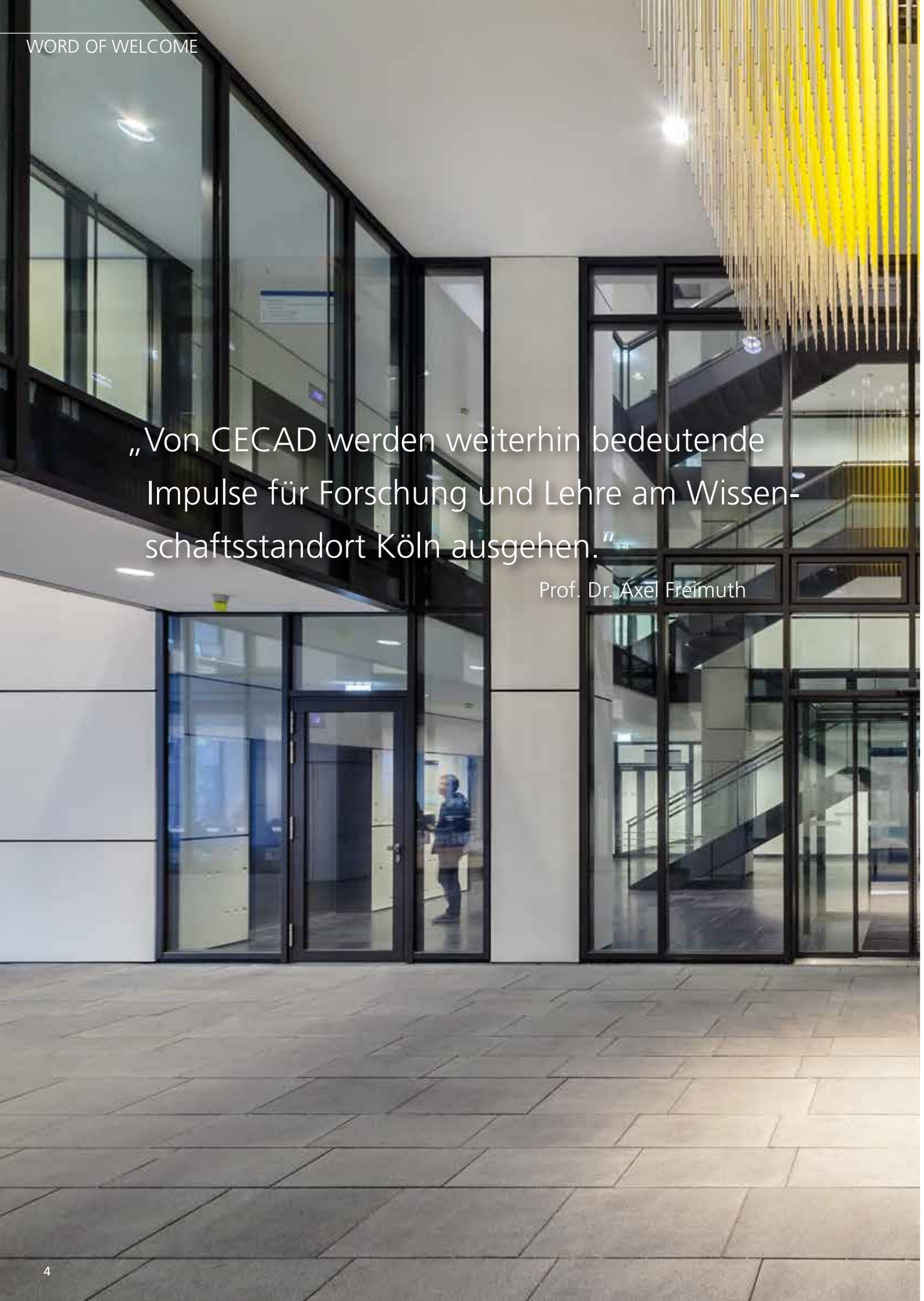
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Prof. Dr. Axel Freimuth

Rector of the University of Cologne

Mit dem Exzellenzcluster CECAD hat sich an der Universität zu Köln ein weltweit einzigartiges Zentrum der Alternsforschung etabliert. Die Erforschung des Alterungsprozesses und alternsassoziierter Erkrankungen wie z.B. Krebs, Schlaganfall, Nierenversagen, Diabetes, chronische Entzündungen oder Neurodegeneration bildet einen wichtigen Aspekt in unserem Zukunftskonzept, das durch die Exzellenzinitiative von Bund und Ländern finanziert wird. Wir leben in einer alternden Gesellschaft – unsere Hochschule leistet in einem international kompetitiven Umfeld einen essentiellen Erkenntnisgewinn in der Grundlagenforschung und einen systematisierten Transfer in neue klinische Therapien.

Das Altern unserer Gesellschaft und die Herausforderungen, die sich für uns alle daraus ergeben, gehören ohne Zweifel zu den „Mega-Themen" unserer Zeit. Die Ergebnisse unserer Forschung möchten wir daher auch in die Praxis übersetzen – mit einer hohen gesellschaftlichen, volkswirtschaftlichen als auch individuellen Relevanz.

Gleichzeitig bildet der Transfer in die Praxis einen starken Anknüpfungspunkt zwischen Wissenschaft und Wirtschaft. Um Therapien zur Anwendungsreife zu entwickeln und schließlich erfolgreich in der Behandlung von Patientinnen und Patienten einsetzen zu können, bedarf es einer engen Zusammenarbeit von Wissenschaft und Wirtschaft, die durch CECAD erfolgreich realisiert wird.

Die Forschungserfolge und vielfältigen Kooperationen machen CECAD damit schließlich auch zu einem Aushängeschild des Wissenschaftsstandorts Köln und der Wissenschaftsregion Rheinland. CECAD ist ein Forschungsverbund, der von der internen wie standortübergreifenden Vernetzung und Kooperation lebt. In CECAD arbeiten über 400 internationale Wissenschaftlerinnen und Wissenschaftler aus der Universität und der Uniklinik sowie aus den beiden Max-Planck-Instituten auf unserem Campus (für die Biologie des Alterns und für die Stoffwechselforschung) sowie dem Deutschen Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft (DZNE). Das im Mai 2013 eröffnete CECAD Forschungszentrum ist ein Katalysator für die wissenschaftlichen Aktivitäten von CECAD.

Die Konzeption des Gebäudes zeigt, wie sehr der Erfolg von CECAD auf Vernetzung und Kommunikation nach innen wie nach außen aufbaut. Modernste Technologien bieten Forschung auf international wettbewerbsfähigem Standard.

Seit dem Start des Clusters im November 2007 hat sich CECAD sehr dynamisch und erfolgreich entwickelt. Die Bewilligung einer zweiten Förderperiode im Rahmen der Exzellenzinitiative des Bundes und der Länder dokumentiert, dass CECAD in den vergangenen Jahren wissenschaftlich außerordentlich erfolgreich war und auch in vorbildlicher Weise strukturbildend gewirkt hat, etwa durch insgesamt 17 Neuberufungen, der wissenschaftlichen Nachwuchsförderung sowie der Schaffung von Infrastrukturen.

Für die weitere Arbeit hat sich CECAD anspruchsvolle Ziele gesetzt, die erwarten lassen, dass von diesem Forschungsverbund auch in Zukunft bedeutende Impulse für Forschung und Lehre am Wissenschaftsstandort Köln ausgehen werden.

Die Schwerpunkte von CECAD sind in vielfältiger Weise mit der Forschungstätigkeit in anderen Disziplinen der Universität zu Köln verknüpft, denn die Herausforderungen des Alterns unserer Gesellschaft sind nicht allein medizinischer Art. Sie umfassen viele Dimensionen und wissenschaftlichen Disziplinen. In den Geistes- und Gesellschaftswissenschaften werden so etwa kulturelle Implikationen und gesellschaftliche Veränderungen erforscht, die sich aus dem demographischen Wandel in sozialer und rechtlicher Hinsicht ergeben.

Ich freue mich sehr über den Erfolg des Clusters, der auch für die Universität zu Köln ein großer Erfolg ist. Der vorliegende Geschäftsbericht des Clusters unterstreicht die hohe Dynamik des Clusters und gibt einen spannenden Einblick in die Forschung von CECAD.

Prof. Dr. Axel Freimuth
Rector of the University of Cologne

Founding the CECAD cluster of excellence, the University of Cologne has established a center for aging research unique the world over. Research into the aging process and age-associated diseases such as cancer, strokes, kidney failure, diabetes, chronic inflammation and neurodegenerative disorders is an essential aspect of our concept for the future, financed by the German federal and state governments through the Excellence Initiative.

We live in an aging society. In an internationally competitive field, our university is generating essential knowledge through basic research and the systematic transfer of findings into new clinical therapies.

The demographic changes currently underway and the challenges they bring are without a doubt one of the key issues of our time. Thus we focus on translating our research findings into practice – a process of high social, economic and individual relevance.

This transfer into practical applications also represents a powerful interface between the scientific and business communities. Science and the private sector need to work in close cooperation to develop mature therapies that can successfully be used to treat patients. This collaborative process is being effectively realized at CECAD.

Productive research findings and a wide range of partnerships make CECAD a flagship for Cologne as a center of scientific research, and for the Rhineland as a science hub. CECAD is a research association that thrives from its networks and partnerships – both within the University of Cologne and spanning multiple locations. Over 400 international scientists from the University of Cologne, the University Hospital Cologne and the Max Planck Institutes for the Biology of Ageing and Metabolism Research on our campus, along with the German Center for Neurodegenerative Diseases within the Helmholtz Association (DZNE), work at CECAD.

Since the new CECAD Research Center opened in May 2013, it has served as a catalyst for CECAD's scientific activities. The building's design is a physical manifestation of the emphasis CECAD places on the networking and communication, internally and externally, so essential to our success. State-of-the-art technologies offer an internationally competitive research environment.

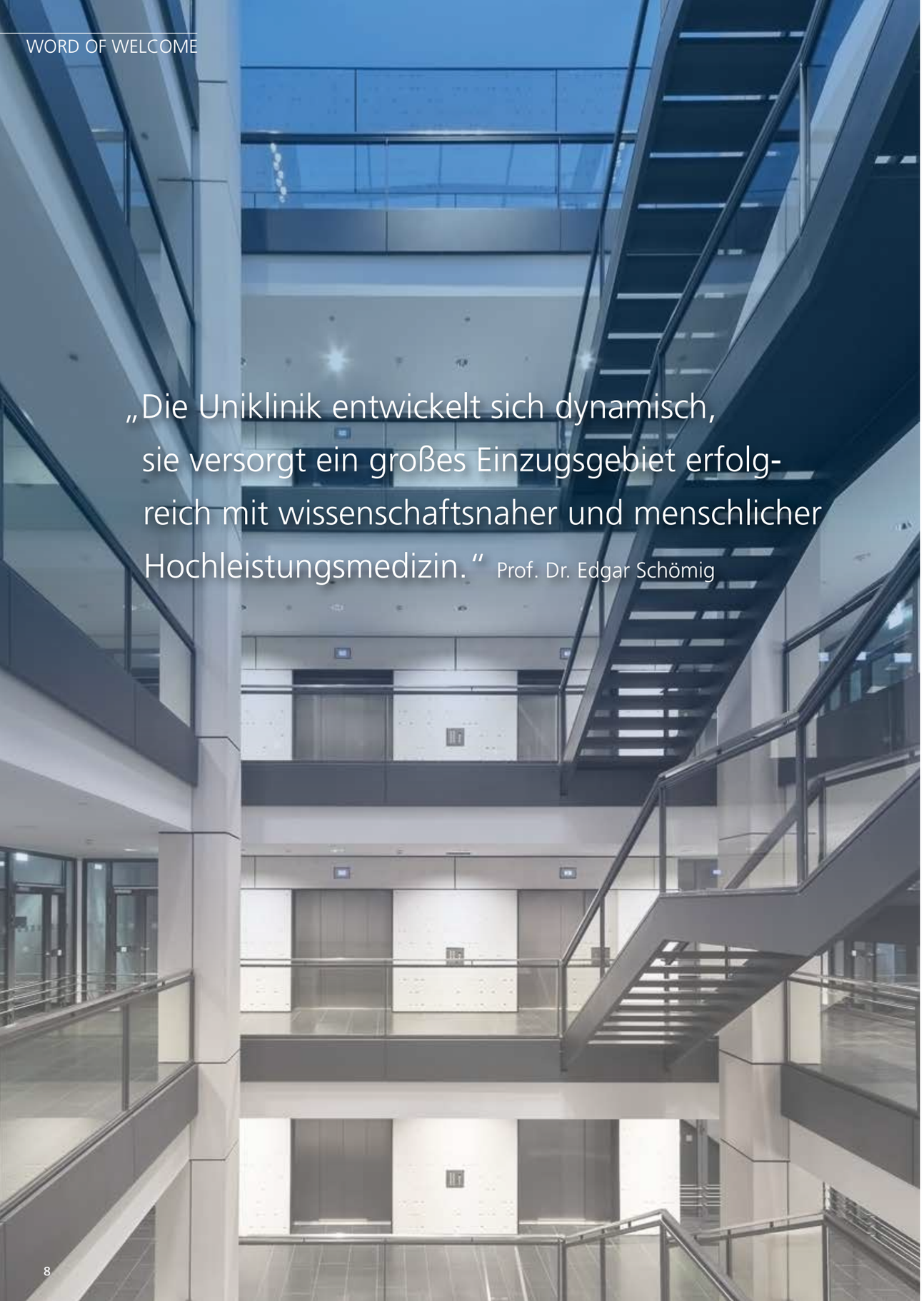
Since the cluster opened its doors in November 2007, CECAD has grown very dynamically and successfully. The approval of a second funding period as part of the German federal and state government's Excellence Initiative is impressive proof of CECAD's extreme scientific success in past years and how exceptionally it has worked to generate structures, including a total of 17 new appointments, our support of young scientists, and by establishing infrastructures.

CECAD has set ambitious goals for its continuing work. We can expect this research association will continue to enrich Cologne as a scientific hub by providing significant impulses for research and teaching in future as well.

CECAD's focal points are linked in a variety of ways with research in other disciplines at the University of Cologne. After all, the challenges posed by the aging of our society cannot be met by medicine in isolation. It involves a wide array of dimensions and scientific disciplines. The humanities and social sciences, for instance, explore the social and legal aspects of the cultural implications and social changes that result from demographic change.

I am very pleased with the Cluster's success, which represents resounding success for the university as well. This annual report emphasizes the cluster's exceptional dynamism and offers an exciting look into the research being done at CECAD.





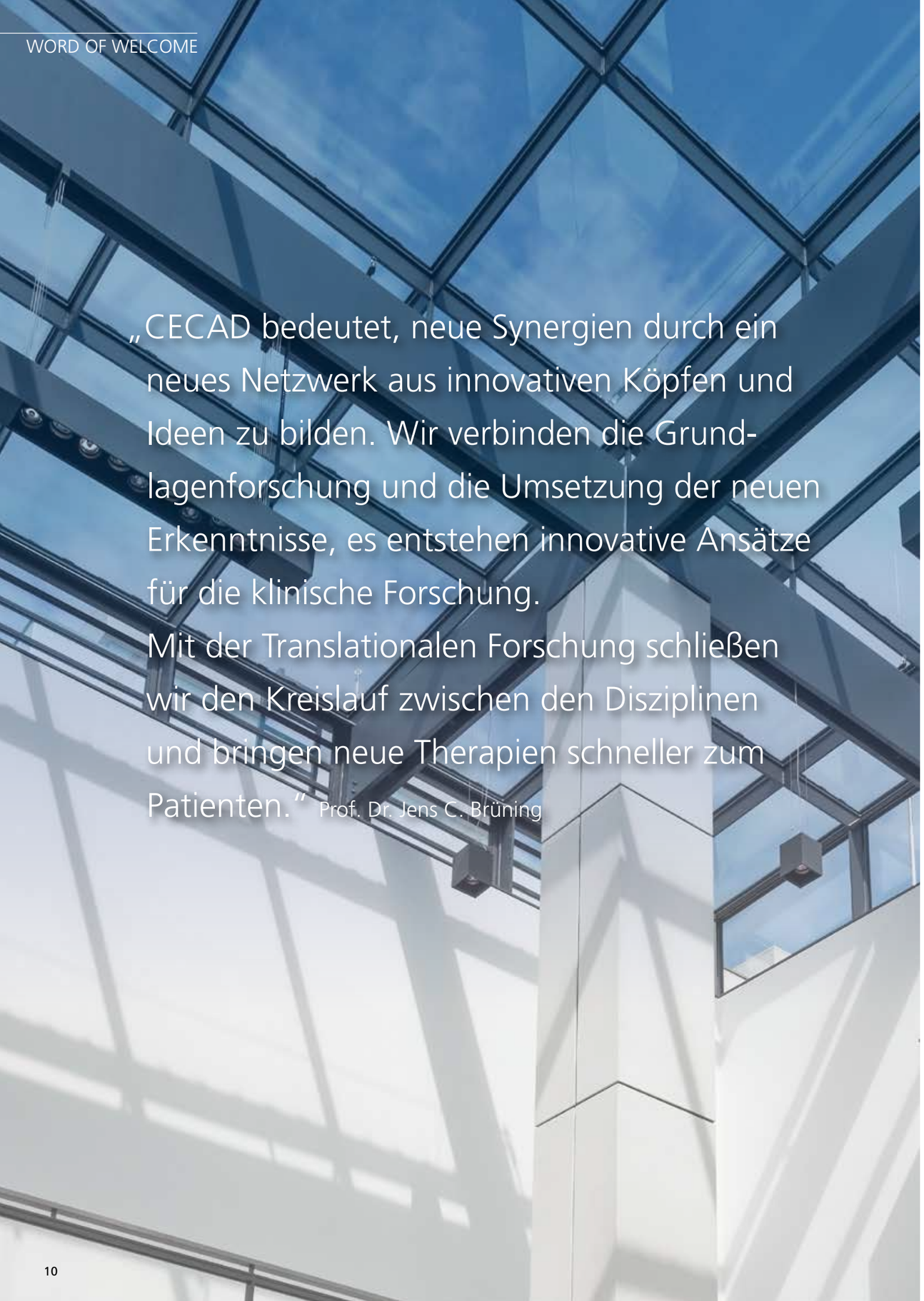
„Die Uniklinik entwickelt sich dynamisch, sie versorgt ein großes Einzugsgebiet erfolgreich mit wissenschaftsnaher und menschlicher Hochleistungsmedizin.“ Prof. Dr. Edgar Schömig

Prof. Dr. Edgar Schömig

Medical Director and Chairman of Executive Board of the University Hospital Cologne

Die Uniklinik Köln arbeitet mit an der Vision von CECAD, der Erforschung der gemeinsamen Ursachen des Alterungsprozesses und altersassoziierter Erkrankungen um daraus neue Therapien für die klinische Therapie zu entwickeln: Ein spannender und zukunftsweisender Prozess mit starken Synergien durch die unmittelbare Nähe vom neuen CECAD Forschungszentrum zum Klinikum und den beiden Max-Planck-Instituten für Biologie des Alterns und für Stoffwechselforschung.
Wir leben in einer alternden Gesellschaft. Die starke gesellschaftliche Relevanz der Forschung von CECAD erleben unsere Ärzte jeden Tag in der Klinik, in der Behandlung der typischen altersassoziierten Erkrankungen wie Neurodegeneration, Krebs, chronische Entzündungen und Nierenerkrankungen, Schlaganfall, oder Diabetes mellitus.
Der interdisziplinäre Fokus des Clusters ist eine große Stärke und Besonderheit: Die Chance, wissenschaftliche Fragestellungen in der Zusammenschau von naturwissenschaftlicher Grundlagenforschung mit medizinisch-therapeutischem Zugang zu betrachten, bietet für die Patienten der Uniklinik einen hohen Nutzen.
Die Uniklinik entwickelt sich dynamisch, sie versorgt ein großes Einzugsgebiet erfolgreich mit wissenschaftsnaher und menschlicher Hochleistungsmedizin. Sie konnte im fünften Jahr in Folge ein positives Jahresergebnis erwirtschaften und die Zahl der Beschäftigten erneut steigern.
Die wissenschaftliche Forschungsleistung von CECAD ist für die Uniklinik Köln von großer Bedeutung. Mit dem Slogan „From bench to bedside and back“ leistet CECAD mit der translationalen Forschung den wichtigen Erkenntnistransfer aus der Grundlagenforschung in die klinische Therapie. Angesichts neuer globaler medizinischer Herausforderungen in der Infektiologie, der Bekämpfung der klassischen Volks- und Alterserkrankungen und der Zunahme von Neuerkrankungen von Krebs und Neurodegeneration ist die Entwicklung neuer medizinischer Strategien und die Vertiefung des Verständnisses von Stoffwechselprozessen im gesamten Organismus von gesellschaftlich extrem hoher Bedeutung.
Vor diesem Hintergrund sind die Forschungsschwerpunkte von CECAD auch in der strategischen Ausrichtung der Uniklinik von großer Bedeutung.
Viele der insgesamt über 400 internationalen CECAD Wissenschaftlerinnen und Wissenschaftler sind auch in unseren Kliniken als Ärzte oder Forscher tätig und leisten durch ihre tägliche Arbeit einen wichtigen Beitrag zum Erkenntnistransfer.
Das im Mai 2013 eröffnete neue CECAD Forschungszentrum ist zentral auf dem Klinikscampus angesiedelt. Es entwickelt sich zu einer zentralen Anlaufstelle des wissenschaftlichen Austauschs, der internationalen Vernetzung und Innovation. Neueste Technologien bieten ein international wettbewerbsfähiges Forschungsumfeld. Forschung braucht Kommunikation, Kommunikation braucht Nähe. Die Uniklinik ist Teil eines weltweit einzigartigen Zentrums für Alternsforschung.

University Hospital Cologne plays an active role in realizing CECAD's vision of exploring the common causes of the aging process and age-associated diseases, and deriving new therapies for clinical treatment. This is an exciting and forward-looking process in which the close proximity of the new CECAD Research Center to the University Hospital and the Max Planck Institutes for Biology of Aging and Metabolism Research generates powerful synergies.
We live in an aging society. Every day at the clinic, in the treatment of typical aging-associated diseases such as neurodegeneration, cancer, chronic inflammation, renal disease, strokes, and diabetes mellitus, our doctors are confronted by the social relevance of the research done at CECAD.
The cluster's interdisciplinary focus is a great strength and unique quality. This opportunity to investigate scientific questions through the interplay of basic scientific research and medical-therapeutic access is a tremendous advantage for University Hospital patients. Our hospital is enjoying dynamic growth: It successfully serves a large area with scientifically advanced, cutting-edge medicine that focuses on the patient. For the fifth year in a row, we have recorded a profit and again increased our staff.
The scientific research pursued by CECAD is very important to University Hospital Cologne. With its "from bench to bedside and back" approach, CECAD is contributing to the crucial process of transferring findings from basic science into clinical therapies via its translational research. In view of the new global medical challenges facing us today in infectology, the fight against wide-spread and aging-associated diseases, and the rising number of new cancer cases and neurodegenerative disorders, developing new medical strategies and deepening our understanding of the metabolic processes taking place throughout the body are essential for our society.
This is why CECAD's research focus is also a key element in determining the University Hospital's strategic direction.
Many of the over 400 international CECAD scientists are also active in our clinics as doctors and researchers. Their daily work is making an important contribution to knowledge transfer.
The new CECAD Research Center, opened in May 2013, is strategically located on the hospital campus. It is developing into pivotal hub for scientific exchange, international networks and innovation. State-of-the-art technologies ensure an internationally competitive research environment. Research requires communication, communication requires close proximity. The University Hospital is proud to be part of this internationally unique center for aging research.



Prof. Dr. Jens C. Brüning

Scientific Coordinator of CECAD Cluster of Excellence at the University of Cologne

Das Altern kommt schleichend, für jeden. Die Forschung des Exzellenzclusters CECAD hat vor diesem Hintergrund eine hohe gesellschaftliche Relevanz und wissenschaftliche Komplexität. Immer mehr Menschen werden immer älter. In einer alternden Gesellschaft ist die volkswirtschaftlich zu erwartende Kostensteigerung im Gesundheitswesen immens. In diesem Spannungsfeld erforscht der Exzellenzcluster CECAD an der Universität zu Köln die Ursachen des Alterungsprozesses und alternsassoziierter Erkrankungen. Unsere Vision ist, daraus neue klinische Therapien für das gesamte Spektrum alternsassoziierter Erkrankungen wie Krebs, Diabetes, Schlaganfall, Nierenversagen oder neurodegenerative Störungen abzuleiten.
CECAD bedeutet, neue Synergien durch ein Netzwerk aus innovativen Köpfen und Ideen zu bilden. Wir verbinden die Grundlagenforschung und die Umsetzung der neuen Erkenntnisse, es entstehen innovative Ansätze für die klinische Forschung.
Mit der translationalen Forschung schließen wir den Kreislauf zwischen den Disziplinen und bringen Therapien schneller zum Patienten.
CECAD ist im Rahmen der DFG-Exzellenzinitiative von Bund und Ländern Ende 2012 erfolgreich in die zweite Förderperiode gestartet.
Mehr als 400 internationale Wissenschaftlerinnen und Wissenschaftler aus der Universität zu Köln, der Uniklinik, den Max-Planck-Instituten für Biologie des Alterns und für Stoffwechselforschung sowie dem Zentrum für Neurodegenerative Erkrankungen (DZNE) arbeiten hier eng vernetzt und interdisziplinär zusammen. So ist in Köln ein weltweit einzigartiges Zentrum für Alternsforschung entstanden.
Erfolgreiche Spitzenforschung basiert auf enger Kooperation und Kommunikation. Nur im Dialog können innovative Ideen zur Lösung komplexer Probleme entstehen. Das im Mai 2013 eröffnete CECAD Forschungszentrum bietet neueste Technologien und die unmittelbare Nähe zwischen den CECAD Forschungsgruppen und den Max-Planck-Instituten. Das besondere Gebäude- und Laborkonzept realisiert optimale Arbeitsbedingungen für Forschung und Innovation. Kliniker und Grundlagenwissenschaftler arbeiten eng zusammen – das impliziert neue Impulse für Wissenschaftler und einen hohen Nutzen für die Patienten der Uniklinik.
Rund 25 % der Fläche sind als „White Space“ reserviert – die besten Nachwuchswissenschaftler/innen bewerben sich auf diese Laborflächen und treten in ihrer täglichen Arbeit in enge Interaktion mit den Forschungsgruppen des Hauses.
CECAD forscht mit einer starken Performance: Um die Ursachen altersassoziierter Erkrankungen zu verstehen und neue Therapien zu entwickeln.

Aging is a constant effect, affecting everybody virtually from birth on. This underscores the social relevance and scientific complexity of the research being done at the CECAD Excellence Cluster.
As average life expectancy increases, more and more people are living longer. In our aging society, the anticipated increased burden to the domestic economy for rising health care costs is immense. Research at the CECAD Excellence Cluster at the University of Cologne into the causes of aging and age-associated disorders is at the interface of this fascinating field of tension. Our vision is to develop new therapies for the entire spectrum of aging-associated diseases, including cancer, diabetes, strokes, renal failure and neurodegenerative disorders.
CECAD stands for creating new synergies through a novel network of innovative minds and ideas. We link basic research and the application of new findings, pioneering new approaches for clinical research. Through translational research, we close the loop, linking disciplines and delivering therapies to patients faster.
As part of the DFG Excellence Initiative supported by the federal and state governments, CECAD successfully entered its second funding period at the end of 2012.
More than 400 international scientists from the University of Cologne, the University Hospital Cologne, the Max Planck Institutes for Biology of Ageing and for Metabolism Research as well as the Center for Neurodegenerative Diseases (DZNE) work together in an interdisciplinary setting at CECAD. Together they have made Cologne an internationally unique hub of aging research. Successful leading research is based on close cooperation and communication. Spectacular ideas for solving complex problems can only emerge from dialogue. The new CECAD Research Center that opened in May 2013 offers the latest technologies and brings the CECAD research groups and the Max Planck Institutes into close proximity. The unique building and laboratory design creates optimal working conditions for research and innovation. Clinicians and basic researchers work closely together, generating new impulses for scientists and great value for patients at the University Hospital.
Around 25% of the area has been reserved as “white space” – the best young rising scientists apply to use this laboratory space and benefit in their daily work from fruitful interactions with research groups in the building.
CECAD excels at high performance research: to understand the causes of aging-associated diseases and develop new therapies.



„Der Exzellenzcluster CECAD hat einen starken Anteil an der Positionierung der Universität zu Köln als Exzellenz-Universität.
Die Medizinische Fakultät unterstützt die Entwicklung des Clusters mit seiner wichtigen strategischen Schnittstellenfunktion zwischen der Universität und der Uniklinik Köln mit großem Engagement. Mit den hervorragenden Forschungsergebnisse aus der ersten Förderperiode konnte die DFG-Weiterförderung bis 2017 erreicht werden.“ Prof. Dr. Thomas Krieg

Prof. Dr. Thomas Krieg

Dean of Medical Faculty of the University of Cologne

Der Forschungserfolg des Exzellenzclusters CECAD und die dadurch ausgelösten Entwicklungen der Infrastruktur tragen wesentlich zur Positionierung der Universität zu Köln als Exzellenz-Universität bei. CECAD hat mit seiner Forschung eine wichtige strategische Schnittstellenfunktion zwischen der Mathematisch-Naturwissenschaftlichen und der Medizinischen Fakultät der Universität zu Köln sowie der Uniklinik Köln. Grundlagenorientierte und klinische Forschungsgruppen arbeiten interdisziplinär und interfakultär eng zusammen und führen mit hochrangig publizierten neuen Erkenntnissen zu tieferem Verständnis des Alterungsprozesses und damit assoziierter Erkrankungen.
Mit großem Engagement hat die Medizinische Fakultät die Entstehung des Clusters unterstützt. Mit den hervorragenden Forschungsergebnissen aus der ersten Förderperiode konnte der Cluster erfolgreich durch die DFG mit Verlängerung der Projektlaufzeit bis 2017 bestätigt werden.
Die Medizinische Fakultät der Universität zu Köln bildet derzeit rund 3.400 Mediziner nach neuestem Wissensstand aus, um die Mechanismen von vielen Erkrankungen zu verstehen und neue therapeutische Konzepte daraus abzuleiten. CECAD bietet die Chance, über die monodisziplinäre Sicht hinaus Erkrankungen interdisziplinär zu betrachten. Alternsassoziierte Erkrankungen wie zum Beispiel Schlaganfall, Krebs, Diabetes, Nierenversagen, erhöhte Infektionsanfälligkeit oder neurodegenerative Erkrankungen werden auf ihre gemeinsamen molekularen Mechanismen erforscht. So werden Synergien gewonnen, die bei einer separaten Betrachtung nicht in den Fokus rücken.
Der Vision, die gemeinsamen Ursachen zu verstehen und daraus neue Therapien abzuleiten, ist CECAD seit dem Start Ende 2007 einen großen Schritt näher gekommen. Forschungsdurchbrüche führten nicht zuletzt durch den systematischen Transfer der Erkenntnisse aus der Grundlagenforschung in die Klinik zu medizinischen Erfolgen. In einer alternden Gesellschaft hat diese Forschung eine hohe gesellschaftliche wie auch individuelle Relevanz.

Etwa 1.800 Wissenschaftlerinnen und Wissenschaftler sind dem Medizinischen Dekanat der Universität zu Köln zugeordnet und verfolgen an über 50 verschiedenen Kliniken, Instituten und Forschungszentren ein gemeinsames Ziel: die Optimierung einer patientenorientierten Spitzenforschung und Hochleistungsmedizin.
Das Medizinische Dekanat engagiert sich in den drei Forschungsschwerpunkten „Gewebshomöostase, Metabolismus und Degeneration“, „Tumor, Infektion und Abwehr“ und „Neuromodulation“. Drei weitere Forschungsschwerpunkte befinden sich derzeit im Aufbau. Das bereits auf dem Campus bestehende „Zentrum für Molekulare Medizin“, die Einwerbung von drei Sonderforschungsbereichen und zwei klinischen Forschergruppen innerhalb der Fakultät und die beiden Max-Planck-Institute in unmittelbarer Nachbarschaft belegen die hohe wissenschaftliche Qualität des Umfeldes, in dem die CECAD-Wissenschaftler/innen interagieren.
Gemeinsam mit CECAD konnte die Medizinische Fakultät neue Professoren und Junior Gruppenleiter in der ersten wie auch in der zweiten Förderperiode rekrutieren und damit einen langfristigen Fokus in einem kompetitiven Umfeld setzen.
Die internationale ‚Cologne Graduate School of Aging Research‘, die von CECAD, den beiden Max-Planck-Instituten und dem Forschungszentrum Caesar betrieben wird, bildet eine neue interdisziplinär arbeitende Wissenschaftlergeneration aus, mit dem Ziel, die Grundlagenforschung zum vertiefteren Verständnis alternsassoziierter Erkrankungen erfolgreich zu optimieren – mit einem hohen gesellschaftlichen Nutzen und einer starken strategischen Positionierung der Uniklinik Köln und der Universität zu Köln.

WORD OF WELCOME

Prof. Dr. Thomas Krieg
Dean of Medical Faculty of the
University of Cologne

The successful research conducted at the CECAD Cluster of Excellence and the infrastructure development it has brought have considerably contributed to the University of Cologne's positioning as a university of excellence. Through its research, CECAD plays a key strategic role as the interface between the Faculty of Mathematics and Natural Sciences and the Faculty of Medicine at the University of Cologne and Cologne University Hospital. Basic and clinical research groups work closely together on both an interdisciplinary and interfaculty level, publishing exceptional new findings that deepen our understanding of the aging process and the disorders associated with it.

The Faculty of Medicine wholeheartedly supported the formation of the Cluster. Based on the outstanding research results from the first funding period, the Cluster has successfully confirmed through the DFG that the project period has been extended until 2017.

Currently, the University of Cologne Faculty of Medicine trains around 3,400 doctors according to the latest state of knowledge in our ongoing effort to illuminate the mechanisms of many diseases and derive new therapeutic concepts from them. CECAD offers an opportunity to move beyond a monodisciplinary perspective and take an interdisciplinary view of disease. The Cluster's work explores the shared molecular mechanisms underlying aging-associated diseases such as stroke, cancer, diabetes, kidney failure, increased susceptibility to infections and neurodegenerative disorders, yielding synergies that would not come to light if they were considered separately.

Since it opened at the end of 2007, CECAD has come a large step closer to its vision of understanding these joint causes and using them as a basis for new therapies. Research breakthroughs have led to medical successes, not least through the systematic transfer of findings from basic research into the clinic. In our aging society, this research is exceptionally relevant to both the individual and society as a whole.

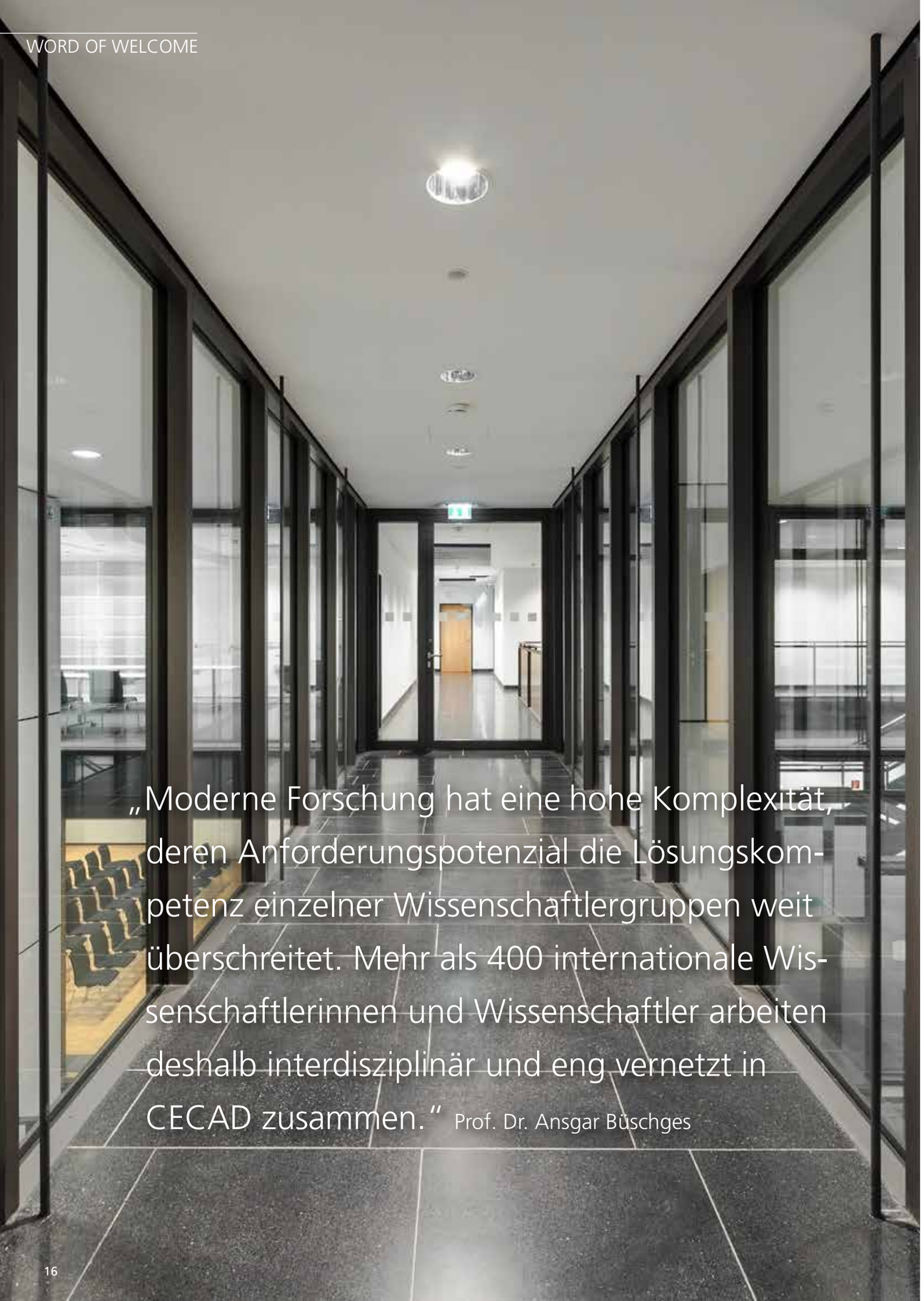
Around 1,800 scientists work under the aegis of the Medical Deanship at the University of Cologne and pursue a common goal at over 50 different clinics, institutes and research centers: optimizing patient-oriented leading research and advanced medicine.

The Medical Deanship actively participates in three core research areas "Tissue Homeostasis, Metabolism and Degeneration", "Tumor, Infection and the Immune Response", and "Neuromodulation". Three additional core research areas are currently under development. The "Center for Molecular Medicine" already on campus, the procurement of three "Collaborative Research Centres" and two "Clinical Research Units" inside the faculty, and the two Max Planck Institutes in close proximity are proof of the exceptional scientific quality of the environment with which CECAD scientists interact.

Together with CECAD, the Faculty of Medicine has been able to recruit new professors and junior group leaders in the first and the second funding period, setting a long-term focus in a competitive environment.

The international 'Cologne Graduate School of Aging Research', operated by CECAD, the two Max Planck Institutes and the Caesar Research Center, is educating a new generation of scientists who work in an interdisciplinary manner with the goal of optimizing basic research aimed at successfully deepening our understanding of aging-associated diseases – extremely useful for society and for the powerful strategic positioning of the University Hospital Cologne and the University of Cologne.





Prof. Dr. Ansgar Büschges

Dean of Faculty of Mathematics and Natural Sciences

Die Alternsforschung ist mit etwa 20 Jahren eine vergleichsweise junge Disziplin. Sie ist ein interdisziplinäres Brennglas wissenschaftlicher Disziplinen und bietet die Chance, die Grundlagenforschung molekularer Mechanismen mit der volkswirtschaftlich dringlichen Erforschung von Volkskrankheiten durch den Transfer neuer Erkenntnisse zu verbinden.
Die Mathematisch-Naturwissenschaftliche Fakultät mit mehr als 160 Professuren und mehr als 15.000 Studierenden an der Universität zu Köln hat ein starkes Interesse an der interdisziplinären Forschung des Exzellenzclusters CECAD. Mit großem Engagement hat die Fakultät mit dem Institut für Genetik die Gründung und Entwicklung des Clusters als Bestandteil der wissenschaftlichen Profilbildung der Universität zu Köln im Rahmen der Exzellenzinitiative unterstützt und durch die interdisziplinäre Forschung mit den Instituten für Biochemie, Zoologie und Entwicklungsbiologie erfolgreich entwickelt.
Aus ihrer langjährigen Kooperation leiteten die Mathematisch-Naturwissenschaftliche und die Medizinische Fakultät 1995 mit der Gründung des Zentrums für Molekulare Medizin (ZMMK) auf dem Kölner Campus eine wegweisende Profilierung auf dem Gebiet der molekularen Medizin ein. Diese Fortschritte in der interdisziplinären Forschung lösten eine weitere profilverstärkende Gründung des international ausstrahlenden Zentrums für Alternsforschung aus. Zusammen mit Wissenschaftlerinnen und Wissenschaftlern der Medizinischen Fakultät, der Uniklinik sowie den beiden Max-Planck-Instituten für Biologie des Alterns und für Stoffwechselforschung entstand ein weltweit einzigartiges Kompetenzzentrum für Alternsforschung.
Mit dem Exzellenzcluster CECAD konnten durch die neu geschaffenen Core Facilities neueste Service-Technologien für alle Kolleginnen und Kollegen aus den Life Sciences zur Verfügung gestellt werden, Forschungsbereiche wie Lipidomics und Proteomics konnten dadurch stimuliert werden.
Die Einbindung eines weiteren fakultätsübergreifenden Zentrums, dem Cologne Center for Genomics (CCG), in beide Fakultäten, in den Exzellenzcluster und in das ZMMK unterstützt die zukunftsgerichtete Forschungsorientierung. Die Gründung neuer Sonderforschungsbereiche (SFB's) wurde durch die hohe Dynamik in den Life Sciences sehr erfolgreich unterstützt. Moderne Forschung hat eine hohe Komplexität, deren Anforderungspotenzial die Lösungskompetenz einzelner Wissenschaftlergruppen weit überschreitet. Mehr als 400 internationale Wissenschaftlerinnen und Wissenschaftler arbeiten deshalb interdisziplinär und eng vernetzt in CECAD zusammen. Die demographische Entwicklung verdeutlicht die hohe Bedeutung der Forschungserfolge: Für eine lange gesunde Lebensspanne im Alter, für das Verständnis des Alterungsprozesses und die damit assoziierten Erkrankungen.

Aging research is still a comparatively young discipline that began around 20 years ago. It is an interdisciplinary burning glass of scientific disciplines and offers opportunities for linking basic research into molecular mechanisms with economically vital research on common diseases through the transfer of new findings.
With more than 160 professors and over 15,000 students, the Faculty of Mathematics and Natural Sciences at the University of Cologne has a vested interest in the interdisciplinary research conducted at the CECAD Excellence Cluster. Together with the Institute for Genetics, the faculty was actively involved in founding and advancing the Cluster as a key element of the University of Cologne's scientific profile in the Excellence Initiative. Through interdisciplinary research with the Institutes for Biochemistry, Zoology and Developmental Biology, the faculty has also been instrumental in CECAD's successful continued development.
Based on their years of cooperation, the Faculty of Mathematics and Natural Sciences and the Faculty of Medicine created an innovative profile in the area of molecular medicine with the founding of the Center for Molecular Medicine (CMMC) on the Cologne campus in 1995. These advances in interdisciplinary research sparked the creation of the internationally influential Center for Aging Research, further strengthening the university's profile. Together with scientists from the Faculty of Medicine, the University Hospital and the Max Planck Institutes for Biology of Ageing and for Metabolism Research, an internationally unique center of excellence in aging research has been formed.
The CECAD Cluster of Excellence has enabled the newly created core facilities to offer all colleagues from the life sciences the latest service technologies and stimulate research areas such as lipidomics and proteomics.
The integration of an additional cross-faculty center, the Cologne Center for Genomics (CCG) into the two faculties, the Excellence Cluster and the ZMMK promotes this future-oriented research approach. The high vitality of the life sciences at the university has resulted in successful support for the founding of new "Collaborative Research Centres" (CRC).
Modern research is so complex, its demand potential goes well beyond the ability of individual research groups to offer comprehensive solutions, so more than 400 international scientists are working in a close and interdisciplinary network at CECAD. Current demographic development illustrates the exceptional importance of successful research: for a long, healthy life into advanced age, and for our understanding of the aging process and the diseases associated with it.

Facts & Figures

CECAD Cluster of Exellence

Scientific Coordinator
Prof. Dr. Jens C. Brüning

- **Deputy Scientific Coordinator**
  Prof. Dr. Thomas Langer (UoC)
- **Deputy Scientific Coordinator**
  Prof. Dr. Michael Hallek (UHoC)

Executive Board

- **Scientific Coordinator**
- **Deputy Scientific Coordinator**
  (UoC, UHoC)
- **Heads of Research Areas**
- **Heads of Research Platforms**
- **Representative of Young Scientists**
- **Permanent Guests**
  Administrative Coordinator
  Head of PR & Marketing
  Financial Project Manager

Central Office

- **Administrative Coordination**
  Dr. Benjamin Köckemann
  Dr. Anja Pfletschinger
- **Assistance of Administrative Coordination**
  Maria Vilgertshofer
- **Financial Projectmanagement**
  Dr. Nora Redemann
- **Head of PR & Marketing**
  Astrid Bergmeister MBA
- **Managing Coordinator for Career Development & Gender Equality,** Dr. Doris Birker
- **Assistance Coordinator for Career Development & Gender Equality,** Jenny Ostermann

Technology Platform

- **Head of Technology Platform**
  Prof. Dr. Peter Nürnberg
- **Head of Imaging Facility**
  Dr. Astrid Schauss
- **Head of Lipidomics Facility**
  Dr. Susanne Brodesser
- **Head of Proteomics Facility**
  Dr. Tobias Lamkemeyer
- **Head of Bioinformatics Facility**
  Dr. Peter Frommolt

Platform for Translational Research
Prof. Dr. Oliver Cornely
Prof. Dr. Michael Hallek

Research Areas

A: Mitochondrial Dysfunction in Aging and Neurodegeneration
Prof. Dr. Thomas Langer
Prof. Dr. Elena Rugarli

B: Disruptions in Protein Metabolism Cause Aging-Associated Diseases
Prof. Dr. Thomas Benzing
Prof. Dr. Thorsten Hoppe

C: DNA-damage responses in Aging-associated Diseases
Prof. Dr. Christian Reinhardt
Prof. Dr. Björn Schumacher

D: The Aging of Membranes
Prof. Dr. Martin Krönke

E: Inflammation in Aging-Associated Diseases
Prof. Dr. Thomas Krieg
Prof. Dr. Manolis Pasparakis

F: Metabolism in Aging Process, Diabetes and Obesity
Prof. Dr. Jens C. Brüning
Prof. Dr. Linda Partridge

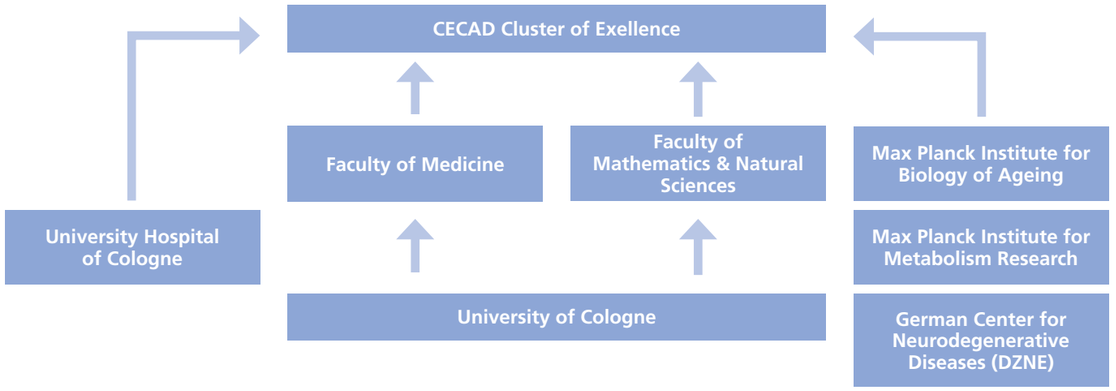
in vivo Research Facility

- **Head of in vivo Research Facility**
  Prof. Dr. Branko Zevnik
- **Scientific Manager in vivo Research Facility**
  Dr. Ylva Mende

Facts & Figures:
CECAD at a glance

An overview of the CECAD Cluster of Excellence – the most important facts and figures:

- → CECAD Cluster of Excellence at the University of Cologne: supported by the Faculty of Mathematics and Natural Sciences and the Faculty of Medicine
- → Funded by the DFG as part of the federal and state Excellence Initiative since November 1, 2007
- → Second five-year funding period began in November 2012
- → May 2013: new CECAD Research Center opened
- → Central office for scientific administration
- → Three central platforms to support research:
  - → Technology Platform with five facilities
  - → Translational Platform
  - → Platform for Career Development, Training, Gender Equality, PR & Marketing



RESEARCH AT THE CLUSTER

Scientists approx. 440 from the University of Cologne, the University Hospital Cologne, the Max Planck Institutes for Metabolism Research and Biology of Ageing, and the Center for Neurodegenerative Diseases (DZNE)
Research areas 6
Principal Investigators 48
Technology facilities 5

THE CLUSTER'S VISION

In an aging society, the CECAD Cluster of Excellence explores the causes of aging processes and aging-associated disorders such as neurodegenerative diseases (Alzheimer's, Parkinson's), diabetes, strokes, kidney failure, chronic inflammation or cancer at the molecular level. The cluster's vision is to understand the common causes of aging and define novel therapeutic approaches for the entire spectrum of aging-associated disorders. This involves identifying the processes that fail as we age and can therefore trigger aging-associated diseases.



FROM LEFT TO RIGHT:
Studierendenhaus, University Hospital Cologne Bettenhaus, Max Planck Institute for Biology of Ageing

VISIBLE VITALITY

With CECAD, the Cologne Life Science Campus has developed a highly dynamic and productive scientific network. Specialized laboratories have been created that reflect the vitality of the cluster in the cityscape as well.

05/2009 CECAD Animal Facility Interim
2013 Max Planck Institute for Biology of Ageing
2013 CECAD Research Center
2014 Restructuring of Max Planck Institute for Metabolism Research (formerly Neurological Research)
These research facilities are in CECAD's immediate vicinity and together create an internationally recognized competence center for aging research.

HIGHTECH FOR RESEARCH

Five facilities offer CECAD scientists an exceptional environment and state-of-the-art technology:

→ Proteomics Facility
→ Lipidomics Facility
→ Imaging Facility
→ Bioinformatics Facility
→ in vivo Research Facility

The CECAD Technology Platform's strategic mission is to promote close cooperation between systems- and molecularly oriented research groups.

CAREER DEVELOPMENT

Exceptional research requires exceptional education: Educating and training young scientific talents is one of CECAD's central focuses. The cluster offers a structured three-year doctorate program in cooperation with the 'Cologne Graduate School of Ageing Research' on campus that has merged with the MPIs and caesar, along with an extensive range of CECAD career development support: numerous seminars, conferences and workshops – also in 'soft skills' – promote sustainable ca-



FROM LEFT TO RIGHT:
Max Planck Institute for Biology of Ageing, CECAD Research Center, Studierendenhaus, Haus Lebenswert

reers.
Equal opportunities for women and men are another of CECAD's important objectives. The vertical 'CECAD Female Faculty Club' network provides female scientists with information about special development opportunities. The cluster also cooperates closely with additional university facilities on equality and family support. The new 'Paramecium' childcare center assists CECAD scientists with small children with their childcare needs.

HIGH POTENTIAL

Strategic development of new appointments in the institutions involved promote CECAD's goals

- → Since 2007: 17 new appointments of internationally successful scientists and the recruitment of new research groups
- → Of these
  - → 6 W3 professorships confirmed through the University of Cologne
  - → 7 new junior research groups set up

CONSTRUCTION OF THE CECAD RESEARCH CENTER

Principals The University of Cologne and the University Hospital of Cologne
Financing Federal government and the federal State of NRW
Construction volume 100 M EUR

Specifications

- → A research center, centrally located on the hospital campus – for short communication channels and efficient working processes
- → Central service facilities, equipped with state-of-the-art technology, to support scientists in the Cluster
- → Identical construction of all laboratory floors to promote intensive communication as a key prerequisite for interdisciplinary research
- → Equipment that allows for close collaboration between clinical and basic research groups
- → Modern laboratory equipment with short distances and divided into laboratory and documentation zones

TECHNICAL DATA

Area Total floor space: 25,000 m²; Useable space: 10,600 m²; Floors: 7 upper floors, 3 basement floors
Realization medfacilities GmbH with architects from von gmp Gerkan, Marg und Partner, Aachen
Ground breaking September 2009
Commencement End of 2009
Roofing ceremony September 2011
Completed Spring 2013
Opened May 2013
Start-up operation Until Autumn 2014
Occupied As of October 2014

Research Center

CECAD Research Center:
Interdisziplinary and cross-linked
Centrally located on the Campus

Modern research is complex and based on the scientists' intensive communication. The new building, which was inaugurated May 2013, enables such close networking through a particular building and laboratory concept. With approximately 10,600 square meters and most modern technologies up to international standards it provides ideal research circumstances. A quarter of the area – the so called "White Space" – is at the disposal of varying highly qualified prospective research groups.
Due to the immediate proximity of the CECAD research groups, the clinicians and the Max Planck Institutes on campus, a world-wide unique center for aging research has been established. The University Hospital's patients profit from the systematical transfer of insights from the university's top-level research to new clinical therapies of a University Hospital with high-end medicine.



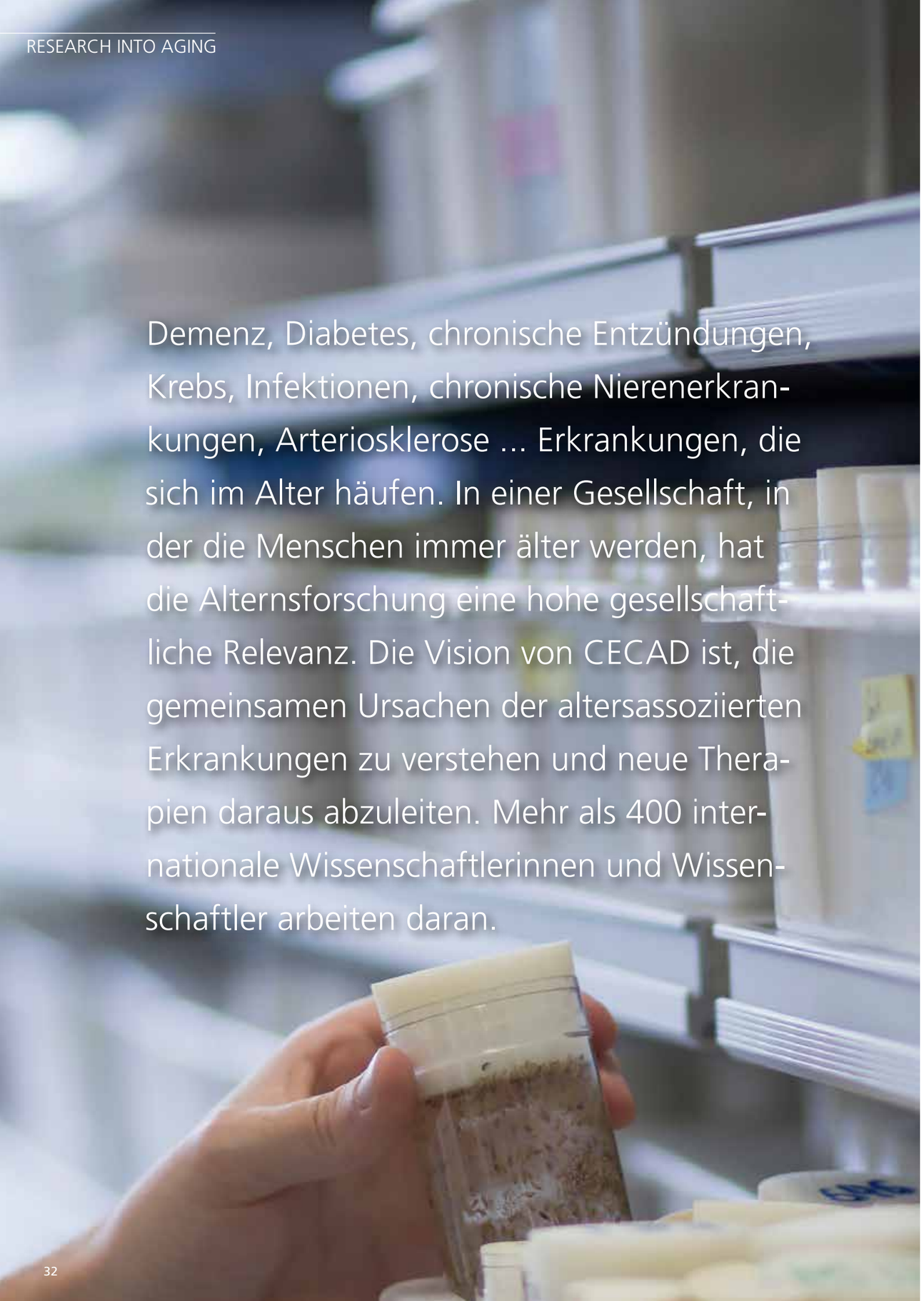


The laboratory floors are arranged like cloverleaves.
In order to enhance synergies, working groups share certain areas such as cell culture laboratories or the histology. State-of-the-art technology-facilities provide analyses and imaging services.

A path on campus, which connects everything from the university's main building to the University Hospital's Bettenhaus – and the CECAD research center which is located as a connection right on this student walkway. On the ground floor the path within public space leads through the building and connects to the glazed communication space on one side. Research requires communication – the latter increases in frequency and intensity congruently to the proximity. The moving-in of the research groups has boosted interdisciplinary cooperation tremendously, a big opportunity for research.

Research into Aging

CECAD’s strong vision



CECAD's vision:
Exploring the Aging Process
Research of Great Social Relevance

Dementia, diabetes, chronic inflammation, cancer, infections, chronic kidney disorders, arterial sclerosis … the prevalence of all these diseases increases with age. In a society in which people are living longer and longer, aging research is of high social relevance. More than 400 international scientists from the University of Cologne, the University Hospital Cologne, the Max Planck Institutes for Metabolism Research and Biology of Ageing, and the German Center for Neurodegenerative Diseases (DZNE) explore the molecular basis of the aging process and age-associated diseases at the CECAD Cluster of Excellence.

Developing new therapies for treating aging-associated diseases requires basic research.
Only if we recognise the molecular processes that trigger the pathogenesis of a disease, we can possibly find research approaches that will give us a new understanding of age-associated disorders. CECAD's vision is to develop new conjoint therapies for aging-associated diseases. To date, neurologists have dealt with dementia, cardiologists with heart disease and oncologists with tumours.
At CECAD we take an interdisciplinary approach: our scientists are looking for shared causes of age-associated disorders. Their goal is to find a central mechanism involved in the aging process that would allow scientists and medical professionals to successfully intervene.

Aging research is still a very young discipline that has explored the molecular causes of aging for around 25 years now. Regarding expectations, it is important to bear in mind that aging is a very complex phenomenon and basic research drives innovation by providing new impulses over a longer period of time. We must also recognise that more than just individual genes play a role in the aging process. As an object of research, the human body is a highly complex network with a multiplicity of interactions, aging-associated changes to biological molecules, and around 25,000 human genes in a considerably larger network of proteins. One of the most important goals is to understand the interplay in and among these networks and not just look at the aging of individual cells. This could define areas of intervention for realising CECAD's vision of effectively countering aging-associated diseases in future.

One of the central mechanisms often disrupted as we age is mitochondrial function. These are the powerhouses of the cells; they release the energy we need to live. All living creatures need working mitochondria to survive. As they operate though, they also release free oxygen radicals that damage the cells and set off a whole chain of failures implicated in the pathogenesis of neurodegenerative diseases.
The effect of DNA on the body is another central mechanism of aging. As we grow older, the cells in many tissues and organs lose partial or total function as DNA defects accumulate over time. This damage to the genes is extremely important because many aging-associated disorders are caused by DNA defects that cannot be repaired. These defects can accumulate in any type of cell, where they may trigger cancer growth, for example, or neurodegenerative diseases such as Alzheimer's and Parkinson's disease in the brain.
DNA defects are highly influential in carcinogenesis because they change how genes function. This may result in the continuous activation of a gene that regulates cell growth. CECAD research findings indicate that the genetic mechanisms that regulate lifespan in model organisms such as fruit flies and threadworms react to DNA damage. A central topic of future research is whether these mechanisms can counteract the dangerous impact of DNA defects, as such preserving tissue and organ function even in advanced age.



Aging effects all the processes and functions inside the cell. In addition to DNA damage, protein aggregates also accumulate. As we age, the cell's quality control mechanisms responsible for "cellular rubbish disposal" can no longer remove the damaged proteins. They accumulate, acting as potential triggers for neurodegenerative diseases such as Alzheimer's and Parkinson's, and can lead to the degeneration of other organs. CECAD scientists are therefore focusing on the processes that lead to this loss of quality control in order to better our understanding of the genesis of these diseases.

The cell membrane also reflects the aging process. Cell membranes consist primarily of lipids (fats) whose composition changes with age. These membranes stiffen, and the cell's ability to protect itself from pathogens drops. Phagocytosis is one of the mechanisms of an intact immune response to pathogens. Here the cell membrane engulfs the invading pathogen. The body's immune cells isolate it and transport it into the cell. A complex process involving hydrolytic enzymes breaks down the pathogen, rendering it harmless to the body. If the composition of lipids in the cell membrane changes as we age, invading pathogens can no longer be engulfed and isolated: the process of phagocytosis cannot be completed. The enzymes no longer destroy the pathogen, and it remains active inside the cell. This is one reason older people are more susceptible to infectious diseases. The scientists at CECAD are exploring the driving factors behind these changes to the cell membrane with age.

Age-associated changes in cell metabolism, such as DNA defects, oxidative stress, mitochondrial dysfunction and metabolic stress, trigger inflammation. They are the intermediaries between cellular stress and tissue damage and influence metabolic homeostasis of the tissue as a whole by disrupting individual cells. Inflammatory processes therefore play a central role in the development of aging-associated diseases.

Research into diabetes and obesity is also exceptionally socially relevant. Metabolic processes are regulated in the brain via the control of nutrient intake and energy expenditure. If faulty signalling at the molecular level throws these processes out of balance, lipid and sugar metabolism in the body is affected. The hormones leptin and insulin play central roles in this process. They regulate metabolic mechanisms that allow the body to age more healthfully and can increase lifespan.

One example of such life-prolonging metabolic mechanisms is a drop in the activity of the insulin-like growth factor: "IGF1". A reduction in IGF1 activity increases the lifespan of many animals. Whether this can be transferred to humans is a question currently under investigation at CECAD. It has been successfully demonstrated in threadworms that not just inhibiting IGF1, but also reducing caloric intake can increase lifespan. If this can be confirmed for human beings as well, developing a drug to trigger this effect could be a promising research approach. Such a breakthrough

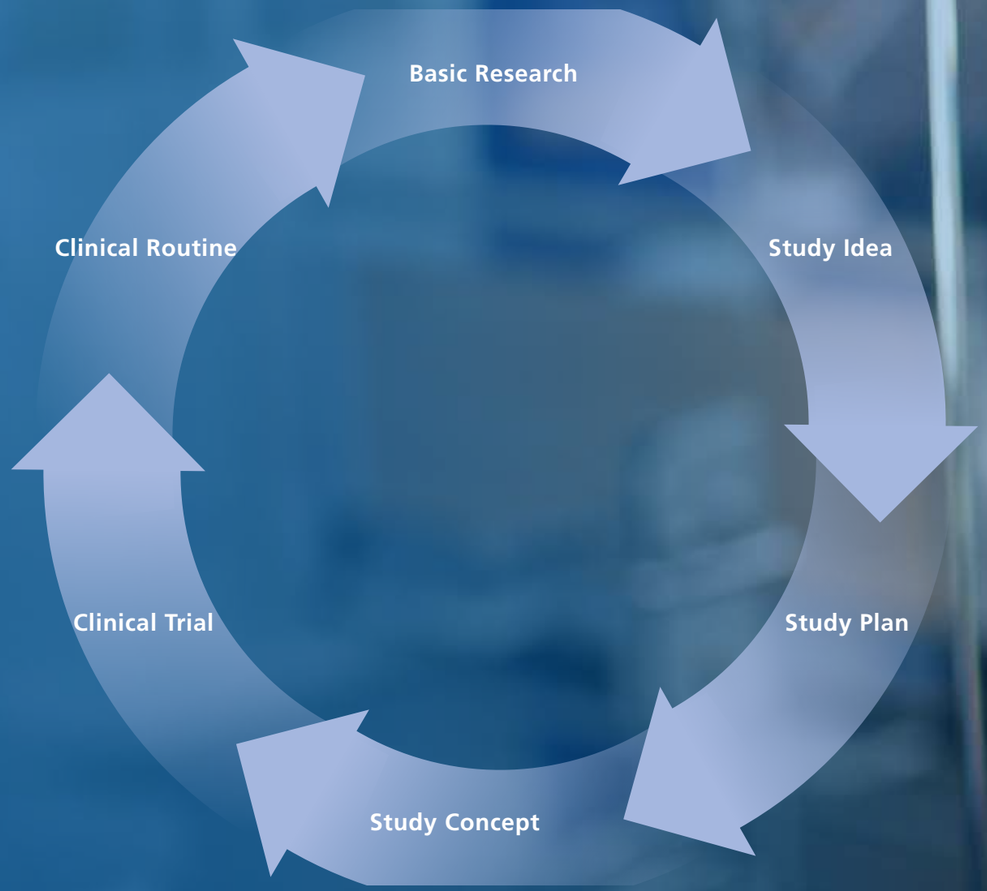


might point the way to realising the CECAD vision.
On the basis of these findings, a clinical study is already successfully underway to see how targeted caloric restriction prior to an operation might protect renal function. The study will also determine if this diet reduces the number of older patients who require dialysis following heart surgery.
It seems that reducing calorie intake places such stress on the body that it becomes less sensitive to external damage for a short period of time. This method might be a way to help protect not just the kidneys, but also other organs from incurring damage as a result of surgery.

This study represents more than just a victory for aging research. It is also an excellent example of CECAD's "translational research" approach. The slogan "from bench to bedside and back", the Translational Platform accelerates the systematic and efficient transfer of findings from basic research into everyday clinical applications, ensuring that patients profit from new research findings as quickly as possible. Partnerships with the private sector and other research institutions help promote these research successes.

From Bench to Bedside and Back

Translational Research at CECAD



Translationale Forschung ist für CECAD ein zentraler Schwerpunkt. Sie verbindet Wissenschaftlerinnen und Wissenschaftler aus der Grundlagenforschung und der Klinik. Die Translationale Plattform von CECAD ist unter der Leitung von Prof. Dr. Oliver Cornely in Kooperation mit dem Zentrum für Klinische Studien Köln (ZKS) effizienter Motor und intelligente Steuerung dieses Prozesses.



↗ http://cecad.uni-koeln.de/Prof-Oliver-Cornely.79.0.html

Prof. Dr. Oliver Cornely

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

Under the leadership of Prof. Dr. Oliver Cornely, the Translational Platform at CECAD systematically searches for findings from basic research that can be translated into promising clinical projects. It serves as a highly dynamic catalyst for collaboration between basic researchers and clinicians. The goal is to maximize the transfer of findings from basic research to realize CECAD's vision of developing novel solutions for aging-associated diseases. The new CECAD Research Center is strategically located on campus near the hospital to facilitate the rapidly rising number of translational research projects. Cologne is one of the most experienced hotbeds for research studies in Europe. Patents awarded and patent applications pending reflect the financial and scientific success of the model.

Our successes: The Translational Platform benefits from funding such as the "Instrument and Method Development for Patient-Oriented Medical Research" program from the Federal Ministry of Education and Research (BMBF). Patents have resulted from some translational projects, such as the research project on catheterless bladder pressure measurement in diagnosing overactive bladder. Translation closes the cycle between disciplines involved.

Our goals: Developing indicators to measure the potential success of translational projects is an important goal for further increasing the Translational Platform's long-term success. Our navigators work in the field of tension between protecting 'intellectual property' and assessing investment and yield. A comprehensive model can be developed based on identified authoritative indicators. If successfully established, this concept can be transferred to other research sites.
Increasing the number of navigators raises the number of translational projects and as such considerably increases our ability to translate basic research findings into clinical application. New partnerships with biotech companies are an important goal in realizing clinical studies.
Our role as the interface between research and companies is a huge responsibility. What often starts with molecules and cells can ultimately lead directly to the patient and improvements of diagnosis and treatment paths.

Our methods/techniques: The navigators at the Translational Platform serve as the interface between basic researchers and clinicians. In keeping with the "Bench to Bedside and Back" principle, seven defined stages move the translation process through the identification of suitable projects, the application process, clinical studies to evaluate and optimize the development of new compounds, medical devices or methods, and ultimately patent application.

PUBLICATIONS

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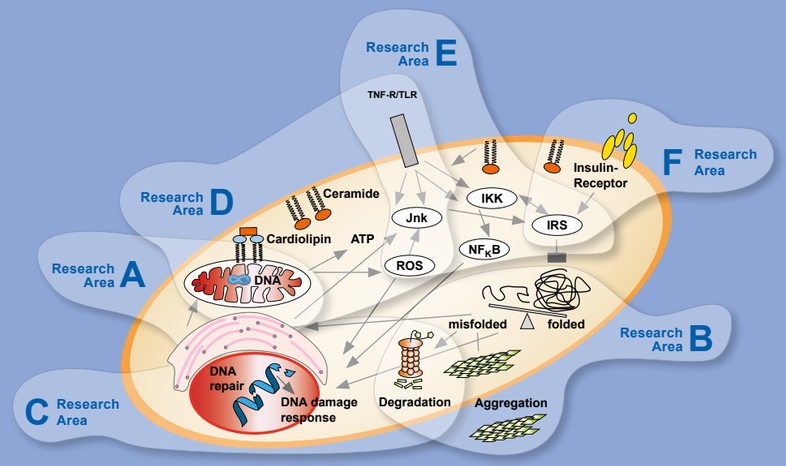
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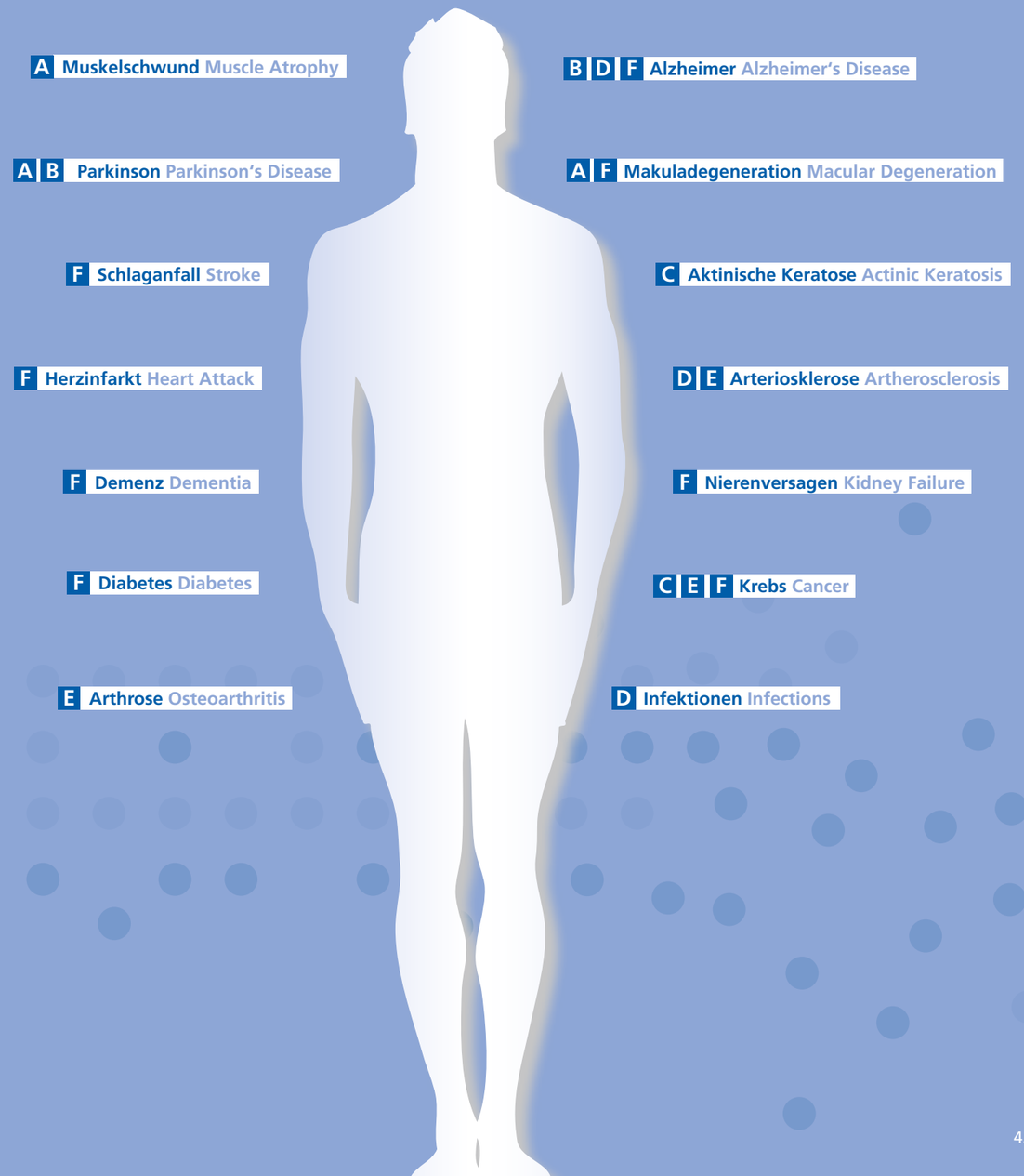
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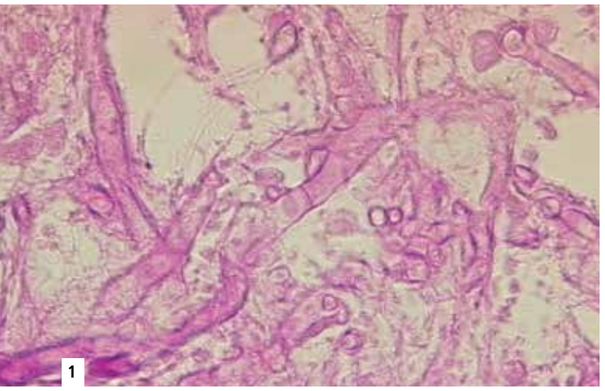
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CECAD hat ein starkes Ziel: Vielversprechende Forschungsergebnisse aus dem Labor schnell in die erfolgreiche klinische Anwendung zu bringen, damit jeder Einzelne in der Gesellschaft vom wissenschaftlichen Fortschritt profitieren kann. Die Translationale Plattform ist der Partner für erfolgreiche Kooperationen zwischen Biotech-Unternehmen, Grundlagenwissenschaft und Klinik. Das umfasst z.B. die klinische Anwendung neuer Medikamente, Substanzen und Verfahren, die Qualitätssicherung von Studien und medizinischen Ergebnissen. Bereits erteilte Patente sowie laufende Patentanträge spiegeln den finanziellen wie wissenschaftlichen Erfolg des Translationsprozesses.





From Bench to Bedside and Back
Successful Project Examples


1


2


3


4

FIGURE 1: Histology of a spleen sample with fungal infiltration (Mucorales)
FIGURE 2: Chest CT scan with typical infiltration indicative for invasive mold infection
FIGURE 3: Cystoscopy with WiCa
FIGURE 4: Prototype: WiCa

PROMISING NEW DIAGNOSTIC METHOD FOR INVASIVE FUNGAL INFECTIONS

Novel diagnostic tests to identify invasive fungal infections provide chronically ill patients, such as those with diabetes and leukemia, with new therapeutic perspectives. In patients with compromised immune systems, fungi cause infections that are very difficult to diagnose and can affect the brain or lungs. In 2014, a national team of scientists around Prof. Oliver A. Cornely from the CECAD Cluster of Excellence at the University of Cologne and the University Hospital achieved a breakthrough led by using fungus-reactive T cells as readout for diagnosing invasive fungal infections.

FLY – FATIGUE WITH LYMPHOMA

Exhaustion and cognitive limitations are two of many undesirable side effects of many cancer therapies and affect up to two-thirds of all cancer patients. Most studies in this area use data based on subjective assessments.
The FLY Project aims to provide an overview of the physiological and molecular aspects of cancer treatments that lead to the symptoms mentioned above. The project combines EEG results and blood analyses with subjective methods to optimize therapeutic options.

CLUD PILOT – TECHNICAL INNOVATION: MEASURING BLADDER PRESSURE WITHOUT A CATHETER

The overactive bladder (OAB) syndrome is a urological disease affecting up to 15.6% of men and 17.4% of women in Europe with a negative impact comparable to diabetes mellitus.
Unfortunately, current standard urodynamic tests have only a small time schedule with an average investigation time of 20 to 30 minutes.
To improve diagnosis and thus to prescribe an accurate treatment, the Department of Urology at the University Hospital of Cologne together with the cooperation of the Faculty of Electrical Engineering and Information Technology in Chemnitz, developed a capsule for longer measurements (WiCa).
The WiCa is inserted into the bladder, where it will continuously record significant bladder pressure changes for up to 3 days. As a result, side effects of antimuscarinic drugs can be avoided and different types of treatments will be offered to OAB patients.
In summary, this project represents trend-setting innovation and advancement for accurately and minimally invasively diagnosis of urinary incontinence pathophysiology. (Wille et al. PloS One 2014)

Clinical Study
Bypass Surgery and Prevention of Kidney Damage

1. QUESTIONS FOR MEDICAL RESEARCH

CURRENT KNOWLEDGE
The kidney is a highly complex organ with a marked sensitivity to a lack of oxygen, e.g. through interruption of circulation. During heart surgery there are times when the blood supply to the kidneys is decreased. Possible result: kidney failure.



QUESTION
How can kidney function be maintained after reduction of blood flow? Are there any medications or interventions that can stabilize kidney function when perfusion is restricted?



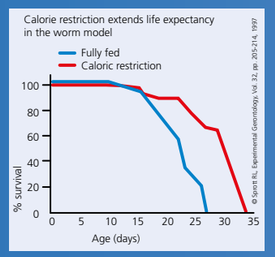
2. WORK ON MODEL ORGANISMS

CURRENT KNOWLEDGE
Facts established through studies on model organisms: Calorie restriction extends life expectancy in yeast, worms, flies and mammals. Metabolic signaling pathways involved in the aging process are subject of intense research.

QUESTION
Reducing calorie intake lengthens lifespan in the mouse model. The mouse is similar to humans. Does this observation also apply to humans?



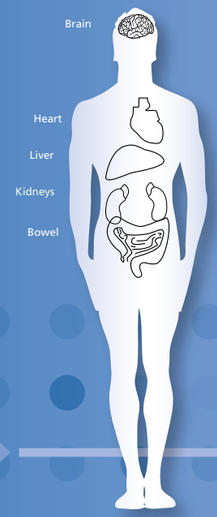


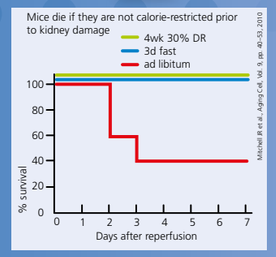


3. CALORIE REDUCTION PROTECTS AGAINST ORGAN DAMAGE

CURRENT KNOWLEDGE
Mice die if their diet has been unrestricted before the onset of kidney failure. This shows that: Calorie reduction gives the mouse a clear-cut survival benefit after kidney failure.

QUESTION
Does this apply to humans? Some organs are particularly vulnerable to a reduced oxygen supply.

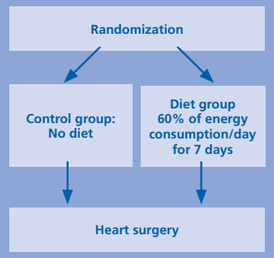




4. DESIGN OF A CLINICAL STUDY

CURRENT KNOWLEDGE
Hypothesis: A special diet before surgery protects against kidney damage after surgery.
Study design: Patients meet the following criteria:
- → Awaiting heart surgery with creatinine levels > 1.5 mg/dl or
- → Renal insufficiency with creatinine > 1.1 mg/dl and one risk factor: diabetes, occlusive arterial disease, heart failure

QUESTION
How would a clinical trial on humans be designed?
Prof. Thomas Benzing, Director of the Department of Medicine II, University Hospital Cologne: "For the first time we will be able to test whether a preoperative diet influences the rate of kidney failure."



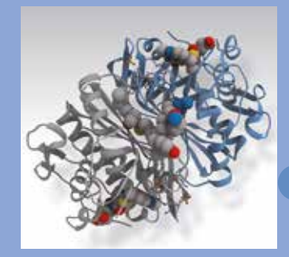
POSSIBLE FUTURE STUDIES
- → Can a diet prevent kidney damage after a heart catheter procedure?
- → Can a diet prevent damage after heart surgery?
- → Can a diet protect organs during chemotherapy?
- → Can a diet improve organ quality in a kidney transplant?

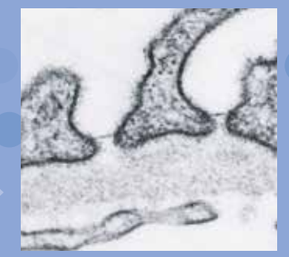
5. BACK TO BASIC RESEARCH

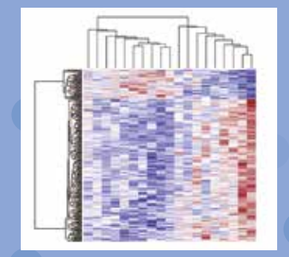
CURRENT KNOWLEDGE
Development of drugs and treatments for the future:
- → What are the key molecules?
- → How can we develop new medications to protect against organ damage?

QUESTION
How indispensable is translational research for medical innovation?

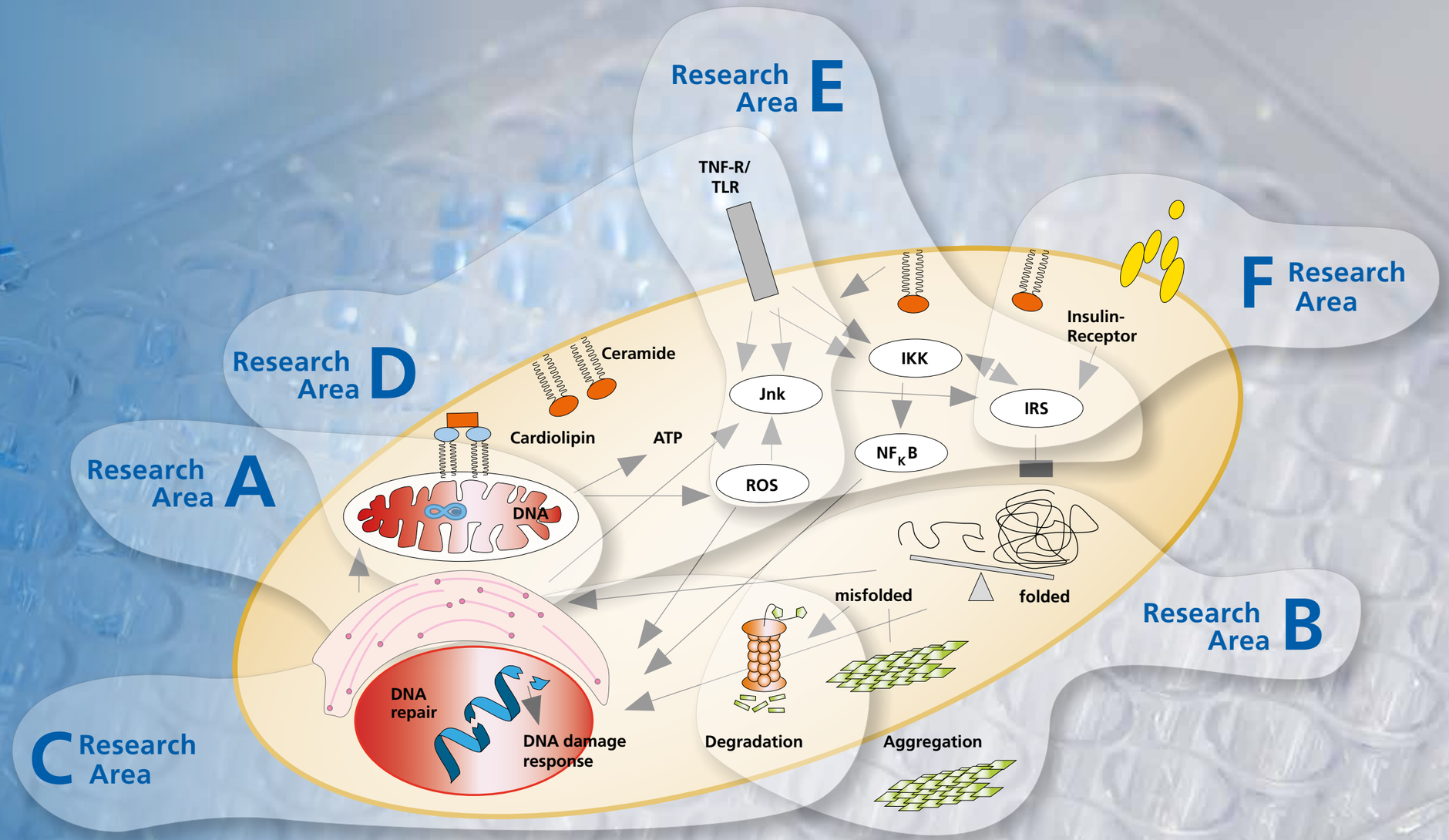
LABORATORY RESULTS
- → Slit diaphragm under the electron microscope
- → Microarray experiment





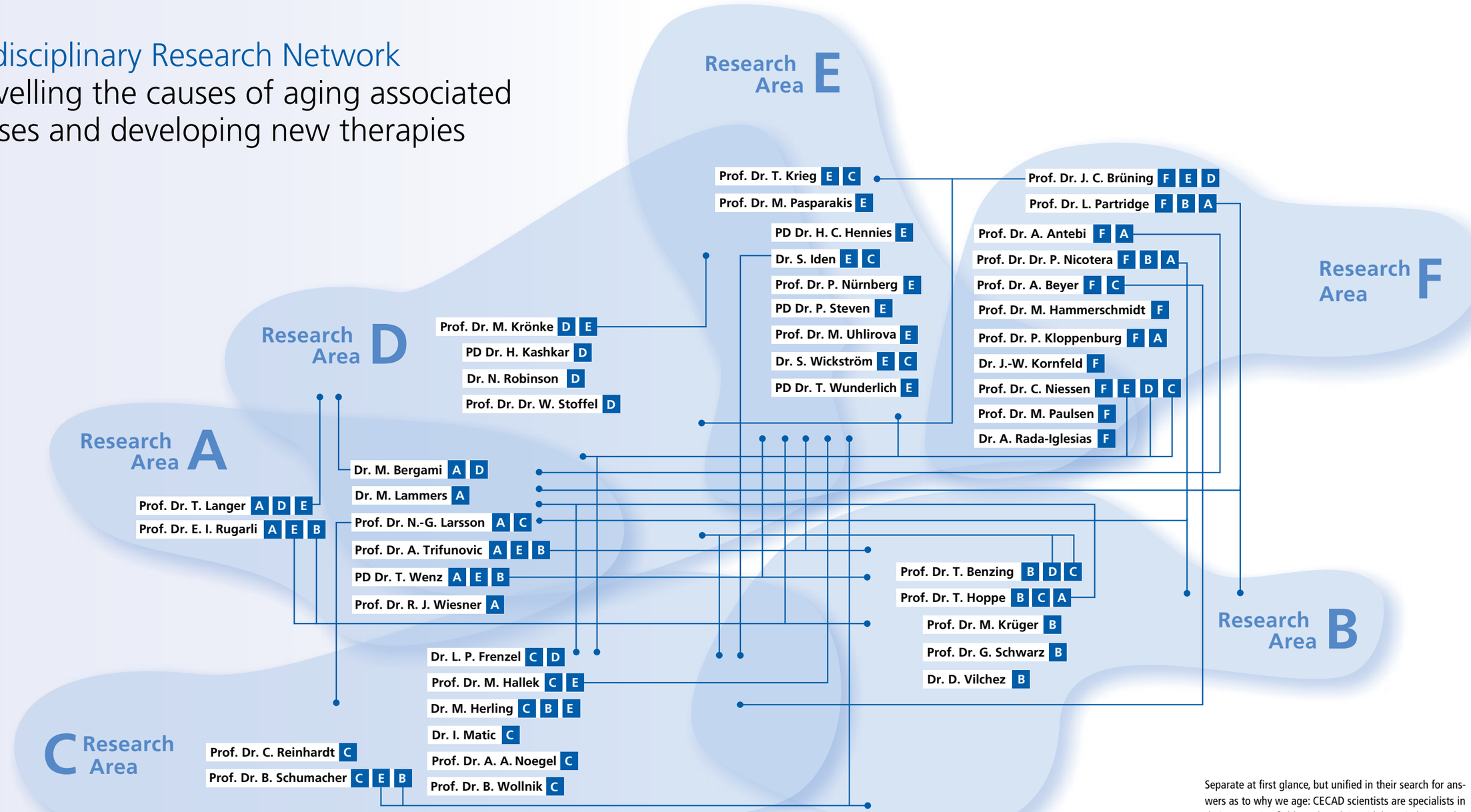


Research Areas

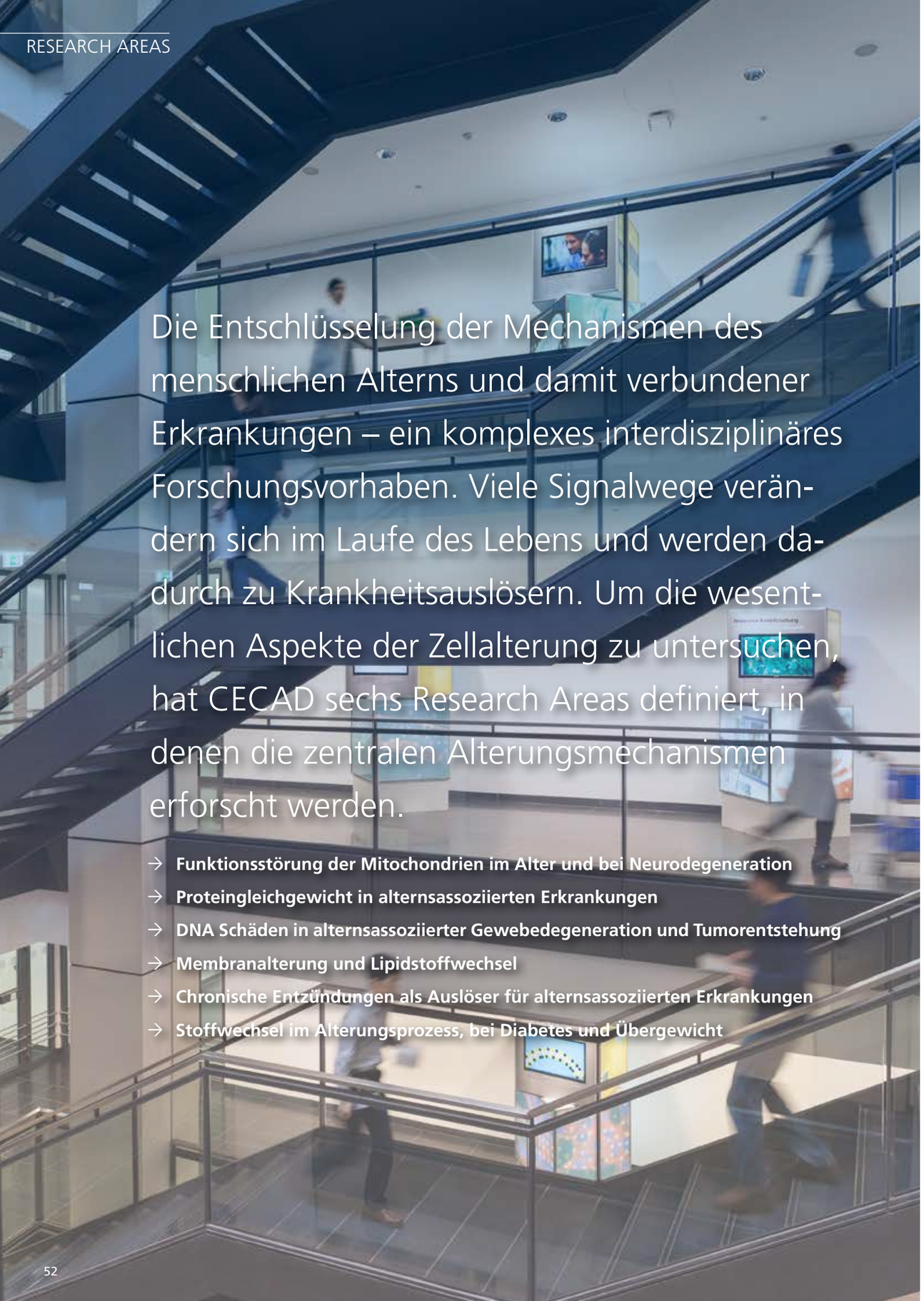


Interdisciplinary Research Network

Unravelling the causes of aging associated diseases and developing new therapies



Separate at first glance, but unified in their search for answers as to why we age: CECAD scientists are specialists in their respective fields and work in widely varied research areas. Through their interdisciplinary cooperation at the research cluster, they identify many key associations – the great answer to the pressing question of why we age.



Die Entschlüsselung der Mechanismen des menschlichen Alterns und damit verbundener Erkrankungen – ein komplexes interdisziplinäres Forschungsvorhaben. Viele Signalwege verändern sich im Laufe des Lebens und werden dadurch zu Krankheitsauslösern. Um die wesentlichen Aspekte der Zellalterung zu untersuchen, hat CECAD sechs Research Areas definiert, in denen die zentralen Alterungsmechanismen erforscht werden.

- → **Funktionsstörung der Mitochondrien im Alter und bei Neurodegeneration**
- → **Proteingleichgewicht in alternsassoziierten Erkrankungen**
- → **DNA Schäden in alternsassoziierter Gewebedegeneration und Tumorentstehung**
- → **Membranalterung und Lipidstoffwechsel**
- → **Chronische Entzündungen als Auslöser für alternsassoziierten Erkrankungen**
- → **Stoffwechsel im Alterungsprozess, bei Diabetes und Übergewicht**

Research Areas
Introduction

RESEARCH AREA A

Mitochondrial Dysfunction in Aging and Neurodegeneration

Mitochondria are the powerhouses of the cell, keeping them supplied with energy. The activity of mitochondria decreases during aging and defects in mitochondria trigger age-associated diseases including neurodegeneration. Research Area A explores the quality control mechanisms that maintain the integrity of mitochondrial processes, and how the disruption of these mechanisms contributes to diseases.

RESEARCH AREA B

Disruptions in Protein Metabolism Cause Aging-Associated Diseases

Cellular differentiation, developmental processes, and environmental factors challenge the integrity of the proteome in every eukaryotic cell. The maintenance of protein homeostasis, or proteostasis, involves repair and degradation of damaged proteins and is essential for human health. It is commonly thought that age-related impairment of protein quality control affects general proteostasis networks and is involved in age-related pathologies.

RESEARCH AREA C

DNA damage responses in Aging-associated Diseases

The genome in each cell of the human body is constantly under attack. Over a lifetime DNA damage accumulates and drives the aging process and causes age-related diseases including cancer. Investigators in Research Area C focus on understanding how DNA repair systems remove the damage and how cells and tissues counteract the detrimental consequences of genome damage.

RESEARCH AREA D

The Aging of Membranes

Cell membranes are integral to our cells and contain enzymes, receptors and ion channels. The composition of their building blocks (lipids) changes over the course of a lifetime. Changes in lipid metabolism play an important role in aging-associated diseases such as hair loss, muscle weakness and obesity. Scientists in Research Area D look into why lipid composition in the cells alters over time and the mechanisms that promote aging-associated diseases.

RESERCH AREA E

Inflammation in Aging-Associated Diseases

When the immune system is not properly regulated it can cause chronic inflammatory reactions. Prolonged inflammation can trigger aging-associated diseases like cancer, chronic wounds, and type 2 diabetes. Research Area E focuses on the different phenomena associated with inflammation, such as the role of chronic inflammation in tissue and aging, or the link between inflammation and carcinogenesis.

RESERACH AREA F

Metabolism in Aging Process, Diabetes and Obesity

Nutrient intake and energy expenditure are controlled by a variety of metabolic and neuronal signaling pathways. Imbalances here can result in diseases such as obesity and type 2 diabetes. The energy-regulating signaling pathways also influence development, growth and the aging process. Scientists in Research Area F work to identify the signaling cascades involved in regulating energy metabolism and explore how their findings might contribute to a longer, healthier life in old age.

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Die Vision des Exzellenzclusters CECAD ist es, die molekularen Grundlagen des Alterungsprozesses zu verstehen. Dazu definieren die Wissenschaftlerinnen und Wissenschaftler Prozesse, deren Fehlfunktion zur Entstehung von alterungsassoziierten Erkrankungen führen. Die Forschungsprojekte im Forschungsbereich A zielen darauf ab, die Rolle der Mitochondrien, den „Kraftwerken der Zelle“, in diesen Prozessen zu erforschen.

Research Area A
Mitochondrial Dysfunction in Aging and Neurodegeneration

The CECAD Excellence Cluster has a vision: to understand the molecular basis of the aging process. To this end, scientists work to identify the processes implicated in triggering aging-associated diseases when they fail. The research projects in Research Area A are designed to explore the role of the mitochondria, the “powerhouses of the cell”, in these processes.

As the human body ages, mitochondrial dysfunctions increase and can lead to neurodegenerative diseases, especially in the brain. Aging correlates with an accumulation of mutations in mitochondrial DNA and a decline in the function of the respiratory chain that generates energy in the presence of the oxygen we breathe in. Whether a deterioration of mitochondrial activities is due to a downregulation of respiratory capacity or the accumulation of defects inside the mitochondria is still unclear.

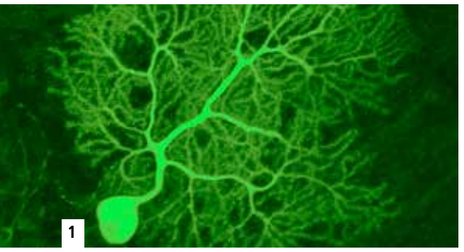
This leads to a central issue CECAD research seeks to address: How can the quality of the mitochondria, their DNA, proteins and lipids be maintained throughout the entire lifecycle? The researchers‘ work focuses on improving the understanding of the mechanisms that maintain the functional integrity of mitochondria with increasing age and protect us from neurodegeneration.

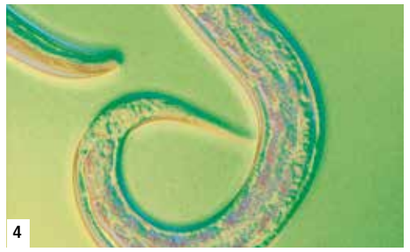
Strengthened by excellent scientific appointments in the first funding period, CECAD scientists in Research Area A are pursuing the following objectives:

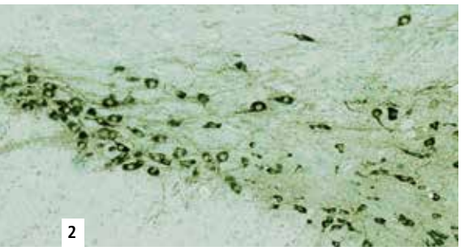
Identifying

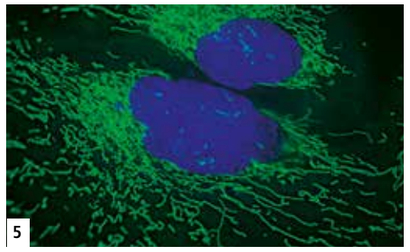
- → The mechanisms that maintain mitochondrial genome integrity and its expression during aging
- → The mechanisms that regulate the production of energy via mitochondrial respiration during the aging process
- → The key components and signaling pathways that mediate increased longevity by regulating mitochondrial function
- → The mitochondrial quality control mechanisms that counteract an aging-association decline in mitochondrial activities
- → The mechanisms that underlie neurodegenerative disorders which are caused by a disruption of mitochondrial quality control

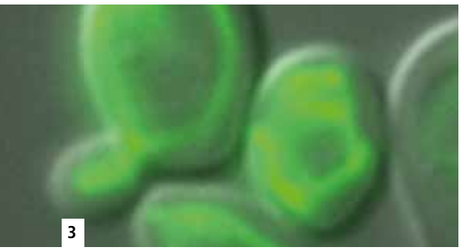
The CECAD scientists in Research Area A use a range of different model systems to explore these topics. Different mouse models are essential for researching neurodegenerative disorders triggered by mitochondrial dysfunction. These disorders include Parkinson’s disease, cerebellar ataxia (lack of muscle coordination caused by a dysfunction of the cerebellum), spastic paraplegia (increasing spasticity in the limbs), and a range of mitochondrial encephalopathies (a term that refers to pathological changes in the brain with a variety of causes and expressions). One important goal of this research is to improve our understanding of the processes that determine the activity and functionality of the mitochondria. These findings could then serve as a basis for developing new, long-term therapeutic approaches to counteract the aging process and the progression of aging-associated disorders.


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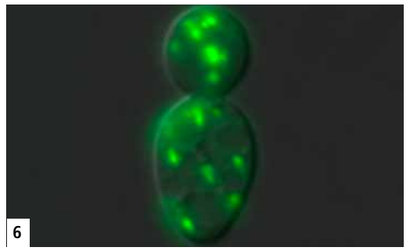

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FIGURE 1: Purkinje nerve cells link the granular to the molecular layer of the cerebellar cortex. This brain region controls balance and muscle coordination.
FIGURE 2: View of the network of nerve cells in the brain.
FIGURE 3 AND 6: Absence of mitochondrial fusion leads to mitochondrial fragmentation and respiratory incompetence. Fzo1 is essential for the presence of tubular mitochondria. Mitochondrial morphology of (a) wild-type and (b) Δfzo1 yeast cells expressing a mitochondrial-targeted GFP protein. Cellular (Nomarsky) and mitochondrial (GFP) morphology were visualized by fluorescence microscopy.
FIGURE 4: An example of a model organism used for research: the threadworm *C. elegans.*
FIGURE 5: Mitochondria are dynamic parts of the cell.

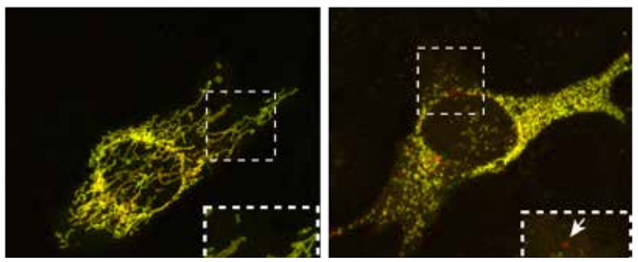
PRINCIPLE INVESTIGATORS MAIN FOCUS

Prof. Dr. T. Langer → p. 59
Prof. Dr. E. I. Rugarli → p. 63
Dr. M. Bergami → p. 67
Dr. M. Lammers → p. 69
Prof. Dr. N.-G. Larsson → p. 71
Prof. Dr. A. Trifunovic → p. 75
PD Dr. T. Wenz → p. 77
Prof. Dr. R. J. Wiesner → p. 79

PRINCIPLE INVESTIGATORS SECOND FOCUS

Prof. Dr. A. Antebi → p. 177
Prof. Dr. T. Hoppe → p. 89
Prof. Dr. P. Kloppenburg → p. 189
Prof. Dr. Dr. P. Nicotera → p. 181
Prof. Dr. L. Partridge → p. 173

Mitochondrien sind als die „Kraftwerke der Zellen“ bekannt. Im Alter nehmen Funktionsstörungen der Mitochondrien zu. Dies führt zu degenerativen Erkrankungen insbesondere der Gewebe, die sich durch einen hohen Energieverbrauch auszeichnen – hier vor allem das Muskelgewebe und das Gehirn. Die Gruppe um Prof. Dr. Thomas Langer erforscht zelluläre Mechanismen, die die Funktion der Mitochondrien während des Alterns überwachen und etwaige Fehlfunktionen korrigiert.



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BACKGROUND FIGURE: Cardiomyocytes, stained for Actinin

FIGURE 1: Mitophagy is a mitochondrial quality control mechanism whereby cells eliminate damaged mitochondria from the mitochondrial network in order to maintain healthy mitochondrial activity. These MEF cells are expressing a fluorescent construct that allows us to quantitatively measure mitophagy. Upon mitochondrial stress (right panel), the mitochondrial network has fragmented and some mitochondria appear as red only structures (arrows). These red mitochondria have been delivered to the cell's waste bins, known as lysosomes, by the mitophagy machinery and are in the process of being degraded.



↗ http://cecad.uni-koeln.de/Prof-Thomas-Langer.98.0.html

Prof. Dr. Thomas Langer

Head of Research Area A – Principal Investigator
Deputy Scientific Coordinator – Institute for Genetics

Mitochondria are cellular organelles that are well known as the powerhouses of the cell. Mitochondrial functions decline with increasing age. This leads to the damage of tissues that are characterized by high energy consumption, such as muscles or the brain. The group of Prof. Dr. Langer studies cellular mechanisms which conduct the functional surveillance of mitochondria during aging. The focus of research is on mitochondrial proteases which serve dual functions: as quality control enzymes, they degrade damaged proteins and prevent their possibly deleterious accumulation within mitochondria; as regulatory enzymes, they degrade or cleave key regulatory proteins affecting diverse mitochondrial activities. The group discovered that various stress conditions lead to the activation of a protease that induces the fragmentation of mitochondria facilitating cell and tissue damage. Inhibition of this pathway prevents dysfunctions of the heart under stress and delays neurodegeneration. The work of the group of Prof. Dr. Langer now aims to explore the relevance of this stress-induced pathway for the onset of a broad spectrum of age-associated disorders.

Our research: Prof. Langer's team studies the role of mitochondrial proteases for the maintenance of mitochondrial activities. These proteases conduct the surveillance of the mitochondrial proteome and degrade misfolded and damaged proteins to prevent their possibly deleterious accumulation within the organelle. Moreover, they maintain the functional integrity of mitochondria by degrading or processing key regulatory proteins that control diverse steps during mitochondrial biogenesis and dynamics. Mutations in several of these proteases cause diverse neurodegenerative disorders and are associated with cardiomyopathies. The work of Prof. Langer and his team aims at understanding the molecular mechanism underlying the pathogenesis of these diseases.

Our successes: Prof. Langer's team succeeded recently to identify key roles of mitochondrial proteases for the regulation of the dynamic behavior of mitochondria under stress and for the control of the phospholipid composition of mitochondrial membranes. Mitochondria form dynamic networks that are maintained by balanced fusion and fission events. Stress conditions lead to the activation of the protease OMA1, which selectively cleaves and inactivates the dynamin-like GTPase OPA1 mediating mitochondrial fusion. Ongoing membrane fission triggers fragmentation of the mitochondrial network, which facilitates the autophagic removal of damaged mitochondria and cell death. The group of Prof. Langer could demonstrate that inhibition of this pathway prevents stress-induced cardiomyopathies and delays the onset of neurodegenerative disorders. In another research line, the work of Prof. Langer´s team identified a crucial role of mitochondrial proteases for the synthesis of cardiolipin, a mitochondria-specific phospholipid, which is essential for the function of mitochondria. Oxidation of cardiolipin is associated with the decline of mitochondrial activities during aging. The group of Prof. Langer could demonstrate that disease mutations leading to cardiomyopathies are caused by disturbances in the cardiolipin metabolism in mitochondria.

Our goals: Prof. Langer's team aims at a detailed molecular understanding as to how mitochondrial proteases contribute to the maintenance of mitochondrial functions in health and disease. This will enable the group to define the cellular mechanisms underlying the decline of mitochondrial activities during aging and the pathogenesis of age-associated diseases that are linked to a dysfunction of mitochondria. Understanding how cells counteract mitochondrial dysfunction and damage accumulation also holds the promise to open up new therapeutic interventions delaying or preventing the onset of disease.

CECAD COOPERATIONS

B Prof. Dr. T. Benzing, Principal Investigator → p. 85
F Prof. Dr. J. C. Brüning, Principal Investigator → p. 169
E Prof. Dr. M. Pasparakis, Principal Investigator → p. 147
A Prof. Dr. E. I. Rugarli, Principal Investigator → p. 63
A Prof. Dr. R. J. Wiesner, Principal Investigator → p. 79

EXTERNAL COOPERATIONS

UC Davis, USA
Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) Madrid, ES

A

Prof. Dr. Thomas Langer
Head of Research Area A – Principal Investigator
Deputy Scientific Coordinator
Institute for Genetics

Our methods/techniques: The group uses a broad spectrum of cell biological, biochemical and genetic approaches to define the proteolytic control of mitochondrial function at a molecular level. Studies include state-of-the-art proteomic, lipidomic and imaging approaches. The combination of mouse models with experiments in simple eukaryotic model organisms allows unraveling the molecular mechanisms of cellular processes and examining their physiological relevance in the pathological context of cardiomyopathies and neurodegenerative disorders.

PUBLICATIONS

Anand R, Wai T, Baker MJ, Kladt N, Schauss AC, Rugarli E, Langer T. (2014) The i-AAA protease YME1L and OMA1 cleave OPA1 to balance mitochondrial fusion and fission. J Cell Biol. 17, 919.

Baker MJ, Lampe PA, Stojanovski D, Korwitz A, Anand R, Tatsuta T, Langer T. (2014) Stress-induced OMA1 activation and autocatalytic turnover regulate OPA1-dependent mitochondrial dynamics. EMBO J. 33, 578.

Potting C, Tatsuta T, König T, Haag M, Wai T, Aaltonen MJ, Langer T. (2013) TRIAP1/PRELI Complexes Prevent Apoptosis by Mediating Intramitochondrial Transport of Phosphatidic Acid. Cell Metab. 18 287-295.

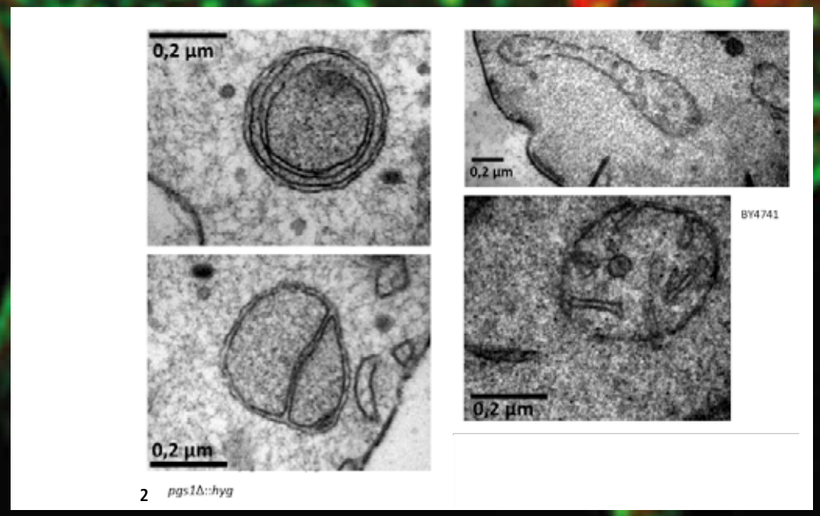
Merkwirth C, Martinelli P, Korwitz A, Morbin M, Brönneke HS, Jordan SD, Rugarli EI, Langer T. (2012) Loss of prohibitin membrane scaffolds impairs mitochondrial architecture and leads to tau hyperphosphorylation and neurodegeneration. PLoS Genet. 8.

Connerth M, Tatsuta T, Haag M, Klecker T, Westermann B, Langer T. (2012) Intramitochondrial Transport of Phosphatidic Acid in Yeast by a Lipid Transfer Protein. Science 338, 815.

So konnte gezeigt werden, dass eine Fragmentierung der Mitochondrien unter Stress das Absterben von Zellen befördert. Die Arbeiten der Wissenschaftler und Wissenschaftlerinnen um Prof. Langer zielen nun darauf ab, Mitochondrien vor diesem Effekt zu schützen, um die Entstehung neurodegenerativer Erkrankungen aufzuhalten.

BACKGROUND FIGURE: Cardiomyocytes, stained for TOMM20 (mitochondrial)

FIGURE 2: TEM microscopy of mitochondria of S.cerevisiae. Disturbed cardiolipin biosynthesis and phospholipid composition of mitochondrial membranes (pgs1Δ::hyg) alters the ultrastructure and function of mitochondria (wildtype: BY4741)



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Prof. Dr. Elena Rugarli und ihr Wissenschaftler/innenteam arbeiten bei CECAD daran, die grundsätzlichen Mechanismen der Entstehung neurodegenerativer Erkrankungen zu entschlüsseln. Der Schwerpunkt ihrer Forschung liegt auf der Hereditären Spastischen Paraplegie (HSP). Die HSP ist eine Gruppe genetischer Krankheiten, die durch den Abbau von motorischen Nervenzellen charakterisiert ist. Die Patienten leiden dadurch unter zunehmender Spastizität und Lähmungserscheinungen in den unteren Extremitäten. Die Arbeitsgruppe konnte bereits mehrere wichtige Mechanismen identifizieren, die zur Entstehung dieser Krankheit führen.



↗ http://cecad.uni-koeln.de/Prof-Elena-I-Rugarli.139.0.html

Prof. Dr. Elena I. Rugarli

Head of Research Area A – Principal Investigator
Cologne Biocenter

Axon degeneration is a characteristic event in many neurodegenerative diseases. Prof. Dr. Rugarli and her group are exploring the mechanisms underlying premature axon death. Her research focuses primarily on hereditary spastic paraplegia (HSP). The team of scientists has succeeded in identifying crucial pathogenic mechanisms that underlie the disease. The ultimate goal is to identify a common process responsible for axonal degeneration independent from the defective gene product. This could lead to the discovery of a central point of attack and a unified therapeutic approach for treating the many different types of HSP.

Our research: Axon degeneration is a process that plays an important role in many neurodegenerative diseases. Premature axon death occurs preferentially in long neurons, such as the corticospinal tract that runs from the cerebral cortex into the spinal cord with axons up to one meter long. Under the leadership of Prof. Elena Rugarli, the CECAD working group is exploring hereditary spastic paraplegia (HSP), a group of rare genetic disorders causing the degeneration of axons of the corticospinal tract. Patients who suffer from HSP experience progressive spasticity and weakness in their lower limbs. In the later stages of the disease, patients may even be confined to a wheelchair. Mutations in many genes are associated with the pathogenesis of HSP. Prof. Rugarli's team is working on exploring the functions of several of these genes to identify the mechanisms behind axonal degeneration. The team's scientists are mainly focusing on two HSP genes: SPG7 and SPAST. SPG7 encodes for paraplegin, a subunit of the mitochondrial m-AAA protease. Remarkably, paraplegin assembles with AFG3L2, which is mutated in another neurodegenerative condition, spinocerebellar ataxia SCA28. Thus, the group is using in vivo models to investigate the role of the mitochondrial m-AAA protease in neurodegeneration. SPAST encodes for spastin, a protein which breaks microtubules along their length. Another goal of the group is to understand a possible role of spastin and other HSP genes in lipid metabolism, an approach that could hold promises to find novel therapeutic strategies for HSP.

Our successes: The scientists in the Rugarli group have contributed to the understanding of the molecular and cell biological function of several HSP genes, thus elucidating pathogenic mechanism underlying axon degeneration in hereditary spastic paraplegia. The group was able to develop an in vivo model for one of the mitochondrial genes. It is currently being used to study both the gene's function and the interaction of the gene product with other proteins. The ultimate goal is to achieve a deeper understanding of the processes in the mitochondria that lead to degeneration and how neurons might be protected in future.

Our goals: The team of scientists led by Prof. Rugarli is currently working on understanding the function of several genes that contribute to the pathogenesis of HSP with the goal of dividing them into functional groups. Since loss of function of several genes cause the development of the same degenerative process, it is important to recognize commonalities and differences in the pathological pathways, in order to be able to devise effective therapeutic strategies and identify groups of patients that might respond to similar therapies. The researchers' ultimate vision is to identify signal cascades in the axons involving a number of defective genes that would allow for interventions at the end of the cascade. This would make it possible to use the same treatment approach on as many patients as possible with a range of different genetic defects.
The Rugarli group's research is also dedicated to understanding how the viability of axons in healthy people is maintained over the course of many decades. Decoding this process is not just important for a better understanding of HSP. The results could also translate to other neurodegenerative diseases such as Parkinson's or Alzheimer's. With her team, Prof. Rugarli is improving our understanding of these age-associated diseases as well.

CECAD COOPERATIONS

A Prof. Dr. T. Langer
Principal Investigator → p. 59

F Prof. Dr. C. Niessen
Principal Investigator → p. 193

E Prof. Dr. M. Pasparakis
Principal Investigator → p. 147

A Prof. Dr. A. Trifunovic
Principal Investigator → p. 75

EXTERNAL COOPERATIONS

Prof. Dr. Elena Rugarli is Project Leader of the NEUROLIPID Consortium at E-rare (ERA-Net for Research Programmes on Rare Diseases), in which an additional German, an Italian and a French team are also involved.

Prof. Dr. Elena I. Rugarli
Head of Research Area A – Principal Investigator
Cologne Biocenter

PUBLICATIONS

Gao J, Schatton D, Martinelli P, Hansen H, Pla-Martin D, Barth E, Becker C, Altmueller J, Frommolt P, Sardiello M, Rugarli EI. (2014) CLUH regulates mitochondrial biogenesis by binding mRNAs of nuclear-encoded mitochondrial proteins. J. Cell Biol. 27, 213-223.

Kondadi AK, Wang S, Montagner S, Kladt N, Korwitz A, Martinelli P, Herholz D, Baker MJ, Schauss AC, Langer T, Rugarli EI. (2014) Loss of the m-AAA protease subunit AFG3L2 causes mitochondrial transport defects and tau hyperphosphorylation. EMBO J. 33,1011-1026.

Merkwirth C, Martinelli P, Korwitz A, Morbin M, Brönneke HS, Jordan SD, Rugarli EI, Langer T. (2012) Loss of prohibitin membrane scaffolds impairs mitochondrial architecture and leads to tau hyperphosphorylation and neurodegeneration. PLoS Genet. 11:e1003021.

Almajan ER, Richter R, Paeger L, Martinelli P, Barth E, Decker T, Larsson N-G, Kloppenburg P, Langer T, Rugarli EI. (2012) AFG3L2 supports mitochondrial protein synthesis and Purkinje cell survival. J. Clin. Invest. 122, 4048-4058.

Rugarli EI, Langer T. (2012) Mitochondrial quality control: a matter of life and death for neurons. EMBO J. 31, 1336-49.

Prof. Rugarli wurde aufgrund ihres Engagements in der Erforschung der HSP im vergangenen Jahr zu einer Projektleiterin des E-Rare (ERA-Net for Research Programmes on Rare Diseases) ernannt.

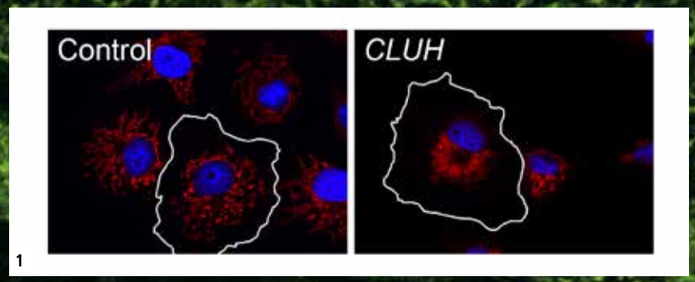
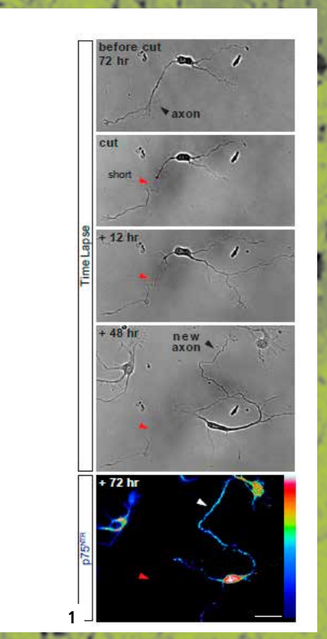
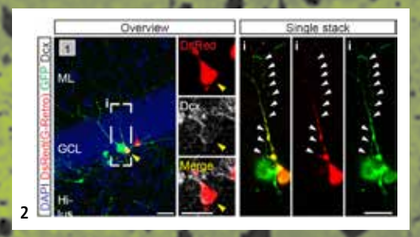


FIGURE 1: Downregulation of CLUH leads to clustering of mitochondria close to the nucleus. Cos7 cells were transfected with control siRNA or siRNA against CLUH. Mitochondria in control cells (left) form a tubular network all over the cell, whereas knock down cells (right) display a mitochondrial clustering on one side of the nucleus. Mitochondria are stained with Mitotracker Red (red) and DNA is stained with DAPI (blue).

A

Die Arbeitsgruppe um Dr. Matteo Bergami erforscht die zellulären und molekularen Prozesse von akuten Gehirnverletzungen und den daraus resultierenden Entzündungsreaktionen.
Im Fokus stehen Mechanismen, die die Neurogenese auslösen. Das Ziel ist, zelluläre Ersatzmechanismen zu identifizieren, um geschädigte neuronale Schaltkreise reparieren zu können.





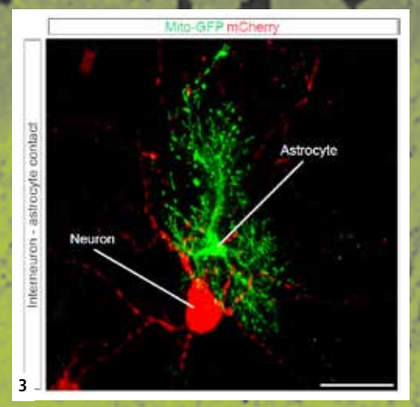


FIGURE 1: Time-lapse images showing a neuron before and after axon cut (red arrow). After 48 hours, one of the short neurites at the time of the axon transaction had grown into a new axon, which showed high p75NTR expression. Scale bar, 20 µm. (Zuccaro et al., 2013).
FIGURE 2: Virus-mediated monosynaptic tracing of neurons presynaptic to newborn neurons in the adult mouse hippocampus. The image shows a dentate gyrus newborn granule neuron at the age of 10 days (in yellow; co-labeled with a DsRed-encoding retrovirus and a GFP-encoding pseudotyped rabies-virus) being in direct contact with a first order presynaptic interneuron (in green; labeled with a GFP-encoding psudotyped rabies-virus only). Single stacks on the right show the emerging axon of the presynaptic neuron contacting the main dendritic shaft of the newborn neuron (arrowheads). (Deshpande et al., 2013).
FIGURE 3: In vivo labeling of the mitochondrial network in a cortical astrocyte (expressing mito-GFP, in green) being in direct contact with a cortical neuron (labeled in red). (Motori et al., 2013).



↗ http://cecad.uni-koeln.de/Dr-Matteo-Bergami.323.0.html

Dr. Matteo Bergami

Principal Investigator
Junior Research Group Leader

In our increasingly aging society, neurodegenerative diseases are extremely relevant. On one hand, Dr. Matteo Bergami and his group investigate the cellular and molecular processes underlying acute brain injury and the ensuing inflammatory response. On the other hand, the team studies the mechanisms that regulate the regeneration of nerve cells with the hope of identifying cell-based replacement approaches towards repairing of damaged brain circuits.

Our research: Nerve cell dysfunction and its progression towards cell death is a primary cause of most aging-associated diseases in the brain. Research developed in recent years has explored new promising approaches for regenerating or replacing the damaged nerve cells. Together with his research group, Dr. Matteo Bergami investigates the mechanisms in the brain that regulate neurogenesis in the adult brain, in order to identify the fundamental principles that may allow nerve cell regeneration following brain damage from trauma and neuroinflammation, for example.

Our successes: For the most part, the adult brain lacks the capacity to regenerate functional brain cells. Neurodegenerative diseases, including brain injury, are characterized by a progressive and irreversible depletion of nerve cells that ultimately affect the integrity of brain circuits. Within this context, new strategies aimed to generate new functional neurons also require establishing the proper connectivity with pre-existing nerve cells.
One success of Dr. Bergami's research is the optimization of a technique that allows the mapping and investigation of how these new connections are formed, thus laying the groundwork for future therapeutic approaches to restore appropriate brain plasticity.

Our goals: Dr. Bergami and his working group focus on the molecular processes that allow the proper formation and connectivity establishment of new nerve cells in the adult brain. Their goal is to identify which mechanisms regulate neuronal regeneration and how these can be manipulated to reinstate functional neurogenesis in the diseased brain.

Our methods/techniques: Research in Dr. Bergami's laboratory is performed using state-of-the-art imaging and molecular techniques. In particular, innovative tracing approaches permit the visualization and mapping of brain circuits under physiological conditions and during pathological states.

PUBLICATIONS

Bergami et al. A critical period for experience-dependent remodeling of adult-born neuron connectivity. Neuron (in press).

Heinrich et al. (2014) Sox2-Mediated Conversion of NG2 Glia into Induced Neurons in the Injured Adult Cerebral Cortex. Stem Cell Reports.

Zuccaro et al. (2014) Polarized expression of p75NTR specifies axons during development and adult neurogenesis. Cell Reports.

Motori et al. (2013) Inflammation-induced alteration of astrocyte mitochondrial dynamics requires autophagy for mitochondrial network maintenance. Cell Metabolism.

Deshpande et al. (2013) Retrograde monosynaptic tracing reveals the temporal evolution of inputs onto new neurons in the adult dentate gyrus and olfactory bulb. Proc Natl Acad Sci USA.

CECAD COOPERATIONS

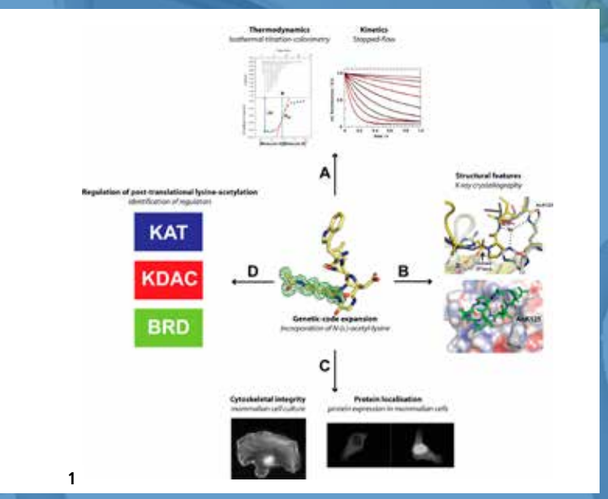
F Prof. Dr. J. C. Brüning — Principal Investigator → p. 169
A Prof. Dr. T. Langer — Principal Investigator → p. 59
A Prof. Dr. N.-G. Larsson — Principal Investigator → p. 71
A Prof. Dr. E. I. Rugarli — Principal Investigator → p. 63
B Dr. D. Vilchez — Principal Investigator → p. 97

EXTERNAL COOPERATIONS

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Prof. Dr. M. Götz, LMU Munich, DE
Prof. Dr. K.-K. Conzelmann, LMU Munich, DE
Prof. Dr. N. Toni, University of Lausanne, CH

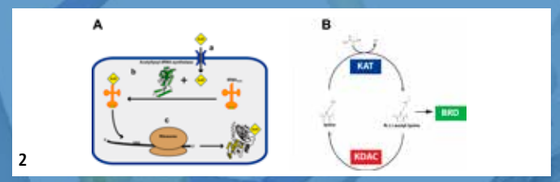
A

Die Arbeitsgruppe von Dr. Michael Lammers untersucht die Modifikation der Aminosäure Lysin durch Acetylierung. Eine Fehlregulation dieses Acetylierungs-Modifikationssystems könnte das Entstehen von neurodegenerativen Erkrankungen sowie Tumoren fördern. Das Wissenschaftlerteam konnte zeigen, dass grundlegende Proteinfunktionen durch diesen Prozess gesteuert werden. Die Forschungsergebnisse bieten einen hoffnungsvollen Ansatz zur Entwicklung neuer nebenwirkungsarmer Medikamente.



1

FIGURE 1: Structural and functional studies of the effect of lysine-acetylation on cytoskeletal protein function. (A) We study the influence of lysine-acetylation on the thermodynamics and kinetics of protein-protein interactions and on the protein-structure (B). (C) We study the impact of lysine-acetylation in eukaryotic cells (D) and want to understand how lysine-acetylation is regulated by KDACs, KATs and targeted by BRD-containing proteins.
FIGURE 2: The genetic-code expansion concept. (A) We use a synthetically evolved acetyl-lysyl-tRNA-synthetase/ $tRNA_{CUA}$ pair from *Methanosarcina bakeri* to site-specifically incorporate N-(ε)-acetyl-L-lysine into proteins. (B) Acetylation is a highly dynamic post-translational modification.



2



↗ http://cecad.uni-koeln.de/Dr-Michael-Lammers.94.0.html

Dr. Michael Lammers

Principal Investigator – Junior Research Group Leader
Institute for Genetics

Dr. Michael Lammers and his team explore the regulation of protein function by post-translational acetylation of lysine side chains. The group's focus is on the regulation of the cytoskeleton. They have successfully incorporated acetyl-lysine site-specifically into different proteins. In the future, using this strategy might allow the working group to develop novel therapeutic approaches including the design of deacetylase inhibitors with fewer side effects compared to known compounds.

Our research: Dr. Lammers and his team explore how lysine-acetylation regulates protein function. Acetylation of lysine side chains is one of the most abundant post-translational modifications comparable in number to phosphorylation. It is dynamically regulated by lysine-acetyltransferases and lysine-deacetylases. The focus of Dr. Lammers and his team is how the cytoskeleton is regulated by lysine-acetylation. The cytoskeleton is involved in many processes essential to the cells' survival. A dysregulation thereof can have drastic consequences for the cellular fate supporting processes such as tumor formation and neurodegenerative cellular disorders.

Our successes: Dr. Lammers and his researchers have observed that these post-translational modifications regulate protein function in a range of different ways. Lysine-acetylation can confer a loss-of- as well as a gain-of-protein function by recruiting bromodomain-containing proteins. Thereby, these processes can lead to modulations of cellular signal transduction pathways.

Our goals: Dr. Lammers long-term goal is to therapeutically tackle the molecular lysine-acetylation machinery. Deacetylase inhibitors have been subject of intensive basic research but they are also in clinical trials in pharmaceutical industry for several years now. However, these compounds often have a low level of target specificity and they show a broad range of unwanted off-target effects. His group focuses on developing more specific therapeutic agents with less side-effects. Mechanistic inhibitors based on non-cleavable acetyl-lysine analogs, such as thioacetyl-lysine, could be used to synthesize highly effective lysine-deacetylase inhibitors.

Our methods/techniques: A range of different biochemical and biophysical methods are used in the lab, including isothermal titration calorimetry, stopped flow, microscale thermophoresis and X-ray crystallography.

PUBLICATIONS

Lammers M, Neumann H, Chin J, James, L. (2010) Acetylation regulates Cyclophilin A catalysis, immunosuppression and HIV isomerization. Nat. Chem. Biol. 6, 331-337.

Price A, Marzetta F, Lammers M, Ylinen L, Schaller T, Wilson S, Towers G, James L. (2009) Active site remodeling switches HIV specificity of antiretroviral TRIMCyp. Nat. Struct. Mol. Biol. 16, 1036-1042.

Lammers M, Meyer S, Kühlmann D, Wittinghofer A. (2008) Specificity of Interactions between mDia Isoforms and Rho Proteins. J. Biol. Chem. 283, 35236-35246.

Lammers M, Rose R, Scrima A, Wittinghofer A. (2005) The regulation of mDia1 by autoinhibition and its release by Rho*GTP. EMBO J. 24, 4176-4187.

Rose R*, Weyand M*, Lammers M*, Ishizaki T, Ahmadian MR, Wittinghofer A. (2005) Structural and mechanistic insights into the interaction between Rho and mammalian Dia. Nature 435, 513-518. (*equal first authors)

CECAD COOPERATIONS

D Dr. N. Robinson → p. 135
Principal Investigator

EXTERNAL COOPERATIONS

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Dr. J. Chin, MRC/LMB Cambridge, UK
Dr. L. James, MRC/LMB Cambridge, UK
Prof. Dr. I. Neundorf, Institute for Biochemistry, University of Cologne, DE
Prof. Dr. T. Outeiro, University Medical Center, Göttingen, DE
Dr. G. Praefcke, Paul-Ehrlich-Institute, Langen, DE
Em. Prof. Dr. A. Wittinghofer, MPI of molecular Physiology, Dortmund, DE

A

Prof. Dr. Nils-Göran Larsson untersucht gemeinsam mit seiner Arbeitsgruppe mitochondriale Gene und ihren Einfluss auf den Alterungsprozess des Menschen. Die Wissenschaftlerinnen und Wissenschaftler konnten neue Erkenntnisse über Mutationen in der Mitochondrien-DNA erlangen, z.B. die Identifikation der Mechanismen, durch die die Vererbung solcher Mutationen verhindert werden kann.



↗ http://cecad.uni-koeln.de/Prof-Nils-Goeran-Larsson.245.0.html

Prof. Dr. Nils-Göran Larsson

Principal Investigator
Managing Director of the MPI for Biology of Ageing

The team supporting Prof. Dr. Nils-Göran Larsson performs research on the mitochondrial genome and also examines the influence of mutations of mitochondrial genes on the aging process. The scientists were able to prove that the combination of mutations, passed on by the mother, and de novo mutations may trigger or amplify illnesses. Furthermore the scientists were able to identify specific mechanisms that prevent the inheritance of DNA mutations in the mitochondria. Currently Prof. Dr. Larsson is cooperating with the Lead Discovery Center, daughter of Max Planck Innovation GmbH, to develop molecules through which the gene expression and thus the performance of the mitochondria can be regulated. This would provide the possibility to influence cell aging or mitochondrial diseases to name two examples.

Our research: The team led by Prof. Dr. Nils-Göran Larsson focuses on examining the mitochondrial genome. Mutations in the mitochondrial DNA may trigger premature aging processes. Prof. Larsson and his team of scientists study the molecular mechanisms through which the mitochondrial genome is passed on. They concentrate on a deeper molecular understanding of the mitochondrial gene expression. The scientists examine the way mitochondrial DNA is transcribed and translated and how mutations influence the aging-process or become the elicitor of aging-associated diseases. The team cooperates with partners in the Lead Discovery Center, daughter of Max Planck Innovation GmbH, in Dortmund on a translational project for the development of so-called "small molecules" which influence the mitochondrial transcription and thus the gene expression.

Our successes: Together with his team Prof. Larsson succeeded in showing that mutations of the mitochondrial DNA induce cell aging. Such mutations are only transmitted by the mother. In combination with newly occurring mutations they can create synergies that may provoke and amplify disease and aging. Unlike the inheritance of nuclear DNA, no recombination of the genetic material takes place. Due to this, defects in the mitochondrial DNA can easily accumulate over generations. The scientists supporting Prof. Larsson were able to identify multiple mechanisms, which prevent the inheritance of DNA damage. By decoding these quality-control-mechanisms, Prof. Larsson's team made a fundamental contribution to the mitochondrial genome research and its role in the aging-process.

Our goals: The team cooperates with partners in the Lead Discovery Center in Dortmund on a translational project for the development of so-called "small molecules". With the aid of these molecules mitochondrial transcription might prospectively be enhanced or constrained and thus influence the gene expression. These molecular tools will henceforth allow the regulation of the mitochondrial functions.

Our methods/techniques: In order to comprehend the structure of the mitochondria and their DNA, the researchers utilized different state-of-the-art techniques, among these high-resolution microscopy of mitochondria and protein structure determination by crystallography. By the means of super-resolution-microscopy, electron microscopy and electron cryotomography Prof. Larsson also examines packaging of the mitochondrial DNA into nucleoids, which holds the genetic material of mitochondria.

CECAD COOPERATIONS

F Prof. Dr. J. Brüning — Principal Investigator → p. 169
A Prof. Dr. T. Langer — Principal Investigator → p. 59
A Prof. Dr. E. I. Rugarli — Principal Investigator → p. 63
A Prof. Dr. A. Trifunovic — Principal Investigator → p. 75

EXTERNAL COOPERATIONS

Prof. Dr. M. Falkenberg Gustafsson, University of Gothenburg, SE
Prof. Dr. A. Filipovska, University of Western Australia, Perth, AU
Prof. Dr. C. Gustafsson, University of Gothenburg, SE
Prof. Dr. S. Jakobs, Max Planck Institute for Biophysical Chemistry, Göttingen, DE
Prof. Dr. W. Kühlbrandt, Max Planck Institute for Biophysics, Frankfurt, DE
Prof. Dr. O. Rackham, University of Western Australia, Perth, AU

Prof. Dr. Nils-Göran Larsson
Principal Investigator
Managing Director of the
MPI for Biology of Ageing

PUBLICATIONS

Kühl I, Kukat C, Ruzzenente B, Milenkovic D, Mourier A, Miranda M, Koolmeister C, Falkenberg M, Larsson NG. (2014) POLRMT does not transcribe nuclear genes (Brief Communications Arising). Nature 2014:514:E7-E11.

Mourier A, Matic S, Ruzzenente B, Larsson NG, Milenkovic D. (2014) The Respiratory Chain Supercomplex Organization Is Independent of COX7a2l Isoforms. Cell Metab. Dec 2;20(6):1069-75.

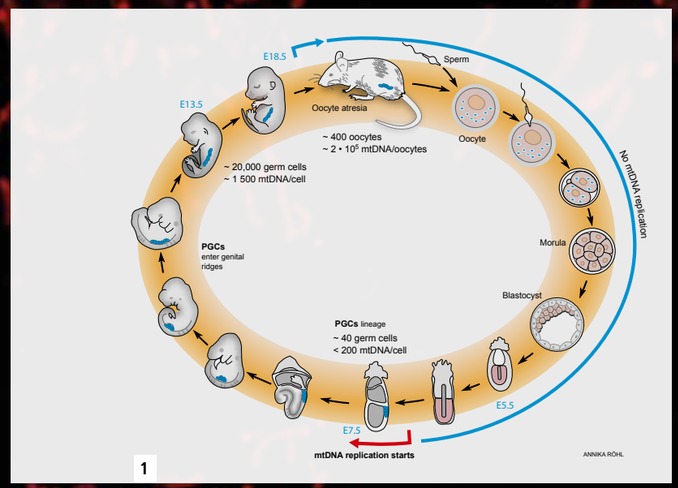
Ross JM, Stewart JB, Hagström E, Brené S, Mourier A, Coppotelli G, Freyer C, Lagouge M, Hoffer BJ, Olson L, Larsson NG. (2013) Germline mitochondrial DNA mutations aggravate ageing and can impair brain development. Nature. 501:412-415.

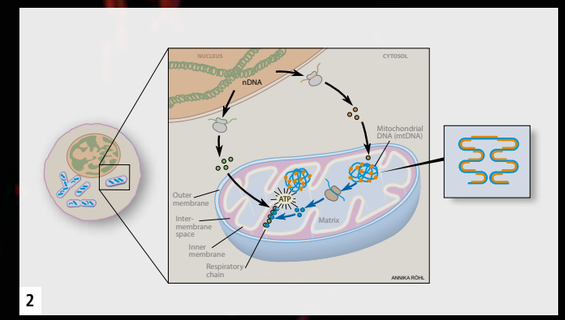
Spåhr H, Habermann B, Gustafsson CM, Larsson NG, Hallberg BM. (2012) Structure of the human MTERF4-NSUN4 protein complex that regulates mitochondrial ribosome biogenesis. Proc. Natl. Acad. Sci. USA. 109:15253-15258.

Freyer C, Cree LM, Mourier A, Stewart JB, Koolmeister C, Milenkovic D, Wai T, Floros VI, Hagström E, Chatzidaki EE, Wiesner RJ, Samuels DC, Larsson NG, Chinnery PF. (2012) Variation in germline mtDNA heteroplasmy is determined prenatally but modified during subsequent transmission. Nature Genetics 44:1282-1285.

Zur Zeit arbeitet Prof. Larsson in Kooperation mit dem Lead Discovery Center, eine Tochter der Max-Planck-Innovation GmbH, an der Entwicklung von Molekülen, über die die Genexpression und damit die Mitochondrienfunktion gesteuert werden kann. Dadurch eröffnen sich neue therapeutische Chancen: Mit der Beeinflussung der Zellalterung könnten auch für mitochondriale Erkrankungen neue Behandlungsoptionen entstehen.

BACKGROUND FIGURE : Mitochondrial network in a mouse fibroblast visualized by Mitotracker staining
FIGURE 1: Schematic drawing of the life cycle of mitochondrial DNA (mtDNA) during the development of oocytes in mice.
FIGURE 2: Schematic drawing of a mitochondrium, mitochondrial DNA and the complexes of protein synthesis. The right window shows a zoom into a part of mitochondrial DNA (blue) that is covered U-shape-like with the TFAM protein (yellow), the main component of the nucleoid.





Mitochondrien sind die Kraftwerke der Zellen. Prof. Dr. Aleksandra Trifunovic erforscht mit ihrer Arbeitsgruppe ihre Funktion in der Entstehung von Erkrankungen. Ihr Fokus liegt auf der Entschlüsselung mitochondrialer Stressreaktionen und der Kommunikation zwischen Mitochondrien und anderen Zellbestandteilen. In diesem Kontext konnte die Arbeitsgruppe bereits relevante Stoffwechselprozesse identifizieren und plant die Evaluation von Medikamenten zur Behandlung mitochondrialer Erkrankungen in Kooperation mit einem Unternehmen.

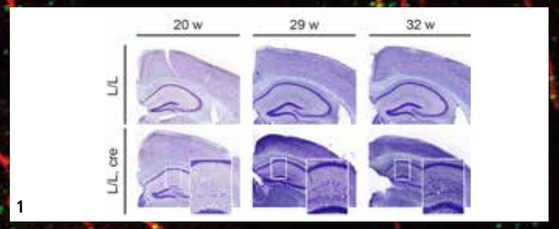


FIGURE 1: Mitochondrial dysfunction causes progressive neuronal loss. Hippocampal area of brains from control (L/L) and aspartyl-tRNA synthentase, forebrain neuron-deficient mice - Dars2 L/L; +/CamKII-cre (L/L, cre) stained by Nissl staining, used to highlight important structural features of different types of neurons. Clear sign of progressive neuronal degeneration are visible in mitochondrial mutant.
FIGURE 2: Histological analysis of mitochondrial dysfunction. Cytochrome c oxidase (COX) activity (brown) highlights integrity of mitochondrial function while succinate dehydrogenase (SDH) activity (blue) increases in respiratory chain deficient cells. In this figure, cross-sections of hearts of DARS2 deficient-mice (a gene essential for mitochondrial translation), show a strong mitochondrial dysfunction (left side). This effect can be partially reversed, if these mice are depleted in addition of CLPP, a mitochondrial matrix protease (right side).



↗ http://cecad.uni-koeln.de/Prof-Aleksandra-Trifunovic.110.0.html

Prof. Dr. Aleksandra Trifunovic

Principal Investigator
Institute for Genetics

Prof. Dr. Aleksandra Trifunovic and her research group are investigating mitochondrial stress responses and the cell's corresponding adaptive reactions. By deciphering the signaling cascades, they are seeking to understand the pathomechanisms of mitochondrial diseases and develop new therapeutic approaches. The group has recently started collaborating with Khondrion, one of the first European companies aiming to develop drugs to treat mitochondrial diseases. Prof. Dr. Trifunovic's group will focus on evaluating the therapeutic effects in model organisms.

Our research: The team led by Prof. Aleksandra Trifunovic is investigating the function of mitochondria in the development of disease and during aging. When mitochondria experience stress or when dysfunction occurs, they send signals to the cell nucleus, which launches different types of adaptive cell responses. Transcription factors are activated and stimulate the expression of specific sets of genes, whose products enable the cell to adapt to the changes. The scientists aim to understand this signaling cascade in detail.

Our successes: The group has successfully advanced research approaches that focus on the communication between mitochondria and other parts of the cell. Causative treatment for mitochondrial disease is not yet available. Since mitochondrial dysfunction affects metabolism in general, serious illness and early death can result. Recently, the group has shown that mitochondrial dysfunction is sensed independently of respiratory chain deficiency, questioning the current view on molecular mechanisms contributing to the development of mitochondrial diseases.

Our goals: The group's main focus is on deciphering the precise signaling cascade of the pathogenic mechanisms leading to mitochondrial diseases, with the ultimate goal of identifying new therapeutic targets.

Our methods/techniques: The group mainly uses in vivo model systems, specifically the roundworm *Caenorhabditis elegans* and transgenic mice to tackle specific questions of mitochondrial pathophysiology. As one of the main aims is to understand the consequences of energy depletion in cells and the organism as a whole, many different bioenergy techniques and approaches are used.

PUBLICATIONS

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Dogan SA, Pujol C, Maiti P, Kukat A, Wang S, Hermans S, Senft K, Wibom R, Rugarli EI, Trifunovic A. (2014) Tissue-specific loss of DARS2 activates stress responses independently of respiratory chain deficiency in the heart. Cell Metab. Mar 4;19(3):458-69.

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CECAD COOPERATIONS

F Prof. Dr. A. Antebi → p. 177
Principal Investigator

F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator

D PD Dr. H. Kashkar → p. 133
Principal Investigator

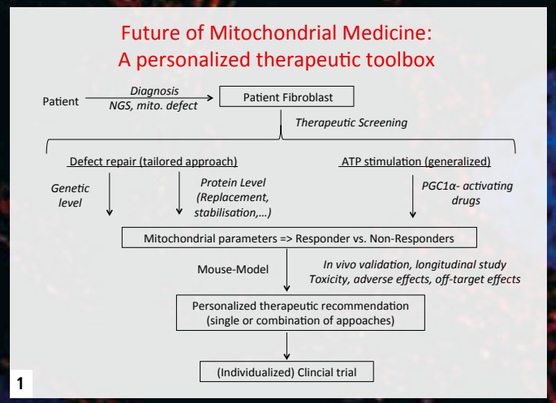
A Prof. Dr. E. I. Rugarli → p. 63
Principal Investigator

EXTERNAL COOPERATIONS

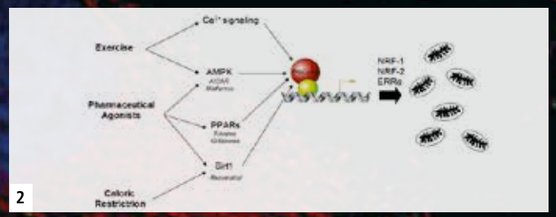
PD Dr. S. Meiners, Helmholtz Zentrum, Munich, DE
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Prof. Dr. A. Suomalainen, University of Helsinki, FI
Prof. Dr. S. Werner, ETH, Zürich, CH

A

Mitochondriale Defekte werden mit vielen alternsassoziierten Erkrankungen wie z.B. neurodegenerative Störungen in Verbindung gebracht. Die Interaktionen sind jedoch im Detail noch nicht erforscht. Die Arbeitsgruppe um PD Dr. Tina Wenz erforscht Mitochondrien und deren Funktionsstörungen, um Erkrankungsmechanismen zu verstehen und therapeutische Optionen zu entwickeln.



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BACKGROUND FIGURE: Cells with mitochondria stained with a fluorescently-labelled mitochondria protein to visualize the organellar network (red). The cell nucleus is stained in blue.

FIGURE 1: Vision for a individualized mitochondrial medicine: Therapeutic screening starts with fibroblasts of a patient with a diagnosed mitochondrial dysfunction (either in mitochondrial disease or common disease, Next generation sequencing (NGS) result patient fibroblasts undergo screening focusing on defect repair or a generalized approach to increase ATP generating capacity. The result of this screening will be then further tested in in vivo models to come up with an personalized therapeutic recommendation.

FIGURE 2: PGC-1α links external cues to mitochondrial biogenesis. Endurance exercise increases PGC-1α expression and activity through increasing cytosolic calcium levels triggered by muscle contraction. The chronic metabolic stress during exercise activates the cellular fuel gauge AMPK, which further activates PGC-1α . In an alternative strategy, PGC-1α can be activated through known pharmaceutical agonist for signaling molecules such as AMPK, PPAR and Sirt1. PGC-1α interacts with the transcription factors NRF-1, NRF-2, and ERR α and thereby coactivating the transcription of their target genes which comprise the mitochondrial biogenesis program.



↗ http://cecad.uni-koeln.de/Dr-Tina-Wenz.114.0.html

PD Dr. Tina Wenz

Principal Investigator
Institute for Genetics

Aging-associated diseases, such as neurodegenerative disorders, are associated with mitochondrial dysfunction, but the role of mitochondria in the development of disease is not yet completely understood. The group led by PD Dr. Tina Wenz investigates the variables controlling the survival of the cell under extreme conditions. The findings could contribute to the development of novel therapeutic options.

Our research: PD Dr. Tina Wenz and her group focus on the investigation of mitochondrial dysfunction and its pathological effect in mitochondrial disease, a rare disorder, as well as on aging and the development of conditions like neurodegenerative disorders or inflammation. Another focus is the behavior of mitochondria in stress situations, for instance their ability to adapt energy generation to changes in nutrient supply. Identifying factors for mitochondrial regulation could lead to new approaches for novel therapeutic options.

Our successes: For her work on rare mitochondrial diseases and establishing a new, patented treatment concept, PD Dr. Tina Wenz was honored with the prestigious Care for Rare Award. Breakthrough findings were the assessment of a small molecular activator for a mitochondrial controlling pathways and the description of a tissue-specific regulator. These results form the basis for development of directed therapeutic approaches in mitochondrial disease.

Our goals: The group is interested in molecular genetic research on tissue-specific regulation. They want to understand how such regulation contributes to the pathomechanism as well as adaptation and recovery in situations of high energy demand. The translational goal is to asses novel therapeutic approaches, which forms the basis for future translation into preclinical testing.

Our methods/techniques: The group uses various methods such as molecular biology, protein isolation, cell culture, model organisms.

PUBLICATIONS

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CECAD COOPERATIONS

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→ p. 40

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→ p. 135

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Prof. Dr. E. M. Verdin, San Francisco, Gladstone Institute, USA

A

Ein zentraler Mechanismus in der Entstehung alternsassoziierter Erkrankungen ist der Funktionsverlust der Mitochondrien, den Kraftwerken der Zelle. Prof. Dr. Wiesner erforscht mit seinem Team die Auswirkung von mutierter mitochondrialen DNA auf die Funktion von Organen. Ein Erfolg ist die Entschlüsselung mitochondrialer Prozesse, die die Entstehung von Diabetes oder Morbus Parkinson beeinflussen.

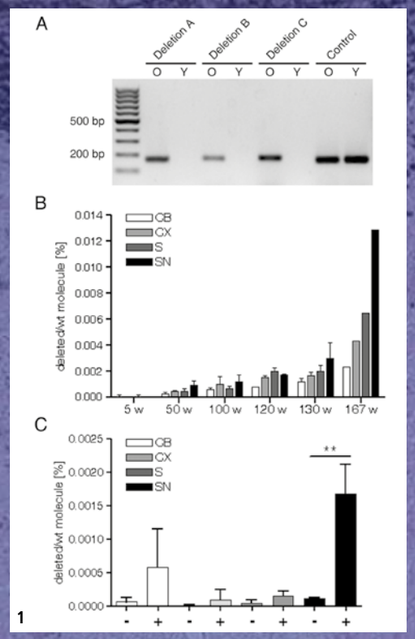
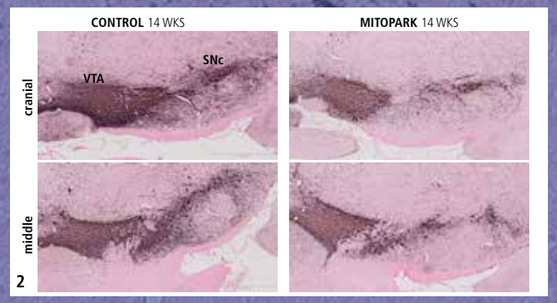


FIGURE 1: Catecholamine metabolism drives mtDNA deletions in aging mouse brain. A) mtDNA deletions in old (> 100 weeks) versus young (5 weeks) mouse striatum; mtDNA molecules harboring a deletion result in specific PCR products; Control: product from D-Loop, present in all mtDNAs. B) Levels of mtDNA deletions in brain tissues. C) Levels of mtDNA deletions in 50-week-old MAOB over-expressing mice. CB: cerebellum; CX: cortex; S: striatum; SN: substantia nigra; +: MAOB induced; –: uninduced.

FIGURE 2: Early death of dopaminergic neurons in the Substantia nigra (SNc), but not in the VTA region, of mice suffering from severe mitochondrial dysfunction in these cells (MitoPark mice, Ekstrand et al., PNAS 104 (2007), resembling the pattern observed in M. Parkinson disease patients.





↗ http://cecad.uni-koeln.de/Prof-Rudolf-J-Wiesner.115.0.html

Prof. Dr. Rudolf J. Wiesner

Principal Investigator
Department of Physiology

Prof. Dr. Rudolf Wiesner's group investigates the mechanisms of mitochondrial loss of function. Mutations in mitochondrial DNA accumulate in the course of life and ultimately lead to functional defects in cells. The group's work centers around deciphering this process to be able to slow it down and delay the resulting organ insufficiency.

Our research: Mitochondria contain their own DNA molecules. The mutations that accumulate in many organs, such as the heart, brain and muscle, are mainly deletions, where a part of the DNA strand is missing. These deletions are not evenly distributed – some cells show massive accumulation, which leads to a loss of function of those cells. A mosaic of normal and heavily impaired cells develops. This process is accelerated in many aging-associated diseases, such as Parkinson's disease or cardiac arrhythmia. The group investigates how these mutations arise, why they accumulate in individual cells, and how they influence tissue function.

Our successes: In collaboration with other research teams, the scientists have uncovered new important aspects of mitochondrial dysfunction in liver and muscle in connection with diabetes. They have shown that in this setting mitochondrial dysfunction is not the cause, but rather a parallel development. The group was able to demonstrate the mutagenic effect of dopamine metabolism on mitochondrial DNA – an important pathomechanism in the development of aging-associated Parkinson's disease. Now they are working on reconstructing the process that damages the mitochondrial DNA. The group was also the first to demonstrate that a very small number of heart muscle cells with mitochondrial dysfunction are sufficient to cause cardiac arrhythmia.

Our goals: The group's goal is to understand in detail how mitochondrial damage – in particular damage caused by mitochondrial DNA deletions – arises and how it leads to organ dysfunction by failure of single cells in a tissue. The aim is to develop therapeutic approaches to slow the process.

Our methods/techniques: The scientists perform behavioral experiments with model organisms, measure organ function, and test mitochondrial DNA for mutations. The collaboration with the Imaging Facility allows mitochondrial function to be observed in situ and in vivo.

PUBLICATIONS

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CECAD COOPERATIONS

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A Prof. Dr. T. Langer → p. 59
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A Prof. Dr. N.-G. Larsson → p. 71
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A Prof. Dr. E. I. Rugarli → p. 63
Principal Investigator

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Prof. Dr. A. Suomalainen-Wartiovaara, Research Program of Molecular Neurology, Helsinki, FI

B

Proteine sind essentielle Bestandteile jeder Zelle. Damit eine Zelle funktionsfähig bleibt, sorgen zelluläre Qualitätskontrollmechanismen dafür, dass defekte Proteine repariert und irreparabel geschädigte Proteine entsorgt werden. Mit zunehmendem Alter nimmt die Aktivität dieser Qualitätskontrollwege deutlich ab, wodurch fehlgefaltete Proteine weniger effizient repariert und entsorgt werden. Die beschädigten Proteine verklumpen und führen zu einer Reihe von schwerwiegenden Erkrankungen. Wissenschaftlerinnen und Wissenschaftler der Research Area B untersuchen den Zusammenhang zwischen Proteinqualitätskontrolle und Alterungsprozessen.

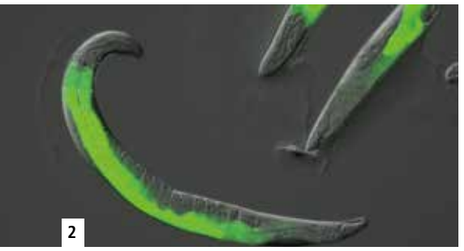
Research Area B
Disruptions in Protein Metabolism Cause Aging-Associated Diseases

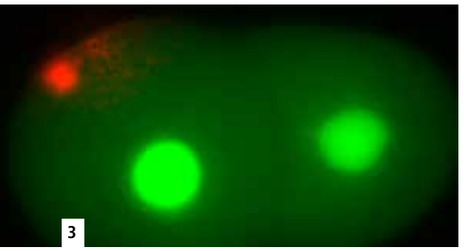
Proteins play a life-sustaining role in the cell – how does it work?
Proteins are essential components of every cell. Protein quality control, the repair of defective and removal of irreparably damaged proteins, is of key importance for maintaining cell function. In human cells, this is accomplished by a range of quality control mechanisms. Special molecules, so-called chaperones, help newly synthesised proteins fold into the right three-dimensional structure. If a protein misfolds despite the presence of a chaperone and therefore cannot function properly, the ubiquitin/proteasome system breaks it down into amino acids, which are then recycled. This quality control no longer functions properly with increasing age. Improperly folded proteins can be neither repaired nor removed. The proteins clump and lead to a series of serious illnesses like Alzheimer's, Parkinson's and muscle disorders, but also to organ degeneration.

New insights into the interplay between protein metabolism, aging and lifespan
Using the *C. elegans* threadworm, CECAD scientists investigate which aging processes are influenced by the disposal and recycling of defective proteins. They have successfully identified components of the ubiquitin/proteasome system that are fundamentally responsible for regulating muscle development. Muscles are comprised of thick and thin protein strands, the myofibrils. These have to be carefully assembled by a complex protein machinery to ensure that the muscle functions under stress. Enzymes regulate this process, and stamp the muscle regulators with an expiration date. In threadworms scientists have successfully manipulated this expiration date, thus keeping damaged muscles active longer. The proper regulation of this system is a prerequisite for developing and maintaining muscle activity. Dysregulation leads to an aggregation of muscle proteins in the human body. They result in inflammation and muscle weakness that can ultimately lead to death. This discovery could be revolutionary for the therapy and diagnosis of some muscle disorders.

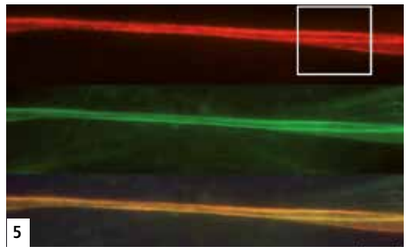
An additional question researchers from Research Area B are looking into is how protein quality control is regulated in individual cells and in united cell structures. They are trying to identify how the control mechanisms can be maintained in response to environmental and physiological challenges. In order to understand specific signalling pathways and reactions in the described proteostasis networks, CECAD scientists are analysing these processes in the tissue of different model organisms.


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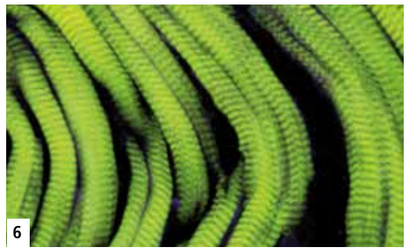

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FIGURE 1: CECAD scientists take advantage of genetic model organisms. Here, the transparent soil nematode *Caenorhabditis elegans* is used to investigate PQC pathways in vivo.
FIGURE 2: *C. elegans* mutants shown in this picture are defective in protein degradation pathways in the intestine, which often cause premature aging phenotypes. The defects are visualized by green fluorescence of a stabilized model substrate.
FIGURE 3 AND 4: *C. elegans* embryos undergo cycles of rapid cell division, which allows following the distribution of labeled proteins by time-lapse microscopy. Here, a DNA replication factor is localized inside the nucleus during S-phase of the cell cycle. Defects in this process result in genomic instability.
FIGURE 5: Myotubes derived from myoblasts of myopathy patients or control cells.
FIGURE 6: are stained for different muscle specific differentiation marker proteins to monitor disease related developmental and structural defects.

PRINCIPLE INVESTIGATORS MAIN FOCUS

Prof. Dr. T. Benzing → p. 85
Prof. Dr. T. Hoppe → p. 89
Prof. Dr. M. Krüger → p. 93
Prof. Dr. G. Schwarz → p. 95
Dr. D. Vilchez → p. 97

PRINCIPLE INVESTIGATORS SECOND FOCUS

Dr. M. Herling → p. 117
Prof. Dr. Dr. P. Nicotera → p. 181
Prof. Dr. L. Partridge → p. 173
Prof. Dr. E. I. Rugarli → p. 63
Prof. Dr. B. Schumacher → p. 107
Prof. Dr. A. Trifunovic → p. 75
PD. Dr. T. Wenz → p. 77

Schwerpunkt der AG von Prof. Dr. Benzing ist die Erforschung altersbedingter Nierenerkrankungen. Progrediente Nierenschäden sind im Alter sehr häufig. Sie erhöhen nicht nur das Risiko für ein dialysepflichtiges Nierenversagen, sondern gelten als potenter Risikofaktor für Schlaganfall, Demenz und Herzinfarkt. Benzing's Team studiert die Funktion konservierter Signaltransduktionsmechanismen der Alterung, Schädigung und Stresstoleranz mit modernsten Techniken der Genetik und Molekularbiologie.

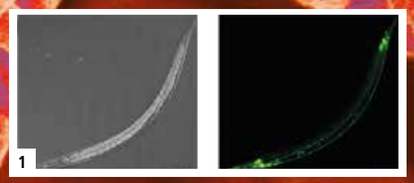


FIGURE 1: The nematode *C. elegans* is one of the model organisms that greatly facilitates these studies, e.g. due to its simple genetic amenability (unpublished image of a worm expressing GFP under the control of the *flcn-1* promoter).
FIGURE 2: We use this model to identify genes that regulate lifespan and stress resistance through modulation of hypoxia-inducible factor (HIF-1) -signaling (shown here for *flcn-1*; modied from Gharbi et al. Aging Cell 2013).



↗ http://cecad.uni-koeln.de/Prof-Thomas-Benzing.84.0.html

Prof. Dr. Thomas Benzing

Head of Research Area B – Principal Investigator
Kidney Research Center Cologne (KRCC)

Age-related kidney diseases are a main cause of morbidity and a major risk factor for stroke, myocardial infarction or dementia. Benzing's team seeks to unravel the molecular networks in age-related renal pathologies. A major aim is to transfer these findings into new treatment strategies. The lab has pioneered molecular nephrology research of the past decade and provided insights into important human diseases.

Our research: An ever-increasing proportion of the aging population is affected by renal disease and hypertension. Although "normal aging" does not necessarily cause dramatic changes in kidney function, a strongly increased incidence of hypertension and a high susceptibility to acute kidney failure are very common findings. The causes of age-related renal pathologies are poorly understood but genetic as well as environmental factors clearly play a role. Benzing's team focuses on the molecular principles of kidney disorders using genetic disorders as a model to unravel the molecular mechanism involved in age-related kidney diseases. They also follow a systems biology approach in studying the underlying signal transduction networks and transfer the findings into the clinics to develop new treatment strategies.

Our successes: In the past decade, Benzing and his team have pioneered the concept of signaling at the slit diaphragm. They showed that this specialized cell junction controls the physiology of the renal filtration barrier and developed tools and techniques to study this regulation. Together with collaborating investigators all over the world they deciphered the function of this signaling complex and its evolutionarily conserved role in controlling intercellular communication and cellular homeostasis in organisms from *C. elegans* over *Drosophila* to mice and humans. Moreover, they have investigated signaling through cilia, longevity and cancer. Seminal studies of the lab have led to the discovery of novel genes involved in controlling the pathogenesis of ciliopathies and a variety of age-related kidney disorders. They recently also identified a novel longevity pathway and showed that deletion of the *vhl-1* gene in *C. elegans* markedly extended lifespan in the nematode. The same pathway reduces susceptibility to various renal insults and slows progression of age-related kidney disease. Benzing's work has been acknowledged with numerous prizes and awards.

Our goals: A central objective is on the identification of signaling 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 they investigate 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 highly recognized clinical expertise provides the unique combination of translating new findings from bench to bedside.

Our methods/techniques: The nephrology lab is headed by Prof. Benzing and Prof. Schermer who also leads his own research team on the molecular pathways of cilia-associated disorders. Their team uses the model organisms *C. elegans* and *Drosophila* as well as genetically engineered mice in combination with genetics, molecular biology, proteomics and live imaging as well as genome-wide mRNA and protein expression techniques to study molecular mechanisms of renal pathophysiology. Benzing and his team are involved in numerous international collaborations and also coordinate the systems biology initiative Systems Biology of Ageing Cologne (Sybacol).

CECAD COOPERATIONS

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Principal Investigator
F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator
C Prof. Dr. M. Hallek → p. 113
Principal Investigator
A Prof. Dr. T. Langer → p. 59
Principal Investigator
E Prof. Dr. M. Pasparakis → p. 147
Principal Investigator
C Prof. Dr. C. Reinhardt → p. 103
Principal Investigator
C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

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Prof. Dr. S. Dryer, University of Houston and Baylor College of Medicine, Houston, USA

Prof. Dr. Thomas Benzing
Head of Research Area B
Principal Investigator
Kidney Research Center Cologne (KRCC)

PUBLICATIONS

Rinschen MM, Wu X, Konig T, Pisitkun T , Hagmann H, Pahmeyer C, Lamkemeyer T, Kohli P, Schnell N, Schermer B, Dryer S, Brooks BR, Beltrao P, Krueger M, Brinkkoetter PT, Benzing T. (2014) Phosphoproteomic analysis reveals regulatory mechanisms at the kidney filtration barrier. J Am Soc Nephrol. 25(7): 1509-22.

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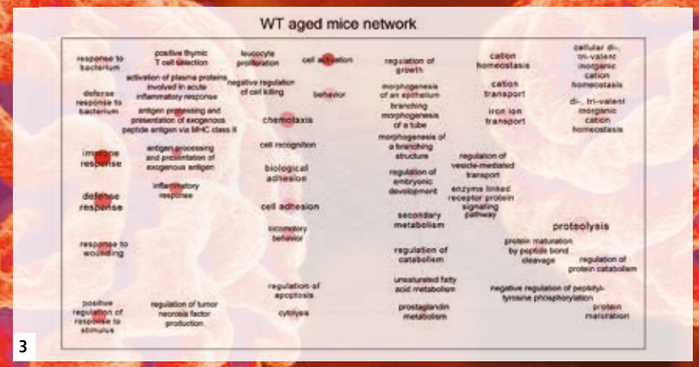
Gharbi H, Fabretti F, Bharill P, Rinschen MM, Brinkkötter S, Frommolt P, Burst V, Schermer B, Benzing T, Müller RU. (2013) Loss of the Birt-Hogg-Dubé gene product folliculin induces longevity in a hypoxia-inducible factor-dependent manner. Aging Cell. 12(4): 593-603.

Höpker K, Hagmann H, Khurshid S, Chen S, Hasskamp P, Seeger-Nukpezah T, Schilberg K, Heukamp L, Lamkemeyer T, Sos ML, Thomas RK, Lowery D, Roels F, Fischer M, Liebau MC, Resch U, Kisner T, Röther F, Bartram MP, Müller RU, Fabretti F, Kurschat P, Schumacher B, Gaestel M, Medema RH, Yaffe MB, Schermer B, Reinhardt HC, Benzing T. (2012) AATF/Che-1 acts as a phosphorylation-dependent molecular modulator to repress p53-driven apoptosis. EMBO J. 31(20): 3961-75.

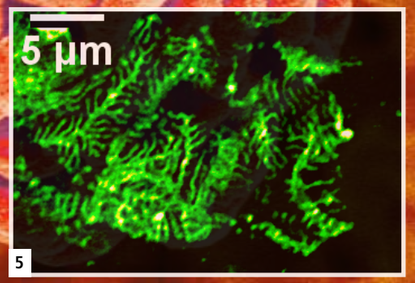
Thadhani R, Kisner T, Hagmann H, Bossung V, Noack S, Schaarschmidt W, Jank A, Kribs A, Cornely OA, Kreyssig C, Hemphill L, Rigby AC, Khedkar S, Lindner TH, Mallmann P, Stepan H, Karumanchi SA, Benzing T. (2011) Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. Circulation. 124(8): 940-50.

FIGURE 3: GO terms that are enriched in the list of differentially regulated genes found in wild type mouse glomeruli are shown. The lower the p-value of term enrichment the darker the bubble color. Bubble sizes reflect the frequency of a respective GO term in the GO database. We find an enrichment of terms associated with immune response, defense response, proteolysis, endocytosis, and regulation of apoptotic processes in aged glomeruli.
FIGURE 4: Minimal state networks of WT mice. The graphs show the minimally connected interaction networks of wild type mice. Pink circles indicate all genes that were differentially expressed. Grey circles indicate linker genes. Both networks contain functional modules associated with chemokine receptor signalling, insulin signaling, anti-apoptotic signalling as well as extracellular matrix and complement signalling.
FIGURE 5: Visualization of single podocytes using mosaic animals. Generation of mosaic expression patterns of Cre recombinase by low-dose tamoxifen induction in R26mT-mG x TPod:Cre glomeruli allows for the visualization of secondary processes. Z-projection (average) of ten consecutive confocal slices, covering 0.75 µm (z-step=0.075 µm). Induction of Cre expression was achieved by feeding with a tamoxifen diet for 6 weeks.

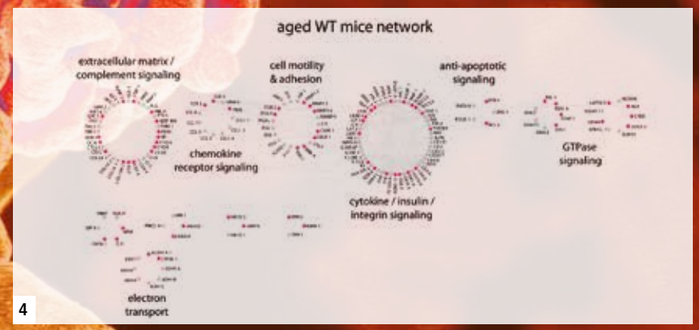
Das Team hat wesentlich zu einem besseren Verständnis von Erkrankungen des Nierenfilters, der glomerulären Mikrozirkulation und alters-bedingten Schädigungen beigetragen und diese Erkenntnisse in neuartige Therapiestrategien umgesetzt. Sie gelten als international renommierte Pioniere auf dem Gebiet der molekularen Nierenforschung.



3



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B

Das Team um Prof. Dr. Thorsten Hoppe beschäftigt sich mit physiologischen und alterungsassoziierten Aspekten verschiedener Proteinabbau-Systeme, der sogenannten zellulären „Müllabfuhr“, und benutzt dazu den Fadenwurm *Caenorhabditis elegans* als Modelorganismus. Die natürliche Struktur von Proteinen kann durch fehlerhafte Translation, oxidative Modifizierungen oder Hitzestress verändert werden. Die Aggregation beschädigter Proteine löst Erkrankungen wie Alzheimer oder Parkinson aus. Bisherige Ergebnisse der Arbeitsgruppe bieten bereits wichtige Grundlagen zur Entwicklung neuer Behandlungsstrategien gegen Demenz und Muskelschwund.



↗ http://cecad.uni-koeln.de/Prof-Thorsten-Hoppe.92.0.html

Prof. Dr. Thorsten Hoppe

Head of Research Area B – Principal Investigator
CECAD Cologne and Institute for Genetics

The ubiquitin/proteasome system (UPS) is a major proteolytic route functioning in a cellular network to maintain the proteome during stress and aging. Another proteolytic system supporting proteostasis is the autophagy-lysosome pathway that degrades proteins inside activated autophagosomes. Age-related impairment of either of these systems causes enhanced protein aggregation and affects lifespan, suggesting functional overlap and cooperation between the UPS and autophagy in stress and aging. The ultimate goal of Prof. Dr. Thorsten Hoppe and his team is to assemble a global picture of the stress-induced proteolytic networks critical for aging and age-related diseases.

Our research: Prof. Thorsten Hoppe and his team are using the nematode *Caenorhabditis elegans* to study physiological aspects of selective protein turnover in the context of aging-associated processes, such as muscle development and regeneration, protein aggregation, and genome stability. They take advantage of fluorescent reporter proteins that allow them to evaluate the activity of both 26S proteasome and autophagy in transgenic worms. This approach has already been used for genetic screening, which provides insight into the regulation of the proteolytic machinery. Initial results indicate that the dynamics of different proteolytic pathways are controlled by stress-induced signaling mechanisms. Identifying the critical regulators would help to characterize the underlying principles. In addition to intracellular proteostasis networks, Hoppe and his team's long-term mission is to understand non-cell-autonomous regulation of protein degradation through paracrine factors. Intercellular communication via stress signals may coordinate cells of different tissues and counteract the aging process of the organism as a whole. The team's goal is to understand the crosstalk between stress-induced proteolytic pathways and the aging of multicellular organisms.

Our successes: Prof. Hoppe's research group has identified regulatory mechanisms that coordinate protein degradation systems and the aging process. Defects in proteolysis often result in the accumulation and aggregation of misfolded proteins in the human brain, causing motor and speech deficits. By manipulating the degradation machinery, Prof. Hoppe and his team were able to delay the aging process and extend the lifespan in *C. elegans*. These findings may be relevant for future therapeutic interventions against degenerative aging-associated diseases, such as Alzheimer's, Huntington's, and Parkinson's disease.
In addition, Prof. Hoppe's studies have identified mechanisms that are involved in inclusion body myopathy. Based on his results, it is possible to prevent the premature loss of central muscle proteins and therefore extend muscle activity. Since muscles lose both structure and stability with age, this topic is highly relevant to current aging research.

Our goals: The scientists aim to understand the role of key proteolytic pathways in triggering aging-associated diseases. Besides intracellular proteostasis networks, the working group's long-term goal is to investigate non-cell-autonomous regulation. The intercellular transduction of stress signals may coordinate cells of different tissues and the aging process of multicellular organisms.

CECAD COOPERATIONS

F Prof. Dr. A. Antebi, Principal Investigator → p. 177
D PD Dr. H. Kashkar, Principal Investigator → p. 133
B Prof. Dr. M. Krüger, Principal Investigator → p. 93
C Prof. Dr. C. Reinhardt, Principal Investigator → p. 103
C Prof. Dr. B. Schumacher, Principal Investigator → p. 107
B Dr. D. Vilchez, Principal Investigator → p. 97
C Prof. Dr. B. Wollnik, Principal Investigator → p. 123

EXTERNAL COOPERATIONS

Prof. Dr. Anat Ben-Zvi, Prof. Dr. Julien Blow,
Prof. Dr. Aaron Ciechanover,
Prof. Dr. Nico Dantuma,
Prof. Dr. Catherine Dargemont,
Prof. Dr. Anton Gartner, Prof. Dr. Markus Glatzel,
Prof. Dr. Michael Glickman,
Prof. Dr. Jörg Höhfeld,
Prof. Dr. Christian Kubisch, Prof. Dr. Eric Miska,
Prof. Dr. Roger Pocock, Dr. Kristijan Ramadan,
Prof. Dr. Michael Ristow, Prof. Dr. Stephan Sigrist,
Prof. Dr. Thomas Sommer,
Prof. Dr. Olaf Stemman, Dr. Stefan Taubert

Prof. Dr. Thorsten Hoppe
Head of Research Area B
Principal Investigator
CECAD Cologne and Institute for Genetics

Our methods/techniques: The research group combines studies in *C. elegans* and primary cell cultures from patients with various diseases. The activity of the proteasome and autophagy is usually monitored by fluorescent marker proteins in transgenic worms. Genome-wide sequencing approaches are used in *C. elegans* to explore the transcriptional regulation of different proteolytic systems.

PUBLICATIONS

Segref A, Kevei E, Pokrzywa W, Schmeisser K, Mansfeld J, Livnat-Levanon N, Ensenauer R, Glickman M.H, Ristow M, Hoppe T. (2014) Pathogenesis of human mitochondrial diseases is modulated by reduced activity of the ubiquitin/proteasome system. Cell Metab. 19, 642-52.

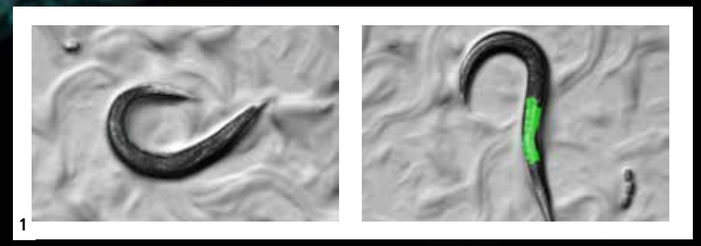
Ermolaeva M.A, Segref A, Dakhovnik A, Ou H.L, Schneider JI, Utermöhlen O, Hoppe T, Schumacher B. (2013) DNA damage in germ cells induces an innate immune response that triggers systemic stress resistance. Nature 501, 416-20.

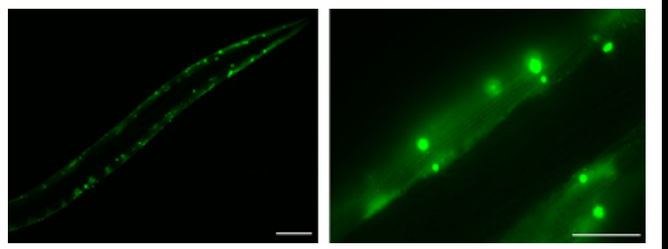
Gazda L, Pokrzywa W, Hellerschmied D, Löwe T, Forné I, Mueller-Planitz F, Hoppe T, Clausen T. (2013) The myosin chaperone UNC-45 is organized in tandem modules to support myofilament formation in *C. elegans*. Cell 152, 183-95.

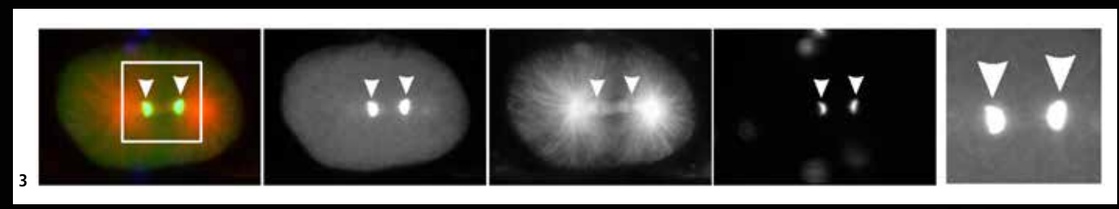
Franz A, Orth M, Pirson P.A, Sonneville R, Blow J.J, Gartner A, Stemmann O, Hoppe T. (2011). CDC-48/p97 coordinates CDT-1 degradation with GINS chromatin dissociation to ensure faithful DNA replication. Mol Cell. 44, 85-96.

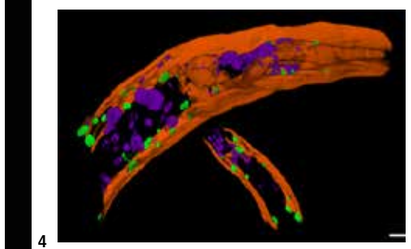
Kuhlbrodt K, Janiesch P.C, Kevei E, Segref A, Barikbin R, and Hoppe T. (2011). The Machado-Joseph disease deubiquitylase ATX-3 couples longevity and proteostasis. Nat. Cell Biol. 13, 273-81.

BACKGROUND FIGURE: We take advantage of the powerful genetic model *Caenorhabditis elegans*, which allows addressing tissue-specific differences in aging relevant proteostasis pathways.
FIGURE 1: Expression of green fluorescent protein (GFP)-based substrates allows rapid quantification of protein turnover in different tissues of *C. elegans*. The right panel shows a mutant worm with proteolytic defects and substrate stabilization.
FIGURE 2: Disease related mutations known to cause huntington's disease challenge tissue specific proteostasis networks. In contrast to wild-type (left), polyglutamine containing proteins form protein aggregates in muscle cells of mutant worms.
FIGURE 3: *C. elegans* embryos depleted for CDC-48$^{UFD\text{-}1/NPL\text{-}4}$ stained with anti-Tubulin (red) and anti-CDT-1 antibodies (green).
FIGURE 4: *C. elegans* body-wall muscle cells (actin in red) with protein aggregates/inclusion bodies (green). Cell nuclei are stained with DAPI (blue).

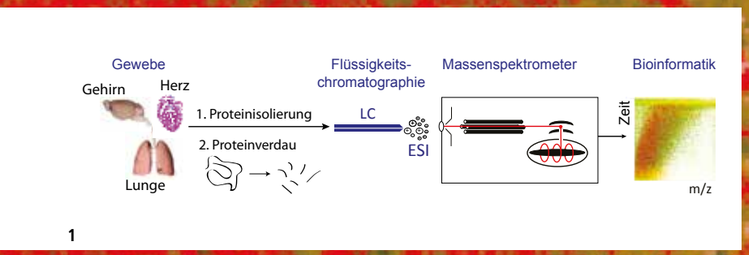

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Die Arbeitsgruppe um Prof. Dr. Marcus Krüger erforscht mit quantitativer Massenspektrometrie Protein-Veränderungen, die durch verschiedene Erkrankungen ausgelöst werden. Ihr Ziel ist es, veränderte Proteine als Angriffspunkte für neue therapeutische Maßnahmen zu identifizieren. Die Wissenschaftler konnten bereits eine Methode zur akkuraten Messung der relativen Protein-Konzentrationen im Gewebe von Modellorganismen wie der Maus entwickeln.



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FIGURE 1: Schematic workflow of a generic shotgun approach. Proteins from biological samples were extracted and digested with proteases. The analysis with liquid chromatography (LC) and mass spectrometry (MS) then results in large data sets of MS and tandem mass spectrometry (MS/MS) data containing quantitative peptide information.



↗ http://cecad.uni-koeln.de/Prof-Dr-Marcus-Krueger.362.0.html

Prof. Dr. Marcus Krüger

Principal Investigator
CECAD Cologne

Prof. Dr. Marcus Krüger and his team are using quantitative high-resolution mass spectrometry to analyze protein changes in various disease models. Their aim is to identify novel disease-related pathways and to identify biomarkers as targets for therapeutic approaches. They use stable isotope labeling of amino acids in cell culture (SILAC) and in living animals to investigate protein dynamics under normal and disturbed conditions.

Our research: The proteome, the whole set of proteins in a cell, cannot be deduced entirely from the genome. For example, post-translational modifications (PTMs) are important for the dynamic regulation of protein activity, translocation, and stability. Moreover, PTMs are critical for signaling pathways and the deregulation of modifying enzymes often leads to diseases, such as cancer and type 2 diabetes mellitus. Prof. Krüger and his research group are applying large-scale quantitative proteomics to investigate signal transduction pathways in various mouse models.

Our successes: The Krüger group is involved in transferring the SILAC technology to various model organisms, including worms, zebra fish, and rodents. This allows them to determine protein concentrations and protein turnover in living animals using mass spectrometry (LC-MS/MS).

Our goals: The group is aiming to identify protein and PTM profiles in living model organisms with relevance to human diseases. With long-term goals of developing new treatment methods, these scientists intend to use the profiles as targets for new therapeutic agents. In personalized medicine of the future, unbiased proteome analysis will be employed in addition to genome-wide strategies for the individual treatment of human patients.

Our methods/techniques: The Krüger laboratory uses SILAC labeling of model organisms to quantify proteins and regulatory PTMs accurately. The group uses the enrichment of PTMs, such as phosphorylation and acetylation, via affinity- and antibody-based methods.

PUBLICATIONS

Krishnan K, Nolte H, Sun T, Kaur H, Sreenivasan K, Looso M, Offermanns S, Krüger M, Swiercz J. (2015) Quantitative analysis of the TNF-α-induced phosphoproteome reveals AEG-1/MTDH/LYRIC as an IKKβ substrate, Nature Communications, accepted manuscript.

Hölper S, Nolte H, Bober E, Braun T, Krüger M. (2015) Dissection of metabolic pathways in the Db/Db mouse model by integrative proteome and acetylome analysis. Molecular BioSystems 17;11(3):908-22.

Nolte H, Hölper S, Housley MP, Islam S, Piller T, Konzer A, Stainier DYR, Braun T, Krüger M. (2014) Dynamics of Fin Regeneration in Zebrafish Using a Pulsed SILAC Approach, Proteomics 15(4):739-51.

Nolte H, Hölper S, Selbach M, Braun T, Krüger M. (2014) Native SILAC flooding dose approach for serum protein dynamics (SILflood) Analytical Chemistry 86 (22), 11033-11037.

Nolte H, Konzer A, Ruhs A, Jungblut B, Braun T, Krüger M. (2014) Global protein expression profiling of zebrafish organs based on in vivo incorporation of stable isotopes. J Proteome Res. Apr 4;13(4):2162-74.

CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator

B Prof. Dr. T. Hoppe → p. 89
Principal Investigator

A Prof. Dr. T. Langer → p. 59
Principal Investigator

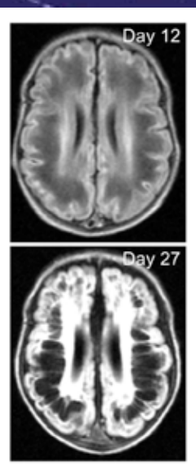
E Prof. Dr. M. Pasparakis → p. 147
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

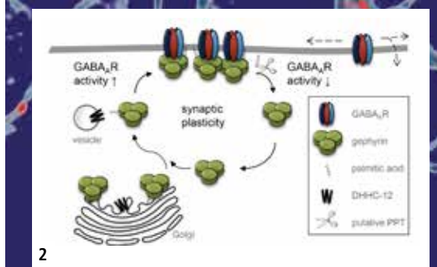
EXTERNAL COOPERATIONS

Prof. Dr. St. Dimeler, University of Frankfurt, DE; Prof. Dr. M. Gautel, Molecular Cardiology, London, UK; Prof. Dr. Zhen Jiang, The Whitaker Cardiovascular Institute, Department of Pharmacology, Boston, USA; Prof. Dr. W. Linke, University of Bochum, DE; Prof. Dr. C. R. Kahn, Joslin Diabetes Center, Boston, USA; Prof. Dr. M. Sandri, Venetian Institute of Molecular Medicine, Padua, IT

Prof. Dr. Günter Schwarz und sein Team erforschen Stoffwechselerkrankungen mit einem besonderen Fokus auf der Molybdän-Kofaktor-Defizienz. Die Wissenschaftlerinnen und Wissenschaftler konnten für diese vererbliche Erkrankung eine Therapie mit einer biotechnologisch hergestellten Vorstufe des Molybdän-Kofaktors entwickeln. Die Mechanismen der Bildung und Funktion inhibitorischer Synapsen und ihre Beteiligung an Epilepsien sind ein weiterer Forschungsschwerpunkt.



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FIGURE 1: Magenetic resonance images of a molybdenum cofactor deficient patient recorded at an age of 12 and 27 days showing rapidly progressing brain damage resulting in brain atrophy and cystic changes in the cerebral cortex.
FIGURE 2: Model for palmitoylation-mediated regulation of gephyrin clustering and plasticity. Gephyrin is palmitoylated by the palmitoyl transferase DHHC-12, which localized to Golgi outposts in primary dendritic shafts. At the synapse, palmitoylated gephyrin stabilizes GABA type A receptors. Silencing of GABAergic transmission leads to gephyrin depalmitoylation via gephyrin nitrosylation, membrane release, and decrease in cluster size.



↗ http://cecad.uni-koeln.de/Prof-Guenter-Schwarz.108.0.html

Prof. Dr. Günter Schwarz

Principal Investigator
Chair in Biochemistry

Prof. Dr. Günter Schwarz and his team are investigating metabolic disorders, focusing on molybdenum cofactor deficiency. Using biotechnology to produce a precursor of molybdenum cofactor, the team has developed a treatment for this inborn error of metabolism. They are also focusing on mechanisms of synaptogenesis and its function in the pathogenesis of epilepsy. In addition, they are trying to ascertain how changes in metabolism cause Huntington's disease.

Our research: Research by Prof. Schwarz's team focuses on two areas. First, the scientists are investigating metabolic disorders such as molybdenum cofactor deficiency, an autosomal recessive disease which presents in neonates with severe seizures that are difficult to treat. The second focus is on neurodegenerative processes, for example, the mechanisms of synaptogenesis and their function in the development of epilepsy.

Our successes: The development of treatment for children with molybdenum cofactor deficiency is one of the group's great successes to date. In the past, these patients could only be treated symptomatically and died in early childhood. Compassionate use of a precursor of molybdenum cofactor, produced in bacteria, has now been successfully used in several patients. Results of this study were accepted for publication in the high-impact journal The Lancet. In their research into neurodegenerative disorders, the scientists have discovered new mechanisms of synaptogenesis in inhibitory neurons. The group also identified a new nitric oxide synthase in mitochondria and is looking now at its function in the nitrite-dependent regulation of blood pressure. In 2010, Prof. Schwarz was awarded the North Rhine-Westfalia Prize for Innovation.

Our goals: The aim of the neurobiological research carried out by the team is to understand which biochemical/molecular processes regulate the formation and elimination of inhibitory synapses. A further aim is to investigate how altered sulfur metabolism impacts the pathogenesis of various diseases. Conditions such as Huntington's disease have been associated with cysteine degradation, as has longevity.

Our methods/techniques: The Schwarz laboratory combines protein biochemistry techniques with methods used in cell and structural biology. Relevant metabolic processes are investigated in proteins, structural or functional changes are analyzed in cell cultures, usually neurons, and the effects of these changes on the morphology of synapses and neuronal development are further observed and verified in various animal models.

PUBLICATIONS

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Wang J, et al., Schwarz G*, Gladwin MT. (2014) Sulfite oxidase catalyzes single electron transfer at molybdenum domain to reduce nitrite to nitric oxide. Antioxidants & Redox Signaling. In press.

Dejanovic B, et al., Schwarz G*. (2014) Gephyrin palmitoylation by DHHC-12 contributes to functional plasticity of GABAergic synapses. PLOS Biology 12:e1001908.

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Belaidi AA, Schwarz G*. (2013) Metal insertion into the molybdenum cofactor: product-substrate channeling demonstrates the functional origin of domain fusion in gephyrin. Biochem. J. 450: 149-57.

CECAD COOPERATIONS

B Prof. Dr. T. Benzing → p. 85
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D PD Dr. H. Kashkar → p. 133
Principal Investigator

F Prof. Dr. P. Kloppenburg → p. 189
Principal Investigator

A Prof. Dr. T. Langer → p. 59
Principal Investigator

E Prof. Dr. P. Nürnberg → p. 155
Principal Investigator

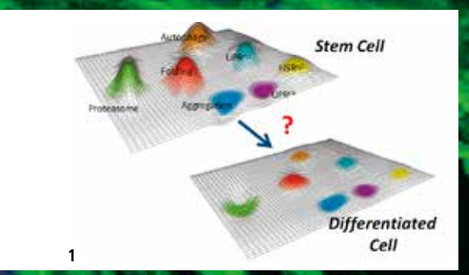
A Prof. Dr. A. Trifunovic → p. 75
Principal Investigator

EXTERNAL COOPERATIONS

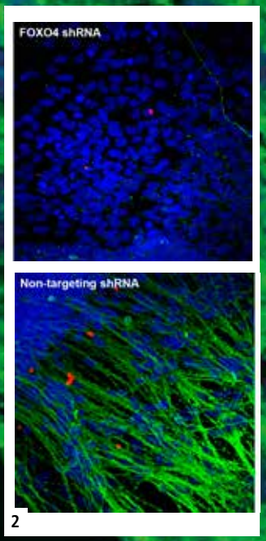
Prof. Dr. A. I. Bush, Melbourne, AU
Prof. Dr. M. T. Gladwin, Pittsburgh, USA
Prof. Dr. R. Hille, Riverside, USA
Prof. Dr. J. C. Meier, MDC Berlin, DE
Prof. Dr. M. Schwab, Stuttgart, DE
Dr. A. Triller, Paris, FR
Prof. Dr. B. Wirth, Cologne, DE

B

Die Qualität der Proteine in einer Zelle nimmt im Alter ab – ein potentieller Auslöser alternsbedingter Erkrankungen. Die Arbeitsgruppe um Dr. David Vilchez erforscht u.a. an Stammzellen, wie sich die Qualität von Proteinen in den Zellen aufrecht erhalten lässt und wie sich daraus Rückschlüsse auf Veränderungen der menschlichen Zellen im Alter ziehen lassen.



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FIGURE 1: We hypothesize that stem cells could have increased mechanisms to maintain the stability of their proteome. Proteostasis landscape schemes adapted from Douglas & Dillin (2010).
FIGURE 2: FOXO4, a forkhead transcription factor, regulates proteasome activity in human embryonic stem cells (hESCs) and is necessary for hESCs differentiation into neural cells. Therefore, our results establish a novel regulation of protein homeostasis in hESCs that links longevity and stress resistance in invertebrates with hESC function and identity (Vilchez et al, 2012b, Vilchez et al 2013). Representative images of immunocytochemistry after neural differentiation assay. Neuronal marker: β-III-tubulin, green. Nuclear staining: DAPI, blue Staining: David Vilchez, Leah Boyer.



↗ http://cecad.uni-koeln.de/Dr-David-Vilchez.363.0.html

Dr. David Vilchez

Principal Investigator – Junior Research Group Leader
CECAD Cologne

Dr. David Vilchez's laboratory is focused on defining the mechanisms underlying protein homeostasis (proteostasis) regulation in stem cells. The final goal is to determine whether intervention of these proteostasis mechanisms slow down aging and protect from the symptoms associated to age-related pathologies by using C. elegans as a model organism.

Our research: Mechanisms that promote proteostasis slow down aging and decrease the incidence of age-related diseases. Since human embryonic stem cells (hESCs) replicate continuously in the absence of senescence, Dr. Vilchez and his team hypothesize that these cells can provide a novel paradigm to study proteostasis and its demise in aging. The scientists mimic proteostasis of hESCs in somatic cells (e.g. *C. elegans*) to examine whether intervention of these mechanisms modulate healthspan and ameliorate age-related diseases.

Our successes: The research team discovered that hESCs exhibit high proteasome activity. This activity is necessary for hESC identity and their differentiation into neural cells. Moreover, they have uncovered that RPN-6, a key proteasomal subunit, is required for this activity and its mode of regulation and conservation in the aging process of *C. elegans*. Their findings established RPN-6 as a regulator of proteasome activity and a determinant of healthspan, providing a powerful candidate to correct proteostatic deficiencies in Huntington's disease. Moreover, their results in *C. elegans* led them to find that FOXO4, a longevity transcription factor, regulates proteasome activity and is necessary for neural differentiation of hESCs. Thus, their findings established a novel regulation of proteostasis that links longevity in invertebrates with hESC identity.

Our goals: Dr. Vilchez and his coworkers aim to define the mechanisms that maintain proteostasis in stem cells. Their final goal is to apply this knowledge for the discovery of pharmaceutical targets to ameliorate Alzheimer's, Parkinson's or Huntington's disease.

Our methods/techniques: The Vilchez lab uses an interdisciplinary innovative approach that combines stem cell research with genetics in *C. elegans*.

PUBLICATIONS

Vilchez D, et al. (2014) The role of protein clearance mechanisms in organismal ageing and age-related diseases. Nature Communications 5: 5659.

Vilchez D, et al. (2013) FOXO4 is necessary for neural differentiation of human embryonic stem cells. Aging Cell 12(3): 518-522.

Vilchez D, et al. (2012) Increased proteasome activity in human embryonic stem cells is regulated by PSMD11. Nature 489(7415): 304-308.

Vilchez D, et al. (2012) RPN-6 determines *C. elegans* longevity under proteotoxic stress conditions. Nature 489(7415): 263-268.

Vilchez D, et al. (2007) Mechanism suppressing glycogen synthesis in neurons and its demise in progressive myoclonus epilepsy. Nature Neuroscience 10(11):1407-13.

CECAD COOPERATIONS

F Prof. Dr. J. Brüning → p. 169
Principal Investigator

B Prof. Dr. T. Hoppe → p. 89
Principal Investigator

B Prof. Dr. M. Krüger → p. 93
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

E PD Dr. T. Wunderlich → p. 163
Principal Investigator

EXTERNAL COOPERATIONS

Prof. Dr. A. Brunet, Stanford University School of Medicine, USA
Prof. Dr. A. Dillin, University of California, Berkeley, USA
Prof. Dr. F. H. Gage, The Salk Institute, USA
Dr. Malene Hansen, Sanford-Burnham Medical Research Institute, USA
Dr. Leo Kurian, ZMMK, Cologne, DE

C

Für CECAD ist das Ziel der Forschung das bessere Verständnis von alternsassoziierten Erkrankungen – die Voraussetzung zur Entwicklung neuer Strategien zur Bekämpfung von Krebs und anderen Alternserkrankungen.

Research Area C
DNA damage responses in Aging-associated Diseases

Human DNA is constantly subjected to attacks by harmful environmental factors such as UV rays, tobacco smoke or toxic substances in food. Even normal metabolism can produce substances that damage the genome. Tens of thousands of DNA lesions occur daily in every cell, requiring highly efficient DNA repair machineries. Unrepaired DNA damage, however, can lead to functional decline of cells ultimately resulting in cell death and tissue degeneration. Given the importance of DNA damage as a casual factor for the aging process, scientists in Research Area C explore the underlying role of DNA damage in aging and cancer.

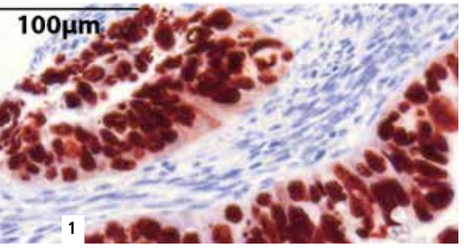
Despite highly complex DNA repair mechanisms constantly surveying the genome, DNA damage inevitably accumulates with increasing age. If the damage is too severe, cell death can occur, ultimately leading to loss of tissue integrity. Erroneous DNA repair, however, can lead to mutations, which in turn can give rise to tumorous cell growth. Consequently, the risk of developing cancer increases dramatically with age. Also, cancer cells may accrue additional mutations that giving rise to resistance against conventional radio- and chemotherapy.

Inborn defects in DNA repair genes can result in accelerated aging and increased cancer susceptibility. Premature aging – so called progeroid- syndromes are rare genetic disorders, in which DNA damage accumulates early in life due to DNA repair deficiencies, thus triggering aging-associated diseases already at a very young age.

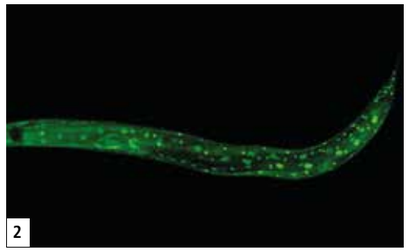
Scientists in Research Area C are specifically seeking answers to the following questions:

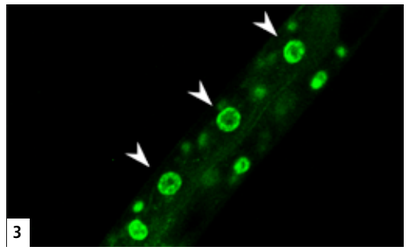
1. How do the highly complex DNA repair mechanisms function at a molecular level?
2. How do cells and tissues respond to the accumulation of DNA damage and which reaction programs can support the maintenance of tissue functioning?
3. Which genome maintenance factors play a role in counteracting the aging process and carcinogenesis?

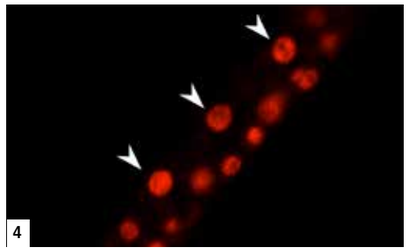
Thus CECAD aims to further our understanding of aging-associated disorders – which will provide the necessary foundation for developing new strategies to extend healthspan and to prevent aging-associated diseases and tumour development.



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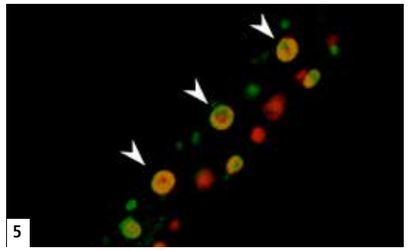

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FIGURE 1: Human endometrial carcinomas were stained with an antibody directed against p53. Accumulation of mutant p53 is represented by intense nuclear staining.
FIGURE 2-5: The longevity assurance factor DAF-16, a homolog of the human FOXO transcription factor, is activated in response to DNA damage in the nematode *C. elegans* (Fig. 2). Confocal imaging of DAF-16 tagged with the green fluorescence protein GFP and the GATA transcription factor EGL-27 tagged with the red fluorescence mCherry show nuclear localization of both DNA damage response factors in animals that were treated with UV (Fig. 3 – 5). EGL-27 mediates the DNA damage response of DAF-16 in antagonizing the detrimental consequences of genome instability during developmental growth and with aging.

PRINCIPLE INVESTIGATORS MAIN FOCUS

Prof. Dr. C. Reinhardt → p. 103
Prof. Dr. B. Schumacher → p. 107
Dr. L. P. Frenzel → p. 111
Prof. Dr. M. Hallek → p. 113
Dr. M. Herling → p. 117
Dr. I. Matic → p. 119
Prof. Dr. A. A. Noegel → p. 121
Prof. Dr. B. Wollnik → p. 123

PRINCIPLE INVESTIGATORS SECOND FOCUS

Prof. Dr. T. Benzing → p. 85
Prof. Dr. A. Beyer → p. 185
Prof. Dr. T. Hoppe → p. 89
Dr. S. Iden → p. 153
Prof. Dr. T. Krieg → p. 143
Prof. Dr. N.-G. Larsson → p. 71
Prof. Dr. C. Niessen → p. 193
Dr. S. Wickström → p. 161

Die Forschungsgruppe um Prof. Dr. Christian Reinhardt erforscht genetische Veränderungen bei Tumorerkrankungen und Leukämien. Zur Entwicklung zukunftsweisender neuer nebenwirkungsarmer Therapien, die das gesunde Gewebe schonen, erforscht die Arbeitsgruppe die Veränderungen in den erkrankten Zellen. Aus dem vertieften Verständnis dieser Prozesse im Vergleich zu gesundem Gewebe lassen sich die entscheidenden Erkenntnisse zur Identifikation von Zielmolekülen für neue therapeutische Substanzen ableiten.



↗ http://cecad.uni-koeln.de/Prof-H-Christian-Reinhardt.140.0.html

Prof. Dr. Christian Reinhardt

Head of Research Area C – Principal Investigator
Department of Internal Medicine I

Prof. Dr. Christian Reinhardt and his team analyze genetic changes in tumor cells. A detailed understanding of the metabolic processes in tumors compared to those in healthy tissue allows molecular dependencies specific to cancer cells to be identified. This is how the group led by Christian Reinhardt works to identify new substances for tumor therapy. The team combines new therapeutic approaches with conventional treatments to systematically test the most successful line of attack.

Our research: Prof. Reinhardt and his team of scientists investigate tumor cells to detect the genomic changes that drive these cells. They use cell cultures and mouse models to identify agents that effectively inhibit these signaling pathways. Tailored treatment that only targets abnormal tissue protects the healthy cells that do not exhibit these genetic mutations, considerably minimizing unpleasant side effects for patients.
The research team uses cell lines with defined molecular changes and reactions to therapeutic agents in their search for ways to combat tumor cells. When a cell responds very effectively to an agent, the genomic characteristics of that cell are explored in detail. This allows genetic specifications to be optimally correlated with the respective therapeutic agent. The research team then tests the results on mouse models with the ultimate goal of speeding up the transfer of basic findings into new standard therapies.

Our successes: One of the working group's most impressive achievements has been the initiation of clinical studies to test the new therapy. Patients are responding very well to treatment with the new active agents developed to target individual tumor cell genotypes. This is an excellent example of how successful translational research works at CECAD and the University of Cologne.

Our goals: The research team led by Prof. Reinhardt aims to develop novel therapies that will optimize treatment success and, as such, improve survival rates for different types of leukemia and solid tumors. Their ultimate goal is to advance the development of personalized therapies based on genetic changes in tumor cells. This would pave the way for the ultimate research objective: to increase therapeutic efficiency, while preserving healthy tissue as effectively as possible, thus prolonging survival while simultaneously improving quality of life.

Our methods/techniques: The research group's standard methods are in vitro screening in combination with extensive validation in autochthonous mouse models. This approach almost ideally reflects the status in patients, which allows 'real' conclusions to be drawn regarding therapy. Once the results have been successfully confirmed, the next step is the transfer of the basic research findings into the clinic.

CECAD COOPERATIONS

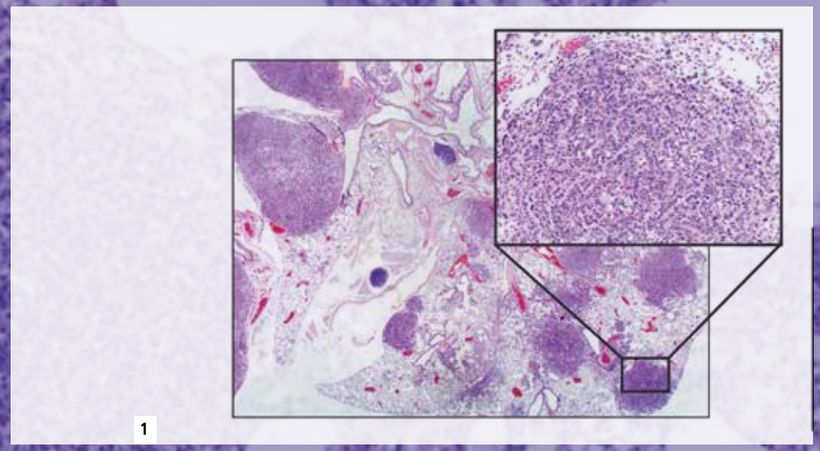
B Prof. Dr. T. Benzing, Principal Investigator → p. 85
C Dr. L. P. Frenzel, Principal Investigator → p. 111
C Prof. Dr. M. Hallek, Principal Investigator → p. 113
C Dr. M. Herling, Principal Investigator → p. 117
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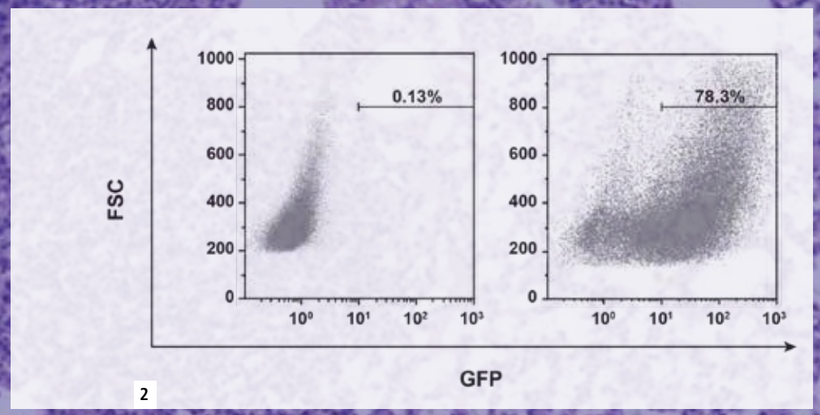
EXTERNAL COOPERATIONS

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Prof. Dr. R. Rad, Munich, DE
Prof. Dr. D. Saur, Munich, DE
Prof. Dr. M.Yaffe, Boston, USA

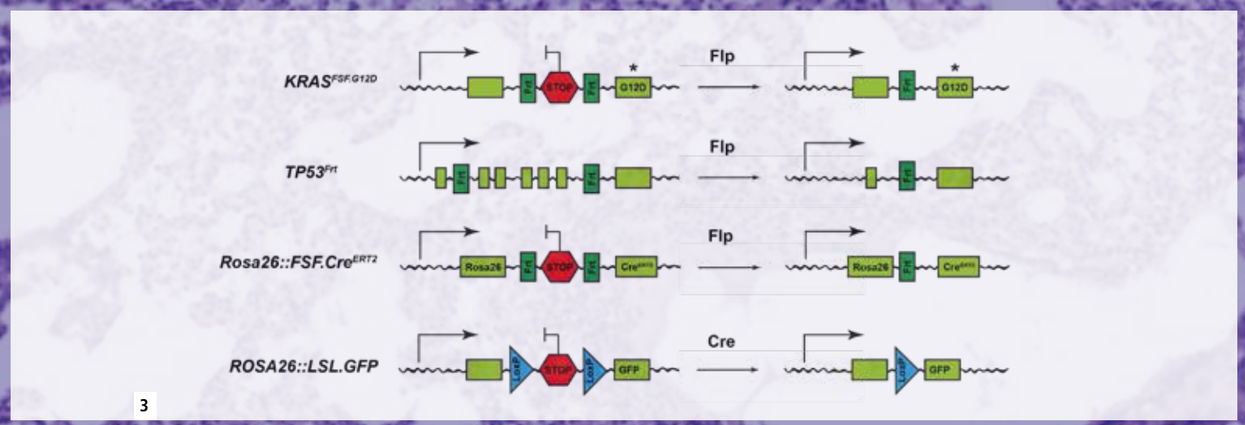
Prof. Dr. C. Reinhardt
Head of Research Area C
Principal Investigator
Department of Internal Medicine I

FIGURE 1: H/E stained tissue section of a tumor-bearing lung. NSCLC was induced in this KRASFrt.STOP.Frt;ROSA26::Frt.STOP.Frt.CreERT2;ROSA26::Lox.STOP.Lox.GFP animal via intratracheal AdenoFlp inhalation.
FIGURE 2: The animals depicted in (4) were treated with a one-week course of intraperitoneal 4OH-tamoxifen 4 weeks after inhalation to activate Cre-recombinase. In this system, Cre activity can only be induced in tumor cells, as only these cells have been previously exposed to AdenoFlp, which is necessary to remove the ROSA26::Frt.STOP.Frt cassette. Cre-mediated deletion of the ROSA26::Lox.STOP.Lox cassette allows for GFP expression, which was detected by flow cytometry of isolated tumor cells. Tumors were harvested 12 weeks after AdenoFlp.
FIGURE 3: Graphic representation of the different alleles used in this proposal.
FIGURE 4: Depicted are µCT images of KRASFrt.STOP.Frt;ROSA26::Frt.STOP.Frt.CreERT2;ROSA26::Lox.STOP.Lox.GFP animals that were intratracheally inhaled with an empty Adeno vector (top) or AdenoFlp (bottom). Lungs were imaged 3 months after inhalation.

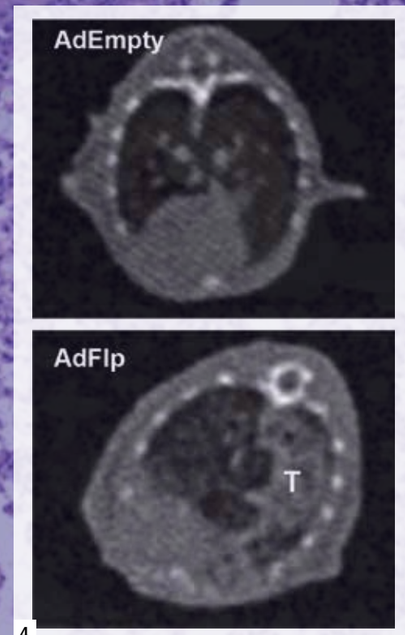

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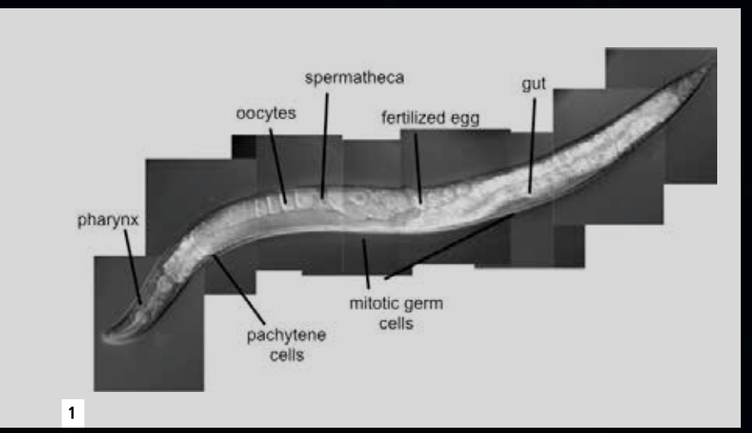
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Das Genom, bestehend aus der DNA, in jeder Zelle des menschlichen Körpers ist ständigen Angriffen ausgesetzt. Die Zellen verfügen über hochentwickelte Reparatursysteme, um Schäden aus dem Genom zu entfernen. Mit zunehmendem Alter sammeln sich aber unweigerlich Schäden in der DNA an und behindern die Funktionen von Zellen, Geweben und Organen. Fehlerhafte DNA Reparatur kann zu Mutationen führen und somit Krebs verursachen. Deshalb steigt das Krebsrisiko mit dem Alter.



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BACKGROUND FIGURE: DNA damage in the *C. elegans* germ line. DNA damage induced by ionizing radiation can be easily visualized in the *C. elegans* germ line using immunofluorescent staining for RAD-51 (red), a protein that is specifically recruited to chromatin (blue) at sites of DNA damage. Recent data from our laboratory show that acute DNA damage can increase organismal stress resistance challenging the classical paradigm that DNA damage has exclusively negative effects on survival and genome stability.
FIGURE 1: The nematode *C. elegans* is a particularly important animal model for aging research. Conserved longevity assurance pathways have been revealed in *C. elegans*. We employ the nematode as simple metazoan model to investigate the complex response mechanisms to genome instability that in humans are linked to cancer development and aging. (Image reproduced form Schumacher & Gartner, Future Oncol 2006).



↗ http://cecad.uni-koeln.de/Prof-Dr-Bjoern-Schumacher.107.0.html

Prof. Dr. Björn Schumacher

Head of Research Area C – Principal Investigator
Chair for Genome Stability in Ageing and Disease

Prof. Dr. Björn Schumacher's research group uses the nematode worm Caenorhabditis elegans to understand the causal role of DNA damage in aging and disease. With increasing age, damage to the genome accumulates and leads to the degeneration of cells and tissues. DNA damage thus plays a causal role in aging-associated diseases. The risk of cancer also increases with age because erroneously repaired DNA leads to mutations that can trigger cancer. Schumacher's team has identified mechanisms that antagonize the detrimental consequences of DNA damage by maintaining tissue integrity and maximizing lifespan, even when the DNA damage cannot be repaired. The Schumacher group has also shown that DNA damage in individual cells impacts the entire organism. The systemic DNA damage responses are mediated by the immune system and increase the general stress resistance of the tissues throughout the body. These findings are particularly important for understanding progeria, disorders that result in premature aging in childhood. Premature aging is caused by congenital dysfunction of the DNA repair processes. Understanding the mechanisms by which organisms respond to accumulating DNA damage with age is pivotal for developing novel therapies to prevent aging-associated diseases and contribute to optimizing cancer treatment.

Our research: The DNA in each cell of the human body experiences many damaging influences over a lifetime. Although the cells have very effective DNA repair mechanisms, DNA damage inevitably accumulates with age. DNA damage leads to a loss of tissue function and the onset of aging-associated diseases. Prof. Björn Schumacher's research group explores how DNA damage affects cells, tissues, and the organism as a whole. This research is important in understanding several congenital diseases caused by defects in the highly complex nucleotide excision repair pathway (NER), including the childhood progeroid (premature aging) diseases, Cockayne syndrome (CS) and trichothiodystrophy (TTD), and xeroderma pigmentosum (XP), which increases the risk of skin cancer. Better understanding of the consequences of DNA repair defects may also lead to new therapeutic options for aging-associated disorders and cancer.

Our success: Prof. Schumacher's group has shown that organisms respond to DNA damage by activating genetic mechanisms that prolong life. The focus is on understanding how this response to DNA damage is regulated so that the organism can maximize its survival even if the DNA cannot be repaired. Schumacher's team has already identified mechanistic links between the genetic aging process and the stochastic accumulation of DNA damage. Schumacher and his team have revealed a previously unknown systemic immune response in *C. elegans*. Their key finding is that an immune response activated in individual cells in response to DNA damage can be transmitted throughout the entire body to promote survival of the organism in the face of further stress. Prof. Björn Schumacher has been awarded the Innovation Prize from the State of North Rhine-Westphalia, holds the ERC starting grant and coordinates the European training network "CodeAge" on chronic DNA damage responses in aging.

CECAD COOPERATIONS

B Prof. Dr. T. Benzing → p. 85
Principal Investigator

B Prof. Dr. T. Hoppe → p. 89
Principal Investigator

F Prof. Dr. C. Niessen → p. 193
Principal Investigator

C Prof. Dr. C. Reinhardt → p. 103
Principal Investigator

EXTERNAL COOPERATIONS

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Prof. Dr. Y. Shiloh, Tel Aviv University, IL
Prof. Dr. B. Schwer and Frederick Alt, Harvard Medical School, USA
International partnerships as part of EU consortia in doctorate programs.

Prof. Dr. Björn Schumacher
Head of Research Area C
Principal Investigator
Chair for Genome Stability in Ageing and Disease

Our goals: Understanding the fundamentals of the aging process is essential for developing new therapies. It is well-known that cancer can be the result of DNA damage. Schumacher's team recently discovered mechanisms through which the entire body responds to DNA damage in specific cells. The organism increases its chances of survival by complex systemic physiological changes. The Schumacher group aims to investigate the regulation of these systematic responses to genome damage. The ultimate goal is to support the development of novel therapies for aging-associated diseases and rare progeroid syndromes.

Our methods/techniques: The nematode *C. elegans* allows scientists to gain insight into the processes of DNA repair and aging, thus revealing how cells, tissue, and the body as a whole respond to DNA damage, how the organism ages, and what mechanisms may prolong survival. The *C. elegans* research is complemented by extending the studies to mice to address disease-specific questions. The mouse models reflect complex diseases very well, allowing researchers to explore novel therapeutic options for humans.

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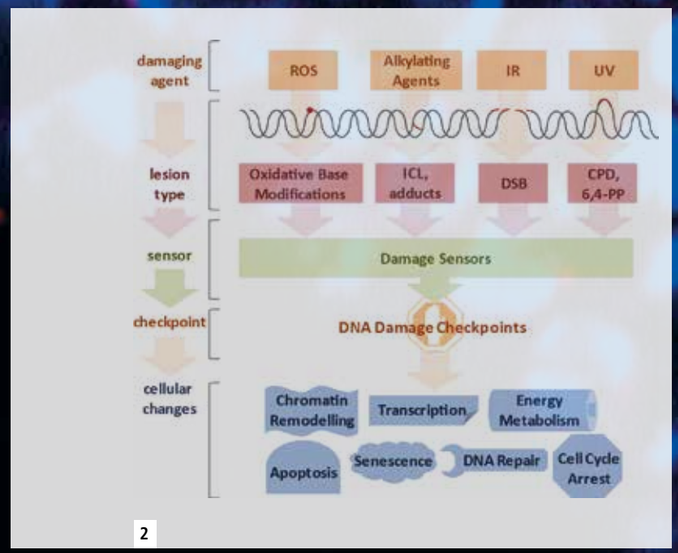
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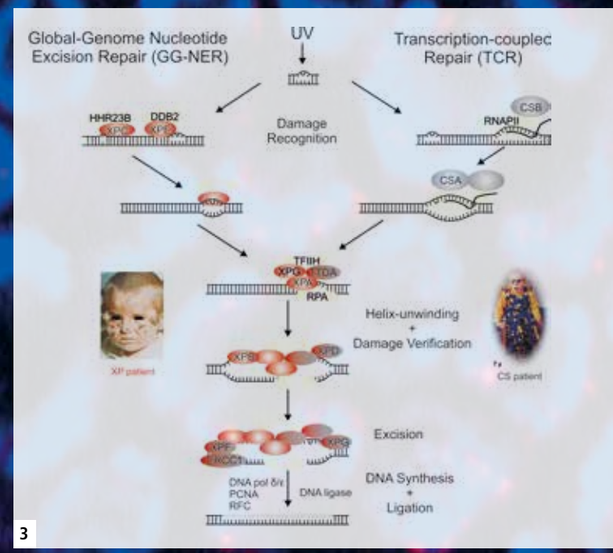
Reinhardt HC, Schumacher B. (2012) The p53 network: Cellular and systemic DNA damage responses in aging and cancer. Trends Genet. Mar;28(3):128-36.

FIGURE 2: Diverse DNA damage lesions trigger specialized DNA damage responses.
The DNA is attacked by various genotoxic insults including reactive oxygen species (ROS) produced during cellular metabolism, alkylating agents that find application in cancer therapy, ionizing irradiation (IR), which is used for radio therapy, or ultraviolet (UV) irradiation presenting a daily threat as it is contained in sunlight. The lesions they inflict are just as diverse, since ROS usually lead to base modifications, alkylating agents give rise to interstrand crosslinks (ICLs) and DNA adducts, IR induces double strand breaks (DSBs), and UV light triggers the formation of cyclobutane pyrimidine dimers (CPDs) and 6,4-photoproducts (6,4-PPs). Cells have a repertoire to sense the different lesions and subsequently activate DNA damage checkpoints. Ultimately, cells respond by chromatin remodeling, modified transcription, fine tuning of energy metabolism, cell cycle arrest, activation of DNA repair pathways and -in case of unrepairable damage load- induction of senescence or apoptosis. (Reproduced from Wolters & Schumacher, Front Genet 2013)
FIGURE 3: The nucleotide excision repair (NER) defects cause cancer and aging. UV lesions and helix-distorting chemical adducts are recognized by global genome (GG-) NER or transcription coupled (TC-) NER and repaired by a multi-protein core NER complex. The clinical outcomes of GG-NER and TC-NER deficiencies are remarkably distinct: GG-NER defects lead to high susceptibility to skin cancer in Xeroderma pigmentosum (XP) patients (red), whereas TC-NER defective Cockayne syndrome (CS) patients prematurely age but remain cancer-free (grey). Mutations in the common NER pathway that both recognition mechanisms funnel into, can lead to cancer-predisposition or premature aging, depending on the effect of the particular point mutation (red-grey). (Reproduced from Schumacher, Bioessays 2009)

Schumachers Team hat genetische Programme aufgedeckt, mit denen Gewebe ihre Funktionsfähigkeit beibehalten, selbst wenn DNA Schäden nicht repariert werden können. Diese Erkenntnisse sind sowohl für die Erhaltung von Geweben im alternden Körper als auch für Patienten von großer Bedeutung, die an vorzeitiger Alterung leiden, weil wichtige DNA Reparaturmechanismen nicht funktionieren.



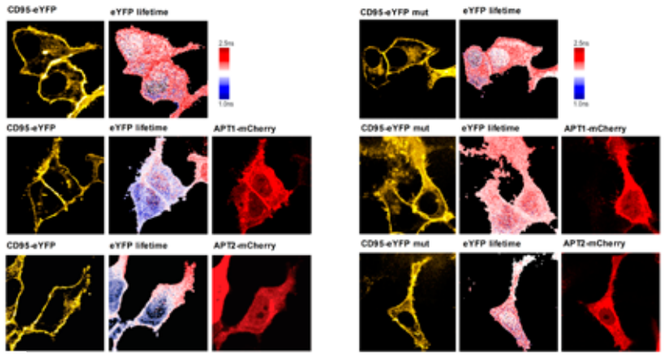
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Deregulierte Apoptosemechanismen in Tumorzellen entscheiden häufig über das Therapieansprechen. Chronische lympahtische Leukämie (CLL) Zellen weisen eine Dysbalance zwischen intrinsischer und extrinsischer Apoptose auf. Dr. Frenzel erforscht mit seiner Arbeitsgruppe diese zentralen Resistenzmechanismen der CLL, mit dem Ziel spezifische, verträgliche und chemofreie Therapien zu entwickeln, von denen vor allem ältere, kranke Patienten profitieren.



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FIGURE 1: CD95 and APTs interact at the plasma membrane. FLIM-FRET (fluorescence lifetime imaging microscopy to Foerster resonance energy transfer) experiments of CD95 with APT1 and APT2 demonstrate that CD95 directly interacts with both proteins (A). The interaction is dependent on the palmitoylation of cysteine 199 (B).
Berg et al., 2015, Blood.



↗ http://cecad.uni-koeln.de/Dr-Lukas-P-Frenzel.221.0.html

Dr. Lukas P. Frenzel

Principal Investigator
CECAD Member

Dr. Lukas Frenzel is carrying out research into the central mechanisms of resistance in chronic lymphatic leukemia (CLL). Together with his team, he wants to identify new targets for overcoming extrinsic apoptosis block and utilizing intrinsic sensitivity to provide targeted, well-tolerated, chemotherapy (CTX)-free treatment, especially for elderly patients with CLL. Such targets for future clinical trials include the mitochondria.

Our research: CLL is the most common form of leukemia in the western world and, so far, remains incurable. Dr. Frenzel and his team are carrying out research into the central mechanisms of resistance in this disease. CLL shows complete resistance to extrinsic apoptosis. On the one hand, it is important to overcome this resistance and, on the other hand, to utilize sensitivity to intrinsic apoptosis in novel treatment concepts. Mitochondria, in particular, represent a meaningful therapeutic target.

Our successes: Starting from the pathological mechanism, the scientists have identified two novel approaches to eliminating CLL cells with CD95 resistance, which are protected by the microenvironment. Their work is based on the previously unknown synergy between two new substances (ABT-199 and ibrutinib), which provides the rationale for future clinical trials.

Our goals: The research group's main aim is to develop targeted, well-tolerated, CTX-free treatment for patients with CLL. Dr. Frenzel and his team are therefore looking at ways of overcoming extrinsic resistance to apoptosis and, via the mitochondria, using intrinsic apoptosis mechanisms in a targeted manner to eliminate CLL cells that have lost p53.

Our methods/techniques: Besides targeted mouse models, the team is using biochemical and imaging procedures, such as click chemistry, acyl-biotin exchange assays, and fluorescence lifetime imaging microscopy.

PUBLICATIONS

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CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning
Principal Investigator → p. 169

D PD Dr. H. Kashkar
Principal Investigator → p. 133

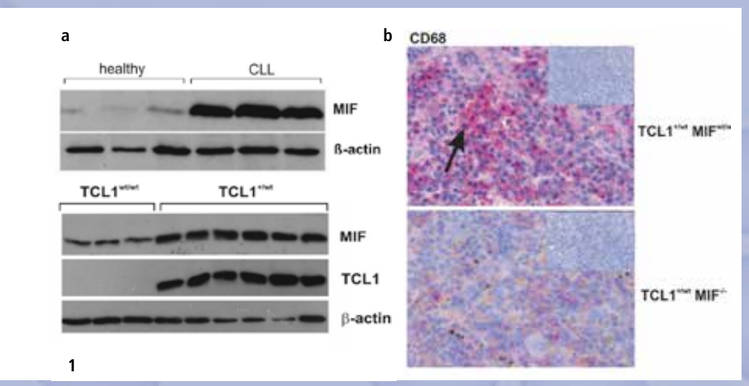
D Prof. Dr. M. Krönke
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C Prof. Dr. C. Reinhardt
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EXTERNAL COOPERATIONS

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Prof. Dr. R. Zeidler, München, DE

Chronische lymphatische Leukämie wird durch genetische Fehler in den Blutzellen, aber auch durch chronische Entzündungen und eine dauerhafte Stimulation von Immunzellen ausgelöst, welche im Laufe des Lebens ihre schädliche Wirkung entfalten. Dies führt zur Entstehung von Leukämien bei älteren Menschen.



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FIGURE 1: MIF deficiency leads to higher apoptosis and a milder CLL presentation in mice. (a) Overexpression of MIF in human and murine B cells. (b) Overexpression of the macrophage marker CD68 in spleens of TCL1+MIFwt/wt mice.



↗ http://cecad.uni-koeln.de/Prof-Michael-Hallek.77.0.html

Prof. Dr. Michael Hallek

Principal Investigator
Deputy Scientific Coordinator

Chronic lymphocytic leukemia (CLL) is caused by the concerted action of genetic events in the cancer cell and of a sustained, chronic inflammation and subsequent stimulation of immune cells. This contributes to leukemogenesis typically in older patients. The team of Prof. Dr. Michael Hallek investigates the signals that influence immune cells in the tumor microenvironment to support the development of leukemia. The aim of the group is to understand the mechanisms by which genetic driver mutations interact with cancer-supporting factors of the microenvironment to initiate and enhance leukemic development. The long-term goal is the development of improved therapeutic concepts for leukemia patients.

Our research: Chronic lymphocytic leukemia (B-CLL), the typical leukemia of the elderly, is triggered by an interaction of genetic aberrations in B cells and their microenvironment. In this disease, leukemic development can be seen as the result of a chronic inflammation and stimulation of the immune system. These events prevent the apoptosis of clonal, long-lived CD5+ B cells which subsequently accumulate and facilitate the development of subsequent mutations. The team of Prof. Hallek investigates the mechanisms that trigger leukemic development through their interaction with the cancer microenvironment. In particular, the group aims to understand which specific pathways are critical for the dialogue between leukemic cells and microenvironmental cells and could serve as targets for novel treatments. Moreover the group is benefitting from a strong clinical trial portfolio of the German CLL study group (head Michael Hallek) that facilitates the translation of novel ideas and concepts into therapeutic reality.

Our successes: Prof. Hallek's laboratory has a long-term interest to study oncogenic signaling events in CLL. More recently, the laboratory has decoded the influence of macrophage migration inhibitory factor (MIF) and its putative receptors, CD 74 and CD 44, on leukemic development. MIF appears to have a strong effect on leukemic development: progression is delayed considerably in the absence of MIF, therapy increasing survival time of CLL-carrying mice. In clinical trials, the group has shown the impact of B-cell-receptor signaling pathway inhibitors and antibodies to induce clinical remissions of this leukemia.

Our goals: This research group is investigating the development of novel therapeutic concepts. One approach to treatment of the future is the use of molecules targeting specific pathways in combination with monoclonal antibodies to interrupt leukemogenic signaling pathways. Combinations of specific therapeutics are applied to specific subgroups of patients in an increasingly personalized way. As a prerequisite, the careful genetic analysis of leukemia cells usually determines treatment, from a watch and wait strategy to immediate therapy with either chemoimmunotherapy or combined use of targeted agents. The goal of our group is clearly to optimize therapy to allow CLL patients to gain a normal life expectancy with a good quality of life.

Our methods/techniques: The team employs a very wide range of laboratory and clinical research methods, including laboratory testing with cell cultures and a variety of different leukemia mouse models. The resultant treatment concepts are being tested in small to large-scale clinical trials (first in man, phase I to III). The laboratory and the GCLLSG currently one of the largest study groups on this disease world-wide (www.dcllsg.de) cooperate with many other centers in world-wide. Clinical trials currently assess studies therapeutic success and form the basis for determining clinical guidelines.

CECAD COOPERATIONS

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Principal Investigator
Translational Research

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C Prof. Dr. C. Reinhardt → p. 103
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
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Prof. Dr. U. Jäger, Vienna, AT
Prof. Dr. W. Lehmacher, Cologne, DE
Prof. Dr. D. Maintz, Cologne, DE
Dr. T. Shanafelt, Mayo Clinic, USA

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Principal Investigator
Deputy Scientific Coordinator

Die Arbeitsgruppe um Prof. Dr. Michael Hallek erforscht, welche spezifischen Signale das Immunsystem so steuern, dass sie zum Auslöser von Leukämien werden. Ziel ist es, die Mechanismen zu entschlüsseln, welche die Wechselwirkung von genetischen Fehlern in den Leukämiezellen und krebsauslösenden Umweltfaktoren steuern und daraus verbesserte Therapieansätze für Leukämiepatienten zu entwickeln.

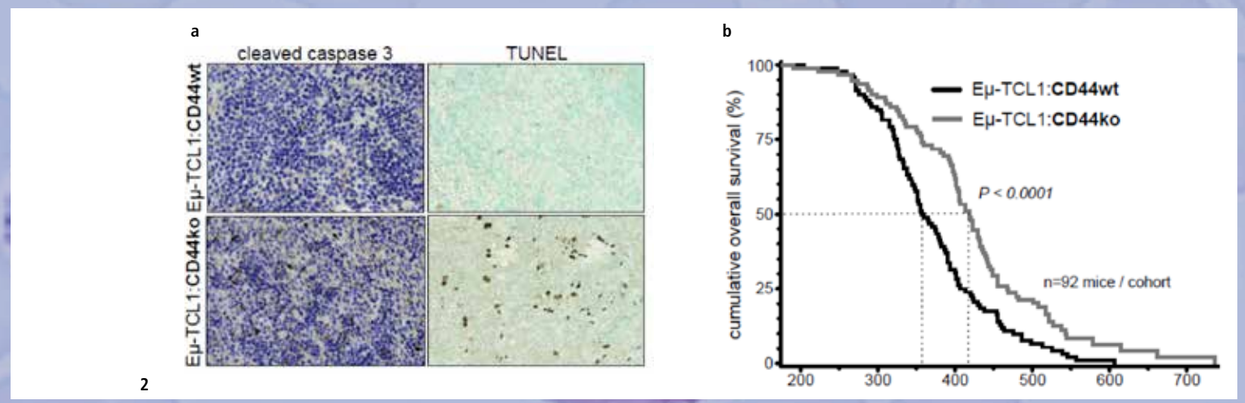
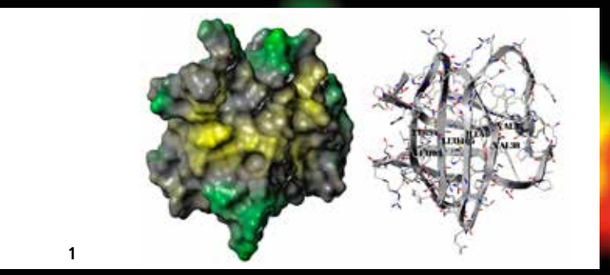


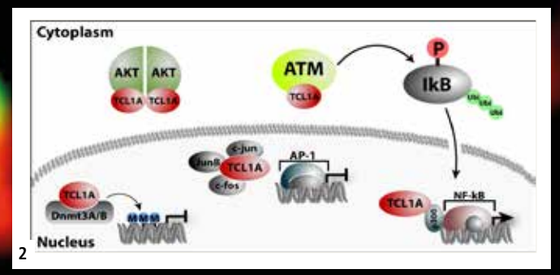
FIGURE 2: CD44 deficiency leads to higher apoptosis and a milder CLL presentation in mice. (a) CD44 deficiency is associated with increased apoptotic CLL cell numbers in vivo. (b) Overall survival of Eμ-TCL1:CD44wt and Eμ-TCL1:CD44ko mice.

T- und B-Lymphozyten sind als Bestandteile des erworbenen Immunsystems unverzichtbar. Sie unterliegen einer engen zellinternen und äußeren Steuerung. Dr. Herling und seine Arbeitsgruppe erforschen die Folgen der Fehlregulation solcher Kontrollmechanismen. Im Fokus stehen abweichende Signalübertragungen in T- und B-Lymphozyten durch das Krebsgen TCL1. Diese können zu unkontrollierter Zellvermehrung und somit zu Leukämien führen. Das Angehen solch abnormer Signalproteine soll die Basis neuer therapeutischer Ansätze sein.

FIGURE 1: Surface domains of the TCL1 adapter protein; hydrophobic areas in yellow.
FIGURE 2: TCL1 can physically engage a multitude of targets and elicit tumorigenic activations of several signaling cascades with a lymphocyte-permissive net effect.



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↗ http://cecad.uni-koeln.de/Dr-Marco-Herling.91.0.html

Dr. Marco Herling

Principal Investigator
CECAD Cologne

Dr. Marco Herling and his team explore in detail the abnormal signal transfer within T and B lymphocytes, which causes them to escape controlled responses to impulses by the microenvironment, which in turn causes them to degenerate into leukemic cells. The laboratory focuses on the adapter protein TCL1. It amplifies signals from the antigen receptor or renders DNA repair inefficient and as such functions as an unconventional oncogene.

Our research: Aberrant intermolecular signaling inside T and B lymphocytes causes these cells to evade a regulated response to growth and apoptotic impulses and to eventually proliferate autonomously. The TCL1 protein plays a central role therein, by acting as an adapter molecule. By amplifying signals from the environment it acts as a sensitizer, especially towards antigen receptor input. It also seems to have a negative influence on the activity of the DNA repair enzyme ATM. The group headed by Dr. Marco Herling is interested in the processes that trigger TCL1 overexpression in the lymphocytic cells. Furthermore, the lab investigates the effector proteins TCL1 binds to and uses for its oncogenic effect alongside possible differences in these mechanisms between T vs B lymphocytes. The overall goal is to understand how such rewired signaling pathways are amenable to interventional approaches.

Our successes: Dr. Marco Herling and his group have successfully established TCL1 as a diagnostic tool and prognostic marker. Moreover, some mechanisms of its dysregulation could be described at the cellular and molecular level. For example, stimuli from stromal cells and abnormally expressed TCL1-repressive micro-RNAs can maintain high cellular concentrations of TCL1. The team also discovered that TCL1 interacts with the kinases AKT and ATM as its major executioners, which in turn can represent targetable Achilles' heels of leukemic cells.

Our goals: The scientists aim to further expand their understanding of the leukemogenic mechanisms of TCL1 by developing a detailed concept of the upstream modes of TCL1 dysregulation and the downstream effects in lymphocytes and their derived tumors. This has to be extended to the role of TCL1 in embryonic stem cells and tumor-initiating cells of solid neoplasms.

Our methods/techniques: The team applies methods that characterize protein-protein interactions, including mass spectrometry. The cell biologic and biochemical effects of TCL1-modulated protein complexes are explored in genetically engineered model organisms such as mice and cell lines (knockdown, mutagenesis, etc.).

PUBLICATIONS

Kiel MJ, Velusamy T, Rolland D, et al. (2014) Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia. Blood. Aug 28;124(9):1460-72.

Fedorchenko O, Stiefelhagen M, Peer Zada AA, et al. (2013) CD44 regulates the apoptotic response and promotes disease development in chronic lymphocytic leukemia. Blood May 16;121(20):4126-36.

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Brechmann M, Mock T, Nickles D, et al. (2012) A PP4 holoenzyme balances physiological and oncogenic nuclear factor-kappa B signaling in T lymphocytes. Immunity Oct 19;37(4):697-708.

Sivina M, Hartmann E, Vasyutina E, et al. (2012) Stromal cells modulate TCL1 expression, interacting AP-1 components, and TCL1-targeting micro-RNAs in chronic lymphocytic leukemia. Leukemia Aug;26(8):1812-20.

CECAD COOPERATIONS

D PD Dr. H. Kashkar → p. 133
Principal Investigator

C Prof. Dr. C. Reinhardt → p. 103
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

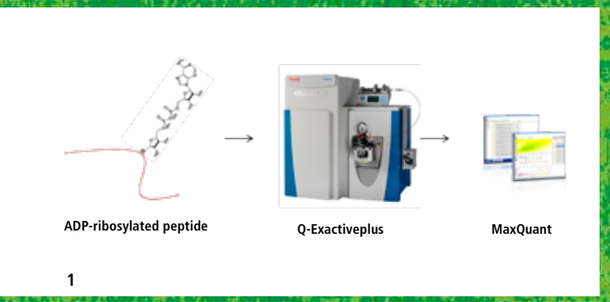
EXTERNAL COOPERATIONS

Prof. Dr. H. Abken, ZMMK, Cologne, DE
Dr. S. Newrzela, Goethe University Frankfurt, DE
Prof. Dr. A. Rosenwald, University of Würzburg, DE
Prof. Dr. M. H. Stern, Institute Curie Paris, FR
Prof. Dr. M. Trepel, Klinikum Augsburg, DE

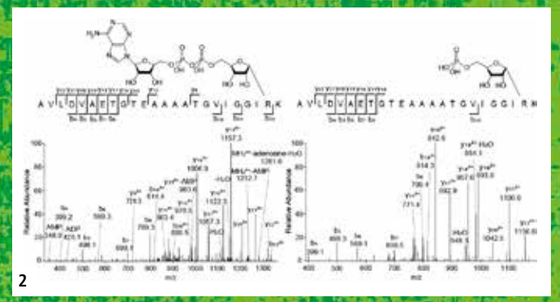
C

Fehler in der DNA-Reparatur führen zur Anhäufung von DNA-Schäden – ein möglicher Auslöser von Krebs. Dr. Ivan Matic und sein Team untersuchen die Funktion einer spezifischen posttranslationalen Modifikation, der ADP-Ribosylierung, für die DNA-Reparaturmechanismen. Das Ziel der Arbeitsgruppe ist es, ein umfassendes Profil dieser Modifikationen zu erstellen, um die molekularen Aspekte der Reparatur von DNA-Schäden detaillierter zu verstehen.

FIGURE 1: Overview of the experimental workflow
FIGURE 2: Fragmentation spectra of a modified peptide from SERPINA3K. Figure from Ivan Matic, Ivan Ahel & Ronald T. Hay Nature Methods. August 2012



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↗ http://cecad.uni-koeln.de/Dr-Ivan-Matic.343.0.html

Dr. Ivan Matic

Principal Investigator – Junior Group Leader
Max Planck Institute for Biology of Ageing

The team led by Dr. Ivan Matic investigates how the ADP-ribosylation of chromatin components functions in DNA repair mechanisms. The aim is to establish a comprehensive profile of these modifications, in order to gain in-depth understanding of molecular aspects in the repair of DNA.

Our research: ADP-ribosylation is a post-translational modification, in which ADP-ribose is coupled to proteins. It is a key mechanism of DNA repair. Specific enzymes, called PARPs, catalyze the ADP-ribosylation of major chromatin components, e.g. histones, creating an environment in which damaged DNA can be repaired. The research group is applying advanced proteomics to determine the molecular mechanisms by which ADP-ribosylation enables DNA repair.

Our successes: Dr. Matic and his team have pioneered the in vivo detection of ADP-ribosylated peptides. They have discovered modifications on amino acids, which had never previously been associated with PARP activity.

Our goals: The research group wants to establish a comprehensive profile of ADP-ribosylation in the context of DNA repair. The scientists are concentrating on the role of chromatin ADP-ribosylation in the DNA damage response. The research program of Dr. Matic's team has the long-term potential to establish a basis for the improved treatment of cancer, a common age-related disease.

Our methods/techniques: The Matic laboratory benefits from state-of-the-art proteomics equipment, including UHPLC and Q Exactive Plus, an Orbitrap mass spectrometer. In addition, the team uses experimental techniques to prepare and enrich specific protein populations for mass spectrometry analysis.

PUBLICATIONS

Tammsalu T1, Matic I1, Jaffray EG, Ibrahim AF, Tatham MH, Hay RT, (2014) Proteome-Wide Identification of SUMO2 Modification Sites. Science Signaling Apr 29, 1Joint first author.

Matic I*, Ahel I, Hay RT. (2012) Reanalysis of phosphoproteomics data uncovers ADP-ribosylation sites. Nature Methods, Jul 30;9(8):771-2 *sole corresponding author - Interview "Dundee ADP-Ribosylation Study Shows Potential and Difficulties of Raw Mass Spec Reanalyses" by the GenomeWeb's ProteoMonitor.

Matic I1, Schimmel J1, Hendriks IA1, van Santen MA1, van de Rijke F, van Dam H, Gnad F, Mann M, Vertegaal AC. (2010) Site-specific identification of SUMO-2 targets in cells reveals an inverted SUMOylation motif and a hydrophobic cluster SUMOylation motif. Molecular cell 39, (4), 641-52, 1Joint first author.

Golebiowski F1, Matic I1, Tatham MH1, Cole C, Yin Y, Nakamura A, Cox J, Barton GJ, Mann M, Hay RT. (2009) System-wide changes to SUMO modifications in response to heat shock. Science signaling 2, (72), ra24, 1Joint first author.

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CECAD COOPERATIONS

B Dr. D. Vilchez → p. 97
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

EXTERNAL COOPERATIONS

Prof. Dr. W. Earnshaw, Edinburgh, UK
Dr. I. Ahel, Oxford, UK

Die Arbeitsgruppe von Prof. Angelika Noegel erforscht die Zellkernhülle und Komponenten der Zelle. Diese umfassen das Zytoskelett, das die mechanische Stabilität und Signalübertragung innerhalb einer Zelle ermöglicht, wie auch Forschungen am Centrosom. Funktionsstörungen dieser beiden Zellkomponenten können zu Erkrankungen z.B. des Herzens oder zu Störungen der Gehirnentwicklung führen.

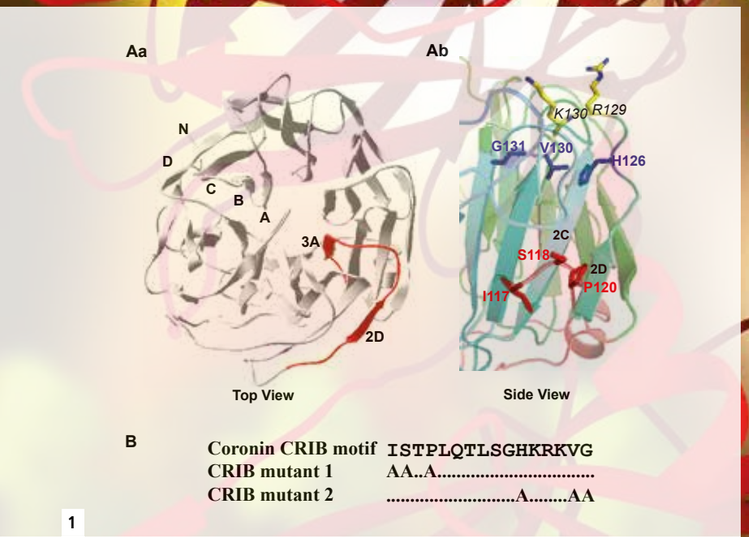


FIGURE 1: Structure of the D. discoideum coronin CRIB domain. The 3D structure of D discoideum coronin was predicted using SWISS-MODEL program using murine coronin 1 (PDB code 2AQ5) as a template. The top view of the modeled D. discoideum coronin is shown. The CRIB domain is highlighted in red and the corresponding strands are labeled. The figure was generated using Jmol (Jmol: anopen-source Java viewer for chemical structures in 3D. http://www.jmol.org/) (taken from Swaminathan et al., 2014).



↗ http://cecad.uni-koeln.de/Prof-Angelika-A-Noegel.101.0.html

Prof. Dr. Angelika A. Noegel

Principal Investigator
Institute for Biochemistry I

Prof. Dr. Noegel's research group focuses on the cytoskeleton, a component of the cell responsible for mechanical stability and signal transmission inside the cell. A group of proteins, which are anchored in the nuclear envelope, binds the actin filaments of the cytoskeleton. The destruction of these links can cause diseases such as laminopathies. Deficiencies of another protein-group, which are found in the M-band of myofilaments, can result in muscle damage, which can trigger cardiomyopathies and other diseases. The group's second research focus is on genetic defects of the centrosome.

Our research: In eukaryotic cells, the nuclear envelope separates the chromosomes from the cytoplasm. Proteins, such as the Nesprins found in the nucleus, fulfill key cell functions. They link the cytoskeleton and the centrosome to the nucleus, thus stabilizing the nucleus. They also modulate signal transduction, and thus are involved in processes of aging. Dysfunctions trigger aging-associated diseases, such as delayed wound healing and muscle damage in the form of cardiomyopathies.

Our successes: One breakthrough by Prof. Noegel's group was the description of Nesprin-1 and -2 as new components of the nuclear envelope, which connect the nucleus to the cytoplasm and cytoskeleton.
Another exciting result was the portrayal of the link between the SUN proteins, inner nuclear membrane proteins, and the Nesprins (proteins in the outer nuclear membrane) which together form the LINC complex. Furthermore,in a successful collaborative project with Prof. Nürnberg, mutations of centromere components were identified as the cause of microcephalies, a failure in cerebral cortex growth.

Our goals: Prof. Noegel's working group explores the principles of cytoskeleton and centrosome regulation. Their research centers on the role of the proteins and the illnesses associated with dysfunctions.

Our methods/techniques: Prof. Noegel's team uses biochemical experimental methods to investigate interactions at the protein level. The biological relevance of the findings is then tested in mouse models.

PUBLICATIONS

Swaminathan K, Müller-Taubenberger A, Faix J, Rivero F, Noegel AA. (2014) A Cdc42- and Rac-interactive binding (CRIB) domain mediates functions of coronin. Proc Natl Acad Sci U S A. 111(1):E25-33.

Hussain MS, Baig SM, Neumann S, Peche VS, Szczepanski S, Nürnberg G, Tariq M, Jameel M, Khan TN, Fatima A, Malik NA, Ahmad I, Altmüller J, Frommolt P, Thiele H, Höhne W, Yigit G, Wollnik B, Neubauer BA, Nürnberg P, Noegel AA. (2013) CDK6 associates with the centrosome during mitosis and is mutated in a large Pakistani family with primary microcephaly. Hum Mol Genet. 22(25):5199-214.

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Hussain MS, Baig SM, Neumann S, Nürnberg G, Farooq M, Ahmad I, Alef T, Hennies HC, Technau M, Altmüller J, Frommolt P, Thiele H, Noegel AA, Nürnberg P. (2012) A truncating mutation of CEP135 causes primary microcephaly and disturbed centrosomal function. Am J Hum Genet.90(5):871-8.

Rashmi RN, Eckes B, Glöckner G, Groth M, Neumann S, Gloy J, Sellin L, Walz G, Schneider M, Karakesisoglou I, Eichinger L, Noegel AA. (2012) The nuclear envelope protein Nesprin-2 has roles in cell proliferation and differentiation during wound healing. Nucleus. 3(2):172-86.

CECAD COOPERATIONS

F Prof. Dr. P. Kloppenburg → p. 189
Principal Investigator

D Prof. Dr. M. Krönke → p. 129
Principal Investigator

E Prof. Dr. P. Nürnberg → p. 155
Principal Investigator

D Dr. N. Robinson → p. 135
Principal Investigator

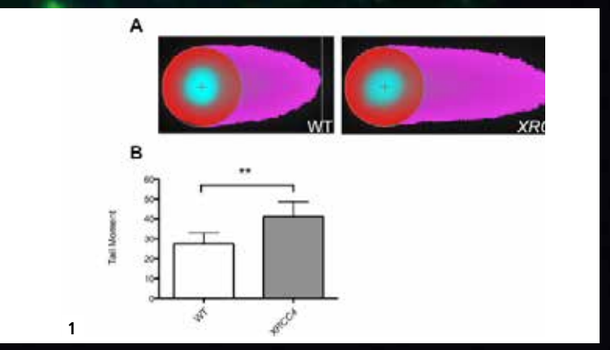
EXTERNAL COOPERATIONS

Prof. Dr. G. Pfitzer, Cologne, DE
Additional international collaborations with clinical groups in Bonn and Singapore

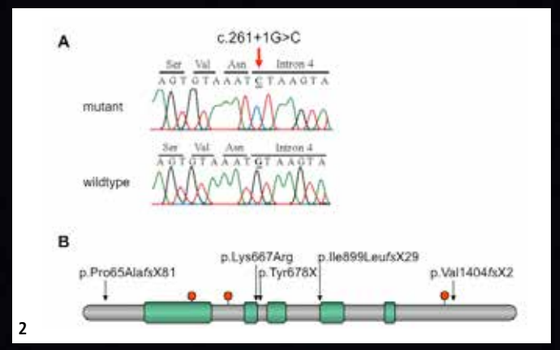
C

Prof. Dr. Wollnik und sein Team erforschen die genetischen Ursachen einer Vielzahl seltener Erkrankungen, speziell aber angeborener Syndrome, die mit einer beschleunigten Alterung des Organismus einhergehen. Die Arbeitsgruppe zielt darauf ab, ursächliche Gene zu finden und nachfolgend die Krankheitsmechanismen zu entschlüsseln. Bislang war das Team bereits an der Identifizierung von über 35 Krankheitsgenen für angeborene, seltene Erkankungen beteiligt – ein großer Erfolg.

FIGURE 1: A homozygous mutation in XRCC4 impairs DSB repair. (A) Representative images of neutral comet assay. (B) Quantification of tail moments after treatment with etoposide.
FIGURE 2: Mutations in CEP152 cause Seckel syndrome.



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↗ http://cecad.uni-koeln.de/Dr-Bernd-Wollnik.116.0.html

Prof. Dr. Bernd Wollnik

Principal Investigator
CECAD Cologne

With his research team, Prof. Dr. Bernd Wollnik investigates inherited forms of rare diseases, especially those which are associated with premature aging phenotypes. The group aims to identify novel genes associated with these diseases and subsequently to elucidate the underlying pathomechanisms. To date the team has successfully identified over 35 new disease-associated genes for various rare diseases, many of them associated with premature aging phenotypes. The research results provide important information about physiological and pathophysiological aging processes.

Our research: Prof. Dr. Wollnik and his group investigate the genetic causes of rare diseases. Their focus is on the processes that trigger accelerated aging in inherited disorders, such as progeria syndromes, but his team also studies genetic factors of craniofacial and skeletal diseases. Patients who suffer from premature aging disorders exhibit very early in life symptoms of premature aging such as osteoporosis, wrinkly skin, hypercholesterolemia and other metabolic changes. The team focuses on decoding in detail the underlying pathomechanisms in order to understand aging processes in both, health and disease.

Our successes: New technologies like next generation sequencing have allowed Prof. Dr. Wollnik and his team to identify over 35 new disease genes so far and the team is currently working on the molecular pathogenesis of many of these yet unpublished genes. The working group is pursuing a strong translational approach between basic research and the newly founded Center for Rare Diseases Cologne at the University Hospital Cologne, which is directed by Prof. Dr. Wollnik.

Our goals: Over the next few years, Prof. Dr. Wollnik and his team aim to discover new pathomechanisms based on the novel disease-associated genes they already identified. Since patients with premature aging phenotypes exhibit strong similarities despite different mutations in different genes, the scientists posit that mutations might affect shared signaling pathways important for aging processes. If the underlying mechanisms can be identified, this information could be used to design therapies that address a wide range of genotypes – an important breakthrough for patients.

Our methods/techniques: The researchers apply human genetic methods, such as whole-genome, whole-exome and Mendeliome sequencing, to identify causative genes and mutations in patients with rare diseases. Subsequently, novel genes and mutations are functionally investigated in in vitro and in vivo.

PUBLICATIONS

Murray JE, et al., Wollnik B, Jackson A. (2014) Extreme growth failure is a common presentation of ligase iv deficiency. Hum Mutat 35: 76-85.

Keupp K, et al., Wollnik B. (2013) Mutations in WNT1 Cause Different Forms of Bone Fragility. Am J Hum Genet 92: 565-574.

Bögershausen N, et al., Wollnik B*, Sacher M, Lamont RE. (2013) Recessive trappc11 mutations cause a disease spectrum of limb girdle muscular dystrophy and myopathy with movement disorder and intellectual disability. Am J Hum Genet 93: 181-190. (*corresponding author)

Asharani PV, et al., Hammerschmidt M, Wollnik B*, Carney TJ*. (2012) Attenuated BMP1 function compromises osteogenesis leading to bone fragility in human and zebrafish. Am J Hum Genet 90: 661-674. (*contributed equally)

Kalay E, et al., Wollnik B. (2011) CEP152 is a novel genome-maintenance protein and its disruption causes genomic instability in Seckel syndrome. Nat Genet 43: 23-26.

CECAD COOPERATIONS

F Prof. Dr. Hammerschmidt → p. 187
Principal Investigator

B Prof. Dr. T. Hoppe → p. 89
Principal Investigator

E Prof. Dr. P. Nürnberg → p. 155
Principal Investigator

C Prof. Dr. C. Reinhardt → p. 103
Principal Investigator

A Prof. Dr. R. J. Wiesner → p. 79
Principal Investigator

EXTERNAL COOPERATIONS

International and national networks: Coordinator of the E-RARE network CRANIRARE-2 and partner of the E-RARE network EuroMicro;
Prof. Dr. H. Kayserili, Istanbul, TR
Prof. Dr. A. Jackson, Edinburgh, UK
Prof. Dr. N. Katsanis, Durham, USA

D

Während des Alterungsprozesses kommt es zu Änderungen in der Zusammensetzung der Lipide (Fette), den Bausteinen der Zellmembranen. Damit verändern sich nicht nur die strukturellen Eigenschaften sondern auch die Funktionen von Zellmembranen.
Die Wissenschaftlerinnen und Wissenschaftler der Research Area D untersuchen an genetisch definierten Modellen von Enzymdefekten im Sphingolipidstoffwechsel ursächliche Mechanismen für altersassoziierte Erkrankungen wie Haarverlust, Muskelschwäche oder Fettleibigkeit. Die neuen Erkenntnisse zu den Alterungsprozessen von Zellmembranen und deren funktionelle Konsequenzen liefern Antworten auf die fundamentalen Fragen nach den Mechanismen des Alterns.

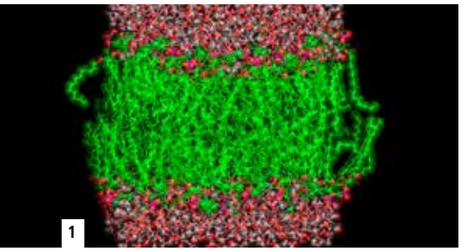
Research Area D
The Aging of Membranes

A key research question is why the lipid composition of the cell membrane changes with age. The aging process seems to alter the composition of lipids (fats), the building blocks of cell membranes. As a result, the structural properties of the cell membrane change as well. The lipid composition of membranes plays an important role in regulating the activity of cell surface membrane receptors, which transmit external signals to the cell interior and thereby control cell fate. In their search for definitive answers, scientists at CECAD combine mass spectrometry of membrane lipids with genetically defined deficiencies for specific enzymes involved in lipid metabolism to gain new insight into the characteristics of age-dependent changes of the lipid composition of cellular membranes and their impact on age-related diseases secondary to loss of cell function. By analysing the cellular lipidome, CECAD scientists have succeeded in improving our understanding of the changes of lipid composition occurring in aging membranes in mice and humans. The structural and functional characterization of aging membranes is an important component of CECAD's ultimate goal: to identify the mechanisms that lead to aging.

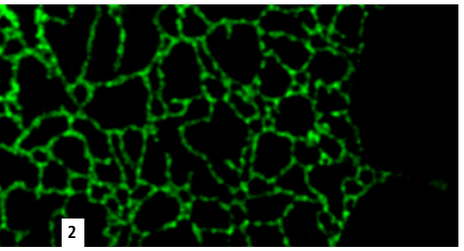
Research Area D investigates the following research topics:

- → A precise understanding of the functional role of specific members of the ceramide synthase family that generate specific ceramide species (sphingolipids that are abundant building blocks of cellular membranes) in aging-associated disorders such as hair loss, muscle weakness or obesity
- → Ceramide-specific control of mitochondrial functions in metabolic homeostasis
- → Research into aging-associated changes in plasma membrane structure and inflammatory status caused by altered saturation and elongation of the polyunsaturated fatty acids (PUFA)
- → Effects of aging-associated changes in the lipids and the effect on mitochondrial membrane permeability and function, and ion channel function at the glomerular filter barrier in the kidney

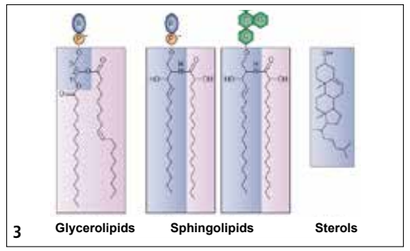
CECAD expects these research activities will contribute considerably to the elucidation of triggers and progression factors driving aging-associated inflammation, neurodegenerative diseases, ceramide synthase-associated metabolic disorders, lipid-associated epidermal barrier function, mitochondrial-linked neurodegenerative diseases, and kidney failure.



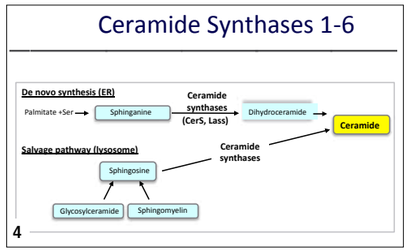
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Suggested name	Fatty acyl CoA	Tissue
CerS1 (lass1)	C18	Skeletal muscle, Brain
CerS2 (lass2)	C20-C24	Liver, Kidney
CerS3 (lass3)	C18/C24	Testis, Skin
CerS4 (lass4)	C18-C22	widely
CerS5 (lass5)	C16	Brain, Skeletal muscle, Testis
CerS6 (lass6)	C16	Skeletal muscle, Kidney

5

FIGURE 1: Lipid bilayer of cellular membranes
FIGURE 2: ER association of GFP-tagged Ceramide synthase 1 in COS cells (super resolution microscopy, stimulated emission depletion (STED))
FIGURE 3: Building blocks of the lipid bilayer
FIGURE 4 AND 5: Enzymatic activity and tissue specific expression of ceramide synthases 1–6

PRINCIPLE INVESTIGATORS MAIN FOCUS

Prof. Dr. M. Krönke → p. 129
PD Dr. H. Kashkar → p. 133
Dr. N. Robinson → p. 135
Prof. Dr. Dr. W. Stoffel → p. 137

PRINCIPLE INVESTIGATORS SECOND FOCUS

Prof. Dr. T. Benzing → p. 85
Prof. Dr. J. C. Brüning → p. 169
Dr. M. Bergami → p. 67
Dr. L. P. Frenzel → p. 111
Prof. Dr. T. Langer → p. 59
Prof. Dr. C. Niessen → p. 193

Eine im Alter oder bei schweren chronischen Erkrankungen häufig beobachtete Muskelschwäche kann bei einzelnen Menschen Pflege- und Hilfsbedürftigkeit auslösen beziehungsweise den Heilungsprozess komplizieren. Den Muskelschädigungen liegt eine altersabhängige, verminderte Aktivität der Ceramid Synthasen-1 und -5 zugrunde, zwei Mitgliedern einer spezifischen Enzymfamilie des Fettsäure-Stoffwechsels. Eine andere Variante dieser Enzymgruppe, Ceramid Synthase-4, konnte für den altersabhängigen Haarverlust von Mäusen identifiziert werden.



↗ http://cecad.uni-koeln.de/Prof-Martin-Kroenke.95.0.html

Prof. Dr. Martin Krönke

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

The CECAD research group led by Prof. Dr. Martin Krönke explores the lipid composition of cell membranes and its alterations in the aging organism. A reduction in the concentration of specific enzymes of sphingolipid metabolism, ceramide synthases-1 and -5, results in changes in the lipid composition in membranes, leading to myopathy of skeletal muscles. In humans, this is associated with frailty of elderly people and of patients suffering chronic critical diseases. One other isoform of the family of ceramide synthases, ceramide synthase-4, has been shown to be involved in the regulation of the hair follicle cycle. Down-regulation of ceramide synthase-4 leads to age-dependent hair loss. The precise mechanisms of action of both ceramide synthase-1,-5, and -4 have not yet been explored. The group's findings will break new ground in the understanding of the impact of age-dependent changes of sphingolipid concentrations in cell membranes and open avenues for novel therapies, especially for older patients.

Our research: Every cell in our body is controlled by cell surface receptors that transmit external signals into the cell. These receptors are located in the plasma membrane and their respective function depends on the lipid composition they are embedded in. The lipid composition of plasma membranes changes during aging, suggesting that this may compromise the function of these receptors.
The laboratory led by Prof. Krönke has discovered that the activity of ceramide synthases-1 and -5, two members of the family of enzymes primarily involved in the production of sphingolipids, decline as we age. A lack of these enzymes triggers myopathy of skeletal muscle in mice, which is reminiscent of critical illness myopathy in humans and of sarcopenia affecting elderly people. A genetic model of deficiency of another member of the ceramide synthase family, ceramide synthase-4, revealed that this enzyme is involved in the regulation of the hair follicle cycle. A loss of ceramide synthase-4 activity causes age-dependent hair loss. The research group is now aiming to elucidate the underlying molecular mechanisms by which ceramide synthase-1 and -4 specifically change the sphingolipid composition of plasma membranes. One goal is the identification of the cell surface receptors that are sensitive to changes of sphingolipids in membranes and respond with transmitting pathogenic signals to the cell interior.

Our successes: The previous findings of Prof. Krönke's research group have contributed to improving our understanding of the function of NADPH oxidases. NADPH oxidases are enzymes that lead to the release of reactive oxygen species (ROS). Increased ROS production has been implicated in serious disorders such as cancer and neurodegenerative diseases and also in the aging of the body. The laboratory has succeeded in identifying the mechanism that regulates the production of ROS triggered by the potent inflammatory cytokine tumor necrosis factor (TNF), whose plasma concentrations are frequently found to be increased in the blood of elderly individuals.

CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator

Prof. Dr. O. Cornely → p. 40
Principal Investigator
Translational Research

D PD Dr. H. Kashkar → p. 133
Principal Investigator

F Prof. Dr. C. Niessen → p. 193
Principal Investigator

E Prof. Dr. M. Pasparakis → p. 147
Principal Investigator

D Dr. N. Robinson → p. 135
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

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Prof. Dr. M. Deckert, Cologne, DE
Prof. Dr. W. Doehner, Berlin, DE
Prof. Dr. A. Futerman, IL

Prof. Dr. Martin Krönke
Head of Research Area D
Principal Investigator
Institute for Medical Microbiology, Immunology and Hygiene (IMMIH)

Our goals: The research group is working on explaining why some elderly individuals or seriously and chronically ill patients develop a unique kind of muscle disorder. One primary research area of the lab focuses on the precise molecular mechanisms by which sphingolipids control membrane integral receptor function. The team's observations suggest ceramide synthases as theurapeutic targets to halt the process of myopathy and to prevent age-dependent hair loss. This translational aspect will be pursued in co-operation with the new CECAD unit ´Translational Research´.

Our methods/techniques: Prof. Krönke's group works with samples from patients and from model organisms that represent the various ceramide synthase disorders. A major advantage of CECAD is the Lipidomics Facility headed by Susanne Brodesser, who is invaluable for the analysis of membrane lipid composition using state-of-the-art mass spectrometry.

Welche Mechanismen zum Aktivitätsverlust der Enzyme führen und warum dieser Verlust sowohl Muskelschädigungen als auch Haarverlust auslösen kann, ist bislang noch nicht im Detail verstanden. Die Arbeitsgruppe von Prof. Dr. Martin Krönke zielt darauf ab, die genauen ursachlichen Mechanismen aufzuklären, auch um neue Therapiekonzepte zu entwickeln.

PUBLICATIONS

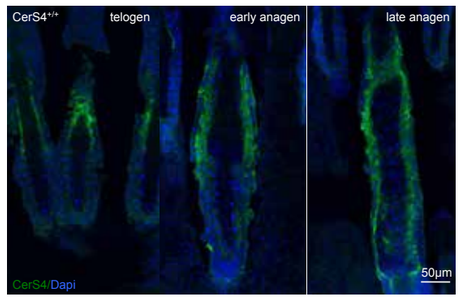
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Boecke A, Sieger D, Neacsu CD, Kashkar H, Krönke M. (2012) Factor associated with neutral sphingomyelinase activity mediates navigational capacity of leukocytes responding to wounds and infection: live imaging studies in zebrafish larvae. J Immunol. 189: 1559-66.

Krause KH, Lambeth D, Krönke M. (2012) NOX enzymes as drug targets. Cell Mol Life Sci. 69: 2279-82.

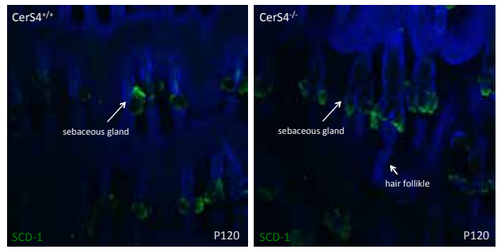
Yazdanpanah B, Wiegmann K, Tchikov V, Krut O, Pongratz C, Schramm M, Kleinridders A, Wunderlich T, Kashkar H, Utermöhlen O, Brüning JC, Schütze S, Krönke M. (2009) Riboflavin kinase couples TNF receptor 1 to NADPH oxidase. Nature. 460: 1159-63.

CerS4 localisation in the hair follicle



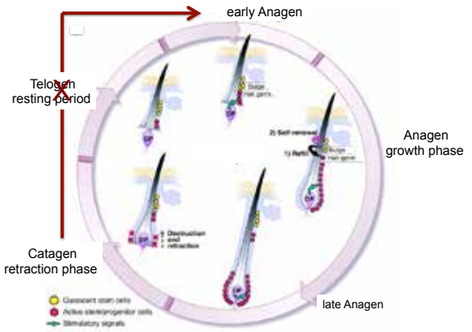
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Ectopic sebaceous glands in CerS4-deficient mice



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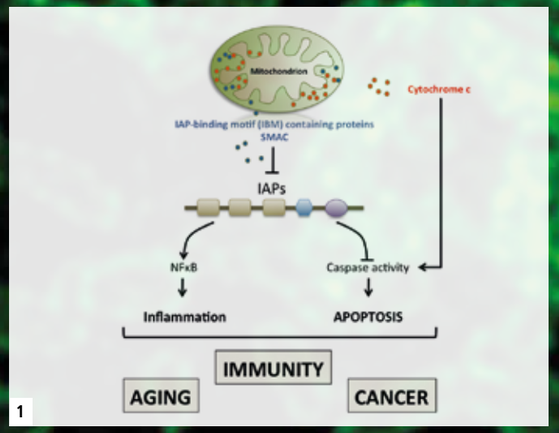
Missing 2° Telogen in CerS4 -/- mice



3

D

PD Dr. Kashkar und sein Team untersuchen, wie der Zelltod durch die Mitochondrien reguliert wird und welche Fehlfunktionen den Zelltod und somit die Gewebefunktion beeinträchtigen. Mitochondriale Fehlfunktionen führen u. a. in Tumorzellen zur Ausbildung einer Zelltodresistenz. Den Wissenschaftlern gelang es, zu der Entwicklung verschiedener ‚small molecules' beizutragen, die eine Aufhebung der Zelltodresistenz erzielen und eine verbesserte Therapie von Krebspatienten ermöglichen.



1

FIGURE 1: Mitochondrial outer membrane permeabilization (MOMP) and the release of several intermembrane space (IMS) proteins including cytochrome c and IBM (IAP-binding motive)- containing proteins including SMAC are known to interfere with cellular death machinery by activating caspases (apoptosis or programmed cell death). Cytosolic cytochrome c induces the proteolytic activation of caspase cascade, whereas cytosolic SMAC antagonizes the inhibitor of apoptosis proteins (IAPs). IAPs have been additionally shown to interfere with cellular immune inflammatory signaling. Our recent data demonstrated that mitochondria impact on inflammation by releasing SMAC and antagonizing IAPs (see Andree et al, EMBO J 2014) and provide the first line evidence how cell death signaling interferes with cellular immune signaling. The dynamic crosstalk between cell death and inflammatory signaling cascades via mitochondria represents a central cellular regulatory circuit involved in immunity, aging and cancer.



↗ http://cecad.uni-koeln.de/Dr-Hamid-Kashkar.93.0.html

PD Dr. Hamid Kashkar

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

PD Dr. Hamid Kashkar and his group investigate how mitochondria impact on cell death and tissue homeostasis. Mitochondrial dysfunction alters cellular death process and culminates in disease stage e.g. cancer. The group has successfully contributed to the development and evaluation of 'small molecules' that target mitochondria and restore cell death in cancer.

Our research: Dr. Hamid Kashkar and his group aim to understand how mitochondria control cell death and tissue immunosurveillance mechanisms. They were able to show that mitochondria simultaneously control cellular death pathways together with cellular immune signaling. Thereby, mitochondria coordinate tissue immunosurveillance and guarantee tissue function. Therapeutic modalities can be developed based on these findings, which will be evaluated in cooperation with clinical partners as treatment for immunocompromised patients, particularly those with cancer.

Our successes: The researchers in Dr. Kashkar's group succeeded in developing and deploying a variety of 'small molecules' to restore proper function of the cell death machinery. The reactivation of cell death in tumor cells through the application of SMAC mimetics, synthesized based on the structure of a mitochondrial protein, sensitizes the tumor cells to the immune system and results in improved immunosurveillance of cancer. At University Hospital Cologne, pre-clinical studies are currently underway on the use of "SMAC mimetics" to treat chronic lymphatic leukemia (CLL) and malignant melanoma.

Our goals: The research focuses on mitochondria and the regulation of tissue immunosurveillance mechanisms, as a treatment concept for cancer and immune diseases. This knowledge has already contributed to design and pre-clinical evaluation of novel therapeutic protocols that are currently under investigation for clinical studies.

Our methods/techniques: Protein biochemistry, cell biology and immunology.

PUBLICATIONS

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CECAD COOPERATIONS

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D Prof. Dr. M. Krönke → p. 129
Principal Investigator

A Prof. Dr. E. I. Rugarli → p. 63
Principal Investigator

A Prof. Dr. A. Trifunovic → p. 75
Principal Investigator

A Prof. Dr. R. J. Wiesner → p. 79
Principal Investigator

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Prof. Dr. T. Tüting, Dermatology, Bonn, DE

D

Im Alter lässt die Funktionsfähigkeit des Immunsystems nach und in Folge nimmt die Infektanfälligkeit zu. Dr. Nirmal Robinson erforscht gemeinsam mit seiner Arbeitsgruppe die molekularen Grundlagen dieses Funktionsverlustes. Im Fokus steht die Bedeutung des Energiestoffwechsels für die Erreger-Abwehr. Die Arbeitsgruppe konnte u.a. ein Protein identifizieren, das ein Bindeglied zwischen Energiehaushalt und Immunsystem darstellt.



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FIGURE 1: Electron microscopical image of Salmonella typhimurium induced autophagosome in a macrophage



↗ http://cecad.uni-koeln.de/Dr-Nirmal-Robinson.270.0.html

Dr. Nirmal Robinson

Principal Investigator
CECAD Junior Group Leader (CECAD CRC Bridging Group)

Dr. Nirmal Robinson and his team are investigating the molecular basis of immunosenescence, looking particularly at the interactions between energy metabolism and the immune system. Their findings have already provided new information on these interfaces, for example, between Salmonella typhimurium bacteria and Sirtuins. The research group aims to explore what significance other metabolic pathways, as well as the hormones insulin and leptin, have to the immune system.

Our research: Functioning of the immune system deteriorates with age. This process is called immunosenescence. Dr. Robinson and his team are investigating the molecular basis of immune senescence. Their goal is to understand how the immune system weakens with age and why older people become more susceptible to infection. The group is looking particularly at the interactions between metabolic pathways and immune responses.

Our successes: Recent research on the interfaces between metabolism and the immune system has enabled the team to demonstrate that pathogenic Salmonella typhimurium bacteria can interfere with metabolic processes in cells of the immune system. A further success has been the elucidation of the role of Sirtuin1 in cell autonomous immune defense mechanisms. This protein, which is frequently lowered in older people, is triggering a balance between anabolism and catabolism in immune cells. These findings illustrate the crosstalk between energy metabolism and immune responses.

Our goals: Based on the way in which glycolysis impacts immune responses, Dr. Robinson's team is exploring the functions of other metabolic pathways, such as glutamine metabolism and fatty acid oxidation, in the body's immune defenses. Research also focuses on the significance of the metabolic hormones insulin and leptin in modulating immunity. As obese and diabetic patients are more susceptible to infection, the scientists hypothesize that these hormones could significantly regulate the immune system.

Our methods/techniques: Besides standard biochemical methods, such as western blots, quantitative PCR, and RNA-sequencing, the Robinson laboratory employs various microscopy techniques and quantitative mass spectrometry.

PUBLICATIONS

Persa OD, Jazmati N, Robinson N, Wolke M, Kremer K, Schweer K, Plum G, Schlaak M. (2014) A pregnant woman with chronic meningococcaemia from Neisseria meningitidis with lpxL1-mutations.Lancet. 384(9957): Epub Nov 21.

Nguyen T, Robinson N, Allison SE, Coombes BK, Sad S and Krishnan L.(2013) IL-10 produced by trophoblast cells inhibits phagosome maturation leading to profound intracellular proliferation of Salmonella enterica Typhimurium. Placenta 34(9):765-774.

Robinson N, McComb S, Mulligan R, Dudani R, Krishnan L and Sad S.(2012) Type-I interferon induces necroptosis in macrophages during Salmonella Typhimurium infection. Nature Immunology 13(10):954-962.

CECAD COOPERATIONS

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Principal Investigator

D PD Dr. H. Kashkar → p. 133
Principal Investigator

D Prof. Dr. M. Krönke → p. 129
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A Dr. M. Lammers → p. 69
Principal Investigator

A PD Dr. T. Wenz → p. 77
Principal Investigator

EXTERNAL COOPERATIONS

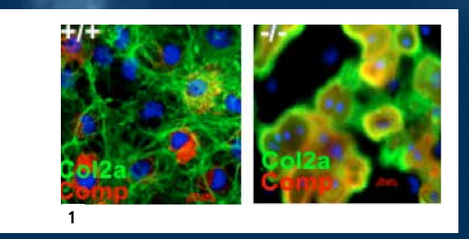
Christoph Dietrich, Max Planck Institute for Biology of Ageing, Cologne, DE
Subash Sad, Department of Biochemistry, Microbiology and Immunology, University of Ottawa, CA
Vidya Velagapudi, Institute for Molecular Medicine Finland, Helsinki, FI
Xiaoling Li, Laboratory of Signal Transduction, National Institute of Environmental Health Sciences, North Carolina, USA

D

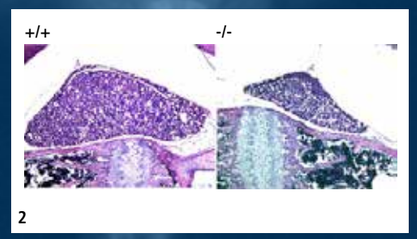
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Die Arbeitsgruppe um Prof. Dr. Dr. Stoffel untersucht die Funktions-Struktur-Beziehungen von Phospho- und Sphingolipiden in der Zellmembran. Genetisch veränderte Mäuse werden phäno- und genotypisch analysiert, um Prozesse mit Schlüsselfunktionen bei der Entstehung systemischer und Knorpel/Knochen bedingter juveniler Wachstumsstörungen und Gelenkerkrankungen zu definieren. Dadurch können neue therapeutische Ansätze entwickelt werden.

BACKGROUND FIGURE: X-ray image of pelvis and hind limb long bone of control (+/+) and smpd3 -/- mouse.
FIGURE 1: Immunhistochemistry unveils disrupted Golgi vesicular protein transport and secretion of extracellular matrix protein (ECM) in smpd3-/- chondrocytes compared to collagen 2A network in ECM.
FIGURE 2: Sagittal section of pituitary gland. SMPD3 deficiency causes hypothalamus-induced combined pituitary hormone deficiency on the basis of systemic hypoplasia.



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↗ http://cecad.uni-koeln.de/Prof-Wilhelm-Stoffel.109.0.html

Prof. Dr. Dr. Wilhelm Stoffel

Principal Investigator
CECAD Cologne

Prof. Dr. Dr. Stoffel's group studies the biochemical and cellular structure-function relationship of complex phospho- (PL) and sphingolipids (SL) in mammalian cell membranes, preferentially in targeted genetically mouse models, which are mimicries of human diseases. Their goal is to understand the molecular impact of the key role of sphingomyelin (SM) metabolism in these mouse mutants, which develop systemic (hypothalamus-pituitary-growth-axis) and cartilage-bone derived juvenile dwarfism and chondrodysplasia, a basis for future novel therapeutic approaches.

Our research: SL, PL and cholesterol form the complex architecture of all mammalian membranes. Stoffel´s group investigates in the current research project the structure-function relationship and the metabolism of SL and their impact on cellular functions. They focus on the regulation of biochemical and cellular processes by Sphingomyelin-Phospho-Diesterase 3 (SMPD3) and its catabolites. The SMPD3-deficient mouse represents a novel form of juvenile systemic hypoplasia (dwarfism) combined with chondrodysplasia.

Our successes: Mouse mutants were generated to unravel the in vivo functions of SL. In the current project, they pinpointed 1. the subcellular localization in the Golgi cisternae, 2. the pivotal role of SMPD3 and SM catabolites in Golgi vesicular protein transport and protein secretion. 3. Lack of SMPD3 in hypothalamic neurosecretory neurons and chondrocytes leads to endoplasmatic reticulum (ER)-protein storage, ER-stress and apoptosis. These results provide crucial insight into the molecular pathobiochemistry of dwarfism combined with chondrodysplasia.

Our goals: The focus of the group is directed towards understanding the molecular basis of hitherto unrecognized functions of SL in the regulation of growth of mouse and man. This research aimed at generating the molecular platform for new therapeutic approaches in the treatment of impaired growth during adolescence. Other rapidly growing cell types will be included in the concept.

Our methods/techniques: The group utilizes lipidomic analysis, genetics, biochemical, cell biological and imaging methods.

PUBLICATIONS

Stoffel W, Hammels I, Jenke B, Binczek E, Schmidt-Soltau I, Brodesser S, Odenthal M, Thevis M. (2014) Obesity resistance and deregulation of lipogenesis in Δ6-fatty acid desaturase (FADS2) deficiency. EMBO R 15, 110-120.

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Schraven S, Franz C, Rüttiger L, Löwenheim H, Lysarowsky A, Stoffel W, Knipper M. (2012) Altered phenotype of the vestibular organ in GLAST-1 null mice. Journal of the Association for Research in Otolaryngology. 13, 323-33.

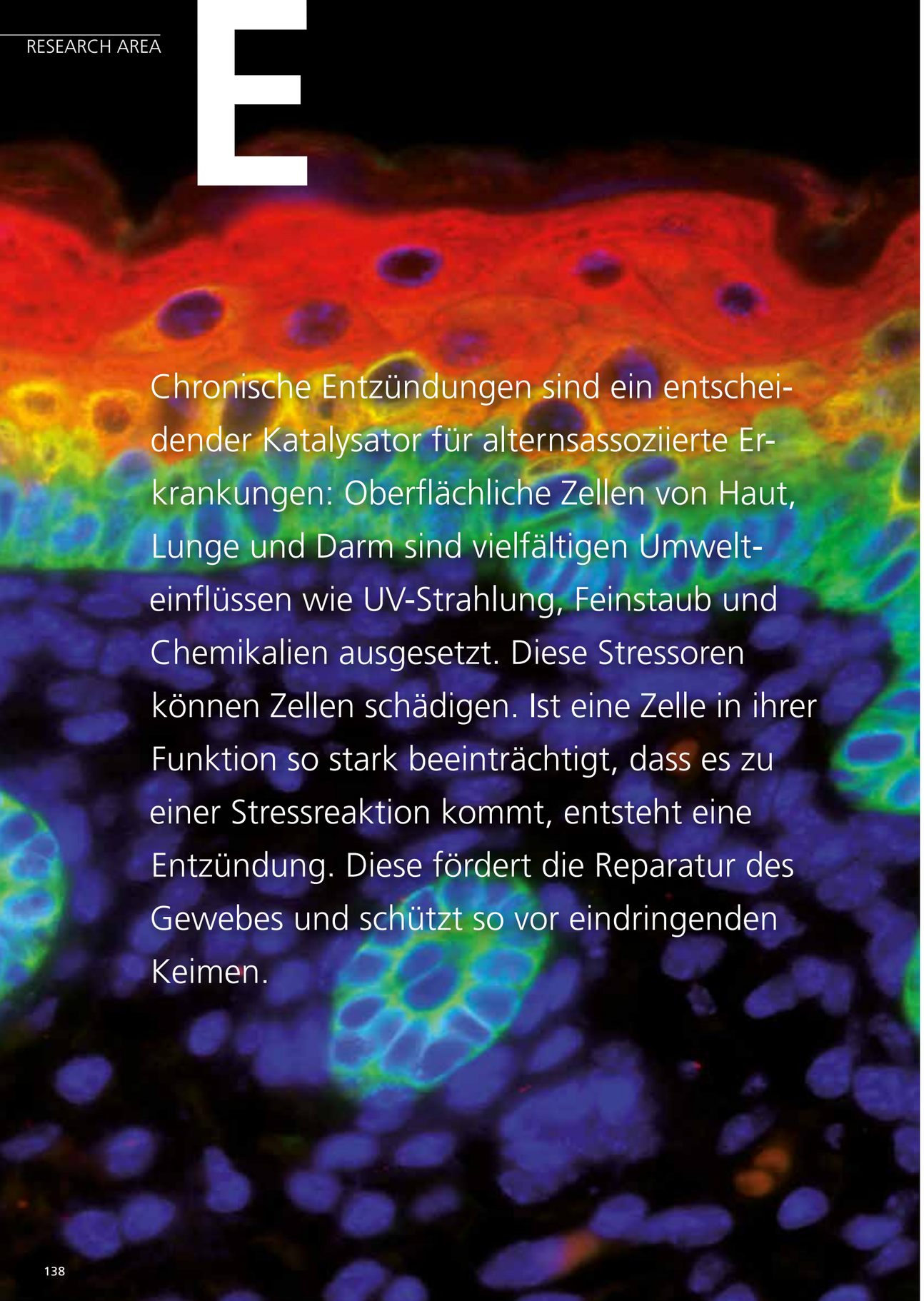
CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator

EXTERNAL COOPERATIONS

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PD Dr. M. Odenthal, Institute for Pathology, Cologne, DE
Prof. Dr. M. Thevis, Institute for Biochemistry, German Sport University Cologne, Cologne, DE

E



Chronische Entzündungen sind ein entscheidender Katalysator für alternsassoziierte Erkrankungen: Oberflächliche Zellen von Haut, Lunge und Darm sind vielfältigen Umwelteinflüssen wie UV-Strahlung, Feinstaub und Chemikalien ausgesetzt. Diese Stressoren können Zellen schädigen. Ist eine Zelle in ihrer Funktion so stark beeinträchtigt, dass es zu einer Stressreaktion kommt, entsteht eine Entzündung. Diese fördert die Reparatur des Gewebes und schützt so vor eindringenden Keimen.

Research Area E
Inflammation in Aging-Associated Diseases

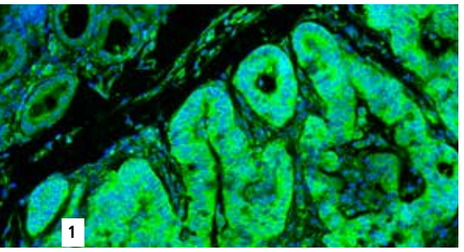
Chronic inflammation contributes to the pathogenesis of aging-associated diseases. Cells covering the surface of tissues such as the skin, lungs and intestines are constantly challenged by a wide range of environmental factors such as UV rays, particulate matter, chemicals as well as microbes. These stressors can damage cells and cause tissue injury that requires repair. Cellular damage induces inflammation, which promotes tissue repair and guards against invading microbes. After successful regeneration, the inflammatory reaction needs to be terminated to establish normal tissue homeostasis. Failure to properly regulate this response may result in uncontrolled chronic inflammation, which causes tissue damage and can result in severe diseases including cancer, chronic wounds, inflammatory bowel disease, psoriasis, type 2 diabetes, hepatitis, and arthritis.

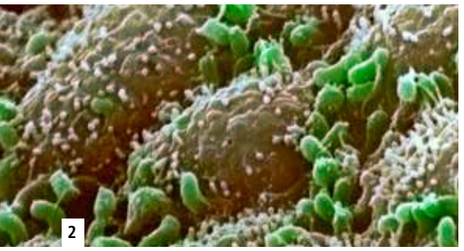
CECAD studies the molecular and cellular mechanisms that cause chronic inflammation and its role in disease pathogenesis. CECAD researchers use state-of-the-art methods and a wide range of model organisms to study the molecules and pathways that regulate inflammation and contribute to disease.

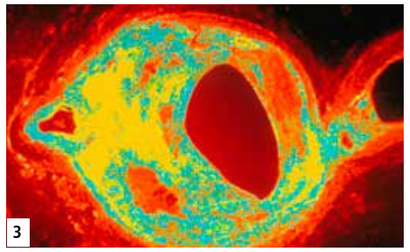
Research Area E focuses on exploring:

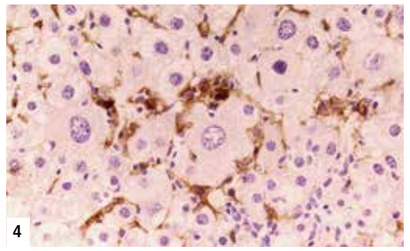
- → The role of inflammation on epithelial tissue homeostasis, equilibrium, degeneration and regeneration
- → Inflammation caused by DNA damage on tissue homeostasis and aging
- → The mechanisms that link inflammation and mitochondrial dysfunction, the onset of neurodegenerative illnesses and metabolic stress
- → The role of the microenvironment in carcinogenesis

CECAD scientists aim to decode the mechanisms that link cellular stress reactions to aging-associated diseases. This could lead to the identification of new therapies for these illnesses.


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BACKGROUND FIGURE: Skin, intestinal epithelium and lung epithelium are surfaces acting as barriers to the outside world. Here the body comes in contact with stressors such as chemicals, germ and UV-light.
FIGURE 1: Chronic inflammation in the gut predisposes to tumor development. Here tumor cells appear intensive green and tightly packed.
FIGURE 2: The intact epithelial lining of the gastrointestinal tract restrains symbiotic bacteria to the lumen. There they importantly contributes to efficient utilization of nutrition.
FIGURE 3: Transverse section through a blood vessel: Inflammatory plaques (yellow and green) at blood vessel walls prevent regular blood flow and can result in vascular occlusion.
FIGURE 4: Macrophages (immune cells) in brown among liver cells.

PRINCIPLE INVESTIGATORS MAIN FOCUS

Prof. Dr. T. Krieg → p. 143
Prof. Dr. M. Pasparakis → p. 147
PD Dr. H. C. Hennies → p. 151
Dr. S. Iden → p. 153
Prof. Dr. P. Nürnberg → p. 155
PD Dr. P. Steven → p. 157
Prof. Dr. M. Uhlirova → p. 159
Dr. S. Wickström → p. 161
PD Dr. T. Wunderlich → p. 163

PRINCIPLE INVESTIGATORS SECOND FOCUS

Prof. Dr. J. C. Brüning → p. 169
Prof. Dr. M. Hallek → p. 113
Dr. M. Herling → p. 117
Prof. Dr. M. Krönke → p. 129
Prof. Dr. T. Langer → p. 59
Prof. Dr. C. Niessen → p. 193
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PD Dr. T. Wenz → p. 77

Degenerative Hautveränderungen und Wundheilungsstörungen treten gehäuft bei älteren Menschen auf. Die Ursachen chronischer Wunden und fragiler Haut sind nicht verstanden. Häufig sind sie mit arteriellen oder venösen Gefäßschäden, Diabetes mellitus und/oder entzündlichen Hauterkrankungen assoziiert. Die Therapie chronischer Wunden und ihrer Komplikationen stellen ein großes medizinisches und sozioökonomisches Problem dar und die Versorgung dieser Patientengruppe ist verbesserungswürdig. Die Arbeitsgruppe um Prof. Dr. Thomas Krieg erforscht Risikofaktoren und Mechanismen bei chronischen Wunden, um neue zukunftsweisende Therapien entwickeln zu können.



↗ http://cecad.uni-koeln.de/Prof-Thomas-Krieg.83.0.html

Prof. Dr. Thomas Krieg

Head of Research Area E – Principal Investigator
Director of Department for Dermatology and Venerology
University Hospital of Cologne

Degenerative skin changes and poor wound healing occur more frequently in older people. The causes of chronic wounds and fragile skin are not yet fully understood. They are often associated with arterial or venous disease, diabetes mellitus and/or inflammatory skin disorders. Treating chronic wounds and their complications is a major medical and socioeconomic problem, and care for this patient group needs improvement.
Prof. Dr. Thomas Krieg's research group explores the risk factors and mechanisms underlying chronic wounds aiming at the development of innovative therapies.

Our research: One key aspect is identifying factors of an increased risk to be affected from poor wound healing and chronic wounds, such as chronic venous insufficiency (CVI). This disease results in inflammatory and fibrotic changes to the skin, which often trigger tissue loss and chronic wounds on the calves and feet. Prof. Krieg and his team of scientists are working to understand the mechanisms of cellular communication and use these findings to help identify the processes that promote degenerative changes in the skin and inhibit the normal healing process.

Our successes: Wound healing mechanisms are regulated by the immune system. Using new mouse models, Prof. Krieg and his working group have successfully proven that specific macrophage populations play a key role in the different wound healing processes and that regulating these influences the quality of the wound healing response.
Additionally the team has shown that mast cells, whose part in triggering fibroses has long been a point of discussion, play more of a subordinate role. The researchers achieved another breakthrough with the identification of new interactions among extracellular matrix molecules in fibrotic skin diseases and with the characterization of the functional consequences for scar formation.

Our goals: The team's basic research has already identified a number of mechanisms essential to the normal wound healing process. Disruptions of these cellular and molecular reciprocal interactions are implicated in chronic wounds and fibrotic disorders. The aim is to use these findings to test therapeutic approaches in the clinic with the ultimate objective of developing a treatment for chronic wounds while limiting scar formation as much as possible.

Our methods/techniques: Prof. Krieg's group uses a variety of experimental approaches. Cell biology methods and molecular techniques in particular are used in basic research. Based on the results from experiments with cell cultures, transgene mice are investigated preclinically as model organisms before new, very promising therapeutic approaches can be tested in clinical studies.

CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator

F Prof. Dr. Hammerschmidt → p. 187
Principal Investigator

F Prof. Dr. C. Niessen → p. 193
Principal Investigator

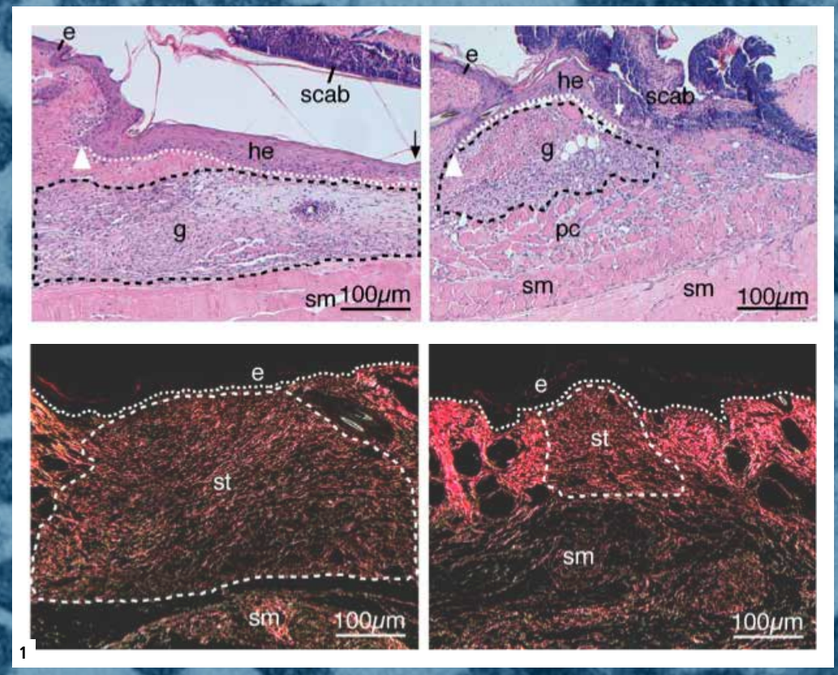
F Prof. Dr. L. Partridge → p. 173
Principal Investigator

E Prof. Dr. M. Pasparakis → p. 147
Principal Investigator

EXTERNAL COOPERATIONS

Prof. Dr. M. Leptin, Cologne, DE

Prof. Dr. Thomas Krieg
Head of Research Area E
Principal Investigator
Director of Department for Dermatology and Venerology University Hospital of Cologne



1

FIGURE 1: Macrophage depletion during the early stage of repair attenuates epithelialization, granulation tissue formation and scar formation.
H&E stainings of wounds in control (LysMCre) and macrophage depleted mice (LysMCre/iDTR) at indicated time points after injury. Whereas in control mice, the day-5 wound is filled with a vascularized granulation tissue in LysMCre/iDTR mice only scarce granulation tissue has formed (black hatched line outlines granulation tissue, white dotted line outlines hyperproliferative epithelial tongue); day-14 wounds in control and LysMCre/iDTR mice are closed, scar tissue is minimal in LysMCre/iDTR mice (hatched line outlines scar tissue).

PUBLICATIONS

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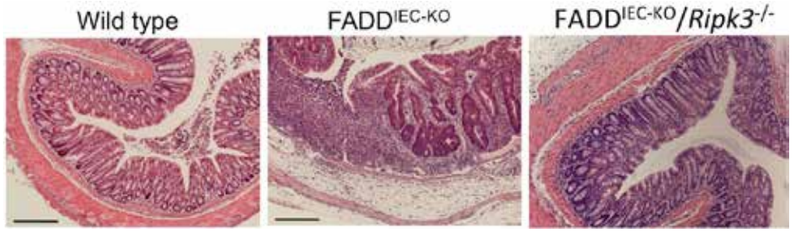
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E

Entzündungsreaktionen schützen den Körper vor mikrobiellen Infektionen und fördern die Wundheilung und Geweberegeneration. Übermäßige oder verlängerte Entzündungen können das Gewebe jedoch schädigen und sind an der Entstehung vieler Erkrankungen beteiligt.



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FIGURE 1: Mice with intestinal epithelial specific knockout of FADD (FADDIEC-KO) show necroptosis of intestinal epithelial cells and develop severe inflammatory colitis. Genetic deficiency of RIPK3 inhibits epithelial cell necroptosis and prevents the development of colitis in FADDIEC-KO mice.



↗ http://cecad.uni-koeln.de/Prof-Manolis-Pasparakis.102.0.html

Prof. Dr. Manolis Pasparakis

Head of Research Area E – Principal Investigator
Institute for Genetics

Inflammatory responses protect the body from microbial infections and promote wound healing and tissue regeneration. However, excessive or prolonged inflammation causes tissue damage and is involved in the pathogenesis of many diseases. The team of Prof. Dr. Manolis Pasparakis studies the mechanisms regulating inflammation and the development of inflammatory diseases. Their research revealed the important role of cell death as a trigger for inflammation in epithelial tissues such as the skin and the intestine. Their long-term goal is to understand the mechanisms that control inflammation and contribute to the pathogenesis of chronic inflammatory diseases.

Our research: Healthy tissue homeostasis is maintained by balanced interactions between epithelial, stromal and immune cells with the commensal microbes that normally reside on the surface of our barrier tissues such as the gut and the skin. Disruption of tissue homeostasis can cause chronic inflammatory diseases and in some cases also cancer. Despite recent progress in identifying factors that contribute to tissue damage and chronic disease, the causes that initiate pathogenic inflammatory responses remain unknown. As a consequence, currently available therapies mainly target the symptoms and aim to achieve stable suppression of the inflammatory response, which requires chronic treatment that causes side effects and increases costs. The group studies the mechanisms that regulate immune responses, with particular interest on identifying molecules and pathways that are responsible for causing chronic inflammatory diseases. They have a long-standing interest on understanding how NF-κB signalling contributes to disease pathogenesis. More recently, they have been interested in studying how different pathways of regulated cell death, such as apoptosis or necroptosis, may contribute to inflammation and the pathogenesis of inflammatory diseases.

Our successes: The group's recent studies contributed to the identification of new mechanisms causing inflammation in epithelial tissues, which may lead to the development of new treatments for inflammatory diseases. Their experiments showed that death of epithelial cells triggers severe chronic inflammation in barrier tissues such as the gut and the skin. In particular, their results revealed that necroptosis, a newly identified pathway or regulated necrotic cell death, of intestinal epithelial cells triggered severe colon inflammation resembling human colitis. In addition, the experiments showed that necroptosis of epidermal keratinocytes also triggered severe skin inflammation. Furthermore, the most recent studies revealed novel functions of RIP kinase 1 that are important for the regulation of epithelial cell survival and the maintenance of immune homeostasis in barrier tissues.

Our goals: The long-term goal is to understand the mechanisms that regulate immune homeostasis and control inflammation. The group's current work focuses on the mechanisms regulating cell death and particularly necroptosis and how this pathway of regulated necrosis contributes to inflammation. Using genetic mouse models they aim to identify basic mechanisms regulating cell death and inflammation. In addition, they aim to assess the potential role of necroptosis in the pathogenesis of human diseases and explore the possible therapeutic application of necroptosis inhibitors in chronic human inflammatory diseases.

CECAD COOPERATIONS

B Prof. Dr. T. Benzing → p. 85
Principal Investigator

A Dr. M. Bergami → p. 67
Principal Investigator

E Prof. Dr. T. Krieg → p. 143
Principal Investigator

A Prof. Dr. T. Langer → p. 59
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

A Prof. Dr. A. Trifunovic → p. 75
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EXTERNAL COOPERATIONS

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University of Massachusetts, USA
University of Frankfurt, DE
Academy Institute of Molecular Biotechnology (IMBA), Vienna, AT

Prof. Dr. Manolis Pasparakis
Head of Research Area E
Principal Investigator
Institute for Genetics

Our methods/techniques: Prof. Pasparakis and his team use genetic mouse models to study the molecules and pathways regulating inflammation and are responsible for the pathogenesis of inflammatory diseases. Since these pathways are conserved between mice and humans, their results are relevant for the better understanding of the mechanisms causing human inflammatory diseases. In addition, they analyze human patient samples in order to assess whether the mechanisms identified to cause disease in mouse models also contribute to the pathogenesis of inflammatory diseases in human patients.

PUBLICATIONS

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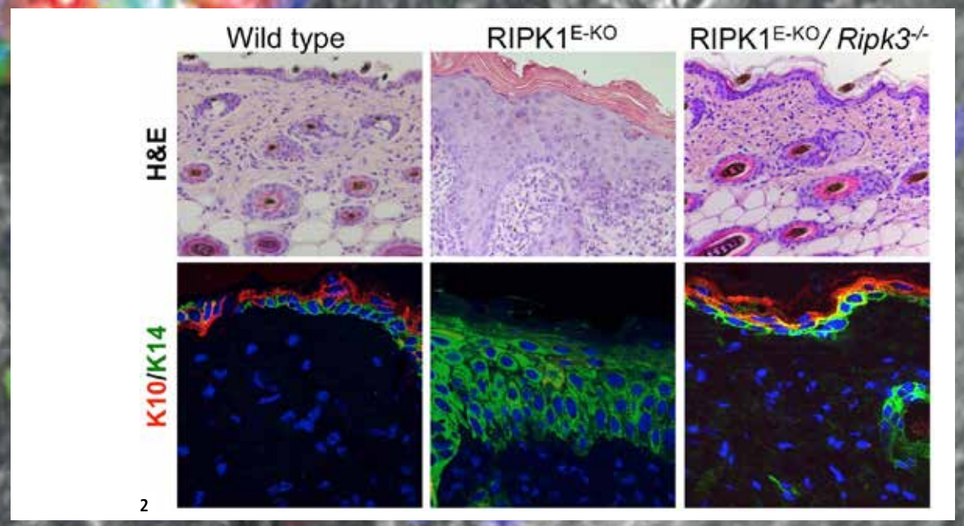
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Vlantis K, Wullaert A, Sasaki Y, Schmidt-Supprian M, Rajewsky K, Roskams T, Pasparakis M. (2011) Constitutive IKK2 activation in intestinal epithelial cells induces intestinal tumors in mice. The Journal of clinical investigation 121: 2781-2793.

FIGURE 2: Mice with epidermal keratinocyte specific knockout of RIPK1 (RIPK1E-KO) show necroptosis of keratinocytes and develop severe skin inflammation characterised by epidermal hyperplasia, increased expression of keratin 14 and decreased expression of keratin 10. Genetic deficiency of RIPK3 prevents keratinocyte necroptosis and inhibits skin inflammation in RIPK1E-KO mice.

Das Team um Prof. Dr. Pasparakis zielt darauf ab, die Mechanismen zu verstehen, die Entzündungsreaktionen regulieren und zu der Entwicklung von chronischen entzündlichen Erkrankungen beitragen. Ihre Forschungsergebnisse könnten dazu führen, neue therapeutische Ansatzpunkte für entzündliche Erkrankungen des Menschen zu finden.



Das Team um PD Dr. Hans Christian Hennies untersucht Ursachen genetisch bedingter Erkrankungen, seltener monogener und häufiger, multifaktorieller Erkrankungen wie der Dupuytrenschen Kontraktur. Ziel ist die Erforschung molekularer Entstehungsmechanismen, um im Rahmen der translationalen Forschung neue Angriffspunkte für Therapien definieren zu können.

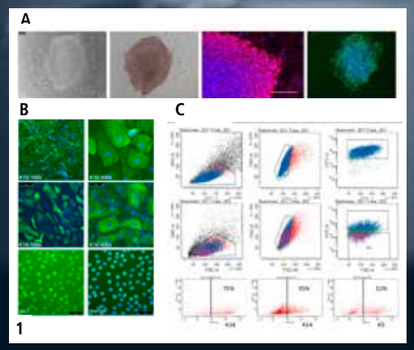
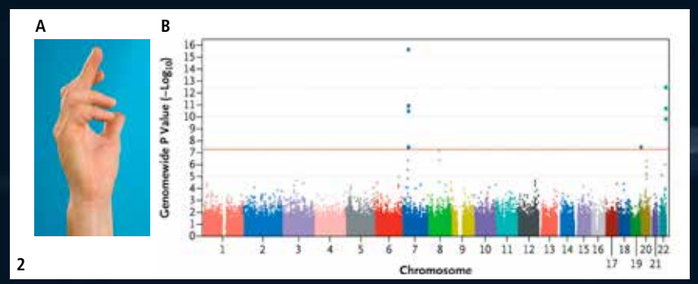


FIGURE 1: Generation of epidermal keratinocytes by differentiation of induced pluripotent stem cells. A) Pluripotent stem cells were obtained by reprogramming of fibroblasts as shown by typical morphology, activity of alkaline phosphatase, and staining signals for Oct4 and Tra1-81 (left to right). B) Differentiation of induced pluripotent stem cells to the ectodermal fate showed synthesis of epithelial marker keratin 18, epidermal marker keratin 14, and ectodermal gatekeeper p63. C) Primary (first row) and iPS-derived keratinocytes were positive for epithelial markers CD104 (first and second row) and keratins 18, 14, and 5 (third row) in FACS analysis.

FIGURE 2: Genome-wide study of genetic association in Dupuytren's disease (Dolmans et al 2011). A) Clinical presentation. B) Manhattan plot of genome-wide P values showed single-nucleotide polymorphisms (SNPs) associated with Dupuytren's disease. The orange line denotes significance threshold ($P = 5 \times 10^{-8}$).





↗ http://cecad.uni-koeln.de/Dr-Hans-Christian-Hennies.90.0.html

PD Dr. Hans Christian Hennies

Principal Investigator
CECAD Cologne

The research group around PD Dr. Hans Christian Hennies investigates the molecular basis of genetic disorders. Many of these are rare monogenic diseases, but especially multifactorial disorders, such as alopecia areata and Dupuytren's contracture, are common. Their goal is to identify the underlying pathomechanisms for these diseases and use them to define new targets for therapies as part of translational research.

Our research: The primary focus of Dr. Hennies and his team is on rare, monogenic diseases, in particular diseases of the skin, hair and connective tissue. They have turned their attention to two more common diseases as well: alopecia areata, hair loss in round patches, and Dupuytren's disease, a contracture of the hand caused by fibromatosis that often occurs at advanced age. Identification of mutations that trigger the conditions is instrumental to decode the underlying pathomechanisms.

Our successes: The greatest advance in research into multifactorial diseases has been an understanding of how diverse genetic loci contribute to cellular mechanisms and affect gene expression in different cell types. One key breakthrough in the study of Dupuytren's disease is new insight into the importance of Wnt signaling: six of nine known chromosomal loci associated with the disease contain genes involved in these pathways. Researchers have demonstrated that Wnt signaling not only exhibits changes at the protein level, but also variants at the DNA level have a direct influence on the Wnt gene. Furthermore, the group has identified mutations in various rare skin diseases, which have revealed the importance of cellular adhesion and lipid metabolism for epidermal integrity and skin barrier function.

Our goals: Dr. Hennies and his team of researchers aim to identify causal genetic variants in order to derive molecular targets for new medicines. The team is also working on the development of cellular models for the different disorders, which facilitate personalized approaches and systematic testing of new substances.

Our methods/techniques: In their research, Dr. Hennies and his team use high-throughput methods in genomics, including next generation sequencing and SNP genotyping. A variety of complex human cell models allows for investigation of fibroblasts, keratinocytes and melanocytes in organotypic cell structures.

PUBLICATIONS

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CECAD COOPERATIONS

E Prof. Dr. T. Krieg → p. 143
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F Prof. Dr. C. Niessen → p. 193
Principal Investigator

E Prof. Dr. P. Nürnberg → p. 155
Principal Investigator

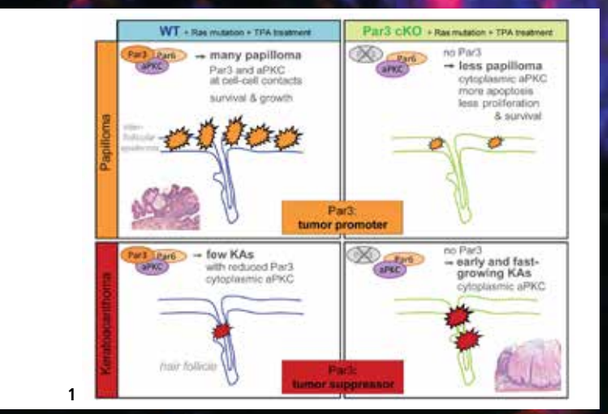
EXTERNAL COOPERATIONS

Prof. Dr. D. Furniss, Oxford, UK; Prof. Dr. D. Kelsell, London, UK; Prof. Dr. M. Schäfer-Korting, Berlin, DE; Prof. M. Schmuth, Innsbruck, AT; Prof. Dr. H. Traupe, Münster, DE; Prof. Dr. P. Werker, Groningen, NL; other cooperations via the ERA-Net project SkinDev

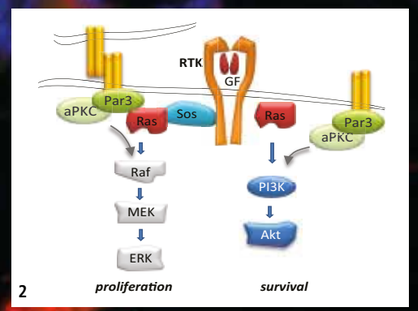
Hautkrebs gehört zu den häufigsten Tumorerkrankungen, und Alter ist ein wesentlicher Risikofaktor. Das Team um Dr. Iden erforscht das Phänomen der Zellpolarität und ihre Bedeutung in der Entstehung von Hauttumoren, um so molekulare Mechanismen der Krebsentstehung zu identifizieren und neue diagnostische Marker und Therapien zu entwickeln.

FIGURE 1: Dual role of Par3 in skin tumorigenesis. Papilloma formation and growth is reduced, and aPKC and components of the Ras pathway are mislocalized when Par3 is lost. In contrast, Par3 KO mice develop significantly more keratoacanthomas, suggesting that Par3 has a tumor-suppressive function in this context (see Iden et al., Cancer Cell 2012).

FIGURE 2: Polarity protein signaling impinges on central cascades that influence tumor formation and progression. Left: In epidermal keratinocytes, Par3 serves to recruit aPKC and Ras signaling components to the plasma membrane, resulting in efficient downstream signaling towards Ras/Raf/MEK/ERK, promoting proliferation and growth of skin papillomas. Right: Par3 and aPKC promote cell survival by the stimulation of PI3K-Akt signaling, thereby counteracting oncogene-induced apoptosis.



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↗ http://cecad.uni-koeln.de/Dr-Sandra-Iden.96.0.html

Dr. Sandra Iden

Principal Investigator – Junior Research Group Leader
CECAD Cologne

The Iden laboratory investigates mechanisms underlying cell and tissue polarization, and how molecular regulators of cell polarity control tissue homeostasis and skin cancer. Using mouse genetics and disease models, the scientists assess the impact of impaired cyto-architecture on oncogenic processes. Next to elucidating basic principles of cancer biology, a major goal is to develop new diagnostic and therapeutic approaches to skin cancers and eventually other types of cancer.

Our research: The Iden laboratory studies the phenomenon of cell polarity. The team aims to decrypt how cell polarity is regulated during the development and homeostasis of epithelial tissues, as well as in pathological conditions of the skin. For this, different in vivo and in vitro models are applied to manipulate polarity signaling and to assess the consequences on cell architecture, skin homeostasis, regeneration, and cancer.

Our successes: Using animal disease models, the team has shown that altered expression of polarity proteins impacts on the development and progression of different epidermal skin cancers. The group established a novel mouse tumor model for investigation of a common skin tumor relevant to human pathology. This and other models now serve to identify molecular mechanisms underlying tumor formation and to develop new therapeutic strategies for skin cancer patients.

Our goals: Current efforts aim at the identification of molecular mechanisms that link cell polarization, growth and differentiation, in the context of a functional skin barrier and various types of skin cancer. Different disease models are used to unravel potential similarities and differences in the way polarity signals contribute to specific skin tumors, and results are compared with normal and malignant human tissues. The aim is to resolve molecular processes that drive skin cancer and to identify new translational approaches to skin cancer diagnosis and therapy.

Our methods/techniques: We combine various in vitro techniques with analysis of genetic mouse models. Simplified, easy-to-manipulate cell culture systems serve for the initial investigation of molecular and cellular processes, as well as oncogenic signaling. Data are then translated into animal (disease) models to test their physiological relevance. Close collaboration with clinician scientists is crucial to connect the findings to human disease. The combination of protein biochemistry, cell culture assays, mouse models, and patient material, will deliver new insights into the role of cell polarity in mammalian tissue homeostasis and disease.

PUBLICATIONS

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CECAD COOPERATIONS

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Principal Investigator

F Prof. Dr. C. Niessen → p. 193
Principal Investigator

C Prof. Dr. C. Reinhardt → p. 103
Principal Investigator

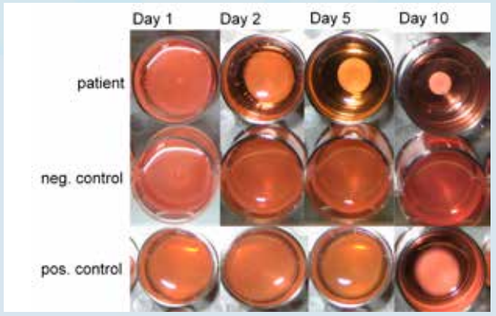
E Prof. Dr. M. Uhlirova → p. 159
Principal Investigator

EXTERNAL COOPERATIONS

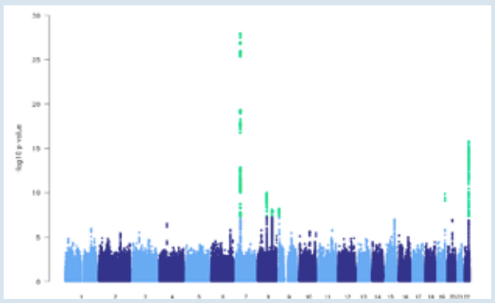
PD Dr. P. Brinkkötter, Prof. Dr. S. Eming,
PD Dr. L. Heindl, Prof. Dr. D. Mörsdorf,
PD Dr. C. Niemann, Dr. S. Schlereth, Cologne, DE
Prof. Dr. T. Tüting, Bonn, DE

E

Die Dupuytrensche Kontraktur zählt zu den häufigsten genetischen Erkrankungen des Bindegewebes in Nordeuropa. Prof. Dr. Peter Nürnberg erforscht mit seiner Arbeitsgruppe die genetischen Ursachen und Mechanismen dieser Erkrankung.



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FIGURE 1: Contraction of fibroblast populated 3-dimensional collagen gels monitored over 10 days. Gel contraction for one patient and one control (normal human fibroblasts) is shown. Patient cells rapidly contract the collagen gel visibly already at day two. The former attached gel detaches itself from the well wall within 24 hours. Control gels detach only after several days, while gels without cells (neg. control) do not contract.
FIGURE 2: Manhattan plot of the GWAS meta-analysis for Dupuytren's disease (N = 5803). The plot shows -log10-transformed P-values for all SNPs (N = 4,350,741). SNPs depicted in green surpass the genome-wide significance level of P<5x10-08.



↗ http://cecad.uni-koeln.de/Prof-Peter-Nuernberg.81.0.html

Prof Dr. Peter Nürnberg

Principal Investigator
Cologne Center for Genomics (CCG)

Dupuytren's contracture (DC) is one of the most common genetic disorders of connective tissue. Prof. Dr. Peter Nürnberg and his team are looking at the pathogenetic mechanisms that lead to the development of this condition. Genome-wide association studies have enabled them to identify variants in nine different gene loci that are associated with the occurrence of the disease.

Our research: Dupuytren's contracture is a multifactorial disease whose causes include genetic variation, cell stress, and inflammatory activity. Prof. Nürnberg's research group is focusing on identifying the many genetic variants that are associated with DC.

Our successes: In a genome-wide association study (GWAS), the team has been able to identify nine significant gene loci that are associated with the onset of DC. Six of these regions contain genes that code for Wnt signaling components. These findings may provide evidence concerning the pathological mechanisms responsible for Dupuytren's contracture.

Our goals: Prof. Peter Nürnberg and his team are looking for functional pathogenetic variants related to the associated gene loci. Their aim is to identify coding and regulatory genetic variants that underlie the GWAS signals. Research is currently focused on direct sequencing of the GWAS region and aimed at the evaluation of the relevance of the identified variants.

Our methods/techniques: The research group has developed methods to determine the contractility of myofibroblasts under various conditions. In this way, age-associated and stress-induced changes can be characterized and distinguished to give a better understanding of the pathology of DC and other fibrotic diseases.

PUBLICATIONS

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CECAD COOPERATIONS

E Prof. Dr. T. Krieg → p. 143
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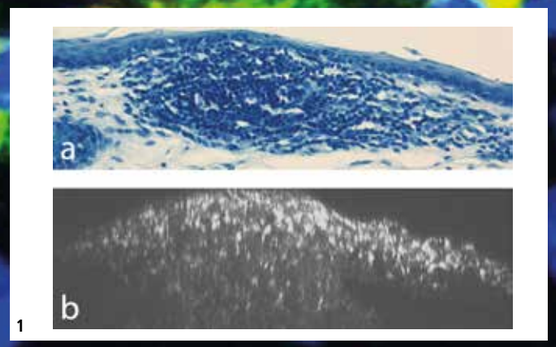
C Prof. Dr. A. A. Noegel → p. 121
Principal Investigator

C Prof. Dr. B. Wollnik → p. 123
Principal Investigator

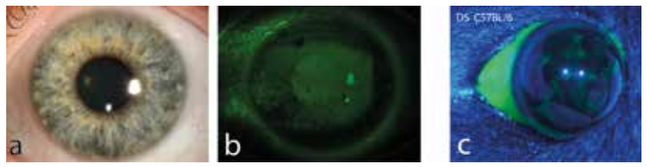
EXTERNAL COOPERATIONS

Prof. Dr. R. Fodde, Erasmus University Medical Center Rotterdam, NL
Prof. Dr. B. Hinz, Laboratory of Tissue Repair and Regeneration, University of Toronto, CA
Prof. Dr. A. Jackson, Institute of Genetics and Molecular Medicine, University of Edinburgh, UK
Dr. S. Sakakibara, Faculty of Human Sciences, Waseda University, Tokorozawa, JP
Prof. Dr. med. S. Tinschert, Medizinische Universität Innsbruck, AT
Prof. Dr. C. Wijmenga, Dept Genetics (MGE), UMCG, Groningen, NL

Viele Menschen leiden unter trockenen Augen. Warum dieses Symptom im Alter gehäuft auftritt, ist noch nicht verstanden. Neben saisonalen, pollenbedingten Allergien leiden Patienten auch unter ganzjährigen okulären Allergien, die mitunter das Sehvermögen bedrohen. Die Arbeitsgruppe von PD Dr. Philipp Steven erforscht das im Alter abnehmende lymphatische Gewebe im Auge, das mit dieser Erkrankung assoziiert ist.



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BACKGROUND FIGURE: Immunohistochemistry of Antigen-presenting cells within Conjunctiva-associated lymphoid tissue (CALT). CALT is thought to play a role in regulating ocular surface immune responses in diseases such as dry-eye, thus serving as a target tissue for novel therapeutic strategies.
FIGURE 1: Conjunctiva-associated lymphoid tissue (CALT) a: histological section of the lymphoid follicle, b: intravital two-photonmicroscopy based on tissue autofluorescence of the corresponding region. Individual cells are visible without the use of artificial dyes.
FIGURE 2: Clinical phenotype of dry-eye disease: a+b female patient with dry-eye due to Sjögren Syndrome. a: The eye appears almost normal in white light illumination. b: using fluorescent dye staining of the cornea and an irregular tearfilm is visible, causing pain and visual distortion. c: a mouse model of dry-eye shows a similar phenotype with staining of the ocular surface.



↗ http://cecad.uni-koeln.de/Dr-Phillip-Steven.340.0.html

PD Dr. Philipp Steven

Principal Investigator
CECAD Cologne

PD Dr. Philipp Steven's group investigates the pathomechanism of dry eye disease. Their goal is to understand the relationship between this inflammatory disease and aging-associated changes in the immune regulation of the eye's conjunctiva-associated lymphoid tissue (CALT) in order to be able to exploit this therapeutically.

Our research: The focus of research is the eye's conjunctiva-associated lymphoid tissue (CALT), a key structure in the pathogenesis of dry eye disease. The group investigates the role of the body's own immune regulation of T cells, dendritic cells and macrophages in the development of this disease and how these immune mechanisms may be put to therapeutic use. Therapeutic approaches using immunosuppressants are already being tested in clinical trials.

Our successes: The scientists were the first to systematically describe the lymphoid tissue CALT in a mouse model. Establishing dye-free two-photon microscopy for intravital imaging of the eye was another important achievement. Since the eye cannot be biopsied, this non-invasive method is crucial for grading, quantifying and characterizing inflammatory processes in the eye by discriminating between macrophages and lymphocytes, and active and inactive cells.

Our goals: Ultimately PD Dr. Steven and his group plan to establish one of the leading research sites for dry eye disease. The animal models established at the Eye Hospital are internationally competitive. The next goal is to test more therapeutic substances in the context of aging processes in CALT.

Our methods/techniques: The group works with cell and organ cultures and complex intravital imaging methods. Molecular biology methods are currently being established. Mouse models are used to investigate specific research questions. Successful approaches are transferred to clinical testing.

PUBLICATIONS

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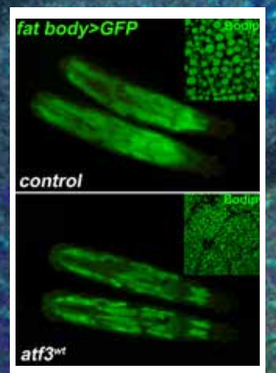
CECAD COOPERATIONS

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Principal Investigator

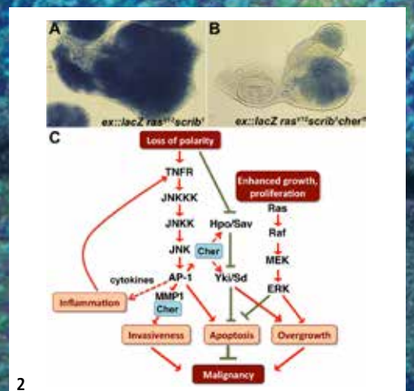
EXTERNAL COOPERATIONS

Prof. Dr. T. Hucho, University Hospital Cologne, DE
Prof. Dr. J. Niederkorn, UT Southwestern Medical Center, Dallas, TX, USA
Dr. M. Stern, Biological Sciences, Allergan Inc., Irvine, CA, USA

Gemeinsam mit ihrer Arbeitsgruppe erforscht Prof. Dr. Uhlirova die Bedeutung von Stress-Signalen in der Erhaltung der Homöostase und der Entstehung von Erkrankungen. Anhand des Modellorganismus *Drosophila melanogaster* gelang es ihnen u.a. einen Schlüsselfaktor für die Homöostase des Stoffwechsels und der angeborenen Immunität zu identifizieren. Zukünftig wollen sie weitere Faktoren entdecken, die in der Regulation des Wachstums, der Zellproliferation oder des Zelltods eine Rolle spielen.



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FIGURE 1: Fat body-specific gain of Atf3 produces lean larvae whose fat body cells are filled with smaller lipid droplets compared to control (insets).
FIGURE 2: Loss of mechanical tension due to deficiency of the actin cross-linking protein Filamin/Cheerio causes downregulation of the Yorkie target gene expression as measured by the *expanded::lacZ* reporter activity (blue), in mosaic *ras*^{V12} *scrib*$^{-}$*cher*$^{-}$ imaginal discs compared to those bearing fully malignant *ras*^{V12} *scrib*$^{-}$ clonal tumors. Model summarizing pleiotropic functions of JNK signaling in malignant tumors induced by Ras activation and polarity loss. Our data show that JNK promotes malignancy downstream of disturbed polarity by modulating tumor microenvironment (MMP1), tumor stiffness and survival (Cher).



↗ http://cecad.uni-koeln.de/Prof-Mirka-Uhlirova.111.0.html

Prof. Dr. Mirka Uhlirova

Principal Investigator
Institute for Genetics

The Uhlirova laboratory uses the powerful genetic model of Drosophila melanogaster to understand how signaling pathways cooperate to ensure homeostasis at the cellular, tissue and whole-body level during normal development and under stress conditions. The group investigates how defects in signaling and regulatory circuits give rise to developmental abnormalities or disease states such as cancer and neurodegeneration.

Our research: The Uhlirova laboratory aims to understand the role of stress signaling in development, homeostasis, and disease states such as cancer and degenerative disorders. Using the relatively simple, yet relevant *Drosophila* model, the team focuses on characterizing the interplay between stress signaling modules and transcription factor networks. In particular, they are interested in determining how developmental and stress signals are translated into meaningful, context-specific responses via the regulation of target gene expression.

Our successes: The team identified the evolutionary conserved bZIP transcription factor Atf3 as a key regulator of metabolic and innate immune homeostasis. Using an established *Drosophila* epithelial tumor model, the group linked the aberrant activity of stress-inducible JNK signaling to enhanced invasiveness of tumors arising from oncogenic Ras activity and disrupted cell polarity. The JNK pathway promotes tumor malignancy through alteration of actin cytoskeleton dynamics and disruption of tissue architecture, highlighting the imapct of tissue mechanics in tumorigenesis. Lastly, the team discovered that the evolutionary conserved protein Ecdysoneless (Ecd) exerts an essential growth function by mediating pre-mRNA splicing.

Our goals: Current research projects attempt to dissect the role of stress signaling pathways and downstream transcription factors (TFs) in the regulation of growth, proliferation, cell death and cell migration. the group concentrates on functional characterization of individual TFs and TF networks downstream of stress-activated MAPK kinase signaling in the process of epithelial morphogenesis, tissue regeneration, wound healing, and tumorigenesis. Further, they explore a link between cellular stress induced by aberrant pre-mRNA splicing, cancer development, and neurodegeneration. Unraveling the molecular mechanisms that orchestrate stress responses is crucial for understanding normal physiology, diseases, and aging.

Our methods/techniques: The scientists take advantage of the genetic accessibility of the *Drosophila* model that facilitates gene discovery, in vivo analysis of gene function and gene interactions. To gain mechanistic insights into a relationship between pathways and their components the scientists combine genetics with cell and molecular biology techniques, biochemistry, and genomic approaches. Collaborations with mouse and human geneticists are crucial to translate their findings to the context of human physiology and diseases.

PUBLICATIONS

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CECAD COOPERATIONS

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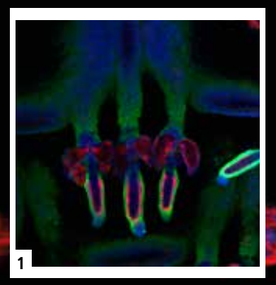
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Dr. D. Stanek, IMG AS CR, Prague, CZ
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Prof. Dr. B. Wirth, University of Cologne, DE

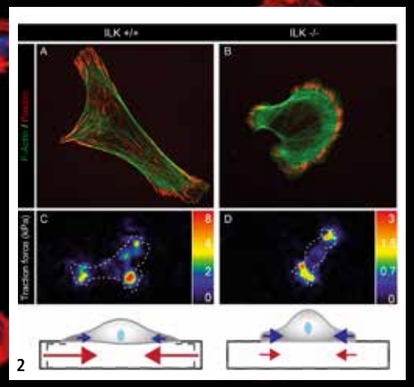
E

Umwelteinwirkungen lösen in der Haut fortwährend Regenerations- und Differenzierungsprozesse aus. Die Arbeitsgruppe um Dr. Sara Wickström erforscht, wie Stammzellen die Erhaltung der Haut als sich selbst ständig erneuerndes Organ ermöglichen, wie diese Prozesse gesteuert werden, sich im Alter verändern und wie in diesem Kontext die Entstehung von z.B. Hautkrebs begünstigt wird.

BACKGROUND FIGURE: Engineering micropatterned surfaces to study stem behavior. To understand how cell density, size and shape affects stem cell behavior, special micropatterned adhesion surfaces can be engineered. The surfaces restrict the adhesive area of the cells, thereby forcing them into a specific shape or density, in this case 30 µm-sized circles. The actin cytoskeleton has been labeled red and nuclei in blue.



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FIGURE 1: Immunofluorescence staining of mouse hair follicle stem cells. Stem cells of the skin and hair follicles (red) are critical for the maintenance and regeneration of the tissue. An important question is how stem cells interact with their environment and how these interactions affect stem cell function and therefore impact tissue regeneration and ageing.

FIGURE 2: Cells sense their environment by generating forces on the surrounding extracellular matrix.
(A) Immunofluorescence staining of the actin cytoskeleton (green) and cell adhesion complexes (red).
(B) A heat-scale map of forces generated by a skin fibroblast on the extracellular matrix. Gene deletion of the adhesion complex component Integrin-linked kinase (ILK -/-) impairs the ability of cells to organize their cytoskeleton and to generate forces (C).



↗ http://cecad.uni-koeln.de/Dr-Sara-Wickstroem.325.0.html

Dr. Sara Wickström

Principal Investigator
Max Planck Institute for Biology of Ageing

The skin is a self-renewing organ constantly exposed to environmental influences, such as injury, UV rays and toxic substances. To maintain a functional tissue, stem cells differentiate to replace cells that are lost through damage or normal turnover. The group led by Dr. Wickström works to identify mechanisms that regulate stem cell differentiation. The central focus is on characterizing fundamental mechanisms of this process and in understanding why skin loses regenerative power as we age, and how stem cell dysregulation promotes the genesis of skin cancer.

Our research: Due to its self-renewing nature skin is optimally suited for stem cell research. Stem cells play key roles in replenishing tissues with differentiated cells that are lost during homeostatic renewal or during injury. Furthermore, stem cell dysfunction leads to tissue degeneration, aging and cancer. Therefore, understanding how stem cells function is critical for understanding how these diseases develop and how they might be treated. The research group led by Dr. Sara Wickström focuses on understanding these processes in detail.

Our successes: Dr. Wickström and her group have shown how the local microenvironment of the stem cells affects their behavior, and its importance for maintaining the stem cell population during aging and for protecting the tissue from cancer. The group has successfully decoded the molecular basis for this process. The scientists are collaborating on translational projects on skin cancer by studying human tumor samples. In another project the group discovered a mechanism by which cells deposit connective tissue. This mechanism is important also in fibrosis, a disease where connective tissue is produced in excess. Therefore this mechanism could be exploited to treat these patients.

Our goals: In future, the research group will focus on more detailed understanding of stem cell regulation in the skin. In addition the group hopes to be able to test some approaches in clinical trials, in particular for treating fibrosis. For this Dr. Wickström and her team work together with Prof. Krieg from the Department of Dermatology, who heads the national network for systemic sclerosis, a severe form of fibrotic disease.

Our methods/techniques: The scientists apply a combination of mouse genetics and cell biology in the following three main areas: (1) mechanisms of force generation in matrix remodeling and tissue repair, (2) role of cell-matrix interactions in stem cell fate, carcinogenesis and aging, and (3) mechanotransduction in skin homeostasis and aging.

PUBLICATIONS

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Zanivan S, Meves A, Behrendt K, Schoof EM, Neilson LJ, Tang HR, Cox J, van Ree JH, van Deursen JM, Trempus CS, Machesky L, Linding R, Wickström SA, Fässler R, Mann M. (2013) In vivo SILAC-based proteomics reveals phosphoproteome changes during mouse skin carcinogenesis. Cell Reports. 21, 552-66.

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CECAD COOPERATIONS

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Obesity

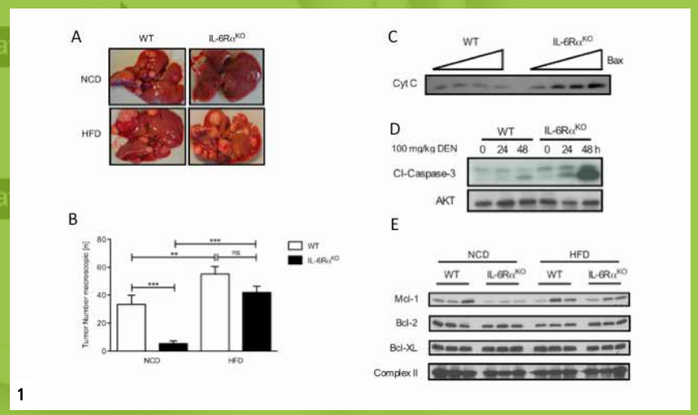
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PD Dr. Thomas Wunderlich und seine Arbeitsgruppe erforschen die Interaktion von chronischen Entzündungen und der Entstehung von Krebs. Im Fokus stehen der Krankheitsverlauf von Leber- und Darmkrebs unter adipösen Bedingungen. Ein wissenschaftlicher Durchbruch gelang PD Dr. Wunderlich mit der Darstellung der Bedeutung von Interleukin 6 für die Leberkrebsentwicklung.

Mcl-1

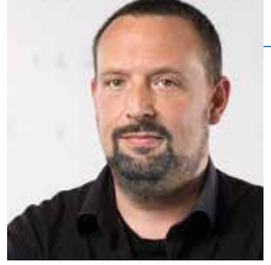
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CytC



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FIGURE 1: Obesity promotes HCC development via Mcl-1 stabilization independent from IL-6Rα signaling. (A) Livers of 8-mo control and IL-6Rαxo mice injected with 25 mg/kg DEN at 15 days of age. (B) Quantitation of macroscopic tumor multiplicity determined by visual inspection in DEN-injected 8-mo control and IL-6Rαxo mice (n=15). (C) Cytochrome C release of isolated mitochondria after treatment with increasing concentrations of recombinant Bax. Mitochondria were isolated from naive 8-wk control and IL-6Rαxo mice fed a NCD. (D) Western blot analysis using cleaved caspase 3 and AKT antibodies on liver tissue from 8-wk control and IL-6Rαxo mice fed on a NCD sacrified at the indicated time points after a 100 mg/kg DEN injection. (E) Western blot analysis using Mcl-1, Bcl-2, Bcl-XL and Complex II antibodies on isolated mitochondria from DEN-injected 8-mo control and IL-6Rαxo mice.



↗ http://cecad.uni-koeln.de/Dr-Thomas-Wunderlich.117.0.html

PD Dr. Thomas Wunderlich

Principal Investigator
MPI for Metabolism Research

PD Dr. Thomas Wunderlich and his working group explore the interaction between chronic inflammation and carcinogenesis. They focus on the progression of liver and colorectal cancers under obese conditions. PD Dr. Wunderlich's scientific breakthroughs have included demonstrating the importance of interleukin 6 in liver cancerogenesis.

Our research: The human immune system combats not only invaders such as viruses and bacteria with an inflammatory response, but also tumors have been shown to be attacked by the immune system. Immunological tolerance develops when inflammation switches from acute to chronic conditions. Thus, the immune system can no longer attack tumor cells; they proliferate and can trigger cancer cell progression. The working group investigates the interaction between chronic inflammation associated with obesity and carcinogenesis in the liver and colon. Chronic inflammation plays a central role in these cancer entities as inflammatory mediators such as interleukin 6 promote the development of cancer in chronic inflammatory environments.

Our successes: In 2013 PD Dr. Wunderlich and his group enjoyed a scientific breakthrough when they decoded the importance of interleukin 6 in liver cancer development. In lean mice, IL-6 signaling is necessary to promote liver cancerogenesis via Mcl-1 stabilization, whereas in obese mice Mcl-1 stabilization occurs independnet of IL-6Rα signaling. Here, another yet to be identified factor that compensates in obesity for IL-6Rα deficiency activates similar signaling pathways that promote HCC development. Thus, identifying this factor might help to combat this often fatal disorder.

Our goals: In addition to promoting cancer, interleukin (IL) 6 and other inflammatory mediators also have beneficial metabolic characteristics for the human body. The research team aims to understand why IL 6 helps the body during acute inflammation, but has a negative effect under chronic inflammatory conditions.

Our methods/techniques: In addition to modern mouse genetics, PD Dr. Wunderlich and his group use metabolic as well as immunological methods including FACS analysis (fluorescence activated cell sorting).

PUBLICATIONS

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Mauer J, et al. (2014) Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. Nat Immunol. May;15(5):423-30.

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CECAD COOPERATIONS

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F Prof. Dr. J. C. Brüning → p. 169
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D PD Dr. H. Kashkar → p. 133
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Prof. Dr. K. Rajewsky, MDC Berlin, DE
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Prof. Dr. A. Waisman, Institute for Molecular Medicine Mainz, DE

F

Warum entsteht Hunger im Gehirn? Auch Fettleibigkeit und Diabetes sind von neuronalen Schaltprozessen abhängig. Der Forschungsbereich F erforscht metabolische Signalwege, d.h. die Stoffwechselprozesse, die durch Nahrungsaufnahme und Energieverbrauch reguliert werden. Diese Signalwege haben in der Entstehung altersassoziierter Erkrankungen eine komplexe Funktion.

Research Area F
Metabolism in Aging Processes, Diabetes and Obesity

Why is the sensation of hunger generated in the brain? Obesity and diabetes depend on neuronal signaling processes. Research Area F explores metabolic signaling pathways, those metabolic processes that regulate food intake and energy expenditure. These signaling pathways play a complex role in the genesis of aging-associated diseases. The TOR signaling network pass on metabolic signals. They play a key role in the development, growth, stress resistance, fertility, and aging process in human beings and so-called model organisms such as worms and flies.

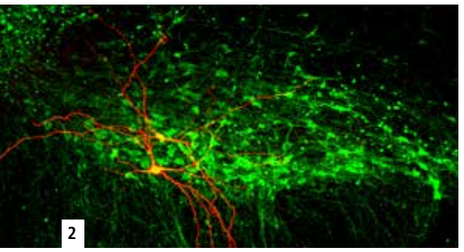
Processes like insulin signaling cascades are crucial for regulating lifespan. Lower signal activity in this metabolic signaling network can increase longevity, improve function and health during aging, and protect from aging-associated diseases such as diabetes. In contrast, altered insulin signaling can also lead to obesity and type 2 diabetes mellitus (T2DM).
Many molecules in the insulin/insulin-like growth factor/TOR signaling networks are potential drug targets. Indeed rapamycin, an effective and specific inhibitor of the kinase enzyme from the TOR network, prolongs the life of fruit flies and mice.

It is therefore essential to identify the exact changes in signalling, gene expression and physiology that promote health and minimise side effects. The central nervous system (CNS) plays a key role in the regulation of the peripheral metabolism. Determining these active mechanisms and identifying other peripheral tissue that further processes and conveys metabolic signals will lead to new drugs.

Here CECAD has derived research projects in three areas:
1. System biology in the metabolic signaling processes
2. Neuronal circuits and metabolic signaling processes
3. New (non-standard) types of tissue as targets for metabolic signaling processes

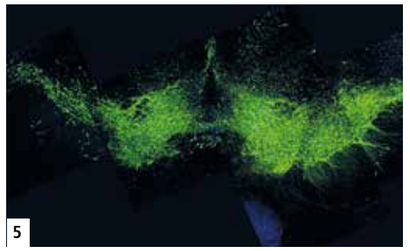
CECAD's research is highly socially relevant. Obesity is on the rise in Western cultures where around 30% of the population is affected. Excess fat and weight are directly linked to the genesis of insulin resistance and as such type 2 diabetes, diabetic complications and a range of skin problems, which come at a high cost to society.


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BACKGROUND FIGURE: Unraveling metabolism in aging, diabetes, obesity: The human brain plays a crucial role in metabolic signaling leading to aging-associated diseases.
FIGURE 1: Important diagnostic: Magnetic Resonance Imaging
FIGURE 2: How does the reward circuitry work? What are the characteristic features of the nerve cells involved? Researchers at CECAD locate individual nerve cells and use techniques such as patch-clamp recordings to study their properties (shown here in the picture).
FIGURE 3: In the laboratory *Drosophila melanogaster* is kept in vials.
FIGURE 4: What is measured on an MRI? The human brain and its structure can be viewed under MRI. With the aid of a functional scanner, it is also possible to measure brain activity, e.g. in the reward center.
FIGURE 5: Focusing on neurons.
Antibody staining of dopamine-secreting nerve cells of the midbrain – some of them are part of the limbic reward center (shown here in green).
FIGURE 6: A fruit fly *(Drosophila melanogaster)* on a grape (picture by courtesy of Sebastian Grönke).

PRINCIPLE INVESTIGATORS MAIN FOCUS

Prof. Dr. J. C. Brüning → p. 169
Prof. Dr. L. Partridge → p. 173
Prof. Dr. A. Antebi → p. 177
Prof. Dr. Dr. P. Nicotera → p. 181
Prof. Dr. A. Beyer → p. 185
Prof. Dr. Hammerschmidt → p. 187
Prof. Dr. P. Kloppenburg → p. 189
Dr. J.-W. Kornfeld → p. 191
Prof. Dr. C. Niessen → p. 193
Prof. Dr. M. Paulsson → p. 197
Dr. A. Rada-Iglesias → p. 199

F

Um ein konstantes Körpergewicht aufrecht zu erhalten, steuert das Gehirn komplexe Prozesse, die die Gewichtszunahme oder den Gewichtsverlust regulieren. Die Forschungsgruppe von Prof. Dr. Jens Brüning untersucht, wie dieses Netzwerk im Detail funktioniert und wie aus einer Fehlregulation Volkserkrankungen wie z.B. Übergewicht und Diabetes mellitus entstehen können. Langfristig zielt seine Forschung darauf ab, neue Therapien für diese gesellschaftlich relevanten Erkrankungen zu generieren. Wissenschaftliche Durchbrüche waren u.a. die Identifizierung der neuronalen Regulation der Aufnahme und des Verbrauchs von Energie und die Entschlüsselung eines Gens, das essentiell die Entstehung von Übergewicht steuert.



↗ http://cecad.uni-koeln.de/Prof-Jens-C-Bruening.75.0.html

Prof. Dr. Jens C. Brüning

CECAD Coordinator – Head of Research Area F
Principal Investigator – MPI for Metabolism Research

Brüning's group explores how the central nervous system regulates food intake and influences energy availability in the body. Altered metabolism can trigger diseases like obesity and diabetes mellitus. The team of scientists led by Prof. Dr. Brüning has succeeded in identifying groups of nerve cells in the brain that control energy homeostasis and in revealing the role of the FTO gene, which is strongly associated with obesity. The group's goal for the future is to deepen our understanding of the control processes the brain uses to integrate the complex impulses that govern our eating behavior.

Our research: Depending on the body's energy stores, the brain regulates nutrient intake as well as energy and sugar metabolism in the body. It coordinates processes in adipose tissue, skeletal muscle, liver and pancreas, that together form a complex system. Dysregulation of this system can trigger diseases like obesity and diabetes, highly relevant to today's society by virtue of their prevalence.
The group led by Prof. Brüning is currently pursuing two research approaches in this area. The team is aiming to understand the neuronal control of the regulatory mechanisms by exploring both the connections between neurocircuits in the brain, and the effect their activity has on human eating behavior and motivation. In addition, the scientists are exploring how these processes deregulated patients who already suffer from a metabolic disorder. The working group hopes to thus decode the fundamental mechanisms behind the normal control as well as alteration in energy homeostasis.

Our successes: In recent years, Prof. Brüning and his team have made a considerable contribution to identifying the neurocircuits in the brain that regulate energy balance. This not only opens up new insights into the regulation of the cells activity in a physiological state, but also enables the scientists to identify signals that lead to the dysregulation of behavior in overweight people. Additionally, the working group has succeeded in decoding the function of the so-called FTO gene. Variations in the FTO gene are strongly associated with obesity in human beings. Experiments have shown that this gene controls the regulation of reward behavior in mice. The researchers' new findings indicate that the gene variations that trigger obesity in humans also produce a change in reward behavior and the regulatory nerve cells.

Our goals: The long-term goal of Prof. Brüning and his scientific team is to understand in detail how fundamental regulatory principles for food intake in the brain are linked to higher brain functions like emotions, or the smell and appearance of a particular food. The integration of all this information leads to the decision about when one eats – and what one eats – and as such whether one becomes overweight. These findings could have a decisive influence on developing new therapeutic approaches to obesity and diabetes mellitus.

Our methods/techniques: Prof. Brüning's group uses mouse models in its basic research to unravel the regulatory mechanisms. The ultimate goal is to translate their findings to humans. Model organisms allow targeted neurocircuits to be stimulated, so scientists can observe the effects on behavioral patterns and metabolic processes. Researchers also use the animal models to validate imaging techniques such as MRI (magnetic resonance imaging) and PET (positron emissions tomography). These non-invasive methods can then be used in the next step: designing clinical trials.

CECAD COOPERATIONS

F Prof. Dr. P. Kloppenburg → p. 189
Principal Investigator

A Prof. Dr. T. Langer → p. 59
Principal Investigator

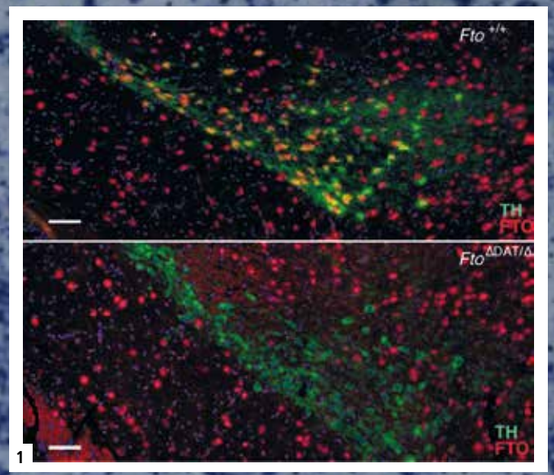
F Prof. Dr. L. Partridge → p. 173
Principal Investigator

EXTERNAL COOPERATIONS

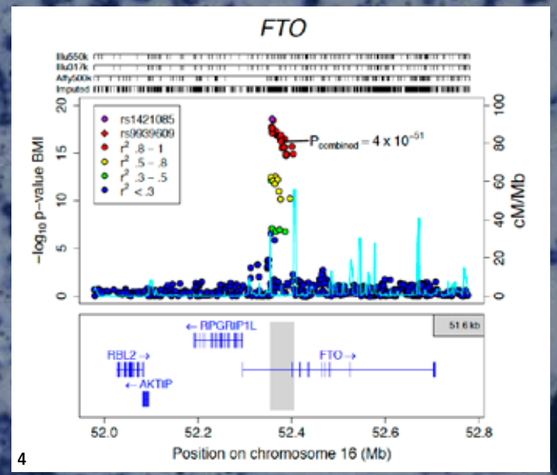
Prof. Dr. T. Horvath, Yale University, USA
Prof. Dr. C. R. Cohn, Harvard Medical School, USA

Prof. Dr. Jens C. Brüning
CECAD Coordinator
Head of Research Area F
Principal Investigator
MPI for Metabolism Research

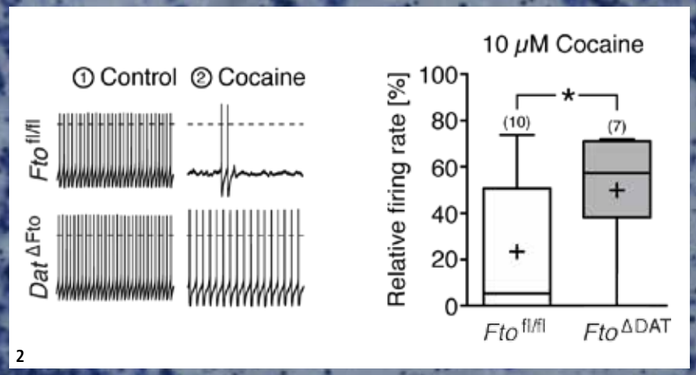
FIGURE 1: Fluorescent staining of a marker for dopaminergic neurons and Fto. Midbrain dopaminergic neurons were stained in FtoΔDAT/Δ and Fto+/+ mice using an antibody directed against the tyrosine hydroxylase (TH, green), a marker for dopaminergic neurons in the midbrain. Further labeling of FTO (red) revealed the absence of FTO in dopamine neuron restricted Fto knock out mice.
FIGURE 2: Effect of cocaine on control and FtoΔDAT DA neurons.
FIGURE 3: Reversible N6-methyladenosine modification. FTO demethylates N6-methyladenosine (m6A) in mRNA (Gerken et al., 2007), thereby presumably playing a role in mRNA processing.
FIGURE 4: Genome wide association studies link FTO to obesity. A cluster of single nucleotide polymorphisms (SNPs) within the first intron of the human FTO gene is significantly associated with increased BMI. Figure adapted from Willer et al. [2009]



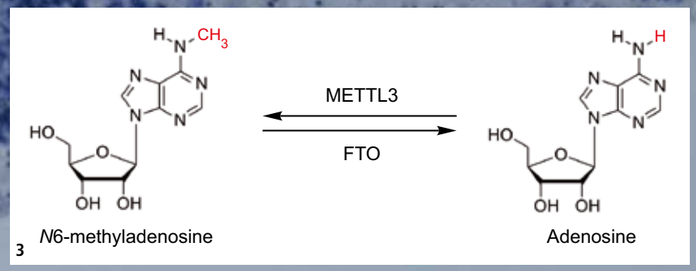
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PUBLICATIONS

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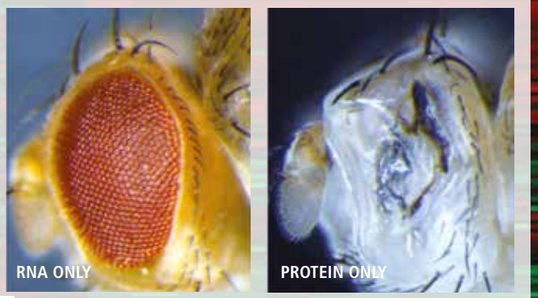
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Klöckener T, Hess S, Belgardt BF, Paeger L, Verhagen LA, Husch A, Sohn JW, Hampel B, Dhillon H, Zigman JM, Lowell BB, Williams KW, Elmquist JK, Horvath TL, Kloppenburg P, Brüning JC. (2011) High-fat feeding promotes obesity via insulin receptor/PI3K-dependent inhibition of SF-1 VMH neurons. Nat Neurosci. Jun 5;14(7):911-8.

Das Forschungsteam um Prof. Dr. Linda Partridge erforscht Mechanismen des Alterungsprozesses. Ein Schwerpunkt bildet dabei der Einfluss, den die Nahrung auf den Alterungsprozess hat und wie bestimmte Diäten einen positiven Effekt auf Lebenszeit und die Gesundheit im Alter ausüben. In diesem Zusammenhang spielen zentrale Signalwege wie z.B. der Insulin oder mTOR Signalweg eine wichtige Rolle und erlauben Einblicke in die molekularen Ursachen des Alterungsprozesses.



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FIGURE 1: *Drosophila* as a model organism to study motor neuron diseases. A hexanucleotide repeat expansion in the human C9ORF72 gene is a major risk factor for frontotemporal dementia and amyotrophic lateral sclerosis. Overexpression of C9orf72 hexanucleotide repeats in the *Drosophila* eye suggests that toxicity is caused by protein translated from the repeats, but not from the RNA itself.



↗ http://cecad.uni-koeln.de/Prof-Linda-Partridge.229.0.html

Prof. Dr. Linda Partridge

Head of Research Area F – Principal Investigator
Director of the Max Planck Institute for Biology of Ageing

A major focus of the research group led by Prof. Dr. Linda Partridge is to explore the effects of nutrition and nutrient-sensing signaling networks on the aging process. Insulin, insulin-like growth factor (IGF), and mTOR (the mechanistic target of rapamycin) signaling are central areas of interest, and they provide information about nutrients, stress and growth factors, and regulate gene expression to match costly activities such as growth, metabolism, and reproduction, to current circumstances. An exact understanding of this network provides hints for identifying appropriate targets that might be responsive to new medications to improve health during aging. This would open new preventative options for aging-related diseases for which we have no effective substances to slow their progression, such as amyotrophic lateral sclerosis (ALS), a motor neuron disease, and Alzheimer's Disease.

Our research: Decoding the network of central signaling pathways for insulin, insulin-like growth factor and mTOR opens new options and targets for medical intervention and might contribute to improved health during aging. Metabolic disorders in particular, such as diabetes mellitus type II, result from dysregulation within this network. Other aging-associated diseases, such as Alzheimer's and amyotrophic lateral sclerosis (ALS), are also associated with these dysfunctions.
The signaling networks have extensive inputs and feedbacks, and can also act systemically to affect other tissues in the body. This results in a complex system where intervention in one area sets off a reaction in others. A deeper understanding of the function of this network will provide answers about control of development, growth, reproduction and different types of stress responses that have an essential effect on metabolism and on the aging process.

Our successes: One of the research group's greatest successes is the discovery that the mechanisms of aging are evolutionarily conserved during evolution from worms to flies and mammals. Signaling pathways and networks can be modified in these animals, resulting in an extended lifetime and improved quality of life for the organism. These findings suggest that interventions into the insulin and TOR network may also be beneficial for human health and lifespan.
Through their research into age-related functional decline, Prof. Partridge and her team have demonstrated that low activity in the insulin signaling pathway is linked to an improved sleep quality at old age. With advanced age, people often fall asleep during the day but find it difficult to fall asleep and to stay asleep at night. This phenomenon has also been observed in fruit flies. Prof. Partridge's group was able to demonstrate that sleep quality of the fruit fly *Drosophila* is considerably improved by feeding Rapamycin, a drug that targets the mTOR signalling pathway. This finding could be applicable to humans and might contribute to improved sleep and consequently also quality of life with advanced age.

Our goals: A central objective of the research group led by Prof. Partridge is a comprehensive understanding of central signaling pathways, including the insulin, insulin-like growth factor and mTOR pathways.
The team also explores Alzheimer's and motor neuron diseases, and has successfully modified the fruit fly *Drosophila* with one of the most important genetic risk factors for motor neuron diseases. Describing the mechanisms that can trigger such illnesses under specific genetic preconditions allows possible points of attack for targeted medications to be identified. These findings are truly groundbreaking, as there are no curative therapeutic approaches to date. The team of scientists now plans to investigate these mechanisms further with the ultimate goal of revealing new treatment possibilities for patients suffering from motor neuron and other neurodegenerative diseases.

CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning – Principal Investigator → p. 169
B Prof. Dr. T. Hoppe – Principal Investigator → p. 89
F Prof. Dr. C. Niessen – Principal Investigator → p. 193

EXTERNAL COOPERATIONS

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Prof. Dr. J. Hardy, UCL, London, UK
Dr. A. Isaacs, UCL, London, UK
Prof. Dr. M. Leptin, EMBL Heidelberg & University Cologne, DE
Dr. M. Piper, UCL, London, UK
Prof. Dr. S. Pletcher, University of Michigan, USA
Prof. Dr. W. Reik, Cambridge, UK

F

Prof. Dr. Linda Partridge
Head of Research Area F
Principal Investigator
Director of the Max Planck Institute
for Biology of Ageing

Our methods/techniques: The scientists around Prof. Partridge work with model organisms like the fruit fly *Drosophila* and mice. They use genetics, behaviour assays, molecular biology and genome wide expression techniques to study the aging process. Their electrophysiological research methods on the fruit fly are unique at the institute to date.

PUBLICATIONS

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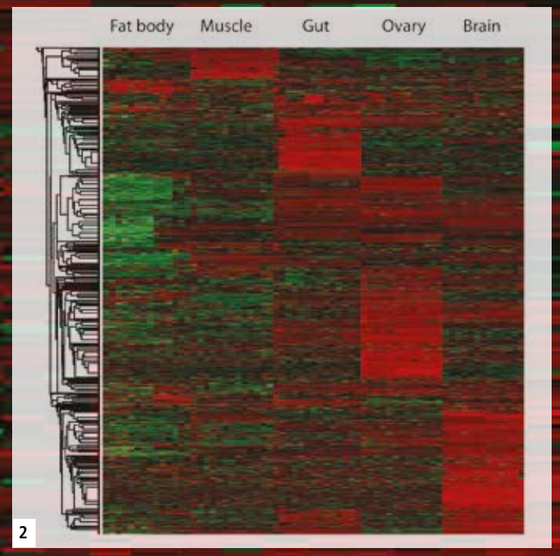
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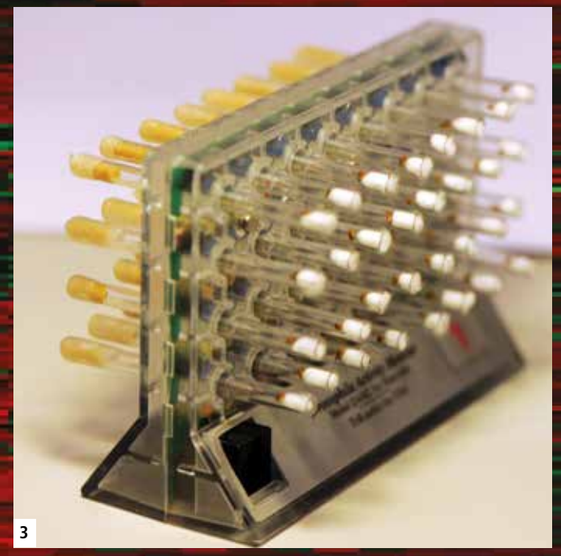
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Das Verständnis dieser zentralen Signalwege auf molekularer Ebene liefert wichtige Hinweise auf neue Medikamente, die zur Entwicklung von Therapien gegen altersbedingte Erkrankungen wie Typ II Diabetes, neurodegenerative Erkrankungen wie Morbus Alzheimer oder der bisher als unheilbar geltenden, amyotrophen Lateralsklerose, einer degenerativen Erkrankung des motorischen Nervensystems, genutzt werden können.

FIGURE 2: Heat map showing differential tissue specific proteomics of *Drosophila*. We detected approximately 6000 proteins in each tissue, revealing highly tissue specific expression profiles in response to reduced IIS.
FIGURE 3: *Drosophila* activity monitor. A *Drosophila* activity monitor allows measuring sleep parameters in fruit flies. Treatment of flies with Rapamycin, an inhibitor of the mTOR pathway, ameliorated the age-related decline in sleep quality.



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Prof. Dr. Adam Antebi und seine Arbeitsgruppe untersuchen, wie Gene und Umweltfaktoren die Lebensspanne von Tieren regulieren. Ihr Fokus liegt auf der Erforschung der molekularen Grundlagen, die diese Regulation der Lebensdauer von Organismen vermitteln und z. B. durch die Nahrungsaufnahme und das Fortpflanzungssystem beeinflusst werden. Sie konnten herausfinden, dass einzelne Gen-Mutationen, aber auch das Nährstoffniveau, die Gesundheit und Lebensdauer von Tieren deutlich verbessern, bzw. verlängern können. Langfristig hoffen die Forscher, ihre Erkenntnisse aus dem Fadenwurm auf den Menschen übertragen zu können, um neue Ansätze zur Therapie alternsbedingter Krankheiten zu finden.



↗ http://cecad.uni-koeln.de/Prof-Adam-Antebi.244.0.html

Prof. Dr. Adam Antebi

Principal Investigator
Director of MPI for Biology of Ageing

Prof. Dr. Adam Antebi's research group focuses on how evolutionarily conserved signal transduction pathways, hormonal mechanisms, and metabolism impact development and longevity in the nematode Caenorhabditis elegans. Such new insights into mechanisms that regulate lifespan may lead to innovative approaches to improve human health into old age.

Our research: Prof. Adam Antebi and his research team focus on the effects of the endocrine system and metabolism on development and life span. Using the nematode *C. elegans* as a model organism, they unravel the molecular mechanisms of how dietary restriction extends health and life span. They also investigate how hormonal signals from the reproductive system alter animal development and longevity. Finally they explore how metabolism and quality control mechanisms impact maintenance of cellular organelles and organismal survival. From a molecular perspective they examine the influence of steroids, insulins and micro-RNAs on animal longevity. Additionally they explore how activation of the hexosamine pathway and other metabolic pathways stimulate protein quality control, which protects cells within the organism from age-related proteotoxicity and neurodegeneration.

Our successes: Early work from Prof. Antebi's research group demonstrated that a steroid receptor in *C. elegans* regulates longevity in response to signals from the reproductive system. They further showed that these pathways also affect the organism´s developmental progression through its 4 larval stages, thus having broad spectrum effects on temporal control at all life phases. The signaling and metabolic inputs onto steroid receptor signaling and their downstream outputs are of great future interest. Furthermore, Dr. Antebi and his team discovered a critical link between steroid receptors and the FOXO transcription factor via let-7 microRNAs, revealing important crosstalk between these longevity factors. Most recently Prof. Antebi and his group have shown that activation of hexosamine metabolism and increased cellular concentration of the hexosamine metabolite N-acetylglucosamine enhances protein quality control. This increases lifespan and eliminates damaging protein aggregates that can act as triggers for neurodegenerative diseases.

Our goals: Future research in the Antebi laboratory will continue to have a focus on unraveling hormonal signaling pathways and downstream mechanisms that improve protein quality control, immunity, and metabolism. Moreover, Prof. Antebi and his team of scientists hope to manipulate the hexosamine pathway in order to stimulate protein quality control mechanisms and attenuate neurodegenerative diseases. If this should prove to be the case, their findings might provide a novel therapeutic approach for many neurodegenerative and aging-associated diseases.

Our methods/techniques: Prof. Antebi's laboratory uses genetics combined with biochemical, cell biological, microscopic, and demographic methods to reveal the functions of genes/pathways of their interest and their effects on lifespan. Additionally the scientists employ a systems biology approaches to uncover the global network of changes in the transcriptome and proteome.

CECAD COOPERATIONS

B Prof. Dr. T. Benzing → p. 85
Principal Investigator

F Prof. Dr. A. Beyer → p. 185
Principal Investigator

F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator

B Prof. Dr. T. Hoppe → p. 89
Principal Investigator

D Dr. N. Robinson → p. 135
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

A Prof. Dr. A. Trifunovic → p. 75
Principal Investigator

EXTERNAL COOPERATIONS

Dr. A. Hsu, University of Michigan, USA
Dr. C. Dietrivh, MPI-Age, DE
Dr. D. Mangelsdorf, UT Southwestern, USA
Dr. C. Murphy, Princeton University, USA
Dr. M. Pagano, NYU, HHMI, USA
Dr. F. Schroeder, Cornell University, USA

Prof. Dr. Adam Antebi
Principal Investigator
Director of MPI for Biology of Ageing

PUBLICATIONS

Horn M, Geisen C, Cermak L, Becker B, Nakamura S, Klein C, Pagano M, Antebi A. (2014) DRE-1/ FBXO11-dependent degradation of BLMP-1/BLIMP-1 governs *C. elegans* developmental timing and maturation. Dev Cell 28, 697-710.

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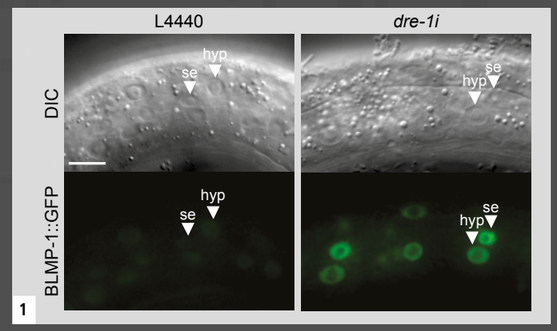
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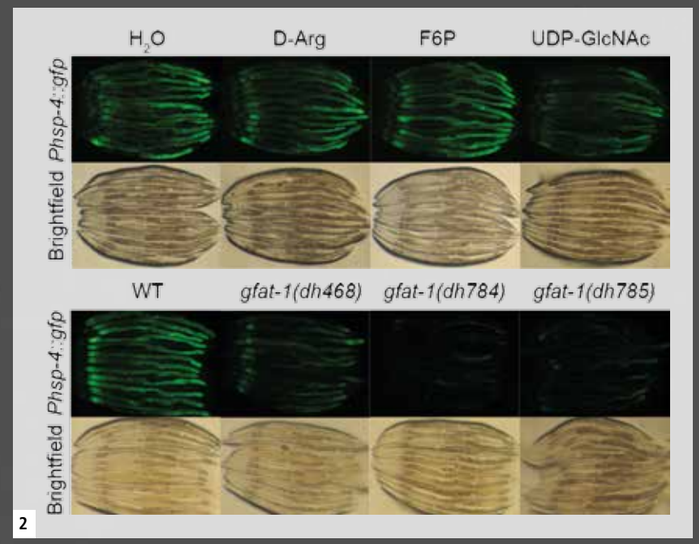
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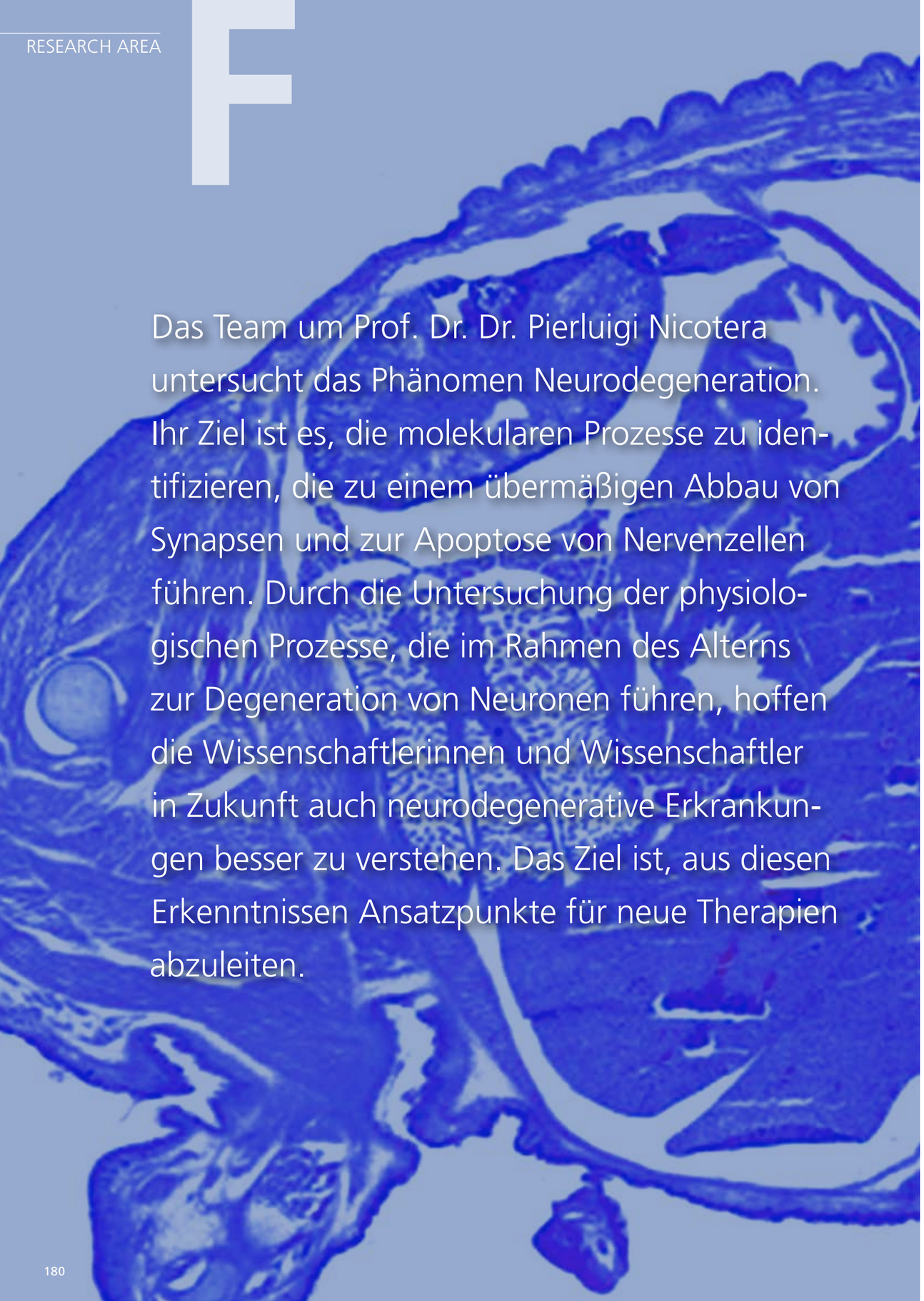
BACKGROUND FIGURE: Microscopic picture of *Caenorhabditis elegans* worm: Blue fluorescence marks the tissues expressing the enzyme GFAT, which is involved in the production of UDP-N-acetylglucosamine, a metabolite of the hexosamine pathway that can prevent toxic protein aggregation.

FIGURE 1: BLMP-1 regulates maturational events in various tissues. BLMP-1::GFP levels peak when epidermal stem cells, called seams, fuse together during a terminal differentiation event. DRE-1/FBXO11 is involved in degrading BLMP-1; upon dre-1/FBXO11 depletion, BLMP-1::GFP is elevated earlier in larval development. DIC and BLMP-1::GFP images of young wt L4 larvae.

FIGURE 2: Wild-type and gfat-1 gain-of-function mutants carrying a marker of ER stress, hsp-4::gfp, were exposed to tunicamycin. Supplementation with UDP-N-acetylglucosamine or presence of the gfat-1 gain-of-function alleles dh468, dh784, and dh785 significantly suppressed hsp-4::gfp induction (green fluorescence) because they neutralize ER stress induced by tunicamycin challenge.







Das Team um Prof. Dr. Dr. Pierluigi Nicotera untersucht das Phänomen Neurodegeneration. Ihr Ziel ist es, die molekularen Prozesse zu identifizieren, die zu einem übermäßigen Abbau von Synapsen und zur Apoptose von Nervenzellen führen. Durch die Untersuchung der physiologischen Prozesse, die im Rahmen des Alterns zur Degeneration von Neuronen führen, hoffen die Wissenschaftlerinnen und Wissenschaftler in Zukunft auch neurodegenerative Erkrankungen besser zu verstehen. Das Ziel ist, aus diesen Erkenntnissen Ansatzpunkte für neue Therapien abzuleiten.



↗ http://cecad.uni-koeln.de/Prof-Dr-Dr-Pierluigi-Nicotera.410.0.html

Prof. Dr. Dr. Pierluigi Nicotera

Scientific Director and Chairman of the Executive Board DZNE

Prof. Dr. Dr. Nicotera and his team are exploring the molecular mechanisms that trigger neurodegeneration. Their current research focus is the significance of microRNAs and mitochondrial DNA in the neuronal aging process and the development of aging-associated diseases. These scientists' goal is to identify the molecular processes that lead to the excessive degeneration of synapses and apoptosis of nerve cells, and to develop new therapeutic approaches based on their findings. Prof. Dr. Dr. Nicotera's team has already succeeded in identifying a mechanism leading to the loss of neuronal spinous processes and subsequent neurodegeneration in patients with Huntington's disease.

Our research: Prof. Pierluigi Nicotera and his research group are investigating the phenomenon of neurodegeneration. Not only the loss of synapses from uncontrolled breakdown but also the controlled death of nerve cells – apoptosis – cause impairment of cognitive and neuronal function and form the basis for neurodegenerative diseases. Prof. Nicotera and his team are exploring the molecular mechanisms that lead to synaptic degeneration or neuronal apoptosis. The current focus of their research is on the function of microRNAs and mitochondrial DNA in the neuronal aging process and the development of aging-associated diseases.

Our successes: If proteins are not folded correctly, abnormal proteins accumulate and cause cell damage or even cell death. Working together with scientists from the University of Leicester, Prof. Nicotera has unraveled the mechanism that causes the loss of spinous processes (spines) of nerve cells and leads to neurodegeneration in patients with Huntington's disease. This mechanism could also have an important role in the development of other neurodegenerative diseases in which incorrectly folded proteins have a toxic effect on neurons. Working with other scientists engaged in research on neurons and neuronal processes, Prof. Nicotera has succeeded in decoding the role of DAXX chaperone in the regulation of histone variants and the transcription of genes in the central nervous system.

Our goals: The aim of Prof. Nicotera's team is the precise identification of the molecular mechanisms that lead to the excessive degeneration of synapses. In order to gain a better understanding of neurodegenerative diseases, these researchers want to elucidate the signaling pathways that result in the loss of synapses and death of neurons under the physiological conditions of aging. The goal is to develop new therapeutic approaches based on their findings.

Our methods/techniques: The team is using model organisms such as mice and *C. elegans* nematodes for research purposes. The physiological significance of individual molecular mechanisms can be studied even further in transgenic mice.

EXTERNAL COOPERATIONS

Prof. Dr. M. Hoch, Universität Bonn, DE
Dr. M. Martins, MRC Toxicology Unit, Leicester, UK
Prof. P. Salomoni, UCL, London, UK
Prof. Dr. A. Zimmer, Life and Brain, Bonn, DE

Prof. Dr. Dr. Pierluigi Nicotera
Scientific Director and Chairman of the
Executive Board DZNE

PUBLICATIONS

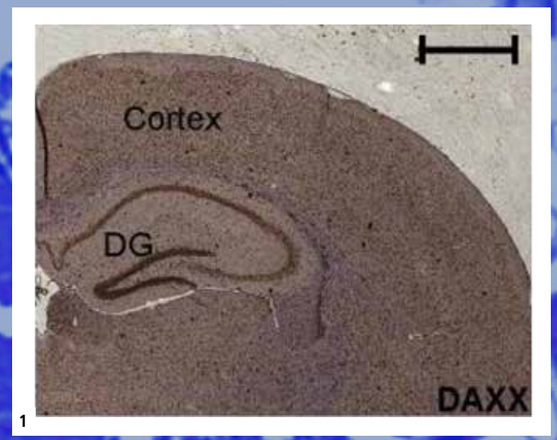
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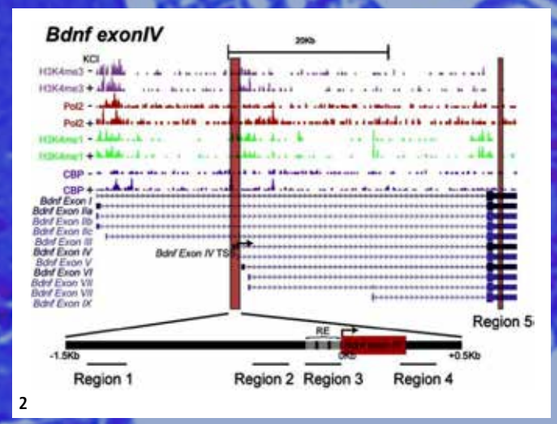
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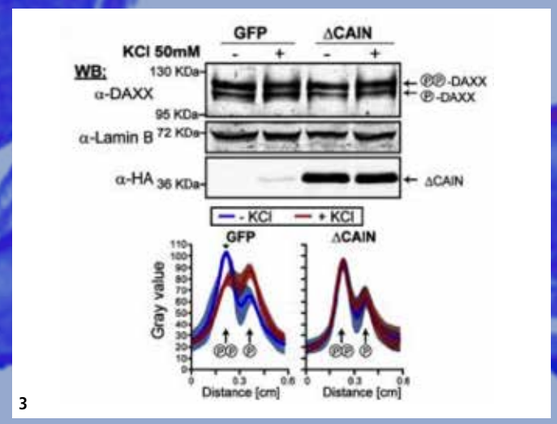
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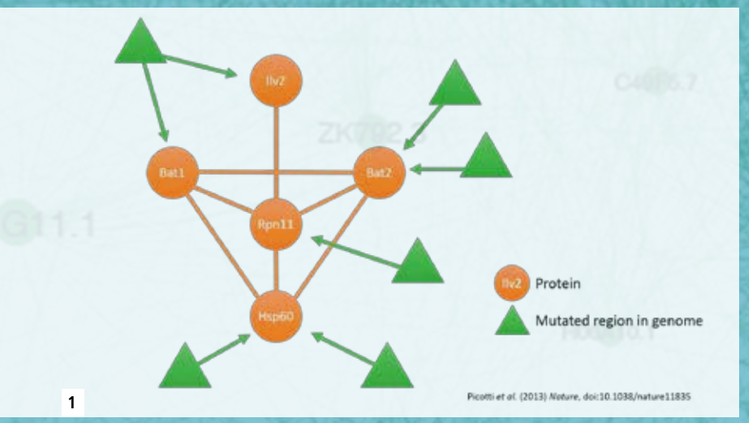
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FIGURE 1: Immunohistochemistry on coronal sections of the mouse brain at P30.
FIGURE 2: Representative Genome Browser image of regulatory element marks for the Bdnf gene in unstimulated and membrane-depolarized neurons (2 hr). H3K4me3 marks promoter regions, whereas H3K4me1 marks enhancer regions. CBP and PolII have been shown to mark both these regions upon neuronal activation. The gene map and the location of primers are shown underneath (regions 1–5). ChIP analysis of DAXX enrichment at the selected regions in DAXXFlox/WT cortical neurons in the absence or presence of 50 mM KCl (3 hr). We performed ChIP by using CRE-infected DAXXFlox/Flox cells as background control.
FIGURE 3: Top: whole-cell lysates were prepared from 5 DIV cortical neurons infected with lentivirus expressing GFP or the calcineurin inhibitor ΔCAIN (1 hr). Extracts were probed with α-DAXX antibody. Bottom: the graphs represent image analysis of band intensity

Prof. Dr. Andreas Beyer entwickelt neue biostatistische und bioinformatische Verfahren, um das Zusammenwirken vieler Gene im Organismus zu untersuchen. Damit können die Wechselwirkungen zwischen tausenden von Eiweißen und anderen Molekülen analysiert werden.



1

FIGURE 1: Network of genomic regions affecting protein levels in yeast. Each triangle is a genomic region affecting the protein level(s) of the respective protein(s). Proteins that are linked are binding to each other. This figure shows the complexity of genetic variation between individuals and to what extent protein levels are affected by those.
FIGURE 2: A gene network determining lifespan extension in the nematode worm *Caenorhabditis elegans*.



2



↗ http://cecad.uni-koeln.de/Prof-Dr-Andreas-Beyer.361.0.html

Prof. Dr. Andreas Beyer

Principal Investigator
Sybacol

Prof. Dr. Andreas Beyer and his group analyze the aging process in the human body and in model species by simultaneously observing the activities of all the genes in an organism. The working group develops algorithms for filtering large amounts of data for relevant information, such as interactions between genes and proteins. Integrating heterogeneous data sets is of particular interest, as this can open approaches to new questions that cannot be answered by evaluating individual data sets in isolation.

Our research: Prof. Dr. Andreas Beyer and his working group use and develop computational approaches for exploring age-associated changes in molecular networks. The integrated analysis of protein concentrations, gene activities, and network information, for example, allows for the identification of specific molecular networks that are subject to activity changes as part of the aging process. This yields information about the mechanisms of the aging process itself, and could help to identify interventions that might delay aging.

Our successes: The working group has made important contributions to further develop a range of biostatistical and bioinformatic methods, such as gene mapping techniques, network biology, and functional genomic screen analysis. The group's work has also yielded fundamental findings on the link between a protein's function and the manner in which its concentration is regulated in the cell.

Our goals: The scientists are interested in the mechanisms of the aging process and their manifestations in molecular networks. The ultimate goal is to use analytical and statistical algorithms to diagnose the individual causes of disease so as to develop a personalized treatment plan. This will improve therapeutic effectiveness and reduce side effects at the same time.

Our methods/techniques: The working group uses computational approaches from biostatistics, machine learning, and network biology to analyze, represent and integrate data from their own, joint, and third-party projects.

PUBLICATIONS

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CECAD COOPERATIONS

F Prof. Dr. A. Antebi → p. 177
Principal Investigator

B Prof. Dr. T. Benzing → p. 85
Principal Investigator

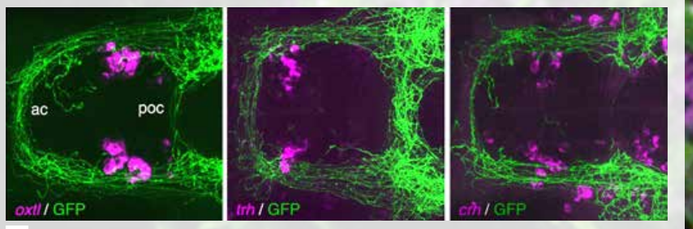
F Prof. Dr. L. Partridge → p. 173
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

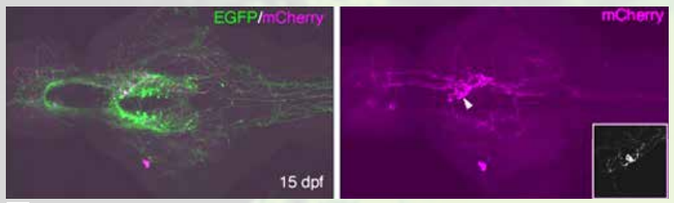
EXTERNAL COOPERATIONS

Prof. Dr. R. Aebersold, ETH-Zurich, CH
Prof. Dr. J. Bähler, UCL, UK; Prof. Dr. J. Berg, Sybacol, DE; Prof. Dr. M. Lässig, Sybacol, DE
Dr. A. Papantonis, CMMC, DE; Prof. Dr. A. Smith, Cambridge Stem Cell Institute, UK
Dr. D. Valenzano, MPI-Age, DE

In der Evolution haben sich viele Stoffwechselprozesse zwischen Fisch und Mensch erhalten. Davon ausgehend erforschen Prof. Dr. Matthias Hammerschmidt und seine Arbeitsgruppe den Energiestoffwechsel an Zebrabärblingen, um daraus neue, auf den Menschen übertragbare Erkenntnisse zur Energiehomöostase abzuleiten.



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3

BACKGROUND FIGURE: Innervation of the pituitary by neuroendocrine cells of the hypothalamus. Live imaging of the hypothalamus-pituitary connection of an adult fish (6 months of age) carrying a otpb:EGFPras transgene (green), marking hypothalamic neurons and a prl:RFP transgene (purple), marking lactotropes of the anterior pituitary.
FIGURE 1: A stable pomca:EGFPras transgenic line reveals the complex projection pattern of pomca neurons in the zebrafish larval brain. Anti-GFP immunohistochemistry of transgenic line at 7dpf, counterstained via in situ hybridization labeling of various second order neurons in the pre-optic region of the hypothalamus: oxtl (oxytocin-like); trh (thyrotropin-releasing hormone); crh (corticotropin-releasing hormone). ac: anterior commissure; poc: postoptic commissure.
FIGURE 2: Single pomca neurons innervate multiple target regions in the larval zebrafish brain. Genetic mosaic labeling was performed by injection of a BAC construct driving mCherry expression under the control of the pomca promoter into fertilized eggs of a stable Tg(pomca:EGFP) line. 15 dpf. The single neuron (purple) projects to all target regions of the pomca circuitry. Inset: magnification of cell body.
FIGURE 3: Dwarf mutants identified in an ENU F3-forward genetic screen. Comparison of body size of mutant fish (4D18-3) to wild-type sibling at 2 months of age.



↗ http://cecad.uni-koeln.de/Prof-Matthias-Hammerschmidt.80.0.html

Prof. Dr. Matthias Hammerschmidt

Principal Investigator
Cologne Biocenter

During the course of evolution, many aspects of the neuroendocrine regulation of energy homeostasis have been preserved in both fish and humans. Even so, there are fundamental differences in that a fish reacts to increased energy supplies by growing in length, while a person puts on weight. Prof. Dr. Hammerschmidt's research group is trying to extrapolate new findings in energy homeostasis to human metabolism.

Our research: Prof. Hammerschmidt and his team have pioneered basic systematic approaches to metabolic research in adult zebrafish and gained insight into related functional aspects. Systematic approaches to functional measurements of energy homeostasis in the zebrafish model are challenging, as there are no isogenic lines and considerable variation in the length, weight, and lifespan of individual fish. In addition, basic investigational methods, such as measuring food uptake and oxygen consumption, first had to be established. The key anatomical structure in this functional research is the hypothalamus, which regulates energy homeostasis in both fish and humans.

Our successes: Functional structures in the human hypothalamus for the regulation of energy homeostasis, such as POMC and AGRP neurons, as well as many second-order neurons, can also be demonstrated in zebrafish. By developing new systematic approaches, the team has succeeded in establishing the fish as a model organism for the basic research of metabolic regulatory networks.

Our goals: Based on the development of new systematic approaches, the research group intends to investigate in detail the regulatory processes of energy homeostasis emanating from the hypothalamus in the zebrafish model, and to extrapolate their findings to neuronal regulation in humans.

Our methods/techniques: Production of transgenic lines for network analysis and functional manipulation of specific neurons (optogenetics, cell ablation); production of genetic mutations in potential regulatory genes by means of CRIPR/Cas9 technology; forward genetics screens after random chemical mutagenesis to isolate mutants with decreased or increased body size.

PUBLICATIONS

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CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator

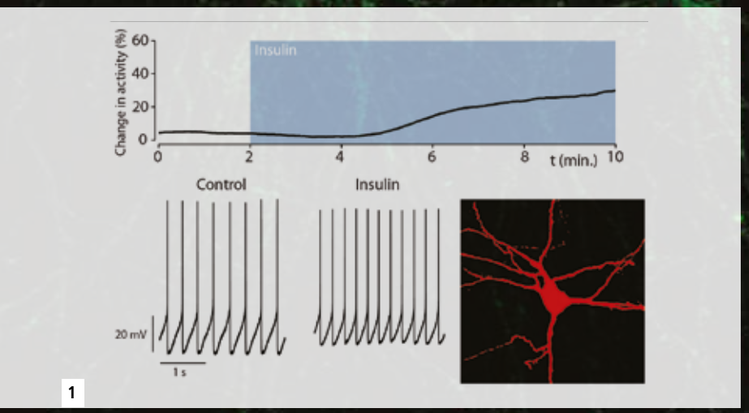
F Prof. Dr. P. Kloppenburg → p. 189
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

EXTERNAL COOPERATIONS

Prof. Dr. S. Ekker, Mayo Clinic Cancer Center, Rochester, MN, USA
Prof. Dr. S. Farber, Carnegie Institution, Baltimore, MD, USA
Prof. Dr. M. Placzek, University of Sheffield, UK

Nahrungsaufnahme und Energiehaushalt werden maßgeblich von kleinen, dynamischen, neuronalen Netzwerken im Gehirn reguliert. Eine Störung dieser Netzwerke kann zu einer Vielzahl von Stoffwechselkrankheiten wie Diabetes Typ 2 führen. Prof. Dr. Peter Kloppenburg untersucht mit seiner Arbeitsgruppe wie Krankheiten, extreme Diäten und Alterung die Funktion dieser Regelkreise auf der zellulären Ebene beeinflussen.



1

BACKGROUND FIGURE: Midbrain dopaminergic neurons integrate signals on food palatability and food-associated reward into the complex control of energy homeostasis. Insulin is a peptide hormone that is part of the metabolic pathway regulating the nutrient concentration in the blood.

FIGURE 1: The figure shows a midbrain dopaminergic neuron and its electrophysiological response to insulin. Elevation of the extracellular insulin concentration increases the action potential frequency. The top panel shows the relative change over time. The lower panels display original traces before and during insulin administration.



↗ http://cecad.uni-koeln.de/Prof-Peter-Kloppenburg.82.0.html

Prof. Dr. Peter Kloppenburg

Principal Investigator
Cologne Biocenter

Obesity and type 2 diabetes are closely linked diseases that are associated with excessive weight and fat mass, and their prevalence is increasing within Western populations. The goal of Prof. Dr. Kloppenburg and his group is to define the mechanisms that regulate body weight and energy homeostasis, and look at how these control mechanisms change under pathophysiological conditions that promote hyperphagia.

Our research: Energy homeostasis is tightly controlled by defined neuronal circuits in the brain to adjust food intake and energy expenditure according to the availability of fuel sources in the periphery of the body. Aging, extreme diets, and diseases can deregulate these neuronal systems. To understand what makes organisms susceptible to metabolic disorders, it is essential to define age and diet-associated changes in this network.

Our successes: The group has shown that high caloric diet-induced obesity can cause functional and structural changes in the adult neuronal networks that control food intake. Another important finding was that a maternal high-fat diet during lactation impaired the proper formation of these circuits in the offspring.

Our goals: One of the Kloppenburg team's main aims is to define the biophysical parameters and cellular mechanisms that cause age- and diet-dependent changes in the intrinsic firing characteristics and synaptic properties of the neuronal circuits that control energy homeostasis. A detailed understanding of the mechanisms that promote or prevent deregulation of these neuronal control circuits may lead to novel approaches for therapeutic intervention in metabolic and neurological disorders.

Our methods/techniques: To achieve these goals, the laboratory is using a combination of various electrophysiological and optophysiological recording techniques.

PUBLICATIONS

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CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator

C Prof. Dr. A. A. Noegel → p. 121
Principal Investigator

B Prof. Dr. G. Schwarz → p. 95
Principal Investigator

A Prof. Dr. R. J. Wiesner → p. 79
Principal Investigator

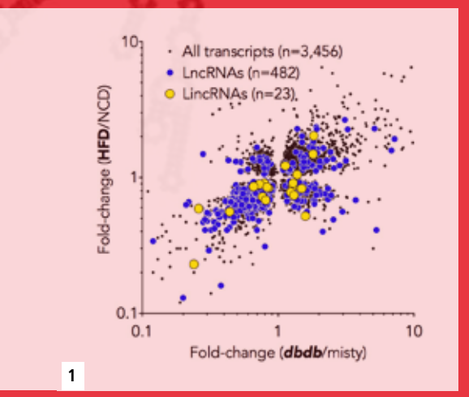
EXTERNAL COOPERATIONS

Prof. Dr. T. L. Horvath, Yale, USA
Prof. Dr. R. Moran, VTC Research Institute, USA
Dr. C. Pouzat, CNRS, FR

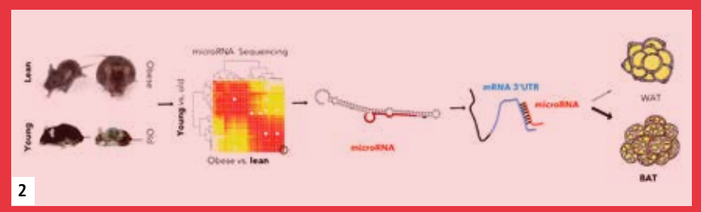
Dr. Jan-Wilhelm Kornfeld erforscht mit seiner Arbeitsgruppe die Rolle von nichtkodierenden RNAs bei der Entstehung und Behandlung Adipositas-assoziierter Erkrankungen wie dem Typ 2 Diabetes. Ein wichtiger Erfolg war die Identifikation einer microRNA, die bei der Entwicklung einer Adipositas-assoziierten Insulinresistenz involviert ist und die ein neuartiges Zielmolekül für die Behandlung metabolischer Erkrankungen im Menschen darstellt.

FIGURE 1: Control of glucose metabolism by lncRNAs. Using deep RNA-Seq we identified >40 lncRNAs correlating with obesity and type 2 diabetes (T2D) in mice. Using transgenic models we study the consequence of in vivo lncRNA loss and identify novel lncRNA targets for obesity intervention.

FIGURE 2: Control of brown adipose tissue (BAT) by microRNAs. Activated BAT controls glucose homeostasis and better understanding BAT function may reveal novel RNA therapeutics for obesity and T2D. We show aging- and obesity-associated loss of BAT function is controlled by a novel microRNA signaling axis that also govern glucose metabolism in mice.



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↗ http://cecad.uni-koeln.de/Dr-Jan-Wilhelm-Kornfeld.317.0.html

Dr. Jan-Wilhelm Kornfeld

Principal Investigator
MPI for Metabolism Research

Dr. Jan-Wilhelm Kornfeld and his group investigate the role of noncoding RNAs in development and treatment of obesity-associated diseases such as type 2 diabetes. One of the group's successes has been the identification of a microRNA involved in obesity-associated insulin resistance which represents a novel target structure for the treatment of metabolic disorders in humans.

Our research: Very little parts of the genomes in higher organisms encode transcripts that serve as template for proteins. In fact, over 90% of the genetic material is never translated into proteins. Current research indicates that this noncoding space of the genome is actively involved in control of cellular differentiation, organismal control of energy metabolism and development of aging-associated diseases like type 2 diabetes and neurodegenerative disorders. Dr. Kornfeld and his group functionally address the role of these noncoding transcripts using transgenic animals. Their focus lies on microRNAs and long, noncoding RNAs (lncRNAs) and testing their aptitude as novel targets for treatment of aging-associated diseases.

Our successes: The team recently demonstrated that microRNA 802 is involved in the development of obesity-associated insulin resistance in both mice and humans. These results deciphered new, exciting therapeutic options for treating metabolic disorders in patients as microRNA inhibitors have been successfully tested in mouse models and nonhuman primates.

Our goals: The group recently started to investigate the role of lncRNAs in controlling energy homeostasis in vivo, as it was shown that lncRNAs are involved in a wide spectrum of cellular signaling mechanisms in higher organisms. Identifying hitherto unknown disease-associated lncRNAs and characterisation of their molecular effector function during development and progression of metabolic- and aging-associated disease represents their main goal.

Our methods/techniques: The group's methodology involves Next-Generation RNA sequencing, epigenomic profiling and computational models to quantify and characterize small and long, noncoding RNAs. Transgenic mouse models are harnessed to study the role of noncoding RNAs in control of glucose metabolism.

PUBLICATIONS

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CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning → p. 169
Principal Investigator

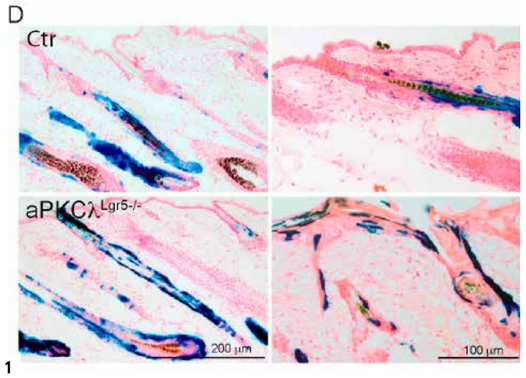
E Prof. Dr. P. Nürnberg → p. 155
Principal Investigator

F Dr. A. Rada-Iglesias → p. 199
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EXTERNAL COOPERATIONS

Dr. A. Bosdorfer Losic, MPI-Age, Cologne, DE
Dr. C. Dieterich, MPI-Age, Cologne, DE
Prof. Dr. J. Heeren, UK Hamburg-Eppendorf, DE
Dr. M. Mori, Federal University of Sao Paolo, BR
Prof. Dr. A. Trarakhovsky, Rockefeller University NY, USA

Prof. Dr. Niessen und ihre Arbeitsgruppe erforschen die Wirkung von Zelladhäsion, Zellform und Polarität auf die Hautbarriere, die uns vor Wasserverlust und externen Einflüssen schützt. Veränderungen der Zell- und Gewebearchitektur können altersassoziierte Erkrankungen wie Krebs und eine verzögerte Wundheilung auslösen.



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BACKGROUND FIG**URE:** Whole mount of adult tail skin stained for K14 (red) and nuclei (blue) visualizing hair follicles morphology.
FIG**URE 1:** Lineage tracing of descendents of bulge stem cells (labeled in blue) showing that upon loss of aPKC stem cells change fate and obtain upper hair follicle and interfollicular identity as indicated by the blue staining in these areas.



↗ http://cecad.uni-koeln.de/Prof-Carien-Niessen.100.0.html

Prof Dr. Carien Niessen

Principal Investigator
Head of Platform Career Development & Gender Equality

The Niessen laboratory asks how control of cell shape and adhesive interactions coordinate formation and maintenance of the skin barrier that protects us from water loss and external insults, such as UV damage by the sun or microbes. Alterations in tissue architecture underlie aging-associated diseases, such as cancer and impaired regeneration. The team has unraveled central mechanisms by which stem cells balance renewal and differentiation to maintain the skin barrier. A major future goal is to gain fundamental insights into how regulation of cell architecture coordinates inflammatory and metabolic responses to control tissue homeostasis.

Our research: How epithelia coordinate cell and tissue structure with growth and metabolic activity to control morphogenesis and homeostasis of tissues is a fundamental question in biology. Altered regulation of epithelial cell/tissue architecture disturbs tissue homeostasis and epithelial barrier function and promotes not only aging but also cancer and a range of inflammatory diseases. The Niessen laboratory asks how key regulators of the cyto-architecture control the formation and maintenance of epithelial tissues. More specifically, the team addresses how cadherin mediated cell-cell adhesion and aPKC- controlled polarity integrate with metabolic insulin/IGF-1 signaling to control stem cell renewal and differentiation, tissue integrity and barrier function in a stratifying epithelium, the epidermis of skin. The Niessen laboratory also asks how external insults such as UV radiation present in the sun alter these processes and whether this results in skin barrier defects and diseases such as cancer.

Our successes: The scientific team around Prof. Niessen has provided important contributions to identify external and internal cues that control stem cell fate decisions in the epidermis likely through regulation of oriented cell division that promote either renewal or differentiation. These results not only provide cues for how stem cell behavior is altered in aged or diseased skin but in the long run might open up novel therapeutic possibilities to rejuvenate stem cells in these conditions. Moreover, the Niessen laboratory has made significant advances in the molecular circuitry through which cadherins control the polarization and integrity of the epidermal barrier. This provides new insight into how interference with adhesion or polarity complex building blocks result in cancer and in auto-immune, genetic and inflammatory diseases in the skin and other epithelial tissues.

Our goals: The long-term goal of Prof. Niessen and her team is to gain a fundamental understanding of the molecular mechanisms that drive polarization in multi-layered epithelia to coordinate cell fate, growth and innate immunity with cell and tissue architecture. This will be central for understanding how stem cells balance self-renewal with differentiation to maintain proper barrier function during normal tissue turnover and how this balance is restored upon insults/damage to the tissue to prevent disease.

Our methods/techniques: The research group of Prof. Niessen combines mouse models with 2D and 3D cell culture models to explore mechanistic insights into control of cell and tissue structure. With the help of state of the art (life) imaging these models allow the scientists to address the impact of interfering with the cyto-architecture of cells and tissues on the formation, maintenance and restoration of the epidermal barrier and follow the individual fate of cells. We combine this with phospho-proteomics and genome-wide analyses to identify downstream mechanisms that in the long run may potentially serve as therapeutic targets.

CECAD COOPERATIONS

F Prof. Dr. J. C. Brüning → p. 169
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E Dr. S. Iden → p. 153
Principal Investigator

D Prof. Dr. M. Krönke → p. 129
Principal Investigator

A Prof. Dr. E. I. Rugarli → p. 63
Principal Investigator

C Prof. Dr. B. Schumacher → p. 107
Principal Investigator

EXTERNAL COOPERATIONS

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Prof. Dr. V. Greco, Yale University, New Haven, USA
Prof. Dr. K. Green, Northwestern University, Chicago, USA
Dr. M. Leitges, University of Oslo, NO

Prof Dr. Carien Niessen
Principal Investigator
Head of Platform Career Development & Gender Equality

PUBLICATIONS

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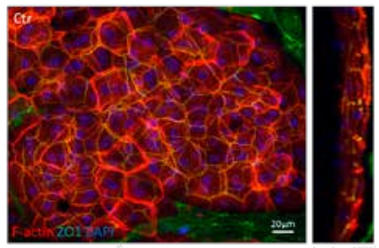
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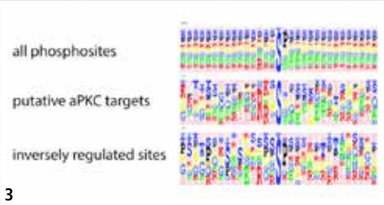
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Dem Team gelang es, zentrale Mechanismen zu entschlüsseln, die Stammzellen in die Lage versetzen, durch Erneuerung und Differenzierung von Zellen die Hautbarriere zu erhalten. Ziel ist es, zu verstehen, wie die Zellarchitektur durch entzündliche und metabolische Reaktionen die Gewebehomöostase kontrolliert.

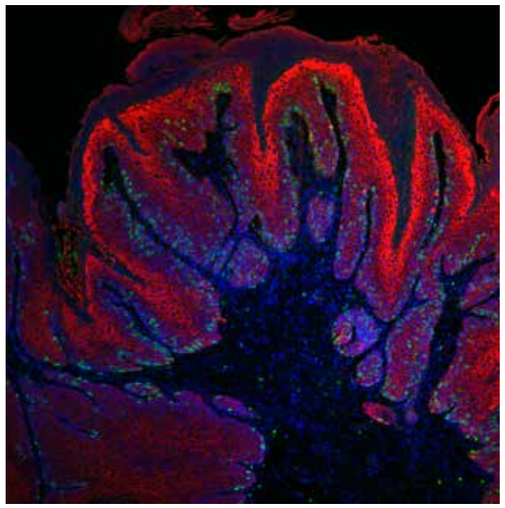
FIG**URE 2:** Whole mount of newborn skin showing that F-actin (red) shows a polarized distribution across the different layers of the epidermis with the highest concentration above the tight junctional barrier labeled by ZO-1 (green). Right panel: XZ- projection.
FIG**URE 3:** Phosphorylation sites identified through SILAC/ mass spectrometry analysis that are reduced upon loss of aPKC are enriched for aPKC consensus sites, indicating that these are putative aPKC targets.
FIG**URE 4:** Skin papilloma stained for K14 (red), BrdU (green) and nuclei (blue) showing enhanced proliferation in these tumors.
FIG**URE 5:** Differentiated keratinocytes stained for ZO-1 (green) and nuclei (red).

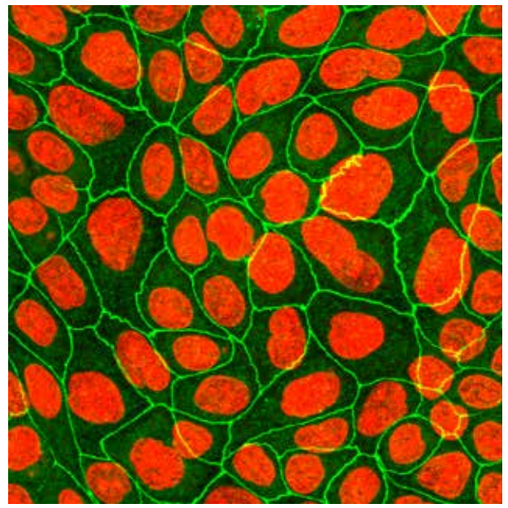


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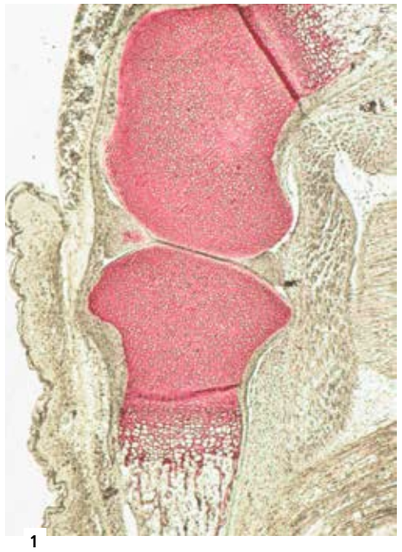
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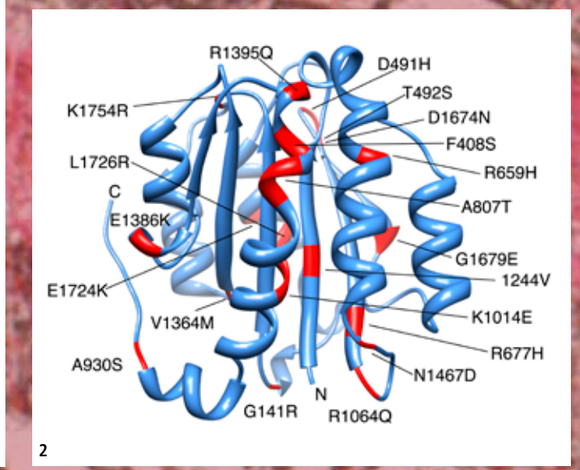

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Prof. Dr. Mats Paulsson und sein Team erforschen die Bedeutung extrazellulärer Proteine für Zellfunktionen und ihren Einfluss auf die Entstehung von Erkrankungen. Sie konnten neue Bestandteile des Kollagen Typ VI identifizieren und darauf aufbauend neue Strukturmodelle entwickeln. Ihr Ziel ist es, den Einfluss extrazellulärer Proteine auf Zytokine und Wachstumsfaktoren zu erforschen.

FIGURE 1: Matrilin-3 expression in a mouse knee joint
FIGURE 2: Muscle disease causing collagen VI mutations mapped onto the new a3N5 domain structure (Becker et al., Structure 22, 199-208)



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↗ http://cecad.uni-koeln.de/Prof-Mats-Paulsson.103.0.html

Prof. Dr. Mats Paulsson

Principal Investigator
Head of Biochemistry II

The research focus of Prof. Dr. Mats Paulsson and his team is the structure and functions of extracellular matrix proteins. Their aim is to understand how the extracellular matrix regulates cell function and how functional disorders can lead to the development of disease. The group has identified new building blocks of type VI collagen and now aims to explore in greater depth the interactions between specific extracellular matrix components, cytokines and growth factors.

Our research: Prof. Mats Paulsson and his research group are looking at the structure and functions of extracellular matrix proteins. Their particular interest lies in the regulation of cell function by the extracellular matrix and the way in which functional disorders can lead to disease. At the present time, these scientists are studying how mutations in matrix proteins may trigger hereditary diseases, such as chondrodysplasias and premature osteoarthritis.

Our successes: The team's greatest recent success has been the identification of three new alpha chains of type VI collagen. Based on these findings, the scientists have developed new structural models of collagen VI, which will contribute to greater understanding of the pathological mechanisms of muscular dystrophies and other diseases.

Our goals: Prof. Paulsson's team aims to gain in-depth understanding of the interactions between microfibrils in the extracellular matrix, cytokines and growth factors. The researchers are working on evidence that mutations in microfibrillar proteins impact on cytokines and various growth processes.

Our methods/techniques: The Paulsson laboratory makes use of recombinant protein expression and protein characterization in combination with high resolution electron microscopy, small angle X-ray scattering (SAXS), and X-ray crystallography to reveal how microfibrillar proteins are linked and to build improved structural models.

PUBLICATIONS

Neacsu CD, Ko YP, Tagariello A, Rokenes Karlsen K, Neiss WF, Paulsson M, Wagener R. (2014) Matrilin-1 is essential for zebrafish development by facilitating collagen II secretion. J. Biol. Chem. 289, 1505-1518.

Becker AKA, Mikolajek H, Paulsson M, Wagener R, Werner JM. (2014) A novel structure of a collagen VI VWA-domain displays N- and C-termini at opposite sides of the protein. Structure 22, 199-208.

Hartmann U, Hülsmann H, Seul J, Röll S, Midani H, Breloy I, Hechler D, Müller R, Paulsson M. (2013) Testican-3: A brain-specific proteoglycan member of the BM-40/SPARC/osteonectin family. J. Neurochem. 125, 399-409.

Groma G, Xin W, Grskovic I, Niehoff A, Brachvogel B, Paulsson M, Zaucke F. (2012) Abnormal bone quality in COMP and matrilin-3 double deficient mice caused by increased TIMP-3 deposition and delayed aggrecan degradation. Arthritis Rheum. 64, 2644-2654.

John S, Thiebach L, Frie C, Mokkapati S, Bechtel M, Nischt R, Rosser-Davies S, Paulsson M, Smyth N. (2012) Epidermal transglutaminase (TGase 3) is required for proper hair development, but not the formation of the epidermal barrier. PLoS One 7, e34252.

CECAD COOPERATIONS

F Prof. Dr. Hammerschmidt → p. 187
Principal Investigator

E Prof. Dr. T. Krieg → p. 143
Principal Investigator

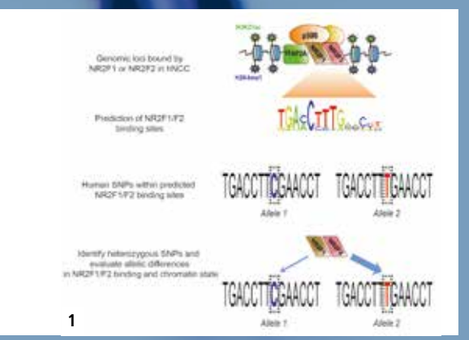
A Prof. Dr. R. J. Wiesner → p. 79
Principal Investigator

EXTERNAL COOPERATIONS

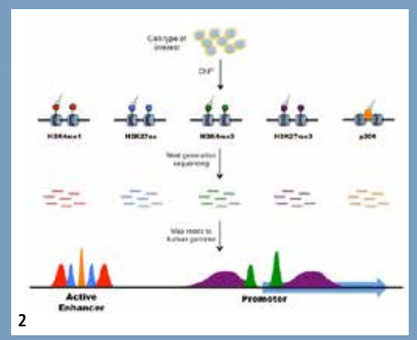
Prof. Dr. C. Baldock, University of Manchester, Manchester, UK
Prof. Dr. P. Bonaldo, University of Padova, Padova, IT
Dr. J. Werner, University of Southampton, Southampton, UK

Dr. Alvaro Rada-Iglesias erforscht die Regulation der Gen-Expression in der embryologischen Entwicklung und ihre Funktion in der Entstehung von Erkrankungen. Gemeinsam mit seinem Team gelang ihm die Entwicklung einer Methode zur Identifikation von regulatorischen DNA-Sequenzen. Das Ziel der Arbeitsgruppe ist es, diese Sequenzen auf Mutationen zu untersuchen, die Aufschluß über die genetischen Grundlagen bestimmter Erkrankungen geben.

FIGURE 1: Combinatorial analysis of ChIP-seq data for a number of histone modifications and transcriptional coactivators (i.e. p300) allows the identification of active enhancers (adapted from Rada-Iglesias et al., Nature 2011).
FIGURE 2: Bioinformatic pipeline employed to predict SNPs occurring within active hNCC enhancers and potentially altering NR2F1/2 binding to these regulatory elements (adapted from Rada-Iglesias et al., Cell Stem Cell 2012).



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↗ http://cecad.uni-koeln.de/Dr-Alvaro-Rada-Iglesias.324.0.html

Dr. Alvaro Rada-Iglesias

Principal Investigator – Junior Research Group Leader
Developmental Genomics Laboratory

The team led by Dr. Alvaro Rada-Iglesias is researching how gene expression is regulated during embryogenesis and how its misregulation might lead to human disease. The research group has developed a method for the genome-wide identification of transcriptional regulatory DNA sequences. The goal is to investigate these sequences for non-coding mutations, in order to decode the genetic basis of human disease.

Our research: Dr. Alvaro Rada-Iglesias and his team are investigating the regulation of gene expression during mammalian development. They are trying to discover how stem cells can develop into specific cell types in early embryogenesis, and what makes further differentiation possible. The researchers believe that changes in this early gene expression due to non-coding genetic variation may contribute to the development of congenital diseases.

Our successes: The scientists have developed a successful method for the genome-wide identification of regulatory DNA sequences. These sequences control DNA expression and are decisive in switching genes on and off during embryological development. The genomic approaches developed by Dr. Rada-Iglesias team are now being used by research groups in other laboratories.

Our goals: Working on the assumption that mutations in regulatory DNA sequences may contribute to human disease, Dr. Rada-Iglesias and his team aim to identify these mutations and characterize their functional consequences. Although focusing on congenital disease, the team's approach should be broadly applicable to many other human disorders. Ultimately, the main goal is to understand the genetic basis of human disease, which might result in the development of novel therapeutic approaches.

Our methods/techniques: The team is working with embryological stem cells in vitro and chick embryos in vivo, using methods belonging to the fields of genomics, biochemistry, and molecular biology. In addition, the group is using next-generation sequencing techniques, such as RNA sequencing (RNA-seq), chromatin immunoprecipitation followed by DNA sequencing (ChIP-seq), and 4C-seq, which allows the investigation of chromatin interactions.

PUBLICATIONS

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Rada-Iglesias A, Prescott SL, and Wysocka, J. (2013) Human genetic variation within neural crest enhancers: molecular and phenotypic implications. Philos. Trans. R. Soc. Lond. B. Biol. Sci. May 368, 20120360.

Rada-Iglesias A. (2013) Pioneering barren land: mitotic bookmarking by transcription factors. Dev Cell. Feb 25;24(4):342-4.

Rada-Iglesias A*, Bajpai R*, Prescott R, Brugmann S, Swigut T and Wysocka J. (2012) Epigenomic mapping annotates human neural crest enhancers and predicts a new role for nuclear receptors NR2F1/2. Cell Stem Cell Nov 2;11(5):633-48.

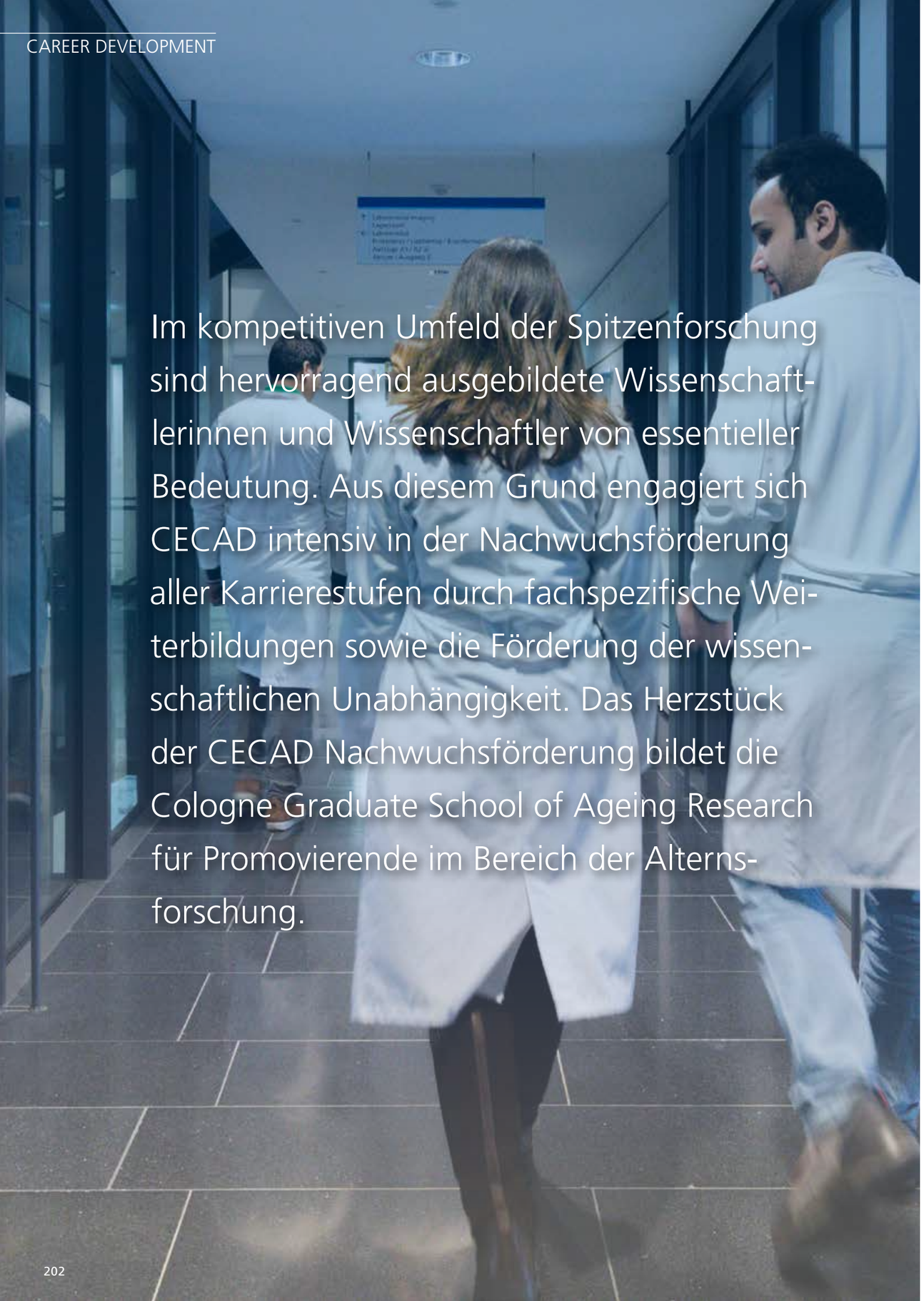
CECAD COOPERATIONS

F Dr. J.-W. Kornfeld
Principal Investigator
→ p. 191

EXTERNAL COOPERATIONS

Dr. R. Andersson, Copenhagen University, DK
Dr. S. Brugmann, Cincinnati Children´s Hospital Medical Centre, USA
Dr. L. Kurian, CMMC, Cologne, DE
Dr. E. Mangold, Institute for Human Genetics, University Hospital Bonn, DE
Prof. Dr. M. Manzanares, CNIC, Madrid, ES
Dr. A. Papantonis, CMMC, Cologne, DE
Dr. T. Saric, Institute for Neurophysiology, University of Cologne, DE

Career Development & Gender Equality



Im kompetitiven Umfeld der Spitzenforschung sind hervorragend ausgebildete Wissenschaftlerinnen und Wissenschaftler von essentieller Bedeutung. Aus diesem Grund engagiert sich CECAD intensiv in der Nachwuchsförderung aller Karrierestufen durch fachspezifische Weiterbildungen sowie die Förderung der wissenschaftlichen Unabhängigkeit. Das Herzstück der CECAD Nachwuchsförderung bildet die Cologne Graduate School of Ageing Research für Promovierende im Bereich der Alternsforschung.



↗ http://cecad.uni-koeln.de/Career-Support.142.0.html

Career Development & Gender Equality

Prof. Dr. Carien Niessen
Head of Career Development & Gender Equality

Young Scientists & Career Development
Promoting young scientists and continuing education at CECAD

The motivated and highly qualified young scientists are a key factor in CECAD's remarkable success. Therefore, at CECAD it is a high priority to offer not just optimal research conditions, but also special programs to promote professional development at any career stage.

The "Model Systems of Ageing and Ageing-Related Diseases" course teaches master's students facts about and how to apply the techniques and methods employed in aging research. Doctoral students in the natural sciences and medicine can deepen their scientific knowledge in a wide range of CECAD seminars and lectures. CECAD also offers a variety of soft skills courses for PhD students and postdocs in diverse areas. Workshops such as "scientific writing" and "scientific poster design" are opportunities to round out scientific training. Travel grants that help students and postdocs attend international conferences and a PhD/Postdoc Retreat support the development of international and regional contact to other researchers. This international networking creates opportunities for wide-ranging collaborations and interesting career opportunities.

To promote scientific independence, each year two CECAD postdocs receive a two-year 10,000 EUR/year research grant. These funds can be used for material expenses. It also covers a technical assistant. This support, together with joint laboratory management seminars and an active exchange with CECAD junior groups has already helped many postdoc grant graduates make the leap to heading up their own research groups at respected research institutes.

Another part of CECAD's mission is to encourage the professional development of junior group leaders. CECAD provides access to excellent resources, mentoring and in-house continuing education. Cologne's role as an optimal aging research network supports this objective. Three CECAD junior research groups have founded a professorship in Cologne, an impressive demonstration of how effectively CECAD promotes young talent. The numerous external research grants awarded to CECAD researchers, such as the Emmy Noether Groups, and diverse scientific prizes are additional proof of the success of CECAD's research groups.



Dr. Doris Birker
Managing Coordinator for
Career Development & Gender Equality



Jenny Ostermann
Assistance Coordinator for
Career Development & Gender Equality

The Cologne Graduate School of Ageing Research
Since 2009, CECAD has offered a very successful structured graduate program in the field of aging research, a highly interdisciplinary area with important implications for the future. The very popular program aims to optimally prepare young scientists for a career in academic research or in the scientific labor market.
The three-year program involves excellent research conditions with intensive mentoring and state-of-the-art technical platforms in an international working environment. This creates an ideal environment in which doctoral students can develop their full scientific potential. The English-language doctoral program is complemented by a wide range of seminars and courses on aging research and practical training. It draws students from Cologne and applicants from all over the world.

Each year doctoral candidates present their projects together with well-respected international experts from their research fields at a graduate symposium, the well-rounded end to the graduate program.

In 2013, the CECAD Graduate School fused with the IMPRS-Age doctoral program from the Max Planck Institute for Biology of Ageing, the Max Planck Institute for Metabolism Research and caesar in Bonn to form the “Cologne Graduate School of Ageing Research”. The program is now even more attractive, since students profit from the synergies of all the institutes involved. This collaboration also allows potential in doctoral programs in aging research to be bundled at the Cologne and Bonn locations. The growing number of applicants is an impressive demonstration of the respected graduate school’s success.





CECAD fördert die Gleichstellung in der Forschung aktiv mit dem langfristigen Ziel, einen ausgeglichenen Anteil von Frauen und Männern innerhalb des Clusters zu erreichen. Daher hat sich CECAD dem „Keep Women on the Scientific Career Path“ Aktionsplan verpflichtet.

Gender and Family Support at CECAD
Pushing forward the “Keep Women on the Scientific Career Path” action plan





While the percentage of excellent young women scientists in research is high, the number of women working in the natural sciences drops considerably at the postdoc level and above. This is likely due to a lack of encouragement to pursue a career in a male-dominated working environment along with an insufficient network that would help women balance the demands of a family and a career. So CECAD specifically targets female scientists to meet its long-term goal of employing an equal number of men and women and to prevent women from dropping out of science.
The “Keep Women on the Scientific Career Path” action plan aims to create networks of women, promote female scientists through custom-tailored workshops, and actively support families.
As part of the structured promotional scholarship program, students receive a monthly stipend for each child in addition to their grants. Since 2012, CECAD has been offering space for children of CECAD employees in the university child care center – with opening times designed to meet scientists’ unique needs. The university also offers emergency child care services during CECAD events and if an employee’s child care falls through at short notice to allow parents to participate in conferences and keep professional appointments. Since the end of 2014 a Family Room is available at the CECAD Research Center. In emergencies, the Family Room is offered to CECAD employees with children who can bring their child to work while looking after him or her. Moreover, the room can be used by nursing mothers.
Close cooperation with the Office of Gender Equality and the family support divisions of the university and other local research institutions is also a key element of the action plan promoting female scientists. Over the past year, together with other DFG-funded institutions at the University and University Hospital Cologne, an attractive continuing education program in the soft skills area and individual coaching for all career stages could be offered. During coaching, women explore their personal goals both in their professional and private lives and draft a plan for achieving these most effectively.

Core Facilities

Neueste Technologien in den ‚Core Facilities' von CECAD ermöglichen die Analyse komplexer Biomoleküle, ein tiefes Verständnis genetischer und molekularer Netzwerke sowie die hochaufgelöste Visualisierung zellbiologischer und physiologischer Prozesse, die Wissenschaftlerinnen und Wissenschaftler von CECAD erforschen . Hochmoderne elektronenmikroskopische und fluoreszenzbasierte Imagingtechnologien, neueste Verfahren der Massenspektroskopie zur quantitativen Analyse von Proteinen und Lipiden und die professionelle bioinformatische Analyse immer größer werdender Datenmengen: Mit diesem Angebot leisten die Core Facilities von CECAD einen wesentlichen Beitrag zum Erfolg der zentralen Forschungsprojekte von CECAD und generieren neue Erkenntnisse in der grundlagenorientierten und translationalen Forschung.



↗ http://cecad.uni-koeln.de/Technology-Platform.27.0.html

Core Facilities Overview

Prof. Dr. Bernhard Schermer
Head of Technology Platform

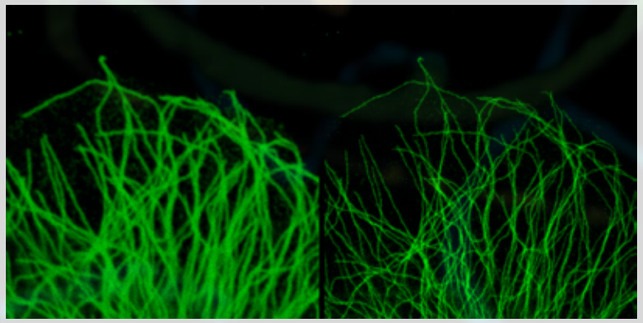


The latest technologies provided by the Core Facilities allow CECAD's scientists to analyze complex biomolecules, gain in-depth understanding of genetic and molecular networks, and perform high-resolution imaging of physiological and cell biological processes.

Our Core Facilities are integral to the success of CECAD's key research projects and contribute critical information for both basic scientific and clinical research. They provide state-of-the-art technical platforms including electron microscopy and fluorescence imaging, modern mass spectroscopy for quantitative protein and lipid analyses, and professional genomic and bioinformatic resources. The Core Facilities lie at the heart of the new CECAD research center and the entire Excellence Cluster.

Prof. Bernhard Schermer is heading the Nephrology Research Laboratory of the Department II of Internal Medicine at the University of Cologne and spokesperson for the five CECAD Core Facilities.

Die Mikroskopie-Plattform bietet allen Wissenschaftlerinnen und Wissenschaftlern des CECAD Exzellenzclusters eine Vielzahl modernster Lichtmikroskope für ihre Forschung.
Die Expertise der Plattform umfasst neben der Wartung und der Betreuung der anspruchsvollen Geräte auch eine direkte individuelle Unterstützung der Forscherinnen und Forscher bei der Planung, Durchführung und abschließenden Auswertung ihrer Experimente.



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BACKGROUND FIGURE: Color coded 3D presentation of mouse retinal blood vessels stained with FITC-Dextran. Two-photon microscopy was performed using an upright laser scanning microscope equipped with an infrared laser source which was tuned to 960 nm (Axel Witt, AG Kashkar).
FIGURE 1: Visualization of the microtubule network of a human cell by classical confocal microscopy (left) and by STED microscopy (right). Stimulated emission depletion (STED) microscopy enables super resolution imaging by bypassing the diffraction limit of light microscopy (Christian Jüngst and Ira Hensen, AG Schauss).



↗ http://cecad.uni-koeln.de/Imaging-Facility.280.0.html

Imaging Facility

Dr. Astrid Schauss
Head of Imaging Facility

In line with the relocation to the new CECAD building at the end of 2013, the Imaging Facility was considerably expanded with the installation of new state-of-the-art microscopes and the recruitment of three new coworkers: one additional microscopist, Dr. Christian Jüngst, for assistance with and maintenance of the existing microscopes, one bioinformatician, Dr. Nikolay Kladt, for data analysis, and one technical assistant, Ira Hensen, for sample preparation and lab organization.

Services: The CECAD Imaging Facility offers a broad range of state-of-the-art microscopes. With the aforementioned additional imaging equipment, it now has a pool of eight different microscopes that cover a broad range of microscopical applications such as FRAP, FLIM and laser ablation, but also advanced techniques like super-resolution microscopy (STED and GSD) and multiphoton microscopy for the intravital imaging of living organisms. All of the systems can be booked online and used after extensive individual training. The facility also advises scientists on their imaging projects, set-up and method selection, and supports them in data analysis.

Scientific achievements: Apart from maintaining the existing microscopes, the facility is very interested in establishing and integrating new imaging techniques. This year, the team worked hand-in-hand with the users to successfully set up two different kinds of super-resolution microscopy (STED and GSD) as well as FLIM (Fluorescence Lifetime Imaging Microscopy) and intravital microscopy. Several custom-tailored analysis pipelines were written to offer users data analysis support.

Future plans: In the coming months, the imaging platform will be extended to include electron microscopy. It has applied for a new transmission electron microscope (TEM) and equipment for EM sample preparation. Two technicians trained in EM services, Beatrix Martiny and Jessica Hausmann, will join the team this month.
At present, the Imaging Facility is used by more than 300 scientists and over 80 research groups. But it is always open to new customers and extremely interested in cooperation projects in which it can actively participate.



PUBLICATIONS

Kondadi AK, Wang S, Montagner S, Kladt N, Korwitz A, Martinelli P, Herholz D, Baker MJ, Schauss AC, Langer T, Rugarli EI. (2014) Loss of the m-AAA protease subunit AFG3L2 causes mitochondrial transport defects and tau hyperphosphorylation. EMBO J. May 2;33(9):1011-26.

Rishmawi L, Pesch M, Juengst C, Schauss AC, Schrader A, Hülskamp M. (2014) Non-Cell-Autonomous Regulation of Root Hair Patterning Genes by WRKY75 in Arabidopsis. Plant Physiol. May;165(1):186-95.

Anand R, Wai T, Baker MJ, Kladt N, Schauss AC, Rugarli E, Langer T. (2014) The i-AAA protease YME1L and OMA1 cleave OPA1 to balance mitochondrial fusion and fission. J Cell Biol. Mar 17;204(6):919-29.

Donovan C, Schauss A, Krämer R, Bramkamp M. (2013) Chromosome segregation impacts on cell growth and division site selection in Corynebacterium glutamicum. PLoS One. 2013;8(2):e55078.

Anton F., Fres J.M., Schauss A., Pinson B., Praefcke G.J., Langer T., Escobar-Henriques M. (2011) Ugo1 and Mdm30 act sequentially during Fzo1-mediated mitochondrial outer membrane fusion. J Cell Sci Apr 1;124(Pt 7):1126-35.

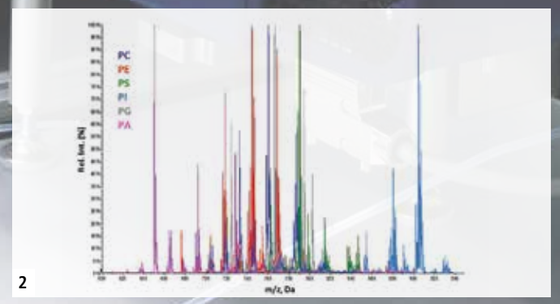
Lipide sind in lebenden Organismen essentiell für den Aufbau von Zellmembranen, als Energiespeicher und als Signalmoleküle im Zellstoffwechsel. Die Lipidomics Facility analysiert Lipide in biologischen Proben unter Anwendung modernster massenspektrometrischer Methoden und leistet damit einen wichtigen Beitrag zur Erforschung ihrer Funktionen.

FIGURE 1: Non-targeted profiling of lipids by Information Dependent Acquisition (IDA): A lipid extract from mouse liver was separated by Liquid Chromatography (LC). The LC eluate was infused into the TripleTOF 5600+ mass spectrometer and monitored by IDA. In IDA experiments MS/MS spectra are recorded automatically when data in the survey MS spectra meet certain criteria. Every data point in the plot represents the retention time and the m/z ratio of a lipid ion that was selected as a precursor ion.



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FIGURE 2: Targeted analysis of lipids by Multiple Precursor Ion Scanning (MPIS): A lipid extract from keratinocyte mitochondria was infused into the QTRAP 6500 mass spectrometer using the chip-based TriVersa NanoMate infusion system. Glycerophospholipid subclasses (phosphatidylcholine, -ethanolamine, -serine, -inositol, -glycerol, and phosphatidic acid) were simultaneously detected by applying specific precursor ion and neutral loss scans for each subclass. Each peak in the mass spectrum represents a glycerophospholipid species with a distinct fatty acid composition.



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↗ http://cecad.uni-koeln.de/Lipidomics-Facility.291.0.html

Lipidomics Facility

Dr. Susanne Brodesser
Head of Lipidomics Facility

In living organisms, lipids are essential for the assembling of cellular membranes, the storage of metabolic energy, and as signaling molecules in cell metabolism. The Lipidomics Facility analyzes lipids from biological samples using the latest mass spectrometric techniques, thus making a key contribution towards exploring their functions.

Services: The Lipidomics Facility offers CECAD scientists the analysis of lipids in biological samples using state-of-the-art mass spectrometric techniques and data processing software. The service also includes help with the experimental design and data interpretation.

Scientific achievements: The Lipidomics Facility originally focused on the targeted analysis of sphingolipids. The Facility's expertise was then subsequently extended to the quantification of further lipid classes such as glycerophospholipids and sterols. Upon move of the Lipidomics Facility into the CECAD Research Center in February 2014, two new-generation mass spectrometers (QTRAP 6500 and TripleTOF 5600+, AB SCIEX) equipped with two Liquid Chromatography systems (1260 Infinity, Agilent; Ekspert MikroLC 200, Eksigent), a chip-based infusion system for Nano-Electrospray Ionization (TriVersa NanoMate, Advion) and an interface for Differential Mobility Spectrometry (SelexION, AB SCIEX) were purchased. Thereby the Facility obtained full flexibility for applying all of the latest lipidomic technqiues. Depending on the lipid class and scientific question analytical methods with (LC-MS/MS) or without (shotgun lipidomics) pre-separation of the lipid extract prior to the mass spectrometric analysis are possible. A comprehensive software package for data processing and evaluation facilitates the handling of large data sets.

Future plans: Whereas the targeted quantification of lipids is well-established in the Lipidomics Facility, the new equipment also enables non-targeted profiling of lipids in complex extracts. In the long term the Facility plans to expand its service towards more general metabolomics applications by integrating metabolites of the glycolysis, the citric acid cycle and the pentose phosphate pathway into the set of service analyses.



PUBLICATIONS

Mourier A, Motori E, Brandt T, Lagouge M, Atanassov I, Galinier A, Rappl G, Brodesser S, Hultenby K, Kühlbrandt W, Larsson N-G. (2015) Mitofusin 2 is required to maintain mitochondrial coenzyme Q levels. J Cell Biol 208(4):429-42.

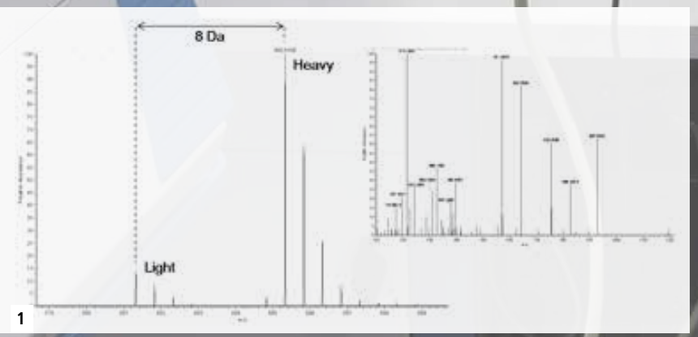
Turpin SM, Nicholls HT, Willmes DM, Mourier A, Brodesser S, Wunderlich CM, Mauer J, Xu E, Brönneke HS, Trifunovic A, LoSasso G, Wunderlich FT, Kornfeld J-W, Blüher M, Krönke M, Brüning JC. (2014) Obesity-induced CerS6-dependent C16:0 ceramide production promotes weight gain and glucose intolerance. Cell Metab 20(4):678-86.

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Schwamb J, Feldhaus V, Baumann M, Patz M, Brodesser S, Brinker R, Claasen J, Pallasch CP, Hallek M, Wendtner CM, Frenzel LP. (2012) B-cell receptor triggers drug sensitivity of primary CLL cells by controlling glucosylation of ceramides. Blood 120(19):3978-85.

Belgardt BF, Mauer J, Wunderlich FT, Ernst MB, Pal M, Spohn G, Brönneke HS, Brodesser S, Hampel B, Schauss AC, Brüning JC. (2010) Hypothalamic and pituitary c-Jun N-terminal kinase 1 signaling coordinately regulates glucose metabolism. Proc Natl Acad Sci USA 107(13):6028-33.

Proteine sind essentielle Bestandteile lebender Organismen und Komponenten fast aller metabolischen Signalwege. Das Proteom ist hochdynamisch und eine systematische Proteincharakterisierung ist wichtig, um zelluläre Regulation unter normalen Umständen und im Falle einer Veränderung durch eine Krankheit oder durch den Alterungsprozess zu untersuchen. Die CECAD Proteomics Facility nutzt hochmoderne Flüssig-Chromatografie in Kombination mit modernen Massenspektrometern (LC-MS) für eine genaue und umfangreiche Proteomanalyse komplexer biologischer Systeme.



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FIGURE 1: SILAC technology: cells are cultured on media containing either light or heavy lysine. Incorporation of this amino acid by the cells into the proteins results in a mass difference of the corresponding tryptic peptides. In this example, each peptide containing a lysine residue will be 8 Daltons heavier than its counterpart in the 'light' cell population. When heavy and light samples are combined, these SILAC pairs can be assigned and the ratio of peak intensities in the mass spectrum reflects the relative protein abundance. The MS/MS spectrum (insert) is used to determine the amino acid sequence of the quantified peptide. Shown are data acquired on a Q Exactive Plus instrument coupled to an EASY nLC 1000 UPLC system.



↗ http://cecad.uni-koeln.de/Proteomics-Facility.273.0.html

Proteomics Facility

Dr. Tobias Lamkemeyer
Head of Proteomics Facility

Proteins are essential building blocks of living organisms and main components of nearly all metabolic pathways. The Proteome of a cell is a highly dynamic entity and systematic protein profiling is important to study cellular regulations under regular and diseased conditions. The proteomics platform uses high performance liquid chromatography in combination with modern mass spectrometers (LC-MS) for an unbiased and comprehensive proteome analysis of complex biological systems.

Services: The CECAD Proteomics Facility applies state-of-the-art methods of mass spectrometry to analyze the aging process on the protein level. The proteomics platform uses the shotgun proteomics approach. Here, sample processing starts with cell lysis, fractionation, and digestion of the proteins. The resulting peptide mixture is separated by reversed phase chromatography using nano-UHPLC system. As the peptides elute from the column they are ionized and detected by an Quadrupole Orbitrap hybrid mass spectrometer. In data-dependent acquisition mode masses of intact peptides are detected by MS scans which are followed by peptide fragmentation to determine the sequence and post-translational modifications of the peptides.

Scientific achievements: To profile the dynamics of protein expression and changes in protein modification with maximum sensitivity the CECAD Proteomics Facility is equipped with latest generation liquid chromatography and mass spectrometers. In continuation of the successful Orbitrap technology, the proteomics platform is now equipped with two Q Exactive Plus LC-MS/MS systems (Thermo Scientific). These instruments combine quadruple precursor ion selection with high-resolution accurate-mass Orbitrap detection. The superior quality of these instruments enables the analysis of complex biological samples in depth and with great confidence.

Future plans: The proteomics platform will continue to develop and apply state-of-the-art liquid chromatography and mass spectrometry. This includes high throughput proteomic analysis of biological samples, the discovery of protein-protein complexes via crosslinkers, and the global identification of post-translational modification (PTM), including phosphorylation and ubiquitination. The facility will develop analytical protocols to measure low-level protein concentrations and will continue its analytical efforts to use targeted proteomics for biomarker analysis.



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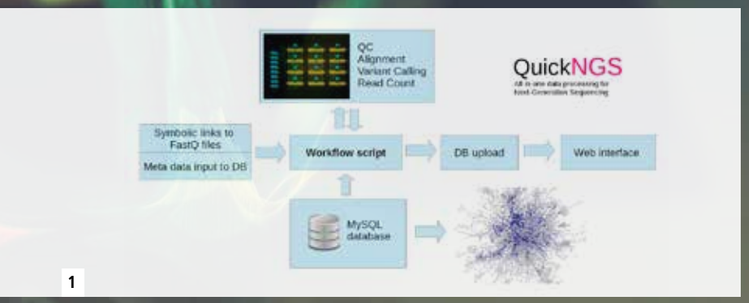
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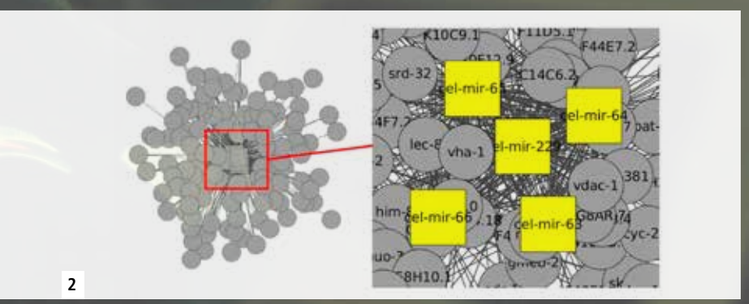
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Erfolgreiche Forschung in einem kompetitiven Umfeld basiert auch auf neuester Informationstechnologie. Die Bioinformatik-Facility unterstützt die CECAD Wissenschaftlerinnen und Wissenschaftler in der biologischen Datenverarbeitung. Sie bietet Technologie zur Verarbeitung der enormen Datenmengen aus Hochdurchsatzanalysen und entwickelt Spezialsoftware zur Bearbeitung datenintensiver Fragestellungen.



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FIGURE 1: The QuickNGS framework developed by the facility combines a broad collection of widely adopted Next-Generation Sequencing (NGS) data analysis softwares into a professional high-end analysis system enabling rapid in-depth analysis of tens or hundreds of samples from NGS experiments with extremely low hands-on time. The sample information simply needs to be fed into a MySQL database by the lab operators and all the rest is running fully automated, ending up in a convenient web interface for easy user access.
FIGURE 2: The lab operates an in-house software package which trains models of molecular regulatory networks by taking advantage of the large and ever increasing RNA-Seq/ChIP-Seq databases behind the QuickNGS framework. Integration of these networks with additional a-priori knowledge from public databases has established a very powerful tool for downstream analysis of RNA-Seq data from the labs within CECAD.
The figure shows a sub-network of a trained miRNA regulatory network in *Caenorhabditis elegans* enriched for genes involved in lifespan regulation and aging.



↗ http://cecad.uni-koeln.de/Bioinformatics-Facility.268.0.html

Bioinformatics Facility

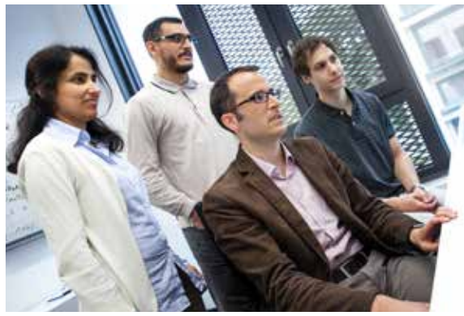
Dr. Peter Frommolt
Head of Bioinformatics Facility

Initially part of the Cologne Center for Genomics (CCG), the CECAD Bioinformatics Facility has been relocated to the CECAD building at the end of 2013. The facility has recruited new co-workers who take responsibility for bioinformatics data analysis and software development. In addition, bioinformatics PhD students from several CECAD labs were embedded into the facility to take advantage of its infrastructure and expertise. The IT hardware used by the Bioinformatics Facility is operated by the Regional Computing Center of the University of Cologne (RRZK).

Services: The newly founded Bioinformatics Facility provides support in all areas of biological data analysis. In particular, it helps with handling the enormous amounts of data from high-throughput technologies in the genomics (Next-Generation Sequencing) as well as the proteomics and metabolomics (Mass Spectrometry) fields. For this purpose, the platform develops very efficient analysis pipelines using state-of-the-art analysis algorithms, but also aims at offering more individualized support.

Scientific achievements: Apart from the basic data processing, the group is particularly interested in innovative data-driven methods for the identification of regulatory molecular circuits. This work relies on public resources as well as large in-house RNA-Seq/ChIP-Seq databases growing with every single sample that is being processed by the analysis pipelines. This data pool is used to establish networks of molecular regulation on the transcriptional as well as the post-transcriptional level which are then made accessible as a high-level support to several collaborative projects with research labs from CECAD.

Future plans: The platform pursues the particular goal to participate in projects involving data integration between different levels of biological information, for instance integrated genomics/proteomics analyses, which open a more system-wide view on biological questions. The Bioinformatics Facility is supported by independent funding from the German Research Foundation (DFG, grant FR3313/2-1 to PF) and the Federal Ministry of Economy and Technology (BMWi, grant KF2429610MS2 to PF).



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Für vielversprechende Forschungsansätze, die erfolgreich in vitro sowie an wirbellosen Tieren entwickelt wurden, ist es in der biomedizinischen Grundlagenforschung essentiell, diese an komplexeren Modellorganismen weiterzuentwickeln. So können Alterungsprozesse und damit assoziierte Erkrankungen verstanden und Therapiemöglichkeiten daraus abgeleitet werden. Physiologisch dem Menschen nahe verwandt und experimentell zugänglich, ist die Maus in spezifischen Fragestellungen das geeignete Modellsystem. Die Tierhaltung ‚in vivo Research Facility' ist ein integraler Teil eines Konzeptes mit hohem gesellschaftlichen und individuellen Nutzen durch die Entwicklung von neuartigen Behandlungskonzepten und Medikamenten gegen z.B. Krebs, Schlaganfall, Diabetes oder neurodegenerative Erkrankungen.



in vivo Research Facility

Prof. Dr. Branko Zevnik
Head of in vivo Research Facility



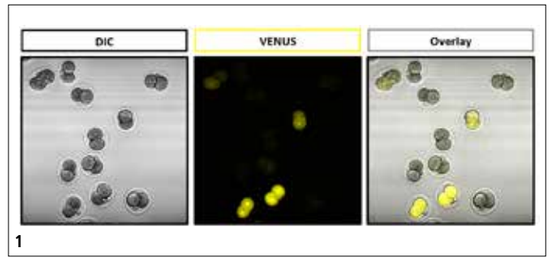
Dr. Ylva Mende
Scientific Manager in vivo Research Facility

CECAD's in vivo Research Facility (ivRF) is an animal facility with state-of-the-art technology, designed and run in line with the latest scientific findings, legislation, ergonomics, and especially animal welfare. Five separate, individually operated barriers allow maximum flexibility for the wide variety of demands made by the research groups. 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 requirements of the 2013 law on the protection of animals used for scientific purposes and consistently adheres to the three R's principle of animal welfare: reduction, refinement, and replacement.

Services: CECAD's in vivo Research Facility has two main departments. The Animal Facility offers CECAD's research groups the opportunity to validate their results in approved and strictly controlled animal studies. The ivRF organizes the import and export of model organisms and biological materials. Scientists experienced in laboratory animal care advise on animal welfare and legal requirements. Ongoing training of qualified staff responsible for animal housing ensures a comprehensive service that includes both professional care and on-site assistance.
The second department is the Transgene Service Unit. This unit is an experimental platform for establishing mouse models in accordance with the latest scientific knowledge, such as genome editing. In addition, it offers laboratory services for embryology, cell biology, and molecular biology.

Scientific achievements: With an innovative concept and in full compliance with current legislation, the ivRF opened its animal facility and transgene service departments in 2014. Strictly controlled hygiene management ensures a high quality of scientific research. Expert advice from the ivRF supports the individual research groups in their various projects.

Future plans: The ivRF supports the work of the scientific research groups by making resources and cutting-edge technology available. A facility providing an environment also suitable for higher safety levels of genetic engineering, as well as a core unit with absolutely reliable hygiene, offers opportunities to build up the range of services.
The goal is to extend the range of transgene services on offer, for example, with high-quality embryonic stem cells for gene targeting, in-house genetic monitoring of mouse lines, and optimising new transgene technology. A planned research priority is to improve the techniques used. In accordance with the three R's principle, the aim is to reduce the number of animals required.



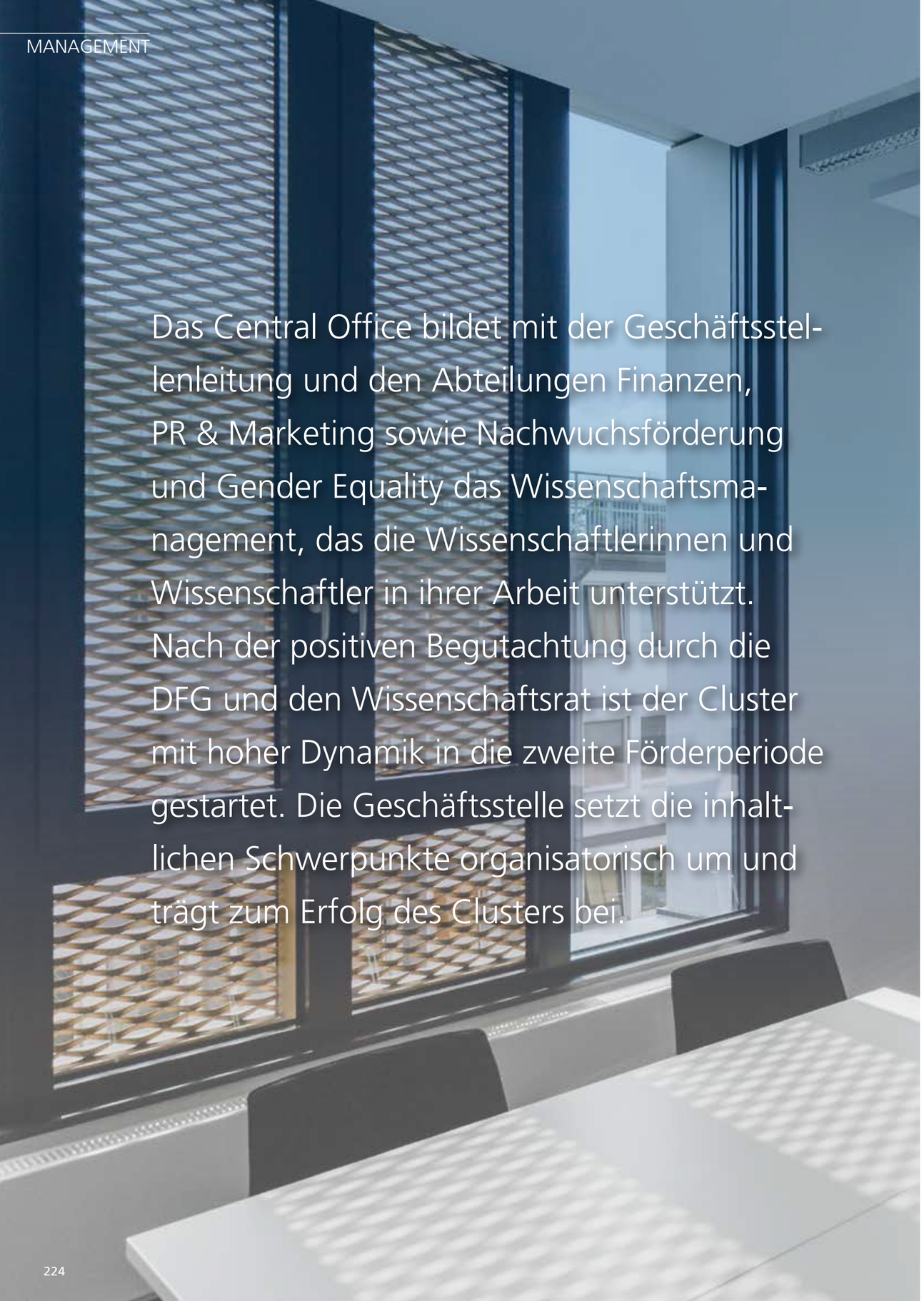
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FIGURE 1: Venus expression from CAG-VENUS plasmid 24 hours after pronuclear injection

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Management





↗ http://cecad.uni-koeln.de/Central-Office.36.0.html

Central Office

Dr. Anja Pfletschinger
Administrative Coordination



Dr. Benjamin Köckemann
Administrative Coordination

With office management and departments of finance, PR & marketing, support for junior researchers, and gender equality, the Central Office is CECAD's administrative hub, providing a research environment that supports its scientists in their work. After positive assessments from the DFG [German Research Foundation] and the *Wissenschaftsrat* [German Council of Science and Humanities], the Cluster has made a dynamic start to its second funding period. The Central Office ensures the implementation of the focus areas and contributes greatly to CECAD's success.

Our Tasks

Professional scientific management organizes the administrative aspects of research in the Cluster of Excellence. The Central Office, with office management and departments of finance, PR & Marketing, support for junior researchers, and gender equality, provides an administrative infrastructure that allows CECAD to optimally support its research scientists in their work.

Modern research is complex – intensive professional communication between research scientists generates synergies and new information. The special architectural and laboratory design of the new CECAD Research Center building, opened in May 2013, allow close networking within its 10,600 m^2. State-of the-art technologies offer optimal conditions for cutting-edge international research. Together with the scientists, the Central Office was closely involved in the planners' work and contributed to the development of a high-performance research center.

The Central Office's tasks include coordinating individual user requests and organizing applications to finance basic equipment, the purchase of large equipment, and commissioning.

Close cooperation between basic scientific and clinical CECAD research groups, the Cologne University Hospital, and the Max Planck Institutes on campus has allowed a unique center for aging research to be established. Patients at the Cologne University Hospital benefit from a systematic transfer of information from cutting-edge research into new clinical treatment at a university hospital providing high-end medicine.



Maria Vilgertshofer
Assistance of
Administrative Coordination





The CECAD Research Center, the Max Planck Institute for Biology of Ageing, and the Max Planck Institute for Metabolism Research form a unique world-class center for aging research in Cologne.

CECAD organizes congresses and participation in conferences, seminars and presentations, as well as international retreats, all of which provide scientists with opportunities for international networking, while discussion of the latest research topics inevitably generates new information.

The scientific development of CECAD was accelerated by the strategic appointment of 17 internationally renowned scientists as professors, the funding of junior research groups, and the consolidation of six professorial chairs at the University of Cologne. These processes require efficient and professional office management.

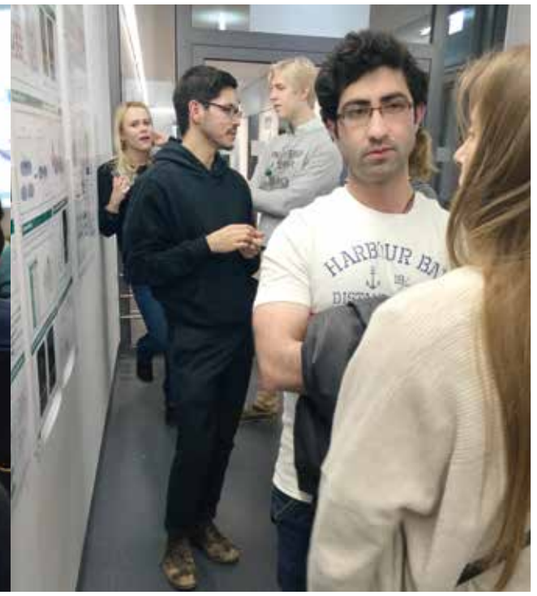
The Central Office cooperates with the University of Cologne and the University Hospital administrative offices, and is in communication with the funding bodies. The Central Office organizes the executive board of the Cluster of Excellence, the faculty board of the Research Center and the administration of the technology platform.

The Cluster of Excellence has made a dynamic start to its second funding period, after positive assessments from the DFG and the *Wissenschaftsrat*. The Central Office ensures the implementation of the focus areas, such as intensifying translational research and promoting young scientists, and contributes greatly to CECAD's success.

Modern laboratories with state-of-the-art equipment allowing a clear separation between lab space and write-up areas are the result of dedicated efforts by the planners, scientists, and the Central Office.









LEFT: CECAD Retreat 2014. CECAD scientists present their current research findings, followed by intensive discussions and exchange of knowledge.
RIGHT: Plenary Meeting 2013. CECAD members vote for their representatives.

Overview Central Office Tasks

Administrative Coordination

- Coordination of Central Office
- Administrative & organisational support of CECAD Research Center, New Groups and Core Facilities
- Support of Executive Board, Faculty Board, Advisory Board
- Organisation of Plenary Meeting, Retreats
- Communication to funding organisations as well as Medical and Nat.Sc.-Faculty

Financial Projectmanagement

- Management DFG third party funding
- Management Cluster basic funding
- Management of the Cluster overheads of the coordinator
- Communication to the University management and funding organisations as well

Promotion of Junior Researchers

- Cologne Graduate School of Ageing Research
- Career Support for CECAD Junior Scientists

Gender and Family Support

- Career Support for female CECAD scientists
- Support for families

PR & Marketing

- Spokesperson of the Cluster
- Marketing
- Strategic and operational external as well internal communications
- Communication of Translational Research

SECOND FUNDING PERIOD

Continuous development of established structures and the scientific research program

→ Recruitment of exceptional scientists at all career stages

→ Modernization and professionalization of the Technology Platform

→ Bundling of activities – Fusion of the CECAD Graduate School with the IMPRS Age Graduate School

→ Further development of CECAD's science communication and research marketing



↗ http://cecad.uni-koeln.de/Central-Office.36.0.html

Funded by the Excellence Initiative

Dr. Nora Redemann
Head of Financial Projectmanagement

Since November 2007, the CECAD Excellence Cluster has received public funding from the federal and state governments as part of the Excellence Initiative through the German Research Foundation (DFG). Following a successful initial funding period, CECAD received a positive evaluation from the DFG and the German Council of Science and Humanities and entered its second funding period in November 2012 that will last until October 2017.

The first funding period

During the first funding period, CECAD became a scientific milestone for the University of Cologne both internally and externally. The large research project involving initially more than 300 scientists presented the university with exciting challenges. CECAD developed new internal funding instruments using DFG project funding of the Excellence Cluster to support innovative research projects acting in the four CECAD Research Areas.

Together with the Faculty of Medicine and the Faculty of Mathematics and Natural Sciences, CECAD successfully appointed top researchers to the University of Cologne in line with the strategic direction of CECAD research.

One of CECAD's unique structural features is its focus on central service facilities to enhance the scientific infrastructure. With five facilities, the Technology Platform (A) offers state-of-the-art laboratory technology. More than 30 % of the DFG project funds of the first funding period were used to finance the platform for career support.

An additional platform (B) offers services for promising young scientists and career development, family support and gender mainstreaming, and PR & Marketing.

The Translational Research Platform (C) systematically transfers findings from basic research into new clinical therapies. CECAD applies DFG third-party funding to this area, thus offering a vital service in meeting the pronounced need for novel approaches to treating age-associated diseases in our aging society.

Second funding period

The second funding period allowed new structures to be established and further developed. Recruiting additional high-ranking scientists at all career stages was highly prioritized for increasing the Cluster's scientific outcomes, and realized from CECAD's German Research Foundation project resources in the financial expenditures for 2013, 2014 and the coming years.

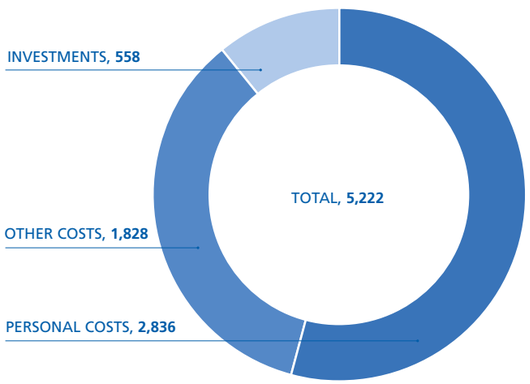
The four research areas (RAs) set up during the first funding period were differentiated into six areas. A substantial percentage of the Cluster's DFG funds went towards new appointments for professorships in Proteomics, the in vivo Research Facility, and the three newly recruited junior groups. One of these new junior groups was set up with the project partner at the Max Planck Institute for Biology of Ageing.

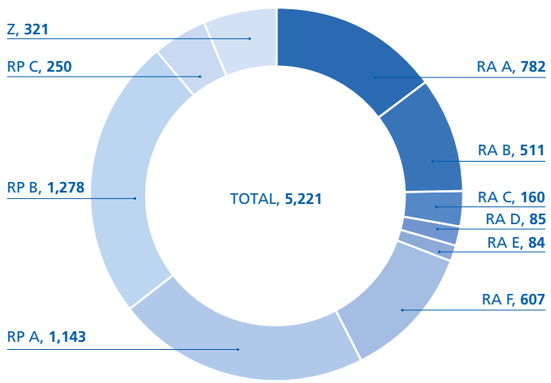
Top research requires excellent young talent. CECAD supports exceptional young scientists at early stages of their careers by offering scholarships for the 'Cologne Graduate School of Ageing Research'. Senior Postdoctoral Fellowships support the step to young postdoctoral researcher's independent stages of their scientific careers. This support has been positively evaluated both internally and externally and will therefore be further intensified in the second funding period (see Research Platform B). A scientific career presents unique challenges for young families and requires a high level of flexibility. So funding equality measures, such as flexible child care, is very important to CECAD (Research Platform B).

Based on the intensive use of the Technology Platform (Research Platform A) by scientists, the Excellence Cluster CECAD supports additional personnel in this area, allowing the service portfolio to be further professionalized.
The move into the CECAD Research Center marked another milestone for the Cluster. The new CECAD Research Center has been equipped with state-of-the-art technologies and offers exceptional working conditions for first-rate research.
Translational research's greatest successes were reflected in the appointment of a W3 professorship. A considerable increase in research activities from this area is expected as a result.
Through professional science communication and research marketing, CECAD has achieved and established the Cluster's strategic positioning with its relevant stakeholders. With a communication and marketing strategy that focuses on research goals, CECAD is realizing intensive public relations on all channels and innovative projects.

Fundraising from additional third-parties
Securing additional third-party funding and the high rate of involvement of CECAD scientists in collaborative partnerships both inside the Cluster and with other scientists on the campus nationally and internationally is a measure of the Cluster's exceptional vitality.
CECAD scientists are involved in several Collaborative Research Centres (CRCs/SFBs) supported by DFG funding and coordinated directly from the CECAD Research Centres. CECAD scientists are also intensively involved in a new CRC Transregio. With a view towards the future, CECAD will continue to focus on attracting additional CRCs.
The high success rate of CECAD applications at the European level is an indication of the Cluster's international visibility. A number of projects receive funding from the EU European Research Council, such as 'International Training Networks' from the European Commission, other ‚European Recearch Council (ERC) Grants', a 'Marie Curie Reintegration Grant' and further grants are currently in preparation.
As part of System Biology for Health in Old Age, the GerontoSys Initiative from the Federal Ministry of Education and Research, the University of Cologne succeeded in procuring an additional professorship with the Sybacol Project. This systems biology approach scientifically compliments CECAD research and has now also been locally integrated into the CECAD Research Center.

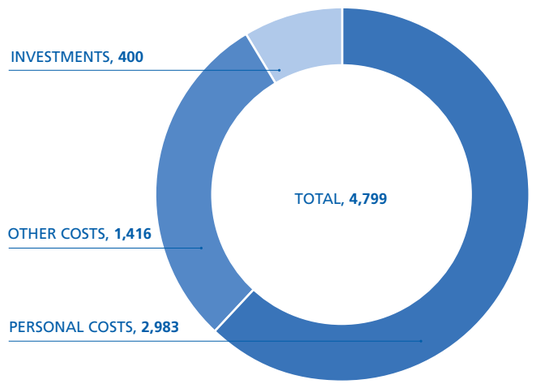
Third party funding by the DFG
2012 November – 2013 December
Costs/Thousand Euro

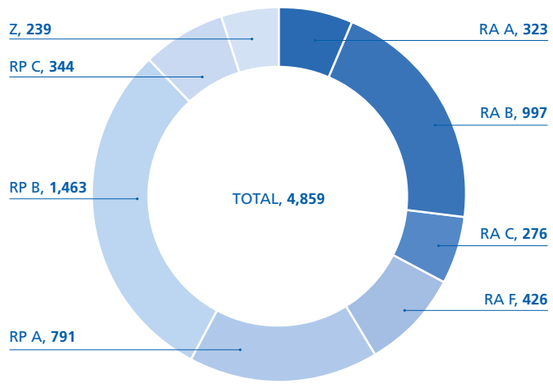




RP Research Platform A – C
RA Research Area A – F
Z Central Management

Third party funding by the DFG
2014 January – December
Costs/Thousand Euro





RP Research Platform A – C
RA Research Area A – F
Z Central Management


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FIGURE 1: Opening of the CECAD Research Center: research based on communication. The musical event reinforced the concept – a new work was performed.
FIGURE 2: Vivid presentation of research: brief film teaser and interview of the lead scientist in each Research Area by the managing editor of *DRadio Wissen*.

FIGURE 3: Eminent guests at the opening ceremony included the German Parliamentary Secretary of State Thomas Rachel, the minister for the sciences in North Rhine-Westfalia Svenja Schulze, the Rector of the University of Cologne, and the Chancellor of the University of Cologne.
FIGURE 4: Get together
FIGURE 5: Press conference (from right to left on the podium): Rector of the University of Cologne, Prof. Dr. Axel Freimuth; Executive Chairman and Medical Director of the University Hospital Cologne, Prof. Dr. Edgar Schömig; Scientific Coordinator of CECAD, Prof. Dr. Jens Brüning; Head of CECAD PR & Marketing, Astrid Bergmeister
FIGURE 6: The NRW Minister for Innovation, Science and Research, Svenja Schulze, delivered a speech to the 300 invited guests from the worlds of politics, administration, science and culture.



↗ http://cecad.uni-koeln.de/About-Communications.37.0.html

PR & Marketing

Astrid Bergmeister MBA
Head of PR & Marketing

CECAD: Synergies via a new network of innovative minds and ideas

'More and more people are living longer and longer. CECAD is looking for solutions leading to a healthy old age.'
The demographic shift in our aging population is one of the greatest challenges of our times. Research into aging and aging-associated diseases is therefore of both individual and societal relevance. CECAD presents its scientists' work to the world beyond the scientific community and raises public awareness of what successful research means for both the individual and society as a whole.

CECAD communicates actively – for both internal and external purposes – using an integrated communication and marketing strategy that harmonizes target groups, messages, goals, and projects in the making. Thanks to its highly developed corporate design, CECAD networks with specific target groups in the scientific community on politics, scientific administration, and economics. New pathways dovetail with conventional channels of information and research transfer. CECAD has increased its national and international impact considerably in the second funding period.



FIGURE 7 AND 8: To coincide with the opening of the Research Center, CECAD hosted the 'First Cologne Aging Conference', with internationally renowned speakers. The event attracted 250 participants.


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FIGURE 3 AND 4: Evening event: 200 invited guests from politics, business, lobby groups, administration, and science experienced an innovative panel discussion on three levels. Switching between differently composed panels, as on the radio, provided an entertaining intense discussion on medical and biological aging research, with all its societal and economic implications.

Together with the Cologne Chamber of Commerce and Industry, CECAD presented the professional interactive exhibition and high-profile evening event that made up 'Aging Science Expedition – CECAD live'.
FIGURE 1 AND 5: Interactive: CECAD carries out research into the causes of aging-associated diseases. The exhibition wall on Translational Research posed and answered the question 'Which diseases are involved in the latest findings from CECAD's basic scientific research and the development of new treatment options?' The exhibition on the ground floor of the Chamber of Commerce and Industry demonstrated the close interactions between cutting-edge research at the University, high-end medicine for translational research at the University Hospitals, and CECAD.
FIGURE 2: The exhibition provided comprehensive and interactive information on all CECAD's research areas.



'Our position at the interface between research and commercial enterprise carries great responsibility. Things often start with a molecule, then a cell, but ultimately concern a patient. It involves people – every single member of our society.'
Translational research is a very dynamic field, systematically transferring basic scientific knowledge into clinical practice. New findings reach patients rapidly and create new therapeutic standards. Nevertheless, the main requirement for developing new treatments to combat age-associated diseases is still basic scientific research. CECAD finds solutions to generate innovations from ideas. These innovative concepts need competent partners – business companies and politicians. Together with the scientists, PR & Marketing has furthered close contact with the city department of economics in Cologne, the Cologne Biocampus, various lobby groups, and commercial enterprises. The translational events 'CECAD Research meets BioRiver Companies' in 2013, and 'CECAD Campus meets BioCampus Cologne' in 2014 were extremely successful.


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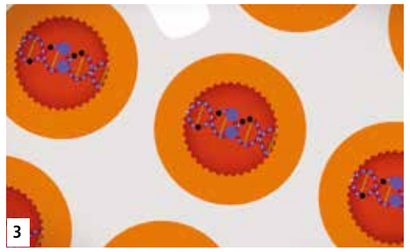
FIGURE 6 AND 7: 'CECAD Campus meets BioCampus Cologne': supported by Ute Berg, the Head of the Department of Economic Affairs, Cologne, CECAD brought scientists and clinicians together with business representatives on translational retreats (in 2013 and 2014).
In a panel discussion, Ute Berg spoke to Executive Chairman and Medical Director of the University Hospitals, Prof. Edgar Schömig, and the scientist Prof. Bernhard Schermer. The aim was to initiate new cooperations.

‘Cancer can affect anyone. Infections increase with age – basic scientific research and translation of the findings go hand in hand. Only in this way can there be new approaches in clinical research.’
CECAD has achieved great renown from successful research marketing that communicates strategic messages to the right target groups. For example, the Chamber of Commerce and Industry was the partner for the project ‘Aging Science Expedition – CECAD live’, which consisted of a professional, interactive exhibition that attracted a large number of visitors and a high-profile evening event geared to the relevant stakeholders in politics, administration, business, and science. The timing was just right, on the evening before the authorization of the second funding period by the DFG und WR was announced, CECAD attracted greater public attention. PR & Marketing had intensively supported the application for the second funding period.

Throw the doors wide open: How do scientists at CECAD carry out their research? What are their visions? What challenges do they face? CECAD communicates actively – the opening of the new Research Center in May 2013 brought research to life for the invited guests. PR & Marketing was responsible for the opening of the CECAD Research Center and for managing the ‘First Cologne Aging Conference’, which ran in parallel.



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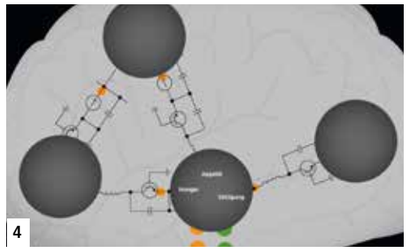
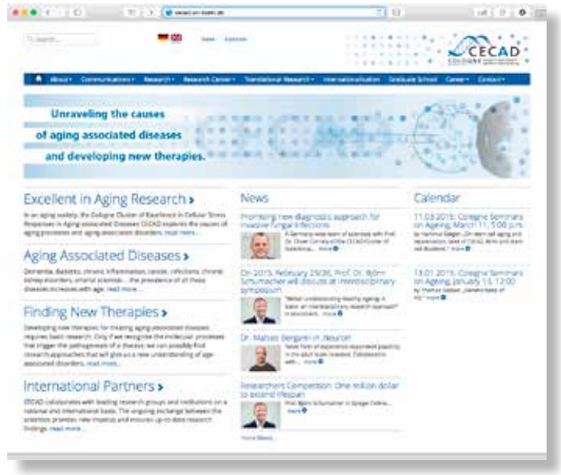

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FIGURE 1 AND 2: Modern research is complex and multi-layered – the CECAD image film communicates this message.
FIGURE 3 AND 4: Research films show easily understood yet fascinating detail on the topics of research being carried out by CECAD. Good examples can be seen in (3) innovative approaches to cancer research and (4) neuronal regulation of energy supply and utilization (metabolism research).

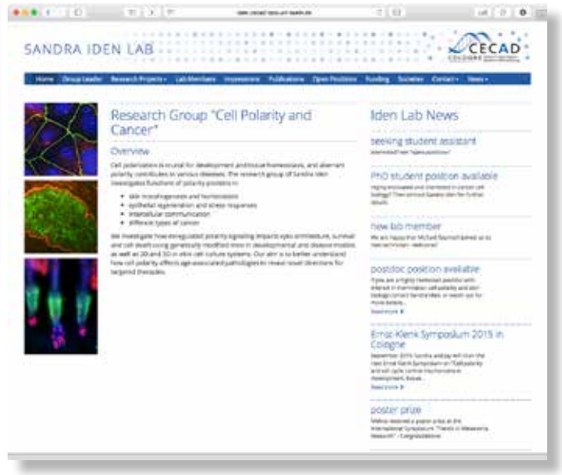
In spring 2015 the CECAD website has successfully been relaunched with optimal target-group-specific presentation of content; incorporation of new features such as ‘Spot on Young Scientists’, in which junior scientists in the Cluster can have their say; changing emphasis on research focus areas; presentation of the Cluster’s strategies to become more international; successful translational research projects; and, of course, the new CECAD Research Center opened in 2013.

The relaunch will be linked to this annual report but will provide far more exciting insights into CECAD research, way above and beyond the information contained in the report itself.
PR & Marketing is managing both projects and providing the key contact for all scientists, other members of staff, and external service providers.

Modern research is complex – it is organized into interdisciplinary projects. Research scientists belong to multiple departments, research centers and clusters, not to mention their own laboratories. CECAD is successful in this multicentric cosmos and is developing a strong sense of in-house identity. An internal newsletter and the intranet developed in 2014 increase networking and the exchange of information.



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FIGURE 5: CECAD website relaunch 2015, home page
FIGURE 6: One component of the new website: presentation of the CECAD Research Center



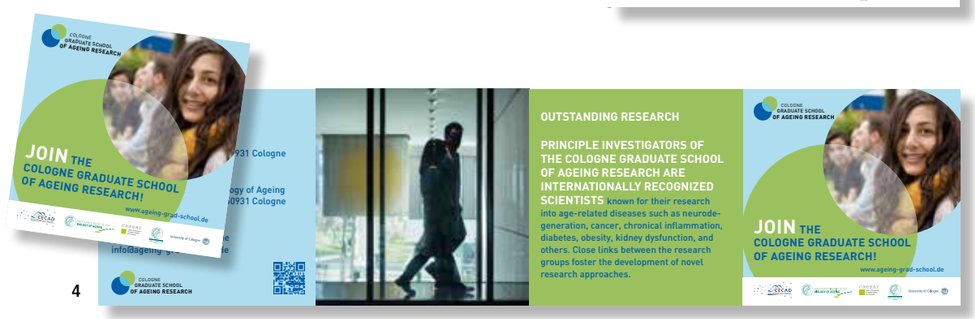
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FIGURE 1– 4: Together with the Max Planck Institute for Biology and Ageing Research, the Max Planck Institute for Metabolism Research, and the Center of Advanced European Studies and Research (caesar), CECAD founded an amalgamated Graduate School in 2013. This educational facility bundles the strengths of all the partner institutes – to the benefit of the Ph.D. students. The figures show the new website and the visual identity.

So that the research is also successful in the long term, the University of Cologne and CECAD encourage young scientists with fellowship programs and the 'Cologne Graduate School of Ageing Research', with the Max Planck Institute for Biology and Ageing Research and the Max Planck Institute for Metabolism Research, and the Center of Advanced European Studies and Research (caesar) as partners. CECAD's PR & Marketing department ensures successful communication, both in-house and externally, by supporting the development of the website for the amalgamated Graduate School, press releases, and publicity campaigns.

Public funding makes cutting-edge research at CECAD possible. For its part, CECAD is developing dynamically and is dedicated to achieving high societal returns from new scientific findings. Given today's aging society, this will benefit not only the economy but also each and every one of us.

The new international CECAD Research Center is a cornerstone of future strategy for both the University of Cologne and the University Hospital.



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FIGURE 5: CECAD's brand-new image

Image Credits

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Jürgen Schmidt (Titel, 2, 4, 7, 8, 10, 12, 15, 16, 22/23, 24/25, 26/27, 34/35, 36/37, 52, 204, 222/223, 224, 225 Fig. LEFT + RIGHT, 226, 227)
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