RESEARCH REPORT

2019/20

LEIBNIZ
FORSCHUNGSINSTITUT
FÜR MOLEKULARE
PHARMAKOLOGIE

SCIENTIFIC ADVISORY BOARD

PROF. DR. KARL-HEINZ ALTMANN
ETH Zürich, Zürich, Schweiz, 2012 – 2019

PROF. DR. NILS BROSE (Chair 2013 – 2019)
Max-Planck-Institut für Experimentelle Medizin, Göttingen, 2012 – 2019

PROF. DR. ULRIKE EGGERT
King's College London, London, Vereinigtes Königreich, 2013 – 2020

DR. MATTHIAS GOTTWALD
Bayer Pharma AG, Berlin, 2016 – 2019

PROF. DR. THOMAS GUDERMANN
Ludwig-Maximilians-Universität München, München, 2013 – 2020

PROF. DR. ECKART GUNDELFINGER
Leibniz-Institut für Neurobiologie, Magdeburg, 2013 – 2020

PROF. DR. THOMAS LANGER
Max-Planck-Institut für Biologie des Alterns, Köln, 2020 – 2023

PROF. DR. BEAT MEIER
ETH Zürich, Zürich, Schweiz, 2013 – 2020

DR. FRANZ VON NUSSBAUM
Innovation Campus Berlin, NUVISAN ICB GmbH, Berlin, 2020 – 2023

PROF. DR. STEFAN OFFERMANNS (Chair since 2020)
Max-Planck-Institut für Herz- und Lungenforschung, Bad Nauheim, 2016 – 2023

PROF. DR. STEFAN RAUNSER
Max-Planck-Institut für Molekulare Physiologie, Dortmund, 2017 – 2020

PROF. DR. MICHAEL SATTLER
Deutsches Forschungszentrum für Gesundheit und Umwelt (DFGU), Helmholtz-Zentrum München, Neuherberg, 2020 – 2023

PROF. DR. PETRA SCHWILLE
Max-Planck-Institut für Biochemie, Martinsried, 2012 – 2019

PROF. DR. REBECCA WADE
ZMBH, Universität Heidelberg und HITS gGmhH Heidelberger Institut für Theoretische Studien, Heidelberg, 2013 – 2020

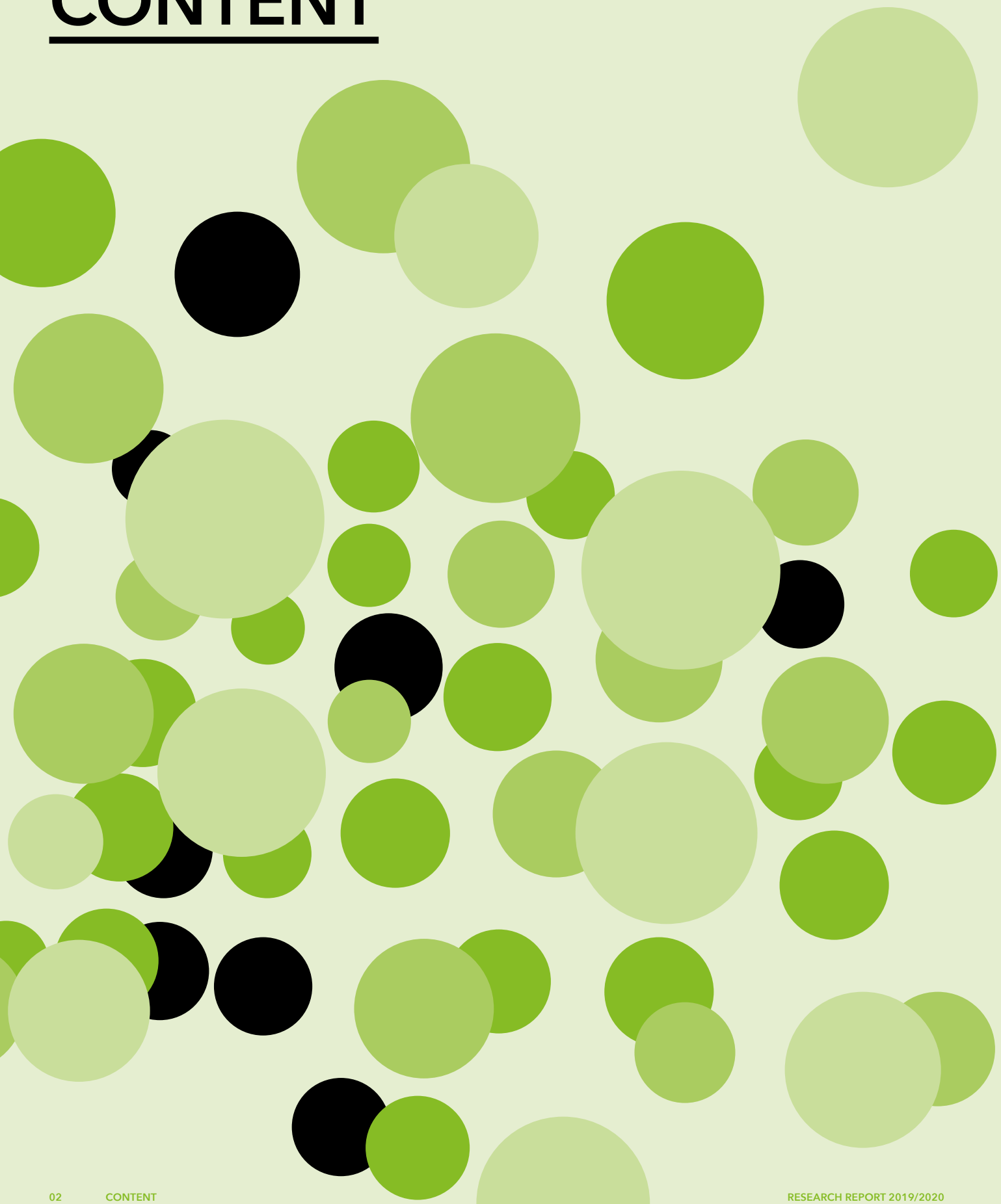
PROF. DR. HELMA WENNEMERS
ETH Zürich, Zürich, Schweiz, 2020 – 2023

RESEARCH REPORT

2019/2020

In 2019/2020, our researchers published 218 articles, including 191 peer-reviewed articles in scientific journals. A number of these articles are presented as highlights throughout the report.
In den Jahren 2019/2020 veröffentlichten unsere Forschenden 218 Publikationen, darunter 191 referierte Beiträge in Fachzeitschriften. Einige von ihnen werden in diesem Bericht auf Highlight-Seiten vorgestellt.

CONTENT



DEAR READERS, DEAR FRIENDS OF THE FMP,

LIEBE LESER*INNEN, LIEBE FREUND*INNEN DES FMP,

→ In the almost three decades since its foundation, the Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP) has established itself as one of the world's most outstanding research centers in molecular pharmacology. Unlike most medical institutions, which conduct disease-based or indication-based pharmacological research, the FMP takes an interdisciplinary approach to molecular pharmacology. This approach involves researchers from structural biology working together with scientists from the fields of genetics, physics, chemical biology or cell biology. The aim of this interdisciplinary mode of research is to develop novel approaches to molecular diagnostics and therapy, helping us create the medicine of tomorrow.

Our research must constantly evolve to remain at the forefront of science. This applies not only to the development or establishment of new technologies, such as CRISPR-based genome engineering or innovative methods of structural biology, but also to the biological topics and systems under study. As a result of our efforts to foster change, we have recruited Noa Lipstein, Daniel Roderer and Johannes Broichhagen as new junior group leaders during the 2019/2020 reporting period. By using innovative genetic, chemical biological and structural biological methods such as cryo-electron microscopy, they seek to explore the causes of neurological disorders and of colorectal cancer in a bid to develop new options for the diagnosis and treatment of these diseases. In turn, junior group leaders Tanja Maritzen and Janine Kirstein have left the Institute to take up professorships at the universities of Kaiserslautern and Bremen, respectively. In this way, the FMP contributes visibly to Germany's role as a science location by acting as a breeding ground for successful early-stage researchers. We would also like to take this opportunity to thank Ronald Kühne and Gerd Krause, group leaders who helped shape and determine research at the FMP and who have now retired.

Successful research has also led to the founding of the spin-off companies Tubulis and ProSion, which take innovative chemical biological and synthetic approaches to disease control. Both companies are a testament to the successful translational research conducted at the FMP and at the Campus Berlin-Buch.

In addition to these examples of successful enterprise creation, we have also enhanced our role as a partner of Berlin's universities in the last two years. For example, Fan Liu, leader of the Structural Interactomics research group, was additionally appointed as Professor for Structural Interactomics at Charité – Universitätsmedizin in 2020; a joint professorship in Structural Chemical Biology with Technische Universität Berlin is now reaching the final appointment stage. These examples illustrate how closely the FMP is linked to Berlin's universities, and to the non-university institutions that have teamed up to form the BR50 alliance, to which the FMP also belongs.

An important development in the reporting period is the further expansion of EU-OPEN-SCREEN – a European high-capacity screening network initiated by the FMP located on Campus Berlin-Buch – and its partner sites at the FMP. As such, Campus Berlin-Buch has established itself as the European gateway for drug screening research.

Last but not least, FMP scientists once again scooped numerous awards and prizes for their successful work in 2019/2020, which we see as a great honor and an incentive to keep up the great work. Turn the page to read more about our research and how the resulting insights

could foster new ways of drug development – from fighting viral-based infectious diseases to brain dysfunction.

I hope you enjoy reading it!
Volker Haucke

→ Das Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP) hat sich in den nahezu drei Jahrzehnten seit seiner Gründung als eines der weltweit herausragenden Forschungszentren der Molekularen Pharmakologie etabliert. Anders als die meisten medizinischen Einrichtungen, die krankheits- oder indikationsbasierte pharmakologische Forschung betreiben, verfolgt das FMP ein interdisziplinäres Konzept der molekularen Pharmakologie, in welchem Forschende aus der Strukturbiologie mit Wissenschaftler*innen der Genetik, Physik, Chemischen Biologie oder Zellbiologie zusammenarbeiten. Das Ziel dieser interdisziplinären Forschung ist es, neue Ansätze der molekularen Diagnostik und Therapie zu entwickeln und so die Medizin von morgen zu erschaffen.

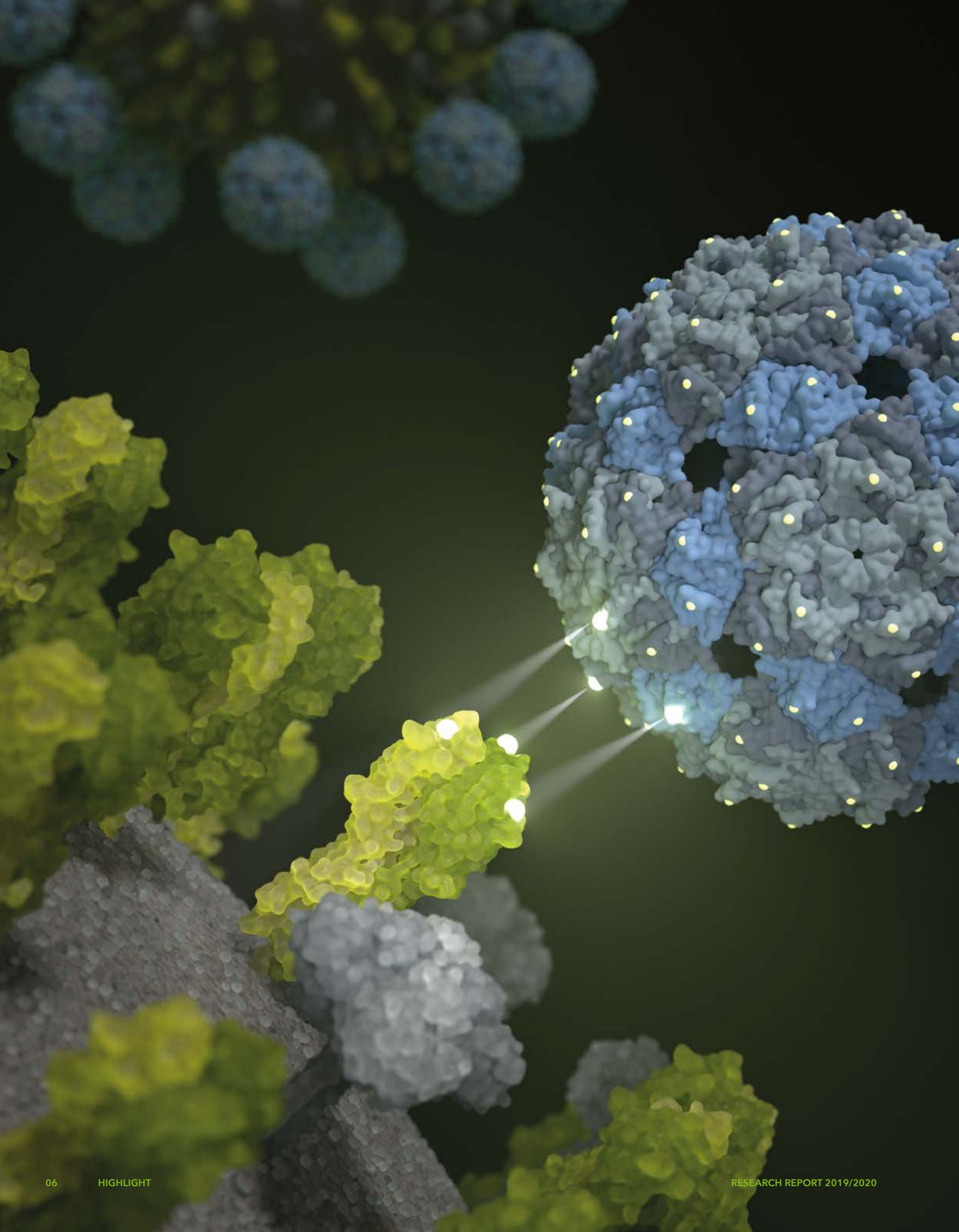
Um am Puls der Zeit zu bleiben, ist unsere Forschung beständiger Veränderung unterworfen. Das betrifft sowohl die Entwicklung oder Etablierung neuer Technologien wie des CRISPR-basierten Genom-Engineerings oder innovativer Methoden der Strukturforschung als auch die biologischen Fragestellungen und Systeme. So haben wir im Berichtszeitraum 2019/2020 Noa Lipstein, Daniel Roderer und Johannes Broichhagen als neue Juniorgruppenleiter*innen gewinnen können, die mit innovativen genetischen, chemisch-biologischen und strukturbiologischen Methoden wie der Kryo-Elektronenmikroskopie die Ursachen neurologischer Störungen und von Darmkrebs-Erkrankungen ergründen wollen, um so neue Möglichkeiten der Diagnostik und Behandlung zu entwickeln. Im Gegenzug haben die Gruppenleiterinnen Tanja Maritzen und Janine Kirstein das Institut verlassen, um Professuren an den Universitäten in Kaiserslautern und Bremen zu übernehmen. Damit trägt das FMP sichtbar als Brutstätte erfolgreicher Nachwuchswissenschaftler*innen zum Wissenschaftsstandort Deutschland bei. Unser Dank gilt auch unseren nunmehr in den Ruhestand eintretenden Gruppenleitern Ronald Kühne und Gerd Krause, die über Jahrzehnte die Wissenschaft am Institut mitbestimmt und geprägt haben.

Erfolgreiche Forschung hat darüber hinaus zur Gründung der Spin-Off-Unternehmen Tubulis und ProSion geführt, die innovative chemisch-biologische und synthetische Ansätze zur Krankheitsbekämpfung verfolgen. Beide Unternehmen sind damit ein Ausweis erfolgreicher translationaler Forschung am FMP und auf dem Campus Berlin-Buch.

Neben diesen Beispielen geglückter Unternehmensgründungen haben wir in den vergangenen beiden Jahren auch unsere Rolle als Kooperationspartner der Berliner Universitäten ausgebaut. So ist Fan Liu, Leiterin der Forschungsgruppe Strukturelle Interaktomik, seit 2020 Inhaberin einer gleichnamigen Professur an der Charité-Universitätsmedizin; eine gemeinsame Professur für Strukturelle Chemische Biologie mit der Technischen Universität Berlin befindet sich im finalen Stadium der Berufung. Diese Beispiele illustrieren die enge Verzahnung mit den Berliner Universitäten, aber auch mit den außeruniversitären Einrichtungen der BR50, zu denen das FMP gehört.

Eine wichtige Entwicklung im Berichtszeitraum ist der weitere Ausbau von EU-OPENSCREEN, eines vom FMP initiierten europäischen Netzwerks für Hochdurchsatz-Screening mit Sitz auf dem Campus Berlin-Buch, und seiner Partnersites am FMP. Damit hat sich der Campus Berlin-Buch als europäische Schnittstelle der screeningbasierten Wirkstoffforschung etabliert. Schließlich haben FMP-Wissenschaftler*innen auch in 2019/2020 für ihre erfolgreichen Arbeiten zahlreiche Anerkennungen und Preise erhalten, die uns Ehre und Ansporn zugleich sind. Lesen Sie auf den folgenden Seiten mehr über unsere Forschung und die Frage, wie die sich daraus ergebenden Erkenntnisse neue Wege der Arzneimittelentwicklung befördern könnten – von der Bekämpfung virusbasierter Infektionskrankheiten bis zu Fehlfunktionen des Gehirns.

Ich wünsche Ihnen viel Vergnügen dabei!
Volker Haucke



PHAGE CAPSID AGAINST INFLUENZA

PHAGEN-KAPSID GEGEN INFLUENZA

A new approach brings the hope of new therapeutic options for suppressing seasonal influenza and avian flu: On the basis of an empty – and therefore non-infectious – shell of a phage virus, a multidisciplinary team of researchers led by Professor Christian Hackenberger has developed a chemically modified phage capsid that "stifles" influenza viruses. Perfectly fitting binding sites cause influenza viruses to be enveloped by the phage capsids in such a way that it is practically impossible for them to infect lung cells any longer. This phenomenon has been proven in pre-clinical trials, also involving human lung tissue.
Lauster, D. *et al.*, Nature Nanotechnology 2020

Image: Phage shell docks on and inhibits the influenza virus.
Visualization: Barth van Rossum

Ein neuer Ansatz macht Hoffnung auf neue Therapieoptionen gegen die saisonale Influenza und Vogelgrippe: Auf Basis einer leeren und damit nicht-infektiösen Hülle eines Phagen-Virus hat ein multidisziplinäres Forscherteam um Prof. Christian Hackenberger ein chemisch modifiziertes Phagen-Kapsid entwickelt, das den Influenzaviren sprichwörtlich die Luft zum Atmen nimmt. Durch passgenaue Bindungsstellen werden die Influenzaviren so von den Phagen-Kapsiden umhüllt, dass sie die Lungenzellen praktisch nicht mehr infizieren können. Das belegen präklinische Tests, unter anderem an menschlichem Lungengewebe.

Bild: Phagenhülle dockt an und inhibiert das Influenzavirus

2019

GUEST PROFESSORSHIP

GASTPROFESSUR

→ Christian Hackenberger was Visiting Professor (Novartis Lecturer) at the New York University (NYU).
Christian Hackenberger war Gastprofessor (Novartis Lecturer) an der New York University (NYU).

CON GRATULA TIONS

APPOINTMENTS

BERUFUNGEN

→ Janine Kirstein has accepted a call to the chair of Cell Biology (W2 professorship) at the University of Bremen.
Janine Kirstein hat einen Ruf auf den Lehrstuhl Zellbiologie (W2-Professur) an der Universität Bremen angenommen.

AWARDS

PREISE

→ Alexander Walter received the Young Investigator Award (€3,345,575) of the Novo Nordisk Foundation in Copenhagen, Denmark.
Alexander Walter erhielt den Young Investigator Award (3.345.575 Euro) der Novo Nordisk Foundation in Kopenhagen, Dänemark.

→ Volker Haucke received the Feldberg Prize 2020, which is awarded annually by the Feldberg Foundation for anglo-german scientific exchange. The aim is to promote scientific exchange between British and German researchers in the field of experimental medicine.
Volker Haucke erhielt den Feldberg-Preis 2020. Die Auszeichnung wird jährlich von der Feldberg Foundation for anglo-german scientific exchange verliehen. Ziel der Stiftung ist es, den wissenschaftlichen Austausch zwischen britischen und deutschen Forscher*innen auf dem Gebiet der experimentellen Medizin zu fördern.

→ Dr. Carl Öster (Lange group) received a research fellowship for young scientists from the Human Frontier Science Program (HFSP, 2019 – 2022, €139.500). Using solid-state NMR, the biophysicist wants to study dynamic processes in potassium-selective and non-selective ion channels.
Dr. Carl Öster (AG Lange) erhielt vom Human Frontier Science Program (HFSP, 2019 – 2022, 139.500 Euro) ein Forschungsstipendium für junge Wissenschaftler*innen. Mithilfe der Festkörper-NMR will der Biophysiker dynamische Prozesse in kaliumselektiven und nicht-selektiven Ionenkanälen untersuchen.

→ Volker Haucke was elected to the renowned "Academia Europaea". The Academia Europaea is a European, non-governmental association that functions as an academy.
Volker Haucke wurde in die renommierte „Academia Europaea" gewählt. Die Academia Europaea ist eine europäische, nichtstaatliche Vereinigung, die als Akademie fungiert.

→ Adam Lange was elected Member of the Executive Board of Einstein Center of Catalysis, Berlin.
Adam Lange wurde zum Mitglied im Vorstand des Einstein Center of Catalysis, Berlin, gewählt.

AWARDS 2020

PREISE

→ Volker Haucke received a prestigious ERC Advanced Grant of the European Research Council (ERC). The biochemist was granted total funding of up to € 2.5 million for a period of five years for his highly innovative research on the assembly of synapses (SynapseBuild project).
Volker Haucke wurde einer der begehrten ERC Advanced Grants des Europäischen Forschungsrates (ERC) zuerkannt. Der Biochemiker erhält für fünf Jahre Fördermittel von rund 2,5 Millionen Euro für seine hochinnovative Forschung zum Aufbau von Synapsen (Projekt SynapseBuild).

→ Fan Liu from the Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP) was awarded a prestigious ERC Starting Grant by the European Research Council (ERC). The scientist was granted a total of up to € 1.5 million (SynLink project)
Fan Liu vom FMP erhielt einen der begehrten ERC Starting Grants des Europäischen Forschungsrates (ERC) für ihre hochinnovative Forschung zu den Interaktionen und der räumlichen Organisation des synaptischen Proteoms. Gefördert wird ihre Forschung mit bis zu 1,5 Millionen Euro (SynLink-Projekt)

→ Christian Hackenberger was honored at the Falling Walls conference with a "Breakthrough of the Year" award in the life sciences. Ten scientific "breakthroughs of the year" were announced on Monday in various disciplines. With this award, the jury recognizes Christian Hackenberger's research on protein-based biopharmaceuticals. These efforts led to the foundation of the highly successful start-up Tubulis (see p. 76)
Christian Hackenberger wurde auf der Falling Walls-Konferenz mit dem „Breakthrough of the Year"-Award ausgezeichnet. Gewürdigt wurde Christian Hackenbergers Forschung in der Kategorie Lebenswissenschaften über proteinbasierte Biopharmazeutika. Diese Forschungserfolge führten zur Gründung des sehr erfolgreichen Start-up-Unternehmens Tubulis. (siehe Seite 76)

→ Dr. Marc-André Kasper from Christian Hackenberger's department was awarded the Humboldt Prize 2020 for the doctoral thesis he completed at the Department of Chemistry at the Humboldt-Universität zu Berlin. In his PhD thesis on "Chemoselective synthesis of functional drug conjugates", he developed an innovative method for producing antibody drug conjugates. He also won the Best PhD Thesis Award 2020, sponsored by the Biochemistry Division of the German Chemical Society (GDCh).
Dr. Marc-André Kasper aus dem Department von Christian Hackenberger wurde für seine Dissertation am Institut für Chemie der Humboldt-Universität zu Berlin mit dem Humboldt-Preis 2020 ausgezeichnet. In seiner Dissertation mit dem Titel „Chemoselective synthesis of functional drug conjugates" hat er eine neuartige Methode für die Herstellung von Antikörper-Wirkstoff-Konjugaten entwickelt. Für seine Dissertation erhielt er zudem den Förderpreis 2020 der GDCh-Fachgruppe Biochemie.

APPOINTMENTS

BERUFUNGEN

→ Tanja Maritzen was appointed to a W2 professorship for Nanophysiology at the Technische Universität Kaiserslautern.
Tanja Maritzen hat den Ruf auf eine W2-Professur für Nanophysiologie an der Technischen Universität Kaiserslautern angenommen.

→ Fan Liu was appointed professor of Structural Informatics. The co-appointment was in collaboration with Charité – Universitätsmedizin Berlin.
Fan Liu wurde zur Professorin für Strukturinformatik ernannt. Die Co-Berufung erfolgte zusammen mit der Charité – Universitätsmedizin Berlin.

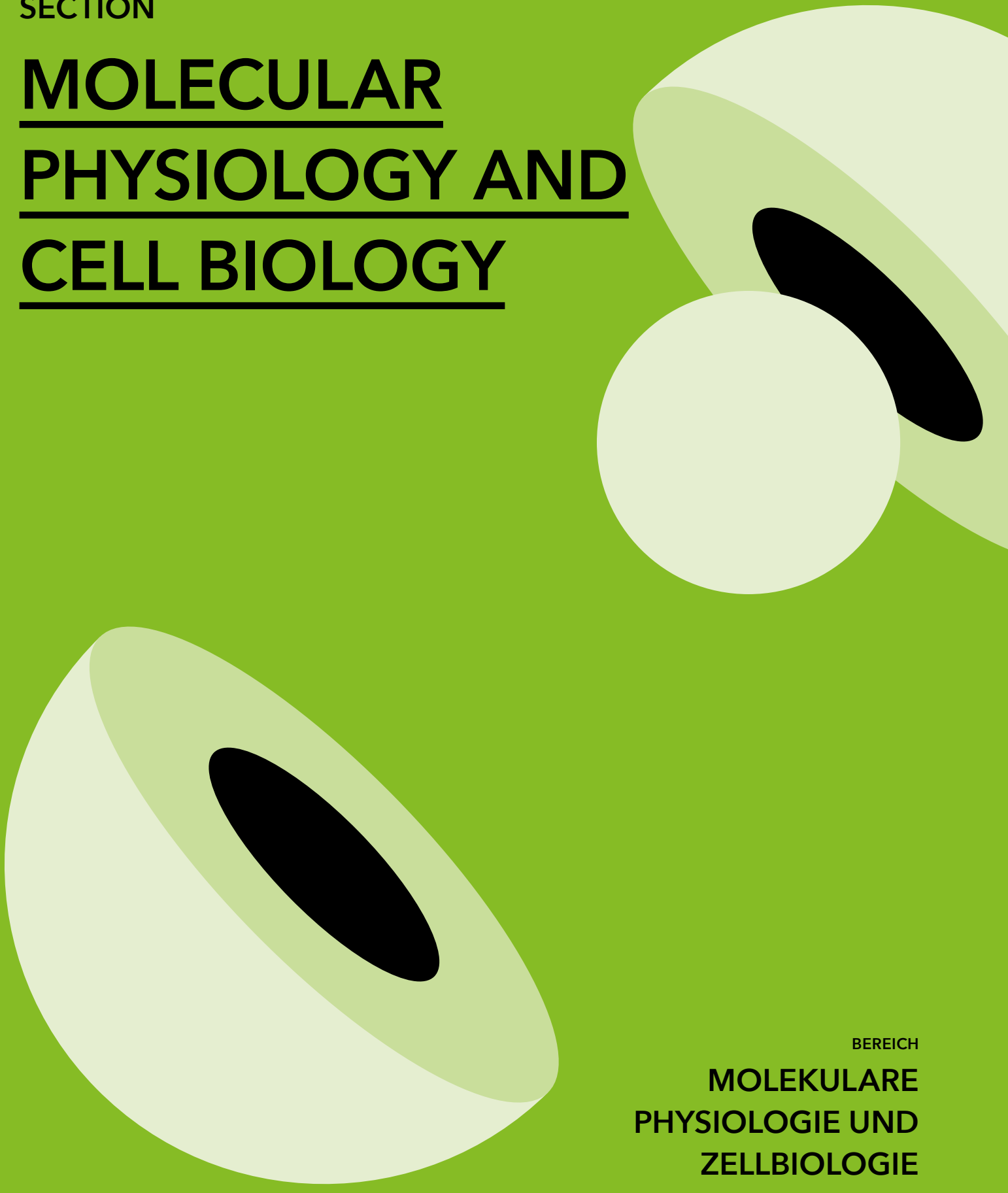
GUEST PROFESSORSHIP

GASTPROFESSUR

→ Volker Haucke was Visiting Professor (Professeur invité) at the Institute of Psychiatry and Neuroscience of Paris, Université Paris Descartes (iPNP).
Volker Haucke war Gastprofessor (Professeur invité) am Institut für Psychiatrie und Neurowissenschaften der Université Paris Descartes (iPNP).

SECTION

MOLECULAR PHYSIOLOGY AND CELL BIOLOGY



BEREICH

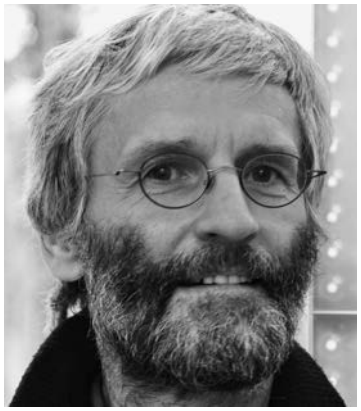
MOLEKULARE PHYSIOLOGIE UND ZELLBIOLOGIE

→ Life is based on complex cellular and physiological mechanisms, and their well-orchestrated interplay. In the case of disease, this interplay becomes unbalanced. Research in the "Molecular Physiology and Cell Biology" section aims to improve our understanding of such mechanisms in molecular detail and to study their dysfunction in disease. Cellular targets for pharmaceutical intervention – many of them membrane proteins such as ion channels or molecules involved in cellular trafficking – are identified and studied in their physiological environment. In addition, their modulation by bioactive compounds is explored. According to our mission to create a broader basis for pharmacology, we study less-explored membrane proteins and molecules of key importance for intracellular trafficking or signaling. A major focus is on neurobiology, with several groups working on trafficking and signal transduction at the synapse. Other research topics include the role of lysosomes in protein degradation and cellular metabolism – an area that is highly relevant for many neurodegenerative diseases – and ion channels and signaling processes, the importance of which extends to tissues beyond the nervous system. We employ a broad arsenal of techniques, ranging from molecular and cellular biology to biochemistry and biophysics, and from sophisticated imaging techniques to whole-animal physiology using genetically modified mice, which often directly model human disease. Our projects benefit greatly from interactions with other FMP sections, including those concerned with structural biology and modeling, drug and siRNA screening, and chemical biology.

→ Leben gründet sich auf komplexe zelluläre und physiologische Mechanismen und deren optimal abgestimmtes Zusammenspiel. Gerät dieses Zusammenspiel aus dem Gleichgewicht, entstehen Krankheiten. Das Verständnis dieser Mechanismen im molekularen Detail sowie deren Störung bei Krankheit ist Ziel der Forschung im Bereich „Molekulare Physiologie und Zellbiologie". Zelluläre Zielmoleküle (Targets) für eine pharmakologische Einflussnahme, darunter Ionenkanäle oder Proteine, die wichtige Signal- und Transportwege steuern, werden identifiziert und in ihrer physiologischen Umgebung untersucht. Zudem werden Substanzen gesucht, die diese Targets modulieren können. Im Sinne unserer Mission, die Basis für pharmakologische Einflussnahme zu vergrößern, ist unsere Forschung darauf ausgerichtet, wenige charakterisierte Membranproteine und Schlüsselmoleküle des intrazellulären Membrantransportes zu untersuchen. Ein wichtiger Fokus unserer Arbeit ist die Neurobiologie. Mehrere Gruppen analysieren Transportprozesse und Informationsverarbeitung an Synapsen. Des Weiteren erforschen wir beispielsweise die Funktion von Lysosomen, die neben ihrer Funktion im Proteinabbau wichtige Schaltzentren für den zellulären Stoffwechsel darstellen und hochrelevant für viele neurodegenerative Erkrankungen sind. Viele der von uns untersuchten Proteine und Prozesse sind keineswegs auf das Nervensystem beschränkt, sondern sind relevant für viele Organe und Pathologien. Zu ihrer Untersuchung setzen wir eine breite Palette von Techniken und Methoden aus Molekular- und Zellbiologie, Biochemie, Mikroskopie, Biophysik und Physiologie ein. Tiermodelle, in der Regel oft direkt krankheitsrelevante genetisch veränderte Mäuse, erlauben uns Studien im Kontext des komplexen Organismus. Unsere Projekte profitieren sehr von der Zusammenarbeit mit den anderen Bereichen des FMP, insbesondere mit der Strukturbiologie und Modellierung, dem Wirkstoff- oder siRNA-Screening sowie der Chemischen Biologie.

PHYSIOLOGY AND PATHOLOGY OF ION TRANSPORT

PHYSIOLOGIE UND PATHOLOGIE DES IONENTRANSPORTS



GROUP LEADER (at the FMP since 2006)
Prof. Dr. Dr. Thomas J. Jentsch

GROUP MEMBERS
Carolin Backhaus, Dr. Sandy Blin, Carlo Barbini, Dr. Xufeng Chen, Dr. Tony Daubitz*, Kerstin Fentker*, Dr. Corinna Göppner*, Petra Göritz, Anika Günther, Dr. Maja Hoegg-Beiler*, Mohamad Kabbani*, Dr. Hülya Kaplan*, Dr. Deborah Knecht (née Elger)*, Janet Liebold, Dr. Karen López Cayuqueo, Dr. Jennifer Lück, Dr. Norma Nitschke, Dr. Anna Oliveras Martínez*, Dr. Ian Orozco*, Dr. Rosa Planells-Cases, Dr. Mayya Polovitskaya, Katrin Räbel*, Patrick Seidler, Judith von Sivers*, Audrey Soria, Fabian Thöne*, Dr. Florian Ullrich*, Viktoriia Vorobeva*, Dr. Felizia Voss*, Mariia Zeziulia*, Dr. Joanna Ziomkowska*

* part of the period

→ leibniz-fmp.de/jentsch

→ We aim to understand ion transport processes from the molecular to the cellular and up to the level of the organism. The latter levels are addressed through an investigation of genetic mouse models and the analysis of human genetic diseases. In particular, we study CLC Cl^- channels and transporters and, more recently, volume-regulated VRAC/LRRC8 and acid-activated ASOR/TMEM206 channels. Key research areas are structure/function analysis, neurobiology, extracellular signaling, volume regulation, and the endosomal-lysosomal system. We investigate many organs, including the brain, inner ear, kidney, the immune system and endocrine organs such as the adrenal gland and endocrine pancreas. After our breakthrough in identifying the long-sought volume-regulated anion channel VRAC in 2014, we now elucidate its diverse functions. Most recently, we found that it is important for innate immunity by transporting the messenger molecule cGAMP. Our recent (2019) identification of ASOR opened yet another new area of research. Our analysis of a large collection of mouse models has already provided novel biological and medically important insights.

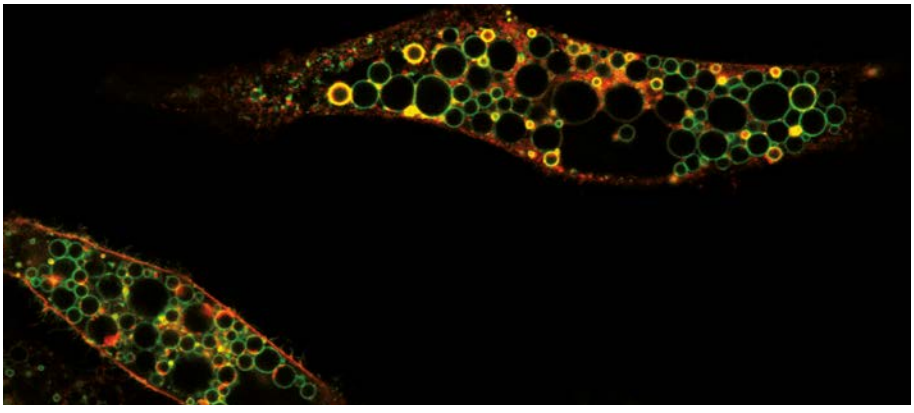
→ Unser Ziel ist es, Ionentransportprozesse von der molekularen über die zelluläre Ebene bis zur Rolle im gesamten Organismus zu verstehen. Letzteres erreichen wir durch Untersuchung der Phänotypen von genetisch veränderten Mäusen und durch die Analyse menschlicher Erbkrankheiten. Unser Fokus liegt auf Anionenkanälen, insbesondere CLC Cl^--Kanälen und -Transportern und den von uns erst kürzlich identifizierten volumenregulierten VRAC/LRRC8- und säureaktivierten ASOR/TMEM206-Kanälen. Wir studieren u. a. ihre Struktur-/Funktions-Beziehungen, Rollen in der Signaltransduktion und im endosomal-lysosomalen System. Dies führt uns zu verschiedenen Organsystemen wie Gehirn, Innenohr und Niere, endokrinen Organen und dem Immunsystem. Nachdem uns 2014 der Durchbruch mit der molekularen Identifizierung des schwellaktivierten Anionenkanals VRAC gelungen ist, klären wir nun seine vielfältigen Rollen auf, beispielsweise im Immunsystem, das VRAC durch den Transport des Botenstoffs cGAMP moduliert. Unsere kürzlich (2019) erfolgte Identifizierung von ASOR eröffnet abermals neue Forschungsrichtungen. Die Analyse einer großen Anzahl von Mausmodellen erlaubt uns schon jetzt wichtige Einblicke in bisher unbekannte physiologische Prozesse und liefert medizinisch relevante Erkenntnisse.

ROLE OF CLC Cl^- CHANNELS AND TRANSPORTERS IN HUMAN DISEASE

Our previous work has shown that the loss of the plasma membrane Cl^- channel ClC-2 leads to male infertility and leukodystrophy, whereas gain of function mutations causes hyperaldosteronism. We investigated the mechanism leading to overproduction of aldosterone and hypertension, using a novel mouse model expressing a hyperactive ClC-2 mutant. We also used cell type-specific ClC-2 KO mice to pinpoint the cell types responsible for the knock-out phenotypes. ClC-3 to ClC-7 are Cl^-/H^+ exchangers on endosomes and lysosomes. Their disruption leads to mainly neuronal pathology in mice and men. We have now shown that the Cl^-/H^+ exchange activity of ClC-3, which forms heteromers with ClC-4, is crucial for its biological role. Our previous ClC-6 KO mouse model showed mild neuronal lysosomal storage, but we were unable to find human *CLCN6* mutations. Together with human geneticists, we have now identified three unrelated children with severe developmental delay and neurodegeneration with exactly the same missense mutation in *CLCN6*. This mutation strongly activates ClC-6 ion transport and generates grossly enlarged lysosome-like vesicles when transfected into cells (Figure 1). Hence this newly described human disorder may be described as lysosomal storage disease.

PHYSIOLOGICAL ROLES OF THE VOLUME-REGULATED VRAC/LRRC8 ANION CHANNELS

We previously found that VRACs are heteromers of up to five different LRRC8 proteins. The specific subunit composition not only determines biophysical properties, but also the range of substrates that can permeate this channel. Intriguingly, VRACs not only transport small ions such as Cl^-, but also a broad range of small molecules such as amino acids and anti-cancer drugs, as we found previously. Together with Hui Xiao (Shanghai), we have now found that VRAC also transports cGAMP, a messenger produced in response to cytosolic double-stranded DNA. By activating the ER-resident STING receptor, cGAMP triggers a signal transduction cascade that leads to increased transcription of interferon genes and activation of downstream targets. DNA is present in the cytosol, e.g. in cancer cells or after infection with DNA viruses. The transfer of cGAMP to neighboring cells, via exit and uptake through VRAC (which depends on its subunit composition), enhances the immune response. Indeed, mice lacking the Lrrc8e VRAC subunit, which we found to be crucial for VRAC's cGAMP transport, exhibited enhanced pathology after infection with a DNA virus. Thus, VRAC plays a role in innate immunity against viral infections, and probably also cancer. To study other roles of VRAC, we have generated mouse lines expressing epitope-tagged LRRC8 subunits and are investigating roles of VRAC in cell type-specific KO mice.



← FIG. 1
Grossly enlarged intracellular vesicles upon transfection of ClC-6^{Y553C}, a mutant of the neuronal late endosomal $2Cl^-/H^+$-exchanger ClC-6 that was identified *de novo* in three patients with severe developmental delay, hypotonia and neurodegeneration (3). The ClC-6 mutant is shown in red. Labeling for Lamp1 (green) reveals that the abnormal vesicles are derived from late endosomes/lysosomes.

SELECTED PUBLICATIONS

Ullrich, F., Blin S., Lazarow, K., Daubitz T., von Kries, JP., Jentsch, TJ. (2019). **Identification of TMEM206 proteins as pore of PAORAC/ASOR acid-sensitive chloride channels.** eLife 8, e49187.

Zhou, C.#, Chen X.#, Planells-Cases, R.#, Chu, J., Wang, L., Cao, L., Li Z., López-Cayuqueo, KI., ... , Qiu, Z.*, Jentsch, TJ.*, Xiao H.* (2020). **Transfer of cGAMP into bystander cells by LRRC8 volume-regulated anion channels augments STING-mediated interferon responses and anti-viral immunity.** Immunity 52, 767–781. (With preview.)

Polovitskaya, MM.#, Barbini, C.#, Martinelli, D.#, Harms, FL., Cole, FS., Calligari, P., Bocchinfuso, G., Stella, L., Ciolfi, A., Niceta, M., Rizza, T., Shinawi, M., Sisco, K., Johannsen, J., Denecke, J., Carrozzo, R., Wegner, DJ., Kutsche, K., Tartaglia, M.*, Jentsch, TJ.* (2020). **A recurrent gain-of-function mutation in CLCN6, encoding the ClC-6 Cl^-/H^+-exchanger, causes early-onset neurodegeneration.** Am J Hum Genet 107, 1062–1077.

[# equal contribution, *corresponding author]

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, "The ClC-2 Cl^- channel in hyperaldosteronism and other pathologies", JE 164/15-1, 01/2019–12/2021, €659,700

Deutsche Forschungsgemeinschaft. FOR 2625, TP 6, "Cell type-specific roles of lysosomal chloride/proton exchange", JE164/14-2, 10/2017-09/2020, €222,950; 10/2017–09/2023 €352,010

European Research Council (Horizon 2020), "Volume regulation and extracellular signaling by anion channels (VOLSIGNAL)", ERC-2016-ADG, # 740537, 10/2017–06/2023, €2,021,112

MOLECULAR PHARMACOLOGY AND CELL BIOLOGY

MOLEKULARE PHARMAKOLOGIE UND ZELLBIOLOGIE

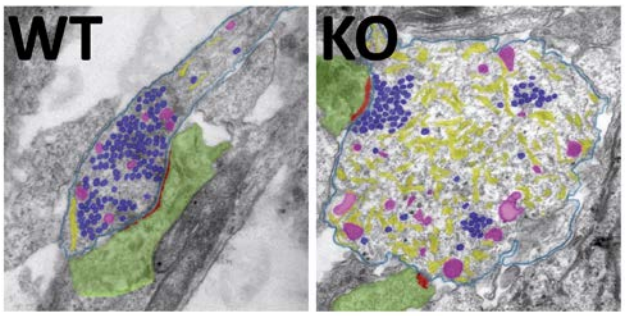
GROUP LEADER (at the FMP since 2012)
Prof. Dr. Volker Haucke

GROUP MEMBERS
Prof. Dr. Michael Krauß, Dr. Gaga Kochlamazashvili, Dr. Gillian Leigh Dornan, Dr. Tania López Hernández , Dr. Marijn Kuijpers, Dr. Tolga Soykan, Dr. Haibin Wang, Dr. Domenico Azarnia Tehran, Dr. Charles Malek, Dr. Michael Ebner, Dr. Manuel Hessenberger, Dr. Wonyul Jang, Dr. Wen-Ting Lo, Dr. Dorien Roosen, Dr. Agata Witkowska, Dr. Alexander Wallroth, Maria Jäpel, Max Lucht, Guan-Ting Liu, Albert Mackintosh, Giulia Russo, Paula Samsó Ferre, Linda Sawade, Dennis Vollweiter, Filiz Sila Rizalar, Hannes Gonschior, Philipp A. Koch, Svenja Bolz, Britta Kristine Oevel, Uwe Fink, Sabine Hahn, Delia Löwe, Maria Mühlbauer, Silke Zillmann

→ leibniz-fmp.de/haucke
→ @VolkerHaucke

→ **HOW DO CELLS COMMUNICATE WITH EACH OTHER?**
Cells communicate with each other by secreting signaling molecules and recognizing those from other cells. For example, nerve cells release neurotransmitters contained in small membrane-bounded vesicles at synaptic cell contacts to elicit responses in neighboring cells. We are studying how nerve cells form and assemble synapses and how synaptic vesicles containing messenger substances are recycled to keep synapses up to speed in fractions of a second. In neurological and neurodegenerative diseases such as Alzheimer's disease, these processes are disrupted. Not only neurons, but almost all cells in our body release or respond to signaling molecules. Growth factors such as insulin and nutrients promote cell growth and division, while suppressing the degradation of metabolites. In cancer cells, this nutrient signaling pathway is often disturbed. We have deciphered cellular mechanisms that regulate nutrient signaling and thus the balance between cell growth and metabolite degradation. Understanding these mechanisms is essential for a better understanding of diseases such as cancer and diabetes. In addition, we use this knowledge to develop new pharmacological approaches for the treatment of such diseases.

→ **WIE KOMMUNIZIEREN ZELLEN MITEINANDER?**
Zellen kommunizieren miteinander, indem sie Signalmoleküle abgeben und solche wiederum von anderen Zellen erkennen. Nervenzellen beispielsweise setzen ihre Botenstoffe aus kleinen membranumhüllten Vesikeln bzw. Bläschen an Synapsen frei, um Antworten in ihren Nachbarzellen auszulösen. Wir studieren, wie Nervenzellen Synapsen bilden und assemblieren und wie synaptische Vesikel, welche die Botenstoffe enthalten, recycelt werden, um Synapsen in Bruchteilen von Sekunden auf dem Laufenden zu halten. Bei neurologischen und neurodegenerativen Krankheiten wie der Alzheimerschen Krankheit sind diese Abläufe gestört. Nicht nur Neuronen, nahezu alle Zellen unseres Körpers setzen Signalmoleküle frei oder antworten auf solche. So fördern Wachstumsfaktoren wie Insulin und Nährstoffe das Zellwachstum und die Zellteilung, während sie den Abbau von Metaboliten unterdrücken. In Krebszellen ist dieser Nährstoffsignalweg oftmals gestört. Wir haben zelluläre Mechanismen entschlüsselt, welche den Nährstoffsignalweg und damit die Balance zwischen Zellwachstum und Abbau von Metaboliten regulieren. Diese Mechanismen zu verstehen, ist grundlegend für ein besseres Verständnis von Krankheiten wie Krebs und Diabetes. Zudem nutzen wir dieses Wissen, um neue pharmakologische Wege der Behandlung solcher Krankheiten zu entwickeln.



← FIG. 1
Electron microscopy images of synapses from wildtype (WT) and autophagy-deficient mice (KO). The endoplasmic reticulum strongly accumulates in KO synapses. Neurotransmitter-containing synaptic vesicles are shown in blue. Photo: Dr. Dmytro Puchkov, FMP. See Kuijpers *et al.* (2020).

→ DESCRIPTION OF PROJECTS

Research within the department covers two major areas: (i) the role of exo-endocytic membrane dynamics in synapse function and neuronal development and (ii) the regulation of membrane homeostasis and cell signaling by phosphoinositides (PIs) and related molecules. We also develop and use super-resolution light (e.g. multi-color STORM and 3D-gSTED, TIRF-SIM), electron microscopy, and correlative light-electron microscopy approaches to study these processes.

i Membrane dynamics in the functioning of the nervous system

Neurons are characterized by an elaborate membrane system that underlies their ability to convey electrical and chemical signals to enable neuronal communication in the brain and in the peripheral nervous system. Using mouse knockout technology, stem cell-derived human neurons, and RNA interference in combination with electron microscopy and optical imaging, including optogenetics and electrophysiology, we aim to dissect the pathways and molecular mechanisms of autophagosomal and endolysosomal membrane dynamics, synaptic vesicle (SV) exo-endocytosis, and axonal transport of SV precursor organelles in the healthy and diseased nervous system. In recent studies, we found that neuronal autophagy, a process that counteracts aging and neurodegeneration, regulates presynaptic neurotransmission by controlling the axonal endoplasmic reticulum (ER) (Kuijpers *et al.*, 2020; Figure 1). Our findings suggest a model where neuronal autophagy controls axonal ER calcium stores to regulate neurotransmission in healthy neurons and in the brain. We also uncovered a molecular mechanism that is responsible for the growth of the myelin sheath, a specialized insulating structure crucial for the fast conduction of nerve impulses. This pathway involves the small GTPase Rab35 and its associated lipid phosphatases MTMR13 and MTMR2, encoded by genes responsible for peripheral Charcot-Marie-Tooth neuropathy types 4B2 and B1 in humans. Pharmacological inhibition of this pathway can ameliorate neuropathic phenotypes, and may thus present a novel therapy for these diseases.

ii Regulation of endocytic and endolysosomal membrane homeostasis and cell signaling by phosphoinositides

Eukaryotic cells internalize nutrients, antigens, growth factors, pathogens, ion channels and receptors via endocytosis. We found that membrane remodeling in endocytosis is tightly linked to the regulated synthesis and turnover of phosphoinositide signaling lipids (PIs), which act by orderly recruitment of PI-binding BAR domain proteins (Lehmann *et al.*, 2019). Other major efforts are directed at elucidating how PI conversion along the endolysosomal pathway is linked to cell signaling processes, e.g. nutrient signaling at lysosomes. In recent studies, we have discovered a pathway for the repression of nutrient signaling by local lipid synthesis via a lysosomal PI 3-kinase isoform that is regulated by protein kinase N (Wallroth *et al.*, 2019). As many PI-metabolizing enzymes are implicated in cancer, diabetes or hereditary disorders such as Charcot-Marie-Tooth disease, we also seek to identify novel pharmacological and chemical inhibitors of select PI-metabolizing enzymes.

SELECTED PUBLICATIONS

Kuijpers, M., Kochlamazashvili, G., Stumpf, A., Puchkov, D., Swaminathan, A., Lucht, MT., Krause, E., Schmitz, D., Haucke, V. (2020) **Neuronal autophagy regulates presynaptic neurotransmission by controlling the axonal endoplasmic reticulum.** Neuron 109 (2), 299–313.e9.

Sawade, L., Grandi, F., Mignanelli, M., Patiño-López, G., Klinkert, K., Langa-Vives, F., Di Guardo, R., Echard, A., Bolino, A., Haucke, V. (2020) **Rab35-regulated lipid turnover by myotubularins represses mTORC1 activity and controls myelin growth.** Nat Commun 11, 2835.

Wallroth, A., Koch, PA., Marat, AL., Krause, E., Haucke, V. (2019) **Protein kinase N controls a lysosomal lipid switch to facilitate nutrient signaling via mTORC1.** Nat Cell Biol. 21, 1093–1101.

SELECTED EXTERNAL FUNDING

BMBF, "Neurobiological basis of polyamine protection from age-induced memory decline (SMARTAGE)", V. Haucke, 07/2015–06/2020, €438,924

Deutsche Forschungsgemeinschaft, Reinhart Koselleck Award (HA 2686/13-1), 01/2017–12/2021, €750,000

European Research Council (ERC) Advanced Grant, Mechanisms of Presynaptic Biogenesis and Remodeling [SynapseBuild], €2,497,000, 01/2021–12/2025

SPECIAL AWARDS/HONORS

2020 ERC Advanced Grant, European Research Council
2020 Feldberg Prize for Research in Physiology and Pharmacology
2020 Professeur invité at the Institute of Psychiatry and Neuroscience of Paris, Université Paris Descartes (iPNP)
2019 Elected Member of the Academia Europaea/Academy of Europe (AE)
2019 Armin Schram Lecture of the German Neuroscience Society

MOLECULAR NEUROSCIENCE AND BIOPHYSICS

MOLEKULARE NEUROWISSEN-SCHAFTEN UND BIOPHYSIK

GROUP LEADER (at the FMP since 2008)
Prof. Dr. Andrew J.R. Plested

GROUP MEMBERS
Saeid Abdolvand, Johann Biedermann, Sebastian Braunbeck, Clarissa Eibl, Yuchen Hao, Florian Heiser, Kordelia Hummel, Benjamin König, Iva Lučić, Sonja Minniberger, Sabrina Mischke, Niccolò Pampaloni, Anahita Poshtiban, Irene Riva, Marcus Wietstruk

→ leibniz-fmp.de/plested
→ @andrewplested

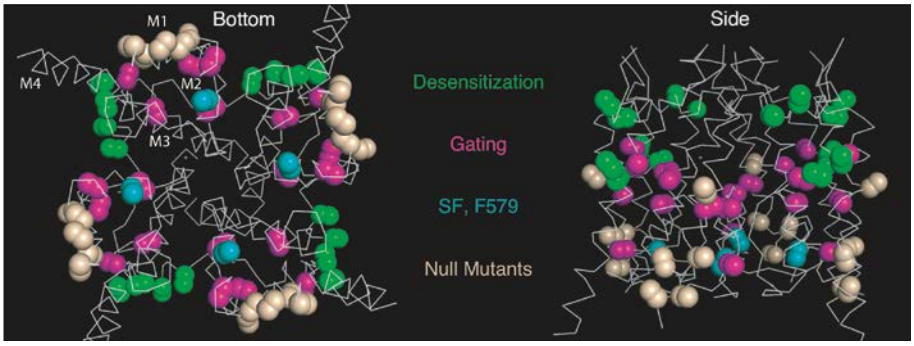
→ Our principal research interests are glutamate receptors and the excitatory synapses in which they reside. These fine connections between nerve cells are implicated in cognition and brain disease. We aim to understand the molecular basis of fast excitatory transmission, and to develop methods to observe and alter synapse activity. To achieve these goals, we study receptor activation with a range of biophysical techniques, including electrophysiology, single-channel recording, fluorescence microscopy and computer simulations. We complement these approaches with investigations of ion channel structure and composition using chemical biology, X-ray crystallography and biochemistry. We employ computational approaches to build novel insights into receptor activation and develop our own software to analyze single receptor activity. A further aspect of our research is to extend these studies to other important components of fast signaling in the brain, such as enzymes and other ion channels.

→ Unsere Forschungsschwerpunkte sind die Glutamatrezeptoren und die exzitatorischen Synapsen, in denen sie sich befinden. Diese feinen Verbindungen zwischen Nervenzellen spielen eine Rolle bei Kognitions- und Gehirnerkrankungen. Wir wollen die molekularen Grundlagen der schnellen exzitatorischen Übertragung verstehen und Methoden zur Beobachtung und Veränderung der Synapsenaktivität entwickeln. Um diese Ziele zu erreichen, untersuchen wir die Rezeptoraktivierung mit einer Reihe biophysikalischer Techniken, darunter Elektrophysiologie, Einkanalaufzeichnung, Fluoreszenzmikroskopie und Computersimulation. Wir ergänzen diese Ansätze durch Untersuchungen der Ionenkanalstruktur und -zusammensetzung mittels chemischer Biologie, Röntgenkristallographie und Biochemie. Wir verwenden computergestützte Ansätze, um neue Erkenntnisse über die Rezeptoraktivierung zu gewinnen, und entwickeln unsere eigene Software zur Analyse der einzelnen Rezeptoraktivitäten. Ein weiterer Aspekt unserer Forschung ist es, diese Studien auf andere wichtige Komponenten der schnellen Signalübertragung im Gehirn auszuweiten, wie Enzyme und andere Ionenkanäle.

→ DESCRIPTION OF PROJECTS

STRUCTURAL AND COMPUTATIONAL STUDIES OF ION PERMEATION IN GLUTAMATE RECEPTORS

Recently, open-state structures of the AMPA-type glutamate receptor were released. These structures were in complex with the auxiliary protein Stargazin,



← FIG. 1
Gating modules of the AMPA receptor pore domain. Using kinetic modeling and unnatural amino acid mutagenesis, we identified three separate activation processes in the transmembrane domain (helices M1-M4). Views from beneath the channel ("Bottom", left) and the membrane ("Side", right). Residues involved in desensitization (green) and the opening of the bundled crossing in the channel core ("Gate", magenta) form contiguous groups. Peripheral residues ("Null Mutants", wheat) are not involved. Surprisingly, the region that selects for permeant ions (SF, F579; blue) has a distinct, unexpected coupling to channel gating and desensitization.

and included the membrane and extracellular domains of the receptor. AMPA receptors are known to open to different configurations, and some measurements of the pore geometry were estimated previously from experiments with large permeant cations. We modified these structures for all-atom simulations of ion permeation by removing the extracellular domains and restraining the loose ends to maintain an open pore. In these computational electrophysiology experiments, we were able to recapitulate a number of known features of the permeation of cations, including the conductance, the ion selectivity and the role of water molecules. The results were robust across different transmembrane voltages, simulation forcefields and temperatures. These simulations show that the open configuration captured in these structural experiments is a good congener of the full open conductance. In complementary experiments, we solved crystal structures of a related cation channel from bacteria (NaK) with its selectivity filter modified to resemble that of an AMPA receptor. These structures, solved in the presence of monovalent and divalent cations, reveal distinct mechanisms of ion permeation and a conversion to two-fold symmetry. We are pursuing similar all-atom simulations based on these structures to investigate ion permeation in the simplest possible system, with the eventual goal of generating and validating simulations of divalent cation permeation.

STRUCTURAL DYNAMICS OF GLUTAMATE RECEPTOR ACTIVATION

Various structures of receptors with auxiliary proteins were published in the past five years, but there was limited validation of the unusual geometries that were found in some experiments. We examined in detail the state-dependence of the LBD layer movement in receptors with and without auxiliary proteins using bifunctional Cysteine crosslinkers. Contrary to previous reports, we found that the receptor is more compact when it is in complex with auxiliary proteins, and that these complexes are quite stable. In the membrane domain, cysteine mutagenesis is problematic because few sites have the solution access needed to complete the experiment. To address the structural dynamics of the membrane segment, we turned to unnatural amino acids that act as UV-triggered crosslinkers. Using kinetic modeling of the UV modification, we were able to identify the selectivity filter as an element that gates ion flow, in multiple states. Most surprisingly of all, the selectivity filter is coupled to the desensitized state.

SELECTED PUBLICATIONS

Poulsen, MH., Poshtiban, A., Klippenstein, V., Ghisi, V. and Plested, AJR. (2019) **Gating modules of the AMPA receptor pore domain revealed by unnatural amino acid mutagenesis.**
PNAS 116 (27), 13358–13367.

Baranovic, J., Plested, AJR. (2018) **Auxiliary subunits keep AMPA receptors compact during activation and desensitization.**
Elife 7.pii: e40548.

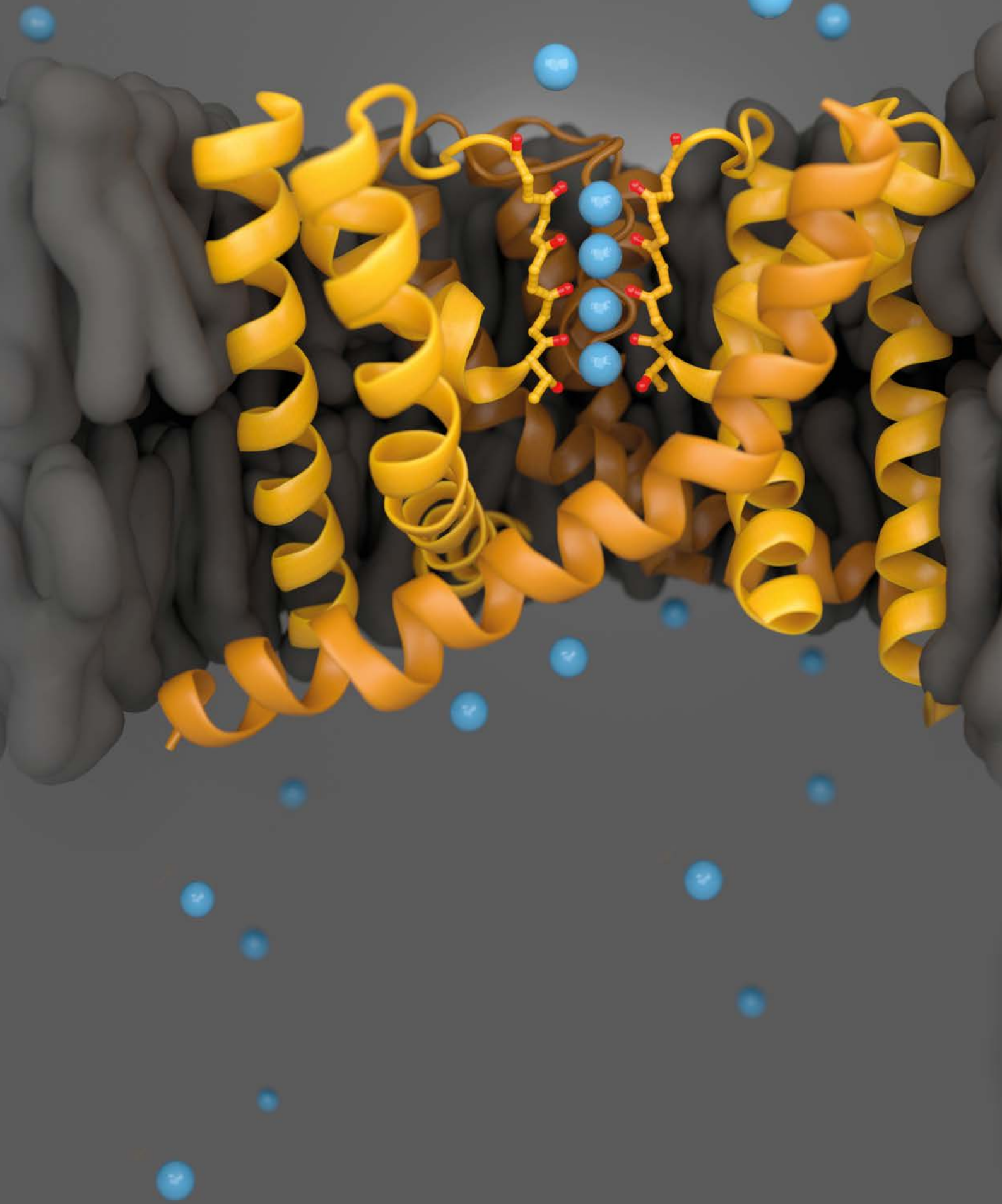
Yu A.#, Salazar H.#, Plested AJR.*, Lau AY.* (2018) **Neurotransmitter funnelling optimizes glutamate receptor kinetics.**
Neuron 97, 139–149.
[# equal contribution, *corresponding author]

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, SFB/TRR 186 A07 "Optical Control of Calcium Switches that Orchestrate Fast Signaling in the Brain" (with Peter Hegemann, HU Berlin) 2016–2020, €295,000

Deutsche Forschungsgemeinschaft, DFG Research Group "Dynlon", FG 2518, P3 "Dynamics of permeation and activation of AMPA Receptors" (with Han Sun, FMP) 2017–2023, €367,000

European Research Council, ERC CoG 647895 "GluActive", 2015–2020, €1,980,000



PHARMACOLOGICAL MASTER KEY DISCOVERED TO CALM NERVE ACTIVITY

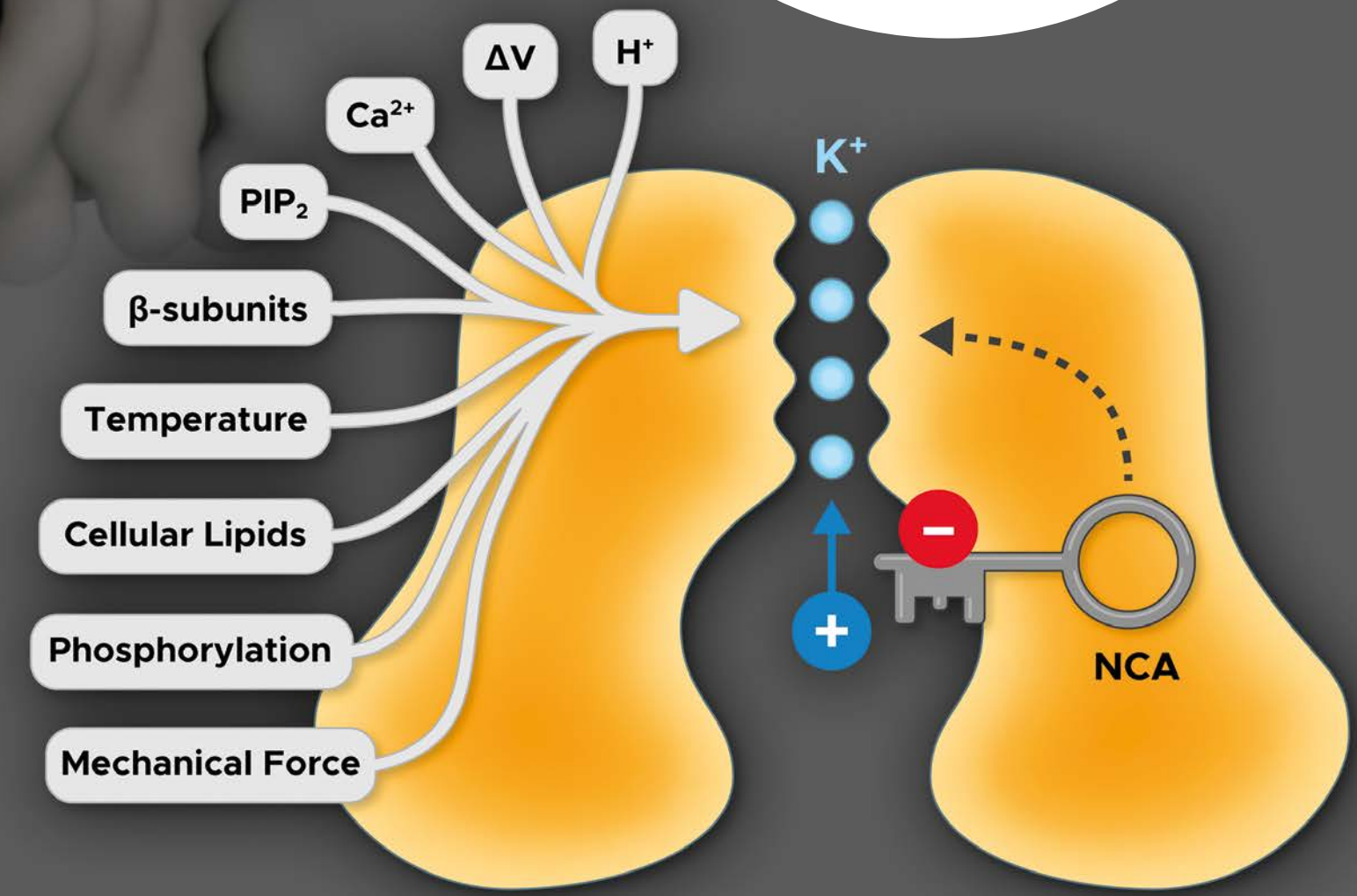
PHARMAKOLOGISCHER GENERALSCHLÜSSEL ZUR BERUHIGUNG VON NERVENAKTIVITÄT ENTDECKT

A research team around Dr. Han Sun discovered a new pharmacological mechanism in potassium channels. This enables excessive electrical activity in nerve or muscle cells to be contained. Scientists of Kiel University (CAU) were furthermore able to pharmacologically influence the mechanism for this and thus finally show – as with a general key – how they can open certain ion channels simultaneously and thus suppress excessive activity in cells. Some of the substances used in this work were synthesized in Marc Nazaré's group.
Schewe, M. *et al.*, Science 2019

Image: Schematic illustration of a potassium channel showing the binding site of the experimental pharmaceuticals (shown here as a key) at the so-called selectivity filter (binding site of the K+ ions). The colored arrows symbolize the multitude of natural mechanisms that open the selectivity filter in cells. Visualization: Barth van Rossum / Physiologisches Institut, CAU

Ein Forscherteam um Dr. Han Sun hat einen neuen pharmakologischen Mechanismus in Kaliumkanälen entdeckt. Mit diesem kann zu hohe elektrische Aktivität in Nerven- oder Muskelzellen eingedämmt werden. Forschende an der Christian-Albrechts-Universität zu Kiel (CAU) konnten zudem hierfür den Mechanismus pharmakologisch beeinflussen und somit schließlich – wie mit einem Generalschlüssel – zeigen, wie sie bestimmte Ionenkanäle gleichzeitig öffnen und dadurch überschießende Aktivität in Zellen unterdrücken können. Teilweise wurden die in dieser Arbeit verwendeten Substanzen am FMP in der Arbeitsgruppe von Dr. Marc Nazaré synthetisiert.

Bild: Schematische Darstellung eines Kaliumkanals, der den Bindungsort der Versuchspharmaka (hier als Schlüssel dargestellt) am sogenannten Selektivitätsfilter (Bindungsort der K+ Ionen) zeigt. Die bunten Pfeile symbolisieren die Vielzahl von natürlichen Mechanismen, die in Zellen den Selektivitätsfilter öffnen.



MOLECULAR AND THEORETICAL NEUROSCIENCES

MOLEKULARE UND THEORETISCHE NEUROWISSENSCHAFTEN

GROUP LEADER (at the FMP since 2015)
Dr. Alexander Matthias Walter

GROUP MEMBERS
Dr. Andreas Till Grasskamp, Dr. Anthony McCarthy, Gabriela Pimenta Dos Reis, Dr. Mathias Böhme, Meida Jusyte, Sabine Hahn, Rukiye Karatepe, Dr. Torsten Götz, Manon Berns

→ leibniz-fmp.de/walter

→ **EXPLAINING THE SIGNAL TRANSDUCTION OF NERVE CELLS AT THE MOLECULAR LEVEL**

Communication between neurons is the basis of survival, cognition and behavior. Synaptic dysfunction is linked to many neurological diseases. We aim to understand the molecular mechanisms of synaptic transmission. We are particularly interested in elucidating how synaptic molecules function together to produce the complex features of neurotransmission, which is not only optimized for speed, but which can also plastically adapt to evade interference or to store information. To do so, we combine experimental and theoretical approaches. Our experimental system is the neuromuscular junction of the fruit fly *Drosophila melanogaster,* a powerful genetic model organism. Despite its simplicity, human and *Drosophila* synaptic genes are remarkably similar. We measure synaptic transmission by electrophysiology and live cell imaging. In addition, super-resolution imaging enables us to uniquely define the topology of the molecular machinery driving transmission on the nanometer scale (a nanometer is a millionth of a millimeter). To arrive at a conceptual framework of how synaptic molecules enable, control and adapt synaptic transmission, we generate mathematical models based on parameters derived from our experiments. These are used to generate hypotheses which are then tested experimentally.

→ **DIE SIGNALÜBERTRAGUNG VON NERVENZELLEN AUF MOLEKULARER EBENE ERKLÄREN**

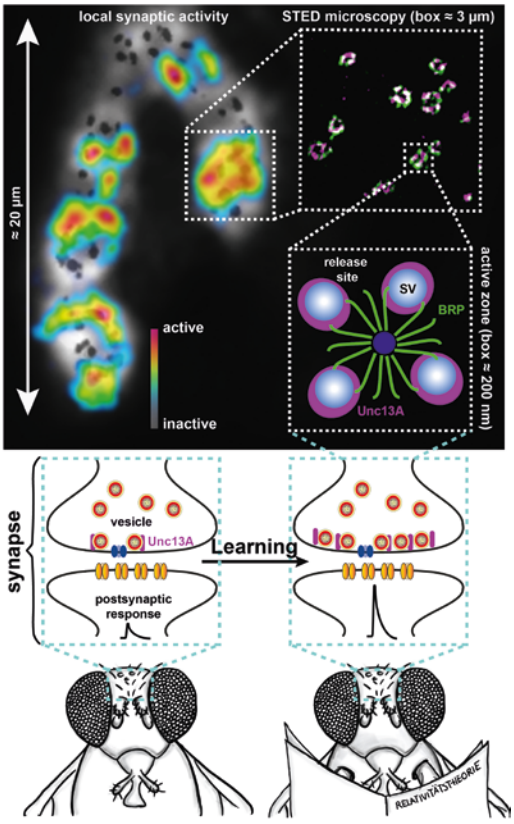
Die Kommunikation zwischen Nervenzellen ist Grundlage von Überleben, Kognition und Verhalten. Sind Synapsenfunktionen fehlerhaft, führt dies zu verschiedenen neurologischen Erkrankungen. Wir möchten die molekularen Mechanismen synaptischer Signalübertragung untersuchen. Insbesondere versuchen wir zu verstehen, wie die einzelnen Moleküle zusammenarbeiten und dazu beitragen, Informationen schnell und verlässlich zu übertragen. Darüber hinaus erforschen wir, wie Synapsen sich anpassen, um störenden Einflüssen entgegenzuwirken und um Informationen zu speichern. Wir untersuchen diese Eigenschaften mithilfe experimenteller und theoretischer Methoden an der Fruchtfliege *Drosophila melanogaster,* deren Synapsen den menschlichen sehr ähnlich sind. Dort messen wir die Signalübertragung mit elektrophysiologischen Methoden oder visualisieren diese mit Mikroskopie. Wir benutzen hochauflösende Mikroskopie, um die „Nano-Maschinerie" zu visualisieren (ein Nanometer ist ein Millionstel Millimeter) mit der Botenstoffe übertragen werden. Um zu verstehen, wie diese Komponenten zur Funktion beitragen, konstruieren wir mathematische Modelle auf der Grundlage experimenteller Daten und nutzen diese, um Hypothesen aufzustellen und experimentell zu testen.

NEUROTRANSMITTER RELEASE SITES–MOLECULAR COMPOSITION AND TOPOLOGY

Neurotransmitters are released from highly specialized locations in a synapse, called release sites, where evolutionarily conserved proteins orchestrate synaptic vesicle (SV) fusion. Action potentials lead to the opening of voltage-gated Ca^{2+}-channels, and local Ca^{2+} influx subsequently triggers SV fusion. The precise positioning of release sites with respect to these channels is therefore crucial for synaptic information processing. In our lab, we investigate which molecules (proteins and signaling lipids) generate release sites and which protein–protein or protein–lipid interactions are required for their correct placement. Using physiology, genetic interference, live imaging, super-resolution STED microscopy and mathematical modeling, we have begun to identify the molecular components of release sites and the interactions between synaptic proteins that operate in precise release site positioning on the nanometer scale, thereby critically determining neural function.

MOLECULAR PRINCIPLES TO REGULATE SYNAPTIC STRENGTH

A remarkable feature of synapses is their capacity to adapt their transmission. This so-called synaptic plasticity allows the nervous system to maintain communication if transmission is challenged, or to store information. In our lab, we therefore investigate the molecular components that allow adaptive transmission on multiple timescales. We particularly focus on how these plasticity mechanisms operate on the level of release sites, for example by changing the number of release sites, or by increasing their efficacy. We investigate plasticity phenomena with physiological readouts and by imaging the changes in the local release site environment using light microscopy. We furthermore address the role of these mechanisms in paradigms to assess how different plasticity mechanisms encode animal behavior, such as learning and memory.



← FIG. 1
(Top) Illustration of synaptic activity and structure in different scale factors. Single synapse activity was determined and shown in different colors according to strength (blue = low activity, red = high activity). The sites where SVs are released (release sites) can be visualized by super-resolution STED microscopy. The function of these sites requires the presence of Unc13A (magenta).

(Bottom) Simplified cartoon of the learning process, during which synaptic signal transmission changes. The release site generating molecule Unc13A plays a key role here. Transmission may get stronger if more Unc13A is incorporated into the synapse (right), because more neurotransmitters can be released. Illustration credits: Mathias Böhme, Meida Jusyte, Andreas Grasskamp and Alexander Walter, FMP

SELECTED PUBLICATIONS

Kobbersmed, JRL., Grasskamp, AT., Jusyte, M., Böhme, MA., Ditlevsen, S., Sørensen, JB., and Walter, AM. (2020) **Rapid regulation of vesicle priming explains synaptic facilitation despite heterogeneous vesicle:Ca2+ channel distances.** eLife 9, e51032.

Bohme, MA., McCarthy, AW., Grasskamp, AT., Beuschel, CB., Goel, P., Jusyte, M., Laber, D., Huang, S., Rey, U., Petzoldt, AG., Lehmann, M., Gottfert, F., Haghighi, P., Hell, SW., Owald, D., Dickman, D., Sigrist, SJ., and Walter, AM. (2019) **Rapid active zone remodeling consolidates presynaptic potentiation.** Nat Commun. 10, 1085.

Reddy-Alla, S., Bohme, MA., Reynolds, E., Beis, C., Grasskamp, AT., Mampell, MM., Maglione, M., Jusyte, M., Rey, U., Babikir, H., McCarthy, AW., Quentin, C., Matkovic, T., Bergeron, DD., Mushtaq, Z., Gottfert, F., Owald, D., Mielke, T., Hell, SW., Sigrist, SJ., and Walter, AM. (2017) **Stable Positioning of Unc13 Restricts Synaptic Vesicle Fusion to Defined Release Sites to Promote Synchronous Neurotransmission.** Neuron 95, 1350–1364.e12.

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, TRR 186, "Molecular switches in the spatiotemporal regulation of cellular signal transduction", 07/2016–06/2024, €471,120

Deutsche Forschungsgemeinschaft, Emmy Noether funding, "Investigating how the active zone cytomatrix orchestrates neuronal exo- and endocytosis", 03/2015–06/2020, €2,051,700

SPECIAL AWARDS/HONORS

2019 Young Investigator Award (€3,345,575), Novo Nordisk Foundation, Copenhagen, Denmark

MEMBRANE TRAFFIC AND CELL MOTILITY

MEMBRANTRANSPORT UND ZELLULÄRE MOTILITÄT

GROUP LEADER
(at the FMP from 2012 to 2020)
Professor Dr. Tanja Maritzen
Tanja Maritzen accepted a professorship in Nanophysiology at the Technische Universität Kaiserslautern in September 2020.

GROUP MEMBERS
Dr. Domenico Azarnia Tehran, Dr. Sai Prasanna Visweshwaran, Lennart Hoffmann Fabian Lukas, Dennis Vollweiter, Hafiza Nayab, Adriano Sanna, Claudia Schmidt

→ leibniz-fmp.de/maritzen
→ @tmaritzen

→ **HOW AND WHY CELLS REGULATE THE UPTAKE OF PROTEINS**

To interact with the extracellular environment, cells rely to a large extent on cell surface-localized proteins. The binding of extracellular signaling molecules to these cell surface receptors triggers diverse intracellular signaling cascades that determine, for example, whether cells start to proliferate, to differentiate or to migrate, and also whether neurons store memories. Accordingly, the number of these signal receptors at the cell surface has to be tightly regulated to ensure the correct response to a specific extracellular cue. The internalization of specifically selected receptors via the remodeling of the surrounding cell membrane into an intracellular hollow sphere (vesicle) in the process of endocytosis constitutes a powerful mechanism for this (Figure 1). However, for many cell surface proteins it is still unclear whether they are in fact internalized by endocytosis, how they interact with the endocytic machinery, and how their internalization is regulated. We investigate the role of endocytic proteins in the physiological function of cell surface proteins by combining cell biological, microscopic and genetic methods.

→ **WIE UND WOZU ZELLEN DIE AUFNAHME VON PROTEINEN REGULIEREN**

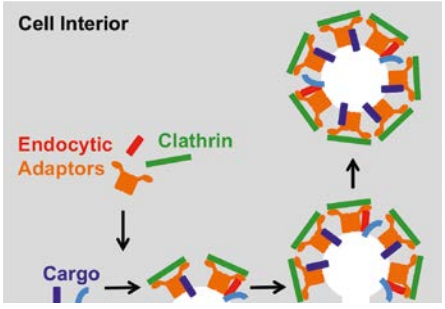
Zellen interagieren mit ihrer Umgebung hauptsächlich über Proteine, die sich an der Zelloberfläche befinden. Die Bindung von Signalmolekülen an solche Zelloberflächenrezeptoren löst vielfältige Signalkaskaden in der Zelle aus. Diese veranlassen Zellen etwa, sich zu teilen, sich in einen anderen Zelltyp zu verwandeln oder sich in Bewegung zu setzen. Bei Nervenzellen bestimmen Signalkaskaden unter anderem auch, ob Erinnerungen gespeichert werden. Um in jeder Situation angemessen auf die jeweiligen Signale zu reagieren, muss die Zelle die Anzahl ihrer Signalempfänger an der Zelloberfläche exakt regulieren. Ein wichtiger Mechanismus dafür ist die Aufnahme ausgewählter Rezeptoren mittels Endozytose. Dabei werden die aufzunehmenden Proteine mithilfe von Adaptoren an eine Maschinerie geknüpft, die die Zellmembran um die Rezeptoren herum zu einem Bläschen umbaut. Dieses Transportbläschen trägt die Rezeptoren dann nach seiner Abschnürung in die Zelle (Abb. 1). Für viele Zelloberflächenproteine ist noch nicht bekannt, ob sie tatsächlich durch Endozytose in die Zelle aufgenommen werden, wie sie mit der Endozytose-Maschinerie interagieren und wie ihre Internalisierung in die Zelle gesteuert wird. Wir untersuchen die Rolle von Endozytoseproteinen für die physiologische Funktion von Zelloberflächenproteinen, indem wir zellbiologische, mikroskopische und genetische Methoden kombinieren.

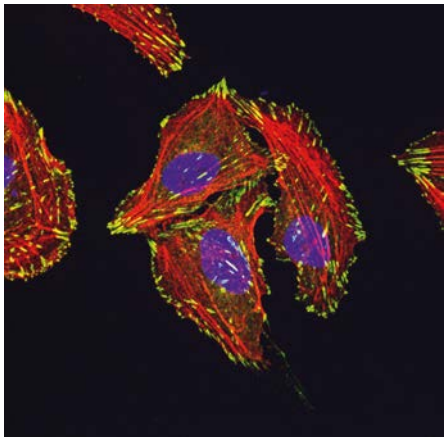
IMPORTANCE OF ENDOCYTIC PROTEINS FOR BRAIN FUNCTION

To enable us to sense our environment, execute actions and form memories, our neurons have to communicate with each other. They do so by releasing signaling molecules from membranous vesicles via their fusion with the cell membrane. These molecules then modulate receptors on the receiving neuron. For the sending neuron, endocytosis is crucial to retrieve vesicle proteins after vesicle fusion because these proteins are needed to generate new vesicles for continued signaling. For the receiving neuron, endocytosis is essential to adjust the amount of surface receptors which relay the signal into the cell because an adaptable signaling strength is the basis for learning and memory. We investigate the importance of specific endocytic proteins for efficient neuronal signaling. We have shown, for example, that the adaptor protein AP180 is crucial for the retrieval of the vesicle protein VAMP2 and thereby protects against seizures. We are currently dissecting the importance of the endocytic protein CALM, an established Alzheimer risk factor, for the uptake of neurotransmitter receptors and thus for learning.

MECHANISMS UNDERLYING FOCAL ADHESION DYNAMICS AND CELL MIGRATION

Our cells adhere to their environment via cell surface proteins, which are organized together with additional factors in complex focal adhesions (FAs, Figure 2). Being transient traction points during cell migration and also signaling platforms, FAs play a role in numerous processes, including the development of our organism, wound healing and immune defense. In addition, altered FAs contribute to diseases such as cancer. In spite of the importance of FAs, our knowledge regarding their disassembly is still fragmentary. While we have studied the importance of endocytosis for FA disassembly, it is clear that additional processes must play a role. To identify these processes, we have depleted all known proteins one by one, and determined the effect of their loss on FA number and size. We are currently investigating the role of proteins whose loss caused FAs to unravel the mechanisms underlying FA disassembly.





← FIG. 1 (LEFT)
Cells employ clathrin-mediated endocytosis to take up surface-localized cargo proteins. In this process, endocytic adaptors select cargo proteins for uptake and recruit the coat protein clathrin. Together with additional endocytic proteins, clathrin reshapes a patch of cell membrane into a spherical vesicle, which is finally pinched off and carries the cargo proteins into the cell.

FIG. 2 (RIGHT)
Cells adhere to their environment via complex protein assemblies, known as focal adhesions (green), which have to be dynamically remodelled to allow for cell migration (cell nuclei in blue, actin cytoskeleton in red).

SELECTED PUBLICATIONS

López Hernández*, T., Puchkov, D., Krause, E., Maritzen*, T., Haucke*, V. (2020) **Endocytic regulation of cellular ion homeostasis controls lysosome biogenesis.** Nat Cell Biol 22 (7), 815–827. [*corresponding authors]

López Hernández, T.*, Haucke*, V., Maritzen*, T. (2020) **Endocytosis in the adaptation to cellular stress.** Cell Stress 4 (10), 230–247. [*corresponding authors]

Azarnia Tehran, D., López Hernández, T., Maritzen, T. (2019) **Endocytic adaptor proteins in health and disease: Lessons from model organisms and human mutations.** Cells 8 (11), 1345.

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, "Dissecting the role of Stonin1 in focal adhesion dynamics and tumor suppression", MA 4735/2-1, 2017–2019, €428,330

Deutsche Forschungsgemeinschaft, "Dissecting the role of the scaffold proteins intersectin 1 and intersectin 2 in insulin secretion", MA 4735/3-1, SCHU750/9-1, with A. Schürmann, 2019–2021, €366,830

Deutsche Forschungsgemeinschaft, "Neuronal function of the endocytic adaptor CALM in the sorting of SNAREs and AMPARs", MA 4735/1-2, HA 2686/8-2, with V. Haucke, 2019–2021, €387,610

PROTEOSTASIS IN AGING AND DISEASE

PROTEINHOMÖOSTASE IM ALTERN UND BEI KRANKHEITEN

GROUP LEADER
(at the FMP from 2013 to 07/2019)
Dr. Janine Kirstein

GROUP MEMBERS
Dr. Sara Ayala Mariscal, Christian Gallrein, Manuel Iburg, Maria Lucia Pigazzini, Kerstin Steinhagen

→ leibniz-fmp.de/kirstein
→ @KirsteinLab

→ **UNDERSTANDING INCORRECTLY FOLDED PROTEINS IN AGING PROCESSES AND ALZHEIMER'S DISEASE**

Proteins are central components of every cell. However, errors in protein folding are more frequent in humans as they grow older or suffer from neurodegenerative diseases: proteins are often misfolded and tend to clump together, and are therefore no longer functional. We want to gain a better understanding of this kind of protein folding, focusing in particular on the complexity, function and dynamics of molecular chaperones. These special proteins help fold newly produced proteins, enabling the folding of unfolded and denatured proteins; they can also dissolve protein aggregates. Our group investigates the function of chaperones during aging and in neurodegenerative diseases. These diseases are characterized by the accumulation of amyloid protein fibrils in cells, i.e. long protein chains that often lead to cell death. We reproduce such scenarios in cell cultures and in the nematode *C. elegans* using targeted synthesis of disease-causing peptides and proteins. In addition, we have established a series of *in vitro* experiments that allow us to investigate how individual chaperones or chaperone complexes influence the structure of amyloid protein fibrils and their stability.

→ **FEHLERHAFT GEFALTETE PROTEINE BEI ALTERUNGSPROZESSEN UND ALZHEIMER VERSTEHEN**

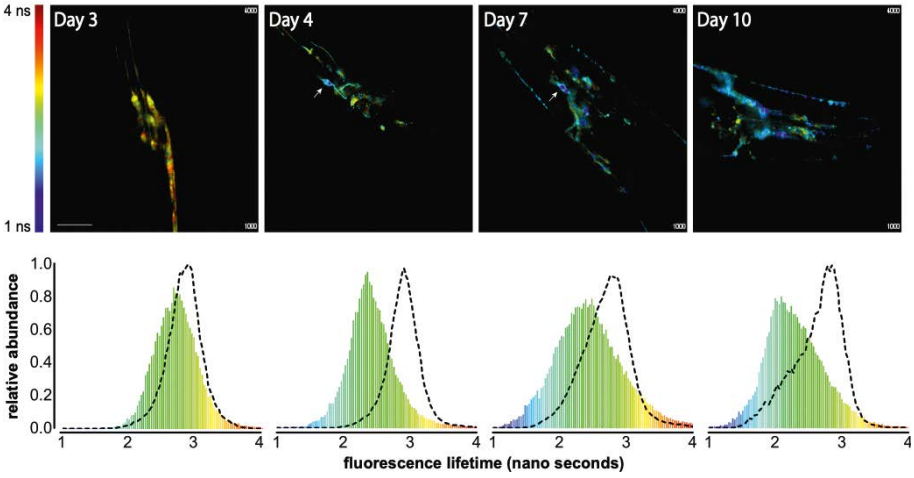
Proteine sind zentrale Bausteine jeder Zelle. Bei Menschen, die älter werden oder an neurodegenerativen Erkrankungen leiden, treten häufiger Fehler bei der Proteinfaltung auf: Proteine sind oft fehlgefaltet, neigen dann zu Verklumpungen und sind somit nicht mehr funktional. Wir wollen diese Proteinfaltung besser verstehen und konzentrieren uns dabei insbesondere auf die Komplexität, Funktion und Dynamik molekularer Chaperone. Diese speziellen Proteine helfen bei der Faltung neu erzeugter Proteine, ermöglichen die Faltung ungefalteter und denaturierter Proteine und können auch Proteinaggregate wieder auflösen. Unsere Gruppe erforscht die Funktion der Chaperone während des Alterns und bei neurodegenerativen Krankheiten. Diese zeichnen sich dadurch aus, dass sich in Zellen amyloide Proteinfibrillen anhäufen, also lange Proteinketten, die meist zum Zelltod führen. Solche Szenarien stellen wir in Zellkulturen und im Fadenwurm *C. elegans* durch gezielte Synthese der krankheitserzeugenden Peptide und Proteine nach. Zusätzlich haben wir eine Reihe von *In-vitro*-Versuchsanordnungen etabliert, die es uns erlauben zu untersuchen, wie einzelne Chaperone oder Chaperonkomplexe die Struktur von amyloiden Proteinfibrillen und deren Stabilität beeinflussen.

NOVEL AMYLOID-BETA PATHOLOGY C. ELEGANS MODEL REVEALS DISTINCT NEURONS AS SEEDS OF PATHOGENICITY

Protein misfolding and aggregation are hallmarks of neurodegenerative diseases such as Alzheimer's disease (AD). In AD, the accumulation and aggregation of tau and the amyloid-beta peptide $A\beta_{1-42}$ precedes the onset of AD symptoms. Modeling the aggregation of Aβ is technically very challenging *in vivo,* due to its size of only 42 amino acids. We established a novel *C. elegans* AD model that sub-stoichiometrically expresses fluorescently tagged $A\beta_{1-42}$ and an excess of untagged $A\beta_{1-42}$. This approach enabled us to monitor aggregation and spreading of Aβ1-42 in the living nematode as aging progressed. Using this model, we were able to establish that untagged $A\beta_{1-42}$ is a prerequisite for amyloid fibril formation. This is the first AD model that shows severe physiological defects, including neuronal dysfunction and neurodegeneration. Fluorescence lifetime imaging microscopy allowed a quantification of the fibrilization with aging, and revealed a heterogenic yet specific pattern of aggregation. Notably, we found that Aβ aggregation starts in a subset of neurons of the anterior head ganglion, the six IL2 neurons. These neurons mark the onset of $A\beta_{1-42}$ aggregation; inhibiting the expression of $A\beta_{1-42}$ in these neurons systemically delayed Aβ aggregation and pathology.

THE SMALL HEAT SHOCK PROTEIN HSP-17 IS A SELECTIVE PROTEIN AGGREGASE

Small heat shock proteins (sHsps) are conserved, ubiquitous members of the proteostasis network. Canonically, they act as "holdases", and buffer unfolded or misfolded proteins against aggregation in an ATP-independent manner. While bacteria and yeast encode only two sHsps, the number is higher in metazoans, suggesting a spatio-temporal as well as functional specialization in higher eukaryotes. We were able to demonstrate that *C. elegans* HSP-17 facilitates aggregation of proteins. This is the first metazoan sHSP that exhibits such a sequestration activity, supporting a hypothesis that protein aggregation deposits may represent less toxic inert structures than unfolded or misfolded soluble proteins. HSP-17 is expressed in the digestive and excretory organs, where its overexpression promotes the aggregation of polyQ proteins and the endogenous kinase KIN-19. Systemic depletion of *hsp-17* shortens the lifespan and severely reduces fecundity and survival upon prolonged heat stress.



← FIG. 1
Fluorescence lifetime imaging analysis of *C. elegans* expressing $A\beta_{1-42}$ and $A\beta_{1-42}$-mScarlet. The heads of animals from Day 3 (young) to Day 10 (old) are shown. The color code depicts the lifetime of $A\beta_{1-42}$ / $A\beta_{1-42}$-mScarlet. The age-dependent increase of $A\beta_{1-42}$ / $A\beta_{1-42}$-mScarlet aggregation can be observed by a reduction of the lifetime (t). Depicted below are histograms showing the distribution of the analyzed cohort. The dashed line indicates the mScarlet control.

SELECTED PUBLICATIONS

Gallrein, C., Iburg, M., Michelberger, T., Koçak, A., Puchkov, D., Liu, F., Ayala Mariscal, SM., Nayak, T., Kaminski Schierle, GS., Kirstein, J. (2020) **Novel Amyloid-beta pathology C. elegans model reveals distinct neurons as seeds of pathogenicity.** Prog Neurobiol 198, 101907.

Iburg, M., Puchkov, D., Brugada, IUR., Bergemann, L., Rieprecht, U., Kirstein, J. (2020) **The non-canonical small heat shock protein HSP-17 from C. elegans is a selective protein aggregase.** J Biol Chem 295 (10), 3064–3079.

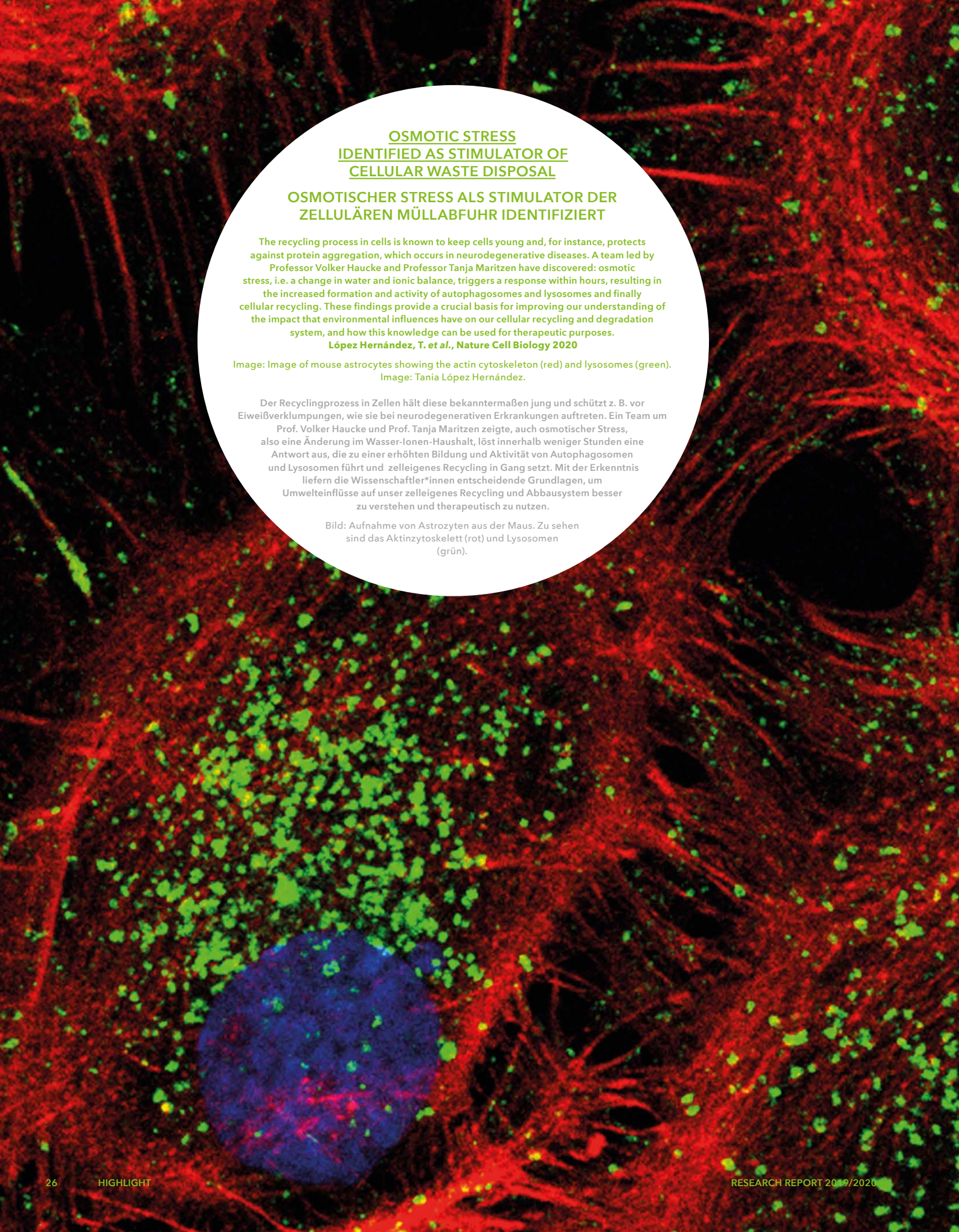
Kreis, P.*, Gallrein, C., Rojas-Puente, E., Mack,TGA., Kroon, C., Dinkel, V., Willmes, C., Murk, K., Tom-Dieck, S., Schuman, EM., Kirstein, J.*, Eickholt, BJ.* (2019) **ATM phosphorylation of the actin-binding protein drebrin controls oxidation stress-resistance and lifespan.** Nat Commun 10(1), 486. [*co-corresponding author]

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, KI-1988/5-1, "Protein homeostasis in dilatative cardiomyopathy-function of Bag3 for the regulation of Hsp70", 01/2019–12/2021, €213,300

DAAD, PPP Programme for Project-Related Personal Exchange with India (National Institute of Pharmaceutical Education and Research (NIPER)), "Aptamer-mediated suppression of Huntingtin aggregation *in vivo*", 2020–2023, € 10,000

Alzheimer Forschung Inititative e.V., Modulating intracellular quality control to prevent spreading of aggregated tau, 12/2020–12/2022, € 50,000



OSMOTIC STRESS IDENTIFIED AS STIMULATOR OF CELLULAR WASTE DISPOSAL

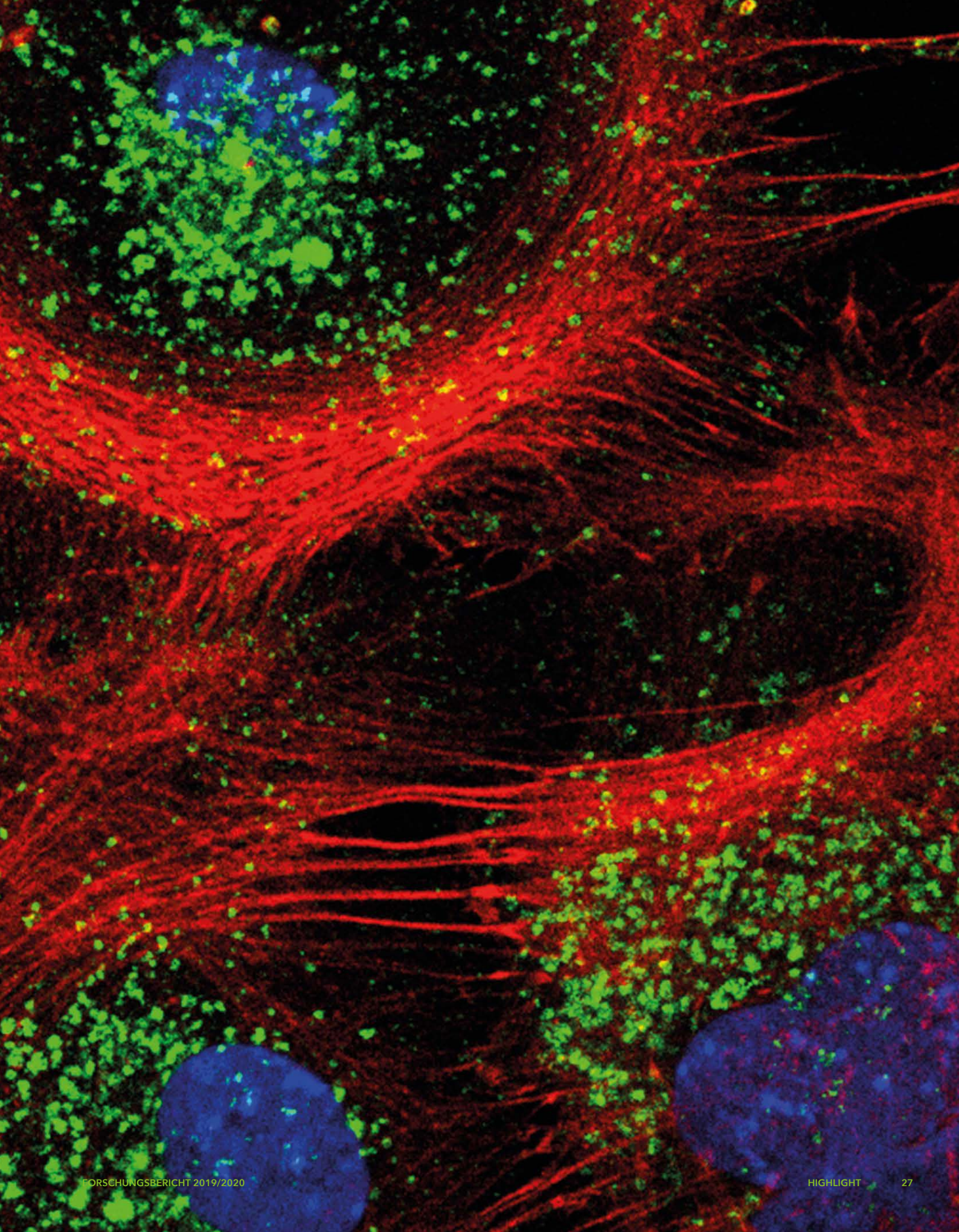
OSMOTISCHER STRESS ALS STIMULATOR DER ZELLULÄREN MÜLLABFUHR IDENTIFIZIERT

The recycling process in cells is known to keep cells young and, for instance, protects against protein aggregation, which occurs in neurodegenerative diseases. A team led by Professor Volker Haucke and Professor Tanja Maritzen have discovered: osmotic stress, i.e. a change in water and ionic balance, triggers a response within hours, resulting in the increased formation and activity of autophagosomes and lysosomes and finally cellular recycling. These findings provide a crucial basis for improving our understanding of the impact that environmental influences have on our cellular recycling and degradation system, and how this knowledge can be used for therapeutic purposes.
López Hernández, T. *et al.*, Nature Cell Biology 2020

Image: Image of mouse astrocytes showing the actin cytoskeleton (red) and lysosomes (green). Image: Tania López Hernández.

Der Recyclingprozess in Zellen hält diese bekanntermaßen jung und schützt z. B. vor Eiweißverklumpungen, wie sie bei neurodegenerativen Erkrankungen auftreten. Ein Team um Prof. Volker Haucke und Prof. Tanja Maritzen zeigte, auch osmotischer Stress, also eine Änderung im Wasser-Ionen-Haushalt, löst innerhalb weniger Stunden eine Antwort aus, die zu einer erhöhten Bildung und Aktivität von Autophagosomen und Lysosomen führt und zelleigenes Recycling in Gang setzt. Mit der Erkenntnis liefern die Wissenschaftler*innen entscheidende Grundlagen, um Umwelteinflüsse auf unser zelleigenes Recycling und Abbausystem besser zu verstehen und therapeutisch zu nutzen.

Bild: Aufnahme von Astrozyten aus der Maus. Zu sehen sind das Aktinzytoskelett (rot) und Lysosomen (grün).



CORE FACILITY

CELLULAR IMAGING

ZELLULÄRE BILDGEBUNG

GROUP LEADER (at the FMP since 2018)
Dr. Martin Lehmann, Light Microscopy

SENIOR SCIENTIST
Dr. Dmytro Puchkov, Electron Microscopy

GROUP MEMBERS
Dr. Christopher Schmied, Hannes Gonschior, Kerem Can Akkaya, Rozemarijn van der Veen, Jenny Eichhorst, Svea Hohensee, Martina Ringling

→ leibniz-fmp.de/imaging

→ **EXPLORING CELLS WITH MICROSCOPY**

As a technology platform, we support over 100 researchers with advanced light and electron microscopy technology and develop new imaging techniques for studying living cells, small organisms and tissue organization. In order visualize proteins and membranes at the nanoscale, we improve our super-resolution microscopes, develop correlative light and electron microscopy, and measure molecular interactions by means of Förster resonance energy transfer (FRET). We apply our technologies to obtain a deeper understanding of mitochondria, paracellular barriers and neuron synapses.

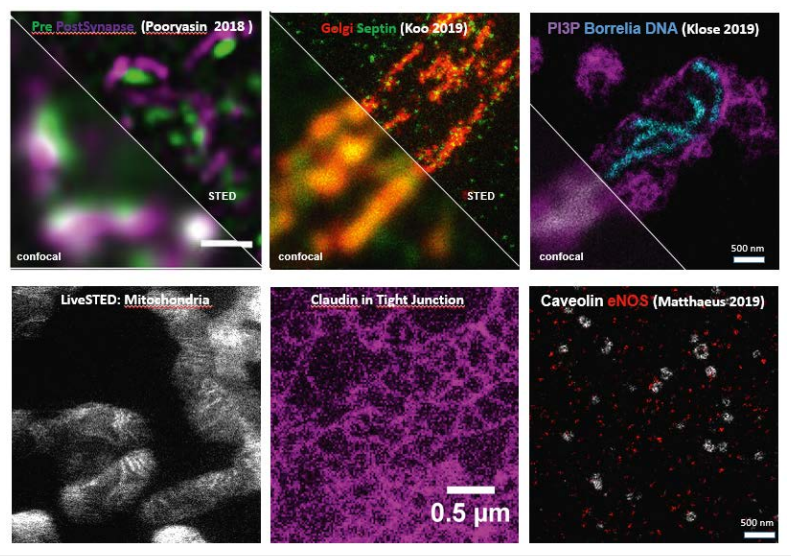
THE LIGHT MICROSCOPY CORE FACILITY

The light microscopy facility supports all research groups within the FMP with fluorescence imaging technology, including labeling and analysis expertise. We apply single-cell and molecular imaging techniques such as FRET, FRAP, FLIM, TIRFM and FCS, as well as ion measurements and caged compounds. Christopher Schmied consults and trains users in applying image analysis techniques to extract meaningful quantitative measurements. Together, we establish automated imaging and quantitative image and data analysis workflows.

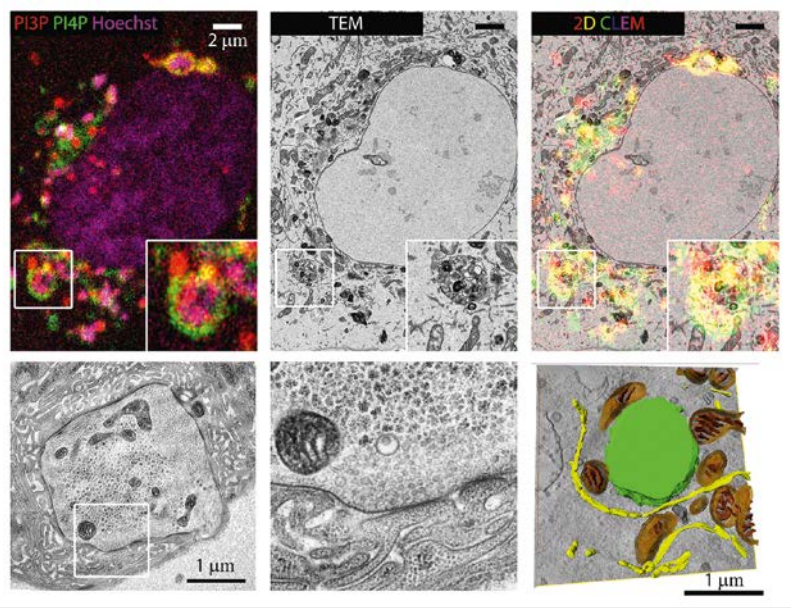
The electron microscopy (EM) unit provides support in the visualization of cellular ultrastructure and in localizing individual proteins at the subcellular level. The lab provides specimen preparation techniques, EM imaging, quantitative analysis, and interpretation for all biological applications, immunogold labeling, correlative light and electron microscopy (CLEM) and tomographical 3D reconstruction.

→ **ZELLEN MITHILFE DER MIKROSKOPIE ERFORSCHEN**

Als Technologieplattform unterstützen wir über 100 Forschende am FMP bei Licht- und Elektronenmikroskopiemessungen und verbessern kontinuierlich unser Angebot zur Superauflösungsmikroskopie für lebende Zellen, Gewebe und Organismen. Ein wichtiger Anwendungsbereich unserer Arbeit ist auch, neue Zielmoleküle für pharmakologische Wirkstoffe zu identifizieren: Dafür setzen wir molekulare Interaktionsmessungen in Zellen mittels Förster-Resonanzenergietransfer (FRET), korrelative Licht- und Elektronenmikroskopie und automatisierte Mikroskopie ein. Wir erforschen Strukturen und Krankheitsmechanismen in Mitochondrien, Zellbarrieren und Synapsen.



← FIG. 1
STED microscopy reveals cellular nanostructure in *Drosophila* brain synapses, Golgi apparatus, endosomal bacteria, live mitochondria, tight-junction proteins and enzyme-coated caveoli structures.



← FIG. 2
Correlative light and electron microscopy (2D CLEM) of confocal fluorescence of lipid sensors (green and red) and LysoTracker (purple) and corresponding TEM image from the same cell. *Drosophila* larvae neuromuscular junction high-pressure freezing, freeze substitution and epoxy embedding. In resin TEM tomography of a lipid droplet (green) and surrounding mitochondria (brown) and endoplasmatic reticulum (yellow).

LICHTMIKROSKOPIE

Die Lichtmikroskopie-Gruppe unterstützt alle Forschungsgruppen des FMP mit Fluoreszenz-Technologien, Beratung bei der optischen Markierung sowie Datenanalyse beim Studium lebender und fixierter Zellen, kleiner Organismen sowie von Geweben und Lösungen. Dazu etablieren wir Einzelzelltechniken basierend auf Weitfeld-, konfokaler und superauflösender Mikroskopie: FRET, FRAP, FLIM, TIRFM, FCS. Unsere Nutzer*innen erhalten bei der automatischen Bildanalyse Unterstützung von Christopher Schmied. Er etabliert automatisierte Mikroskopie und quantitative Bild- und Datenworkflows und schult Nutzer*innen in der Anwendung von Bildanalyse-Software.

Die Elektronenmikroskopie Unit unterstützt die Visualisierung zellulärer Ultrastrukturen und die Lokalisierung einzelner Proteine auf subzellulärer Ebene. Das Labor stellt Probenpräparationstechniken, mikroskopische Aufnahmen und quantitative Analysen für alle biologischen Applikationen, Immunogold-Markierungen, für die correlative Licht- und Elektronenmikroskopie (CLEM) sowie für tomografische 3D-Rekonstruktionen bereit.

SELECTED PUBLICATIONS

Schneider, AFL., Kithil, M., Cardoso, MC., Lehmann, M., Hackenberger* CPR., (in press) **Cellular uptake of Large Biomolecules Enabled by Thiol-reactive Cell-penetrating Peptide Additives.**
Nat Chem. (in press)

Song, K., Gras, C., Capin, G., Gimber, N., Lehmann, M., Mohd, S., Puchkov, D., Rödiger, M., Wilhelmi, I., Daumke, O., Schmoranzer, J., Schürmann, A., Krauss, M. (2019) **https://pubmed.ncbi.nlm.nih.gov/30709970/ A SEPT1-based scaffold is required for Golgi integrity and function.**
J Cell Sci. 132 (3), 225557.

Lehmann*, M., Lukonin, I., Noé, F., Schmoranzer J., Clementi, C., Loerke, D. , Haucke*, V. (2019) **Nanoscale coupling of endocytic pit growth and stability.**
Sci Adv 5, eaax5775
[*equal contribution]

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, GRK 2318 "Tight junctions and their proteins: molecular features and actions in health and disease", 10/2017–10/2022, € 348,000

CORE FACILITY

ANIMAL FACILITY

TIERHALTUNG

GROUP LEADER (at the FMP since 2013)
Dr. Natali Kristina Wisbrun

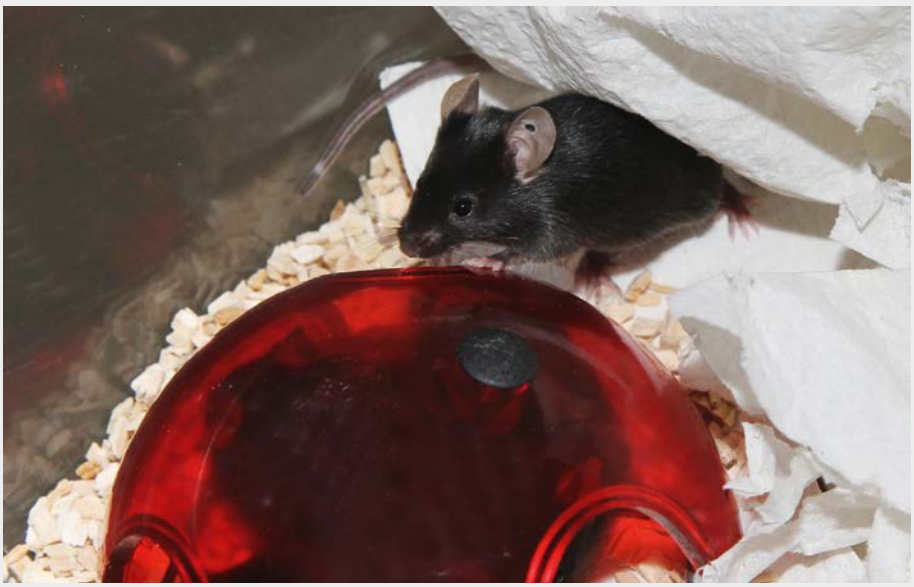
GROUP MEMBERS
Dr. Nadja Heinrich, Nadja Daberkow-Nitsche, Petra Göritz, Martina Lauersdorf, Eva Lojek, Sina Scholz, Maximilian Schülein, Jeannette Unnasch

→ leibniz-fmp.de/animal_facility

→ The Animal Facility manages and organizes the breeding and keeping of laboratory animals for use in scientific projects. Animal welfare legislation and the highest scientific standards are enforced to obtain highly relevant scientific results. We provide support and advice to scientists in all issues related to the planning and execution of experiments involving animals. We also provide practical support, such as taking samples and keeping proper documentation. Furthermore, we organize the global import and export of laboratory animals as well as embryonal stem cells.

→ Unsere Aufgabe besteht darin, Versuchstiere zu züchten und zu halten, die im Rahmen der Bearbeitung wissenschaftlicher Fragestellungen eingesetzt werden. Die Anforderungen des Deutschen Tierschutzgesetzes werden dabei umfassend berücksichtigt. Wir unterstützen und beraten die Forschenden des FMP bei allen Fragen zur Planung und Durchführung von Tierversuchen. Dazu gehört auch die praktische Unterstützung, etwa bei der Probengewinnung und der Dokumentation. Zudem organisieren wir den Export und Import von Versuchstieren und Embryonalzellen weltweit.

→ The Animal Facility team helps ensure that FMP scientists use animals for experiments in compliance with the Animal Welfare Act and with the oversight of an Animal Welfare Officer. The service supplies animal environment housing and manages genetically modified mice, as well as frogs and rats under performance standards. It also provides veterinary care and qualified animal care, using standard operation procedures, and prepares documentation. The service furthermore includes providing education and training to animal care staff, staff involved in carrying out experimental procedures (research technicians), and scientists involved in experimental trials with animals. The team's aim is to establish a well-planned, well-designed, well-constructed and properly maintained laboratory animal facility that is responsible for animal care in compliance with applicable laws and regulations.



← FIGS. 1 & 2
At the FMP, we run an animal care facility for rodents (mice/rats) and African clawed frogs that meets modern hygienic and technical standards.

SELECTED PUBLICATIONS

Zhao, X., Zhang, K., Daniel, P., Wisbrun, N., Fuchs, H., Fan, H. (2019) **Delayed allogeneic skin graft rejection in CD26-deficient mice.** Cell Mol Immunol. 16(6), 557–567.

Pohlmann, A., Karczewski, P., Ku, MC., Dieringe, B., Waiczies, H., Wisbrun, N., Kox, S., Palatnik, I., Reimann, HM., Eichhorn, C, Waiczies, S., Hempel, P., Lemke, B., Niendorf, T., Bimmler, M. (2014) **Cerebral blood volume estimation by ferumoxytol-enhanced steady-state MRI at 9.4 T reveals microvascular impact of α1-adrenergic receptor antibodies.** NMR Biomed. 27, 1085–1093.

SECTION

STRUCTURAL BIOLOGY

BEREICH

STRUKTURBIOLOGIE

→ The Structural Biology Section addresses atomic structures and functional dynamics of proteins and protein complexes in their natural environment. This includes membrane proteins in the context of native-like lipid bilayers, fully assembled molecular machines, and soluble proteins within live cells. Furthermore, the Section investigates larger systems such as organelles, cells, tissue and even organisms using structural proteomics and imaging approaches.

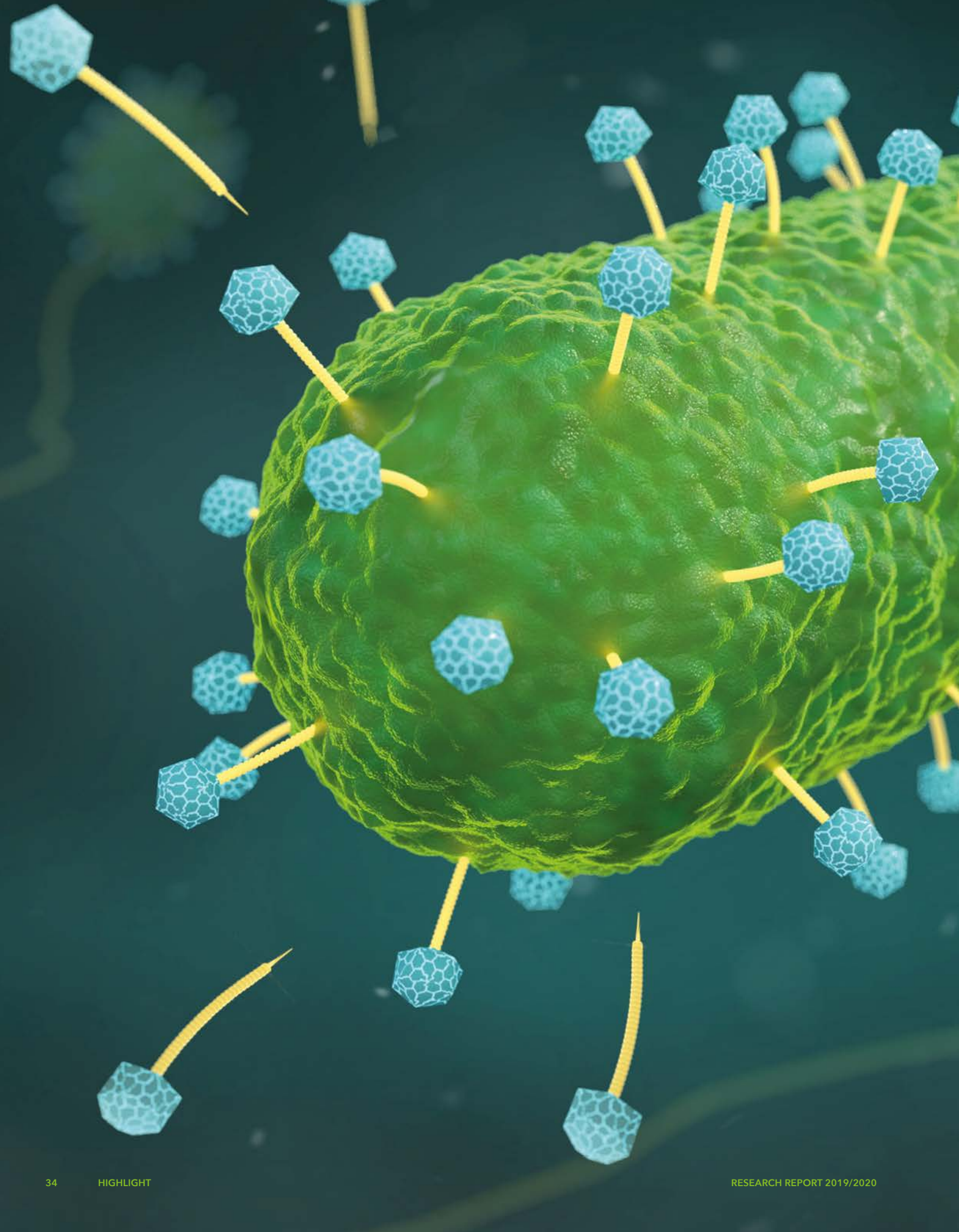
To achieve these aims, an integrated structural biology strategy is adopted that combines solid- and solution-state nuclear magnetic resonance (NMR; Lange, Oschkinat), mass spectrometry (MS; Liu), and cryo-electron microscopy (cryo-EM; Roderer). These experimental techniques are supported by first-class core facilities (Schmieder, Liu) and combined with state-of-the-art computational approaches such as structure-based drug design and atomistic molecular dynamics simulations (G. Krause, Kühne). Structural knowledge obtained from these studies is also translated into magnetic resonance imaging diagnostic tools (Schröder).

The planned research for forthcoming years will capitalize on methodological improvements (e.g. DNP, solid-state NMR using proton detection, cryo-EM and hybrid structure calculation) as well as investments in infrastructure (e.g. MS facility, GHz NMR and cryo-EM). Furthermore, new and contemporary biologically relevant systems (dense protein–water phases, biofilms, rhomboid proteases, etc.) have been established recently. The installation of a new cryo-EM junior research group (Roderer) adds a key technique to the methodology of the Section, further strengthening its focus on integrated structural biology.

→ Die Sektion Strukturbiologie beschäftigt sich mit den atomaren Strukturen und der funktionell wichtigen Dynamik von Proteinen und Proteinkomplexen in ihrer natürlichen Umgebung. Dazu gehören Membranproteine im Kontext nativer Lipidmembranen, vollständig assemblierte molekulare Maschinen und lösliche Proteine in lebenden Zellen. Darüber hinaus untersucht die Sektion größere Systeme wie Organellen, Zellen, Gewebe oder sogar ganze Organismen mit Ansätzen der strukturellen Proteomik und bildgebenden Techniken.

Um diese Ziele zu erreichen, wird eine integrierte strukturbiologische Strategie verfolgt, die Kernspinresonanz im festen und gelösten Zustand (NMR; Lange, Oschkinat), Massenspektrometrie (MS; Liu) und Kryo-Elektronenmikroskopie (Kryo-EM; Roderer) umfasst. Diese experimentellen Techniken werden durch erstklassige Core Facilities (Schmieder, Liu) unterstützt und mit modernsten, computergestützten Ansätzen wie dem strukturbasierten Wirkstoffdesign und atomistischen Molekulardynamiksimulationen (G. Krause, Kühne) kombiniert. Die aus diesen Studien gewonnenen Erkenntnisse werden auch in diagnostische Werkzeuge der Kernspintomografie umgesetzt (Schröder).

Die für die kommenden Jahre geplante Forschung profitiert von methodischen Verbesserungen (z. B. DNP, Festkörper-NMR mit Protonendetektion, Kryo-EM und Hybridstrukturberechnung) sowie von Investitionen in die FMP-Infrastruktur (z. B. MS Facility, GHz-NMR und Kryo-EM). Darüber hinaus wurden in jüngster Zeit neue und zeitgemäße biologisch relevante Systeme (u. a. dichte Protein–Wasser-Phasen, Biofilme, Rhomboid-Proteasen) etabliert. Die Einrichtung einer neuen Nachwuchsgruppe zum Thema Kryo-EM (Roderer) erweitert die Methodik der Sektion um eine Schlüsseltechnik und stärkt somit nochmals den Fokus auf die integrierte Strukturbiologie.



LIGHT SHED ON THE ATOMIC RESOLUTION STRUCTURE OF PHAGE DNA TUBE

STRUKTUR VON PHAGEN-DNA-TUNNEL IN ATOMARER AUFLÖSUNG AUFGEKLÄRT

Phages are able to destroy bacteria and, with growing antibiotic resistance, have again become the focus of increased research interest. Professor Adam Lange's research group is particularly interested in the tube used by phages to implant their DNA into bacteria. In collaboration with colleagues from Forschungszentrum Jülich and Jena University Hospital, the researchers have now revealed the 3D structure of this crucial phage component in atomic resolution. The key to success was combining two methods – solid-state NMR and cryo-electron microscopy.
Zinke, M. *et al.*, Nature Communications 2020

Image: Artistic representation of phages of the Siphoviridae family (yellow and blue). Visualization: Barth van Rossum

Phagen können Bakterien vernichten und sind im Zuge der zunehmenden Antibiotikaresistenzen wieder verstärkt in den Blick der Forschung geraten. Die Arbeitsgruppe von Prof. Adam Lange interessiert sich insbesondere für den Tunnel, durch den die Phagen ihre DNA in Bakterien einschleusen. Nun haben die Forscher zusammen mit Kolleg*innen des Forschungszentrums Jülich und des Universitätsklinikums Jena die 3D-Struktur dieser entscheidenden Phagen-Komponente in atomarer Auflösung aufgeklärt. Die Kombination zweier Methoden – der Festkörper-NMR und der Kryo-Elektronenmikroskopie – war der Schlüssel zum Erfolg.

Bild: Künstlerische Darstellung von Phagen der Familie Siphoviridae (gelb und blau)

MOLECULAR BIOPHYSICS

MOLEKULARE BIOPHYSIK

GROUP LEADER (at the FMP since 2014)
Prof. Dr. Adam Lange

GROUP MEMBERS
Dr. Chaowei Shi, Dr. Sascha Lange, Dr. Veniamin Shevelkov, Dr. Tillmann Utesch, Dr. Juan Li, Pascal Sanchez Carranza, Dr. Stamatios Liokatis, Dr. Carl Öster, Dr. Oxana Krylova, Dr. Reiner Haseloff, Kitty Hendriks, Claudia Bohg, Maximilian Zinke, Songhwan Hwang, Heike Nikolenko, Dagmar Michl, Susanne Bischoff, Marleen van Rossum, Stefanie Schneider, Julia Ruta, Katja Frenzel, Jan Horlebein, Leonard Constien, Berke Türkaydin

→ leibniz-fmp.de/lange

→ DETECTING THE STRUCTURE OF PROTEINS

Proteins are long-chain macromolecules that are usually folded three-dimensionally into a complex architecture. To understand the function of a protein, it is helpful to know its structure. Researchers usually study proteins in soluble or crystalline form. However, not all proteins can be investigated in this way. We also use solid-state nuclear magnetic resonance spectroscopy (solid-state NMR) to analyze the structure and dynamics of proteins. This technique allows us to investigate chemical details, interaction with water and lipid molecules, and functionally relevant protein dynamics. The latter aspect is important because proteins are not rigid structures with a fixed architecture, but have moving parts similar to machines. To conduct solid-state NMR investigations, we place samples in a strong superconducting magnet (external field up to 20 T, i.e. ~400,000 times stronger than the earth's magnetic field), rotate them rapidly (up to 100,000 revolutions per second; magic-angle spinning) and investigate them spectroscopically using radio waves. Important applications of our work are the analysis of membrane proteins in their natural lipid environment and the 3D structure determination of molecular machines in the cell.

→ DIE STRUKTUR VON PROTEINEN ERKENNEN

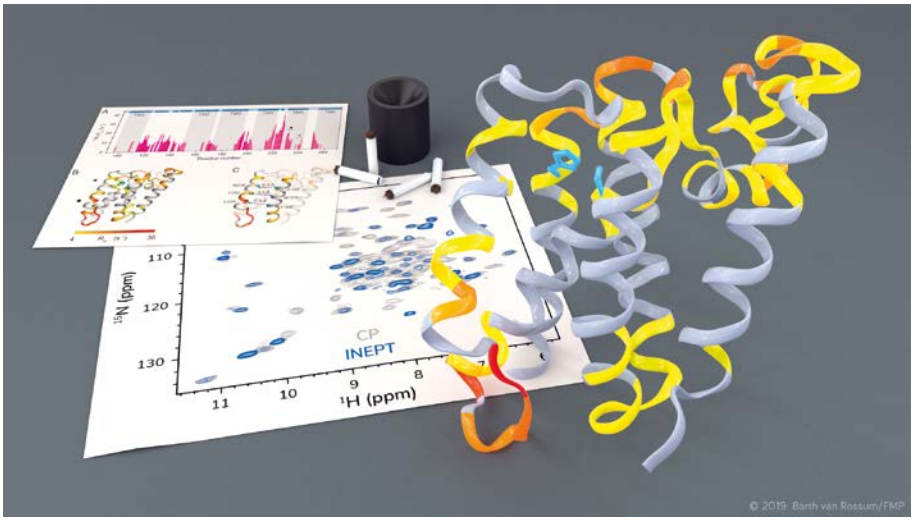
Proteine sind langkettige Makromoleküle und meist dreidimensional zu einer komplexen Architektur gefaltet. Um die Funktion eines Proteins zu verstehen, ist es hilfreich, seine Struktur zu kennen. Dazu nutzen Forschende in der Regel Verfahren, bei denen die Proteine gelöst sind oder kristallisiert werden. Nicht alle Proteine lassen sich jedoch auf diese Weise untersuchen. Wir nutzen zusätzlich Festkörper-Kernspinresonanzspektroskopie (Festkörper-NMR), um die Struktur und Dynamik von Proteinen zu analysieren. Diese Technik erlaubt die Untersuchung chemischer Details, der Wechselwirkung mit Wasser- und Lipidmolekülen und der funktionell relevanten Proteindynamik. Der letzte Aspekt ist wichtig, da Proteine keine starren Gebilde mit einer festen Architektur sind, sondern ähnlich wie Maschinen bewegliche Teile besitzen. Für Festkörper-NMR-Untersuchungen bringen wir die Proben in einen starken, supraleitenden Magneten (mit Feldstärken bis zu ~20 Tesla und damit ca. 400.000-mal so stark wie das Magnetfeld der Erde), versetzen sie in eine schnelle Rotation (bis zu 100.000 Umdrehungen pro Sekunde; Magic-Angle-Spinning) und untersuchen sie spektroskopisch mittels Radiowellen. Wichtige Anwendungen unserer Arbeit sind die Analyse von Membranproteinen in ihrer natürlichen Lipidumgebung und die 3D-Strukturbestimmung molekularer Maschinen in der Zelle.

MEMBRANE PROTEINS

Membrane proteins are a major focus of our group's work. Unlike other methods in structural biology, solid-state NMR enables us to study membrane proteins in native-like lipid bilayers at room temperature and under physiological buffer conditions. Current projects involve non-selective cation channels such as NaK, a bacterial homolog of the cyclic nucleotide-gated ion channel that plays a crucial role in sensory transduction (Shi 2018). In collaboration with the Sun group (Chemical Biology Section, which performs advanced atomistic MD simulations), we revealed for the first time the importance of conformational plasticity in the selectivity filter for ion non-selectivity. In a related study on the selective K^+ channel NaK2K, our group showed that the selectivity filter is entirely occupied by K^+ ions, and not – as previously thought – alternatingly occupied by water and K^+ (Öster 2019). Furthermore, we recently investigated the functional dynamics of the GlpG protein, an intramembrane protease that hydrolyzes peptide bonds directly within the lipid bilayer (Shi 2019, see Figure 1).

INTEGRATED STRUCTURAL BIOLOGY

With regard to determining atomic structures, we introduced a general hybrid approach for determining the structures of supramolecular assemblies based on cryo-EM (global information) and solid-state NMR (local information and dynamics) (Demers 2014). On the biological side, one of the most exciting results was the determination of the structure of the bactofilin BacA using solid-state NMR alone (Vasa 2015 and Shi 2015). We discovered that bactofilins adopt a β-helical architecture, a structural motif that has not been observed before for any other cytoskeletal filament. Bactofilins are a new class of cytoskeletal proteins that are involved in key cellular processes; they represent an interesting pharmacological target for treating bacterial infections. The rather complex proton-detected solid-state NMR methods used to determine the structure of bactofilin were further developed by us into a user-friendly protocol and published in Nature Protocols (Fricke 2017). Very recently, we succeeded in solving the structure of a large and flexible supramolecular assembly: the SPP1 bacteriophage tail tube. Use of tailored proton-detected 4D experiments, also developed by the lab (e.g. Zinke 2017), enabled us to readily investigate the complex system. Distance restraints from solid-state NMR were combined with cryo-EM, yielding an atomic-resolution structure. In addition, we assessed the dynamics of the system, revealing a spinal column architecture with rigid hexameric rings connected by flexible linkers (Zinke 2020).



← FIG. 1
Investigation of the rhomboid protease GlpG by solid-state NMR. (Barth van Rossum, FMP)

SELECTED PUBLICATIONS

Zinke, M., Sachowsky, K.A.A., Öster, C., Zinn-Justin, S., Ravelli, R., Schröder, GF., Habeck, M., Lange, A. (2020) **Architecture of the flexible tail tube of bacteriophage SPP1.** Nat Commun 11 (1), 5759.

Shi, C., Öster, C., Bohg, C., Li, L., Lange, S., Chevelkov, V. and Lange, A. (2019) **Structure and dynamics of the rhomboid protease GlpG in liposomes studied by solid-state NMR.** J Am Chem Soc 141(43), 17314–17321.

Öster, C., Hendriks, K., Kopec, W., Chevelkov, V., Shi, C., Michl, D., Lange, S., Sun, H., de Groot, BL. and Lange, A. (2019) **The conduction pathway of potassium channels is water free under physiological conditions.** Sci Adv 5 (7), eaaw6756.

SELECTED EXTERNAL FUNDING

European Research Council, ERC Starting Grant "3D structures of bacterial supramolecular assemblies by solid-state NMR", assemblyNMR, grant agreement no. 337490, 2014–2019, € 1,456,000

Deutsche Forschungsgemeinschaft, DFG "own position" (Dr. Stamatios Liokatis) "Cross-regulation of post-translational protein modifications and effects on the histone H3 tail conformations/dynamics: A structural and mechanistic study on whole nucleosomes by Nuclear Magnetic Resonance (NMR) spectroscopy", LI 2402/2-2, 04/2017–09/2019, € 281,000

Unifying Concepts in Catalysis – Cluster of Excellence, now: **Unifying Systems in Catalysis (UniSysCat; DFG),** "Regulated catalysis by intra-membrane proteases"; 11/2017–12/2022, € 59,000 (HU Berlin) + € 422,000 (FMP)

SPECIAL AWARDS/HONORS

Since 2019 Executive Board Einstein Center of Catalysis, Berlin

NMR-SUPPORTED STRUCTURAL BIOLOGY

NMR-UNTERSTÜTZTE STRUKTURBIOLOGIE

GROUP LEADER (at the FMP since 1998)
Prof. Dr. Hartmut Oschkinat

GROUP MEMBERS
Dr. Anne Diehl, Dr. Barth-Jan van Rossum, Dr. Matthias Herrera Glomm (Hiller), Dr. Miguel Arbesu, Dr. Wing Ying Chow, Dr. Kelsey Collier, Nils Cremer, Natalja Erdmann, Daniel Friedrich (Stöppler), Michel-Andreas Geiger, Lisa Gerland, Amira Gutmann-Trieb, Liselotte Handel, Martina Leidert, Florian Lindemann, Dr. Elena Matei, Johanna Münkemer, Kristina Rehbein, Andrea Steuer, Arndt Wallmann

→ leibniz-fmp.de/oschkinat

→ **INVESTIGATING HIGHLY COMPLEX STRUCTURAL INFORMATION**

Magic-angle spinning (MAS) solid-state NMR spectroscopy provides high-resolution structural information on heterogeneous samples, independent of the molecular weight of the investigated proteins or nucleic acids. It is an attractive method for structural investigations on "difficult" systems such as small proteins embedded in lipid bilayers, large polydisperse complexes (Figure 1) or biological macromolecules in their natural environment. NMR provides a direct view of protons and connected exchange processes, and allows distinctions to be made between rapidly interconverting structural states on the basis of their characteristic chemical shifts. In a pharmacological context, we carry out investigations within the "real space" of a cell, capitalizing on a 20-100-fold increase in the signal-to-noise ratio afforded by the use of dynamic nuclear polarization (DNP). Furthermore, we apply very fast MAS (100,000 rotations per second) for studying protein structure so that high-resolution proton spectra can be obtained using a minimal sample quantity. This enabled, for example, studies of the binding of small molecules to the neonatal Fc receptor. Using these techniques, we investigate protein systems involved in protein homeostasis, biological systems undergoing phase separation, signaling processes and biofilms.

→ **HOCHKOMPLEXE STRUKTURINFORMATIONEN UNTERSUCHEN**

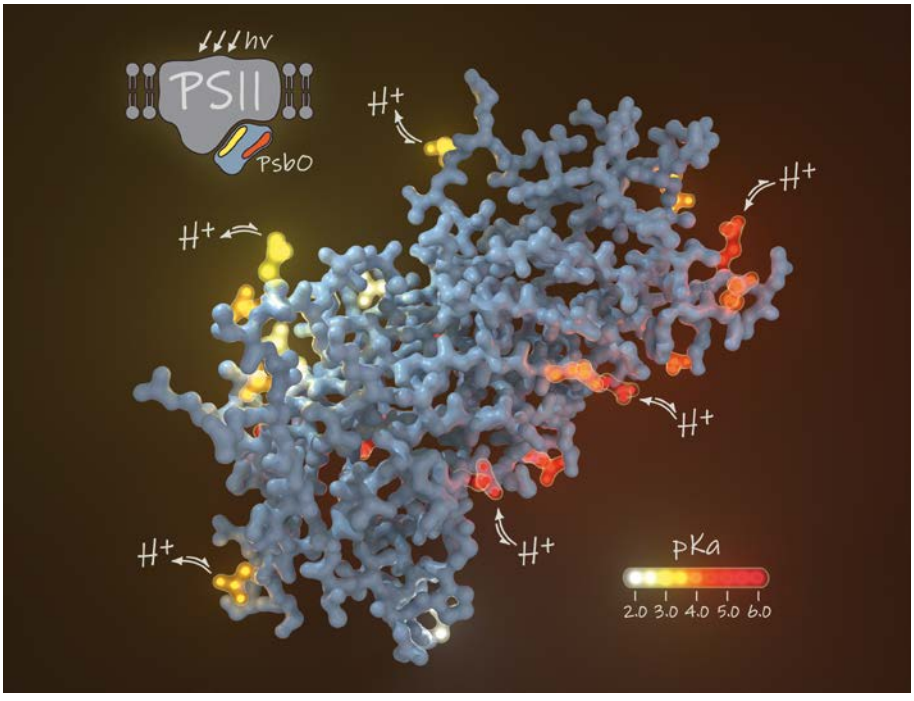
Die Festkörper-NMR-Spektroskopie mit Magic-Angle-Spinning (MAS) ist in der Lage, hochauflösende Strukturinformationen von komplexen Proben biologischer Makromoleküle zu liefern, unabhängig von deren Molekulargewicht. Die MAS-NMR-Spektroskopie ist eine attraktive Methode für strukturelle Untersuchungen an kleinen Proteinen, die in Lipiddoppelschichten eingebettet sind, großen polydispersen Komplexen (Abb. 1) oder Proteinen in ihrer natürlichen Umgebung. Wir führen strukturelle Untersuchungen im „realen Raum" einer Zelle durch, wobei wir langfristig von einer 20-100-fachen Erhöhung des Signal-Rausch-Verhältnisses durch den Einsatz der dynamischen Kernpolarisation (DNP) profitieren. Alternativ wird eine schnelle Rotation der Proben (100.000 Rotationen pro Sekunde) angewendet, beispielsweise zur Untersuchung der Bindung kleiner Moleküle an den neonatalen Fc-Rezeptor. Mit diesen Techniken untersuchen wir große dynamische und polydisperse Proteinsysteme, die an der Proteinhomöostase beteiligt sind, biologische Systeme, die in Phasentrennung involviert sind, zelluläre Signalketten sowie Biofilme.

CLUSTERING OF PH-DEPENDENT PROTON AFFINITY IN PSBO ENABLES LOCAL BUFFERING AND TRIGGERS STRUCTURAL CHANGES

Photosystem II (PSII) catalyzes the splitting of water, releasing protons and dioxygen. Its highly conserved subunit PsbO extends from the oxygen-evolving center into the thylakoid lumen, and stabilizes the catalytic Mn_4CaO_5 cluster. High conservation of accessible negatively charged surface residues in PsbO suggests additional functions, as a local pH buffer or by affecting the flow of protons. Our investigations delivered pK_a values of water-accessible aspartate and glutamate side-chain carboxylate groups, with high pKa values around 4.9 clustered on the luminal PsbO side and values below 3.5 on the side facing PSII. Changes in backbone chemical shifts indicate pH-triggered conformational changes. PsbO may thus function as a pH sensor in photosystem II.

DISCOVERY OF A NEW MECHANISM IN THE RARE GENETIC DISEASE ALKAPTONURIA

Alkaptonuria (AKU) is a rare genetic disease that is characterized by high levels of homogentisic acid and unusual tissue pigmentation. The so-called ochronotic pigment causes brown-black deposits that lead to cartilage degradation and severe joint pain. Skin, heart and kidneys can also be affected. As part of multi-disciplinary research in collaboration with the FU Berlin and the universities of Liverpool and Cambridge, new insights have been gained into the mechanisms of pigmentation and cartilage destruction. With the help of DNP NMR, it was revealed that fractions of the collagen triple-helix structure in the cartilage had been destroyed. Electron spin resonance showed that the pigment triggers redox reactions involving glycine residues, creating transient glycyl radicals breaking hydrogen bonds in collagen. These results lead to the proposal of a new mechanism of collagen degradation in alkaptonuria that may also apply to osteoarthritis, as suggested by experiments with corresponding patient tissue.



← FIG. 1
Distribution of glutamic acid and aspartic acid pK_a values on the PsbO surface. (Scientific Image: Barth van Rossum)

SELECTED PUBLICATIONS

Chow, WY., Norman, BP., Roberts, NB., Ranganath, LR., Teutloff, C., Bittl, R., Duer, MJ., Gallagher, JA., Oschkinat, H. (2020) **Pigmentation chemistry and radical-based collagen degradation in alkaptonuria and osteoarthritic cartilage.** Angew Chem Int Ed Engl 59 (29), 11937–11942.

Friedrich, D., Brüning, FN., Nieuwkoop, AJ., Netz, RR., Hegemann, P., Oschkinat, H. (2020) **Collective exchange processes reveal an active site proton cage in bacteriorhodopsin.** Commun Biol 3(1), 4.

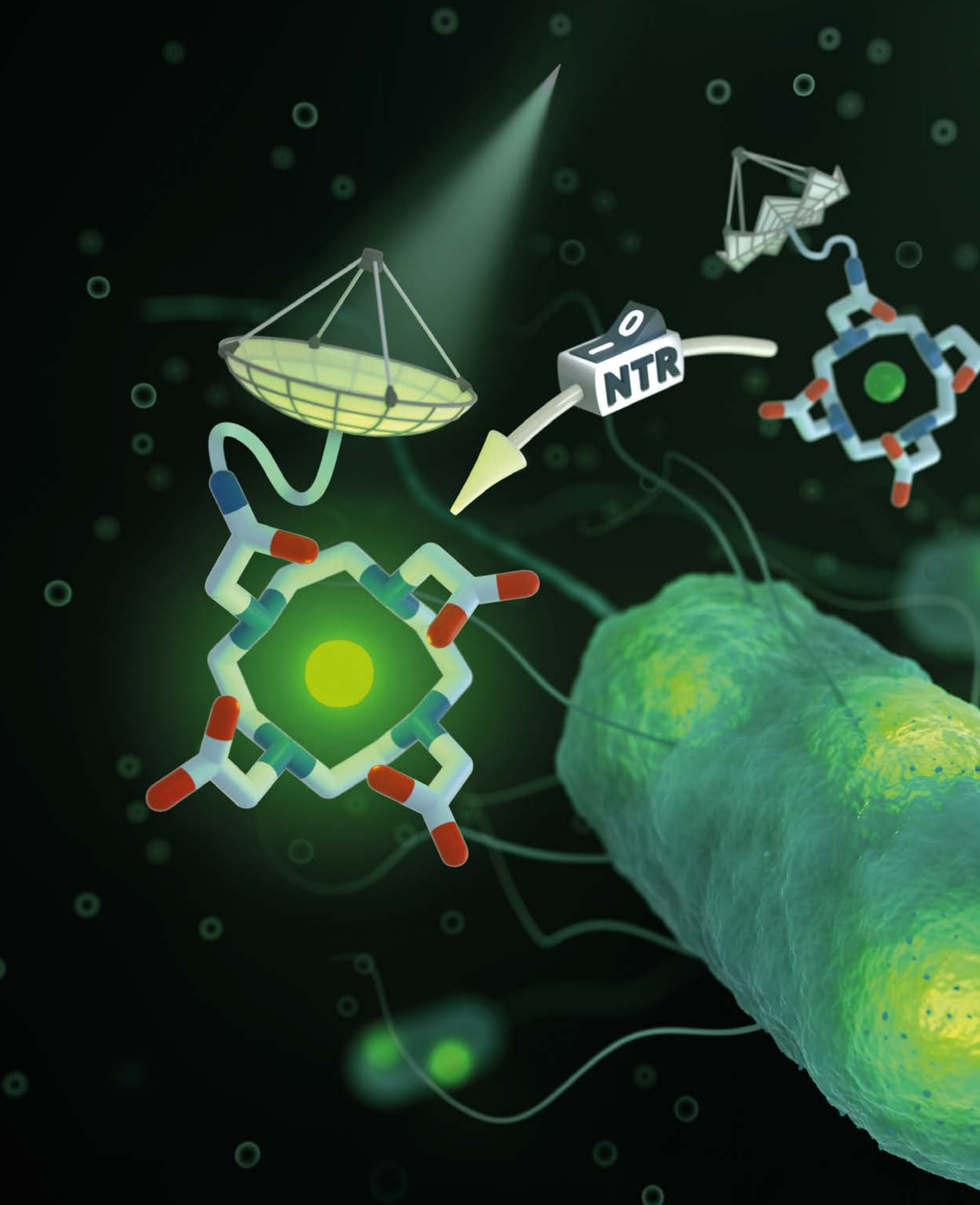
Gerland, L., Friedrich, D., Hopf, L., Donovan, EJ., Wallmann, A., Erdmann, N., Diehl, A., Bommer, M., Buzar, K., Ibrahim, M., Schmieder, P., Dobbek, H., Zouni, A., Bondar, AN., Dau, H., Oschkinat, H. (2020) **pH-dependent protonation of surface carboxylate groups in PsbO enables local buffering and triggers structural changes.** Chembiochem 21 (11), 1597–1604.

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, SFB 1078, TP B01, Structural Dynamics of Channelrhodopsins, 01/2017–12/2020, €699,121, continued until 12/2024 (€299,520)

European Commission, EU 8. RP/H2020 iNext, Integrating Infrastructures for Structural Biology, 09/2015–08/2019, €438,609

Deutsche Forschungsgemeinschaft, OS 106/17-1, Strukturbiologie von Bacillus Subtilis Biofilmen, 08/2020–07/2023, €263,200


NTR

MEDICAL DIAGNOSTICS: DETECTING MULTIDRUG-RESISTANT PATHOGENS

MEDIZINISCHE DIAGNOSTIK: DETEKTION MULTIRESISTENTER KRANKHEITSERREGER

Multi-resistant pathogens are responsible for the majority of hospital infections. A team led by Dr. Marc Nazaré has succeeded in developing the first luminescent lanthanoid turn-on probe for the highly selective and sensitive detection of nitroreductase (NRT). This probe could be used for the development of diagnostic tools for bacterial infections.
Benjamin Brennecke, *et al.*, Angewandte Chemie Int. Ed. Engl. 2020

Image: The illumination of bacterial pathogens by a specific lanthanide luminescent turn-on probe. A non-fluorescent caged precursor is intracellularly activated by bacterial NTR to form a sensitizing, light-harvesting antenna, enabling energy transfer to the lanthanoid. Entrapment of the activated probe inside bacterial cells allows for precise localization of live bacteria by fluorescence lifetime imaging. Visualization: Barth van Rossum

Multiresistente Erreger sind für die Mehrzahl der Krankenhausinfektionen verantwortlich. Einem Team um Dr. Marc Nazaré ist es gelungen, die erste aktivierbare lumineszente Lanthanoidsonde für den hochselektiven und sensitiven Nachweis von Nitroreduktase (NRT) in Bakterien zu entwickeln. Diese Sonde könnte für die Entwicklung von Diagnosewerkzeugen für bakterielle Infektionen verwendet werden.

Bild: Die Markierung bakterieller Pathogene durch eine spezifische Lanthanoid-Lumineszenz-Einschaltsonde. Ein nicht-fluoreszierender, gekapselter Vorläufer wird intrazellulär durch bakterielle NTR zu einer sensibilisierenden, lichtsammelnden Antenne aktiviert, die einen Energietransfer zum Lanthanoid ermöglicht. Der Einschluss der aktivierten Sonde in Bakterienzellen erlaubt eine präzise Lokalisierung lebender Bakterien durch Fluoreszenzlebensdauer-Mikroskopie.

MOLECULAR IMAGING

MOLEKULARE BILDGEBUNG

GROUP LEADER (at the FMP since 2009)
Dr. rer. nat. Leif Schröder

GROUP MEMBERS
Tahoe Fiala, David Hernandez Solarte, Dr. rer. nat. Martin Kunth, Hen-Amit Morik, Dr. rer. nat. Jabadurai Jayapaul, Dr. rer. nat. Jan Oliver Jost, Ursula Pfeiffer, Dr. rer. nat. Patrick Schünke, Patrick Werner, Dr. rer. nat. Lars Winkler

→ leibniz-fmp.de/schroeder

→ **BIOSENSORS FOR IMPROVED MRI DIAGNOSTICS**

Magnetic resonance imaging (MRI) is an indispensable tool for diagnostic imaging in drug development and therapy monitoring. Its limited sensitivity makes conventional MRI rely on the detection of tissue water. To unleash the full potential, it is necessary to integrate concepts of spin hyperpolarization techniques into diagnostic imaging. This will make MRI useable for precision medicine and visualize the distribution of dilute molecular markers in deep tissue. Our work on targeted molecular reporters optimizes the steps of preparation, manipulation and encoding of spin magnetization to obtain ultra-sensitive NMR reporters. A key concept is the development of biosensors that are only loaded in situ with hyperpolarized nuclei, significantly expanding the application range. To explore this potential, we successfully engage in highly competitive programs such as the Reinhart Koselleck program of the DFG and the Human Frontier Science Program to obtain MRI contrast from molecular targets at extremely low concentrations and sense molecular interactions within a few minutes, where conventional MRI protocols would require thousands of years.

→ **BIOSENSOREN FÜR EINE VERBESSERTE MRT-DIAGNOSTIK**

Die Magnetresonanztomographie (MRT) ist ein unverzichtbares Werkzeug für die diagnostische Bildgebung bei der Arzneimittelentwicklung und für die Therapieüberwachung in der Präzisionsmedizin. Aufgrund ihrer begrenzten Empfindlichkeit ist die herkömmliche MRT auf die Detektion von Gewebswasser angewiesen. Um das volle Potenzial auszuschöpfen, ist es notwendig, die Konzepte der Spin-Hyperpolarisierung in die diagnostische Bildgebung zu integrieren. Dies wird es ermöglichen, die MRT für die Präzisionsmedizin nutzbar zu machen, und die Verteilung molekularer Marker frühzeitig in tiefliegendem Gewebe zu visualisieren. Unsere Arbeiten an zielgerichteten molekularen Markern optimieren die Schritte zur Vorbereitung, Manipulation und Kodierung der Spin-Magnetisierung, um ultraempfindliche NMR-Reporter zu ermöglichen. Ein Schlüsselkonzept ist die Entwicklung von Biosensoren, die erst in situ mit hyperpolarisierten Kernen beladen werden und somit den Anwendungsbereich erheblich erweitern. Um dieses Potenzial auszuloten, engagieren wir uns erfolgreich in hoch kompetitiven Programmen wie dem Reinhart Koselleck-Programm der DFG und dem „Human Frontier Science Program“, um MRT-Kontrast von molekularen Markern bei extrem niedrigen Konzentrationen zu erhalten und molekulare Wechselwirkungen innerhalb weniger Minuten zu erfassen, für die herkömmliche MRT-Protokolle Tausende von Jahren erfordern würden.

QUANTIFICATION OF EXCHANGE KINETICS IN DRUG CARRIERS AND MRI REPORTERS

Spin exchange between different chemical environments is an important observable for characterizing chemical exchange kinetics in protein folding, host – guest interactions in drug carriers, and imaging reporters. This project introduces a novel type of highly simplified exchange kinetics analysis by relying on hyperpolarized ^{129}Xe as a freely exchanging ligand reporter. This technique allows the detection of otherwise inaccessible analyte concentrations with a single spin echo train (only 0.01% of the detected spins need to be transiently bound to the molecule). The Xe hosts cryptophane-A monoacid and cucurbit[6]uril represent two exemplary families of analytes (the latter also serving as drug delivery vehicles). By including principles of MRI, multiple samples can be studied simultaneously to determine the effective exchange rate; temperature-dependent measurements quantify the activation energy from simple relaxometry analysis. The concept is transferable to many applications where Xe is known to bind into hydrophobic cavities of proteins and drug carriers.

SIZE-OPTIMIZED REPORTERS FOR MRI-BASED CELL TRACKING

There is an urgent need to improve diagnostic imaging and therapy by targeted compound delivery to pathological areas and across biological barriers. This project focuses on preferred uptake of nanoscopic molecular reporters into blood–brain barrier (BBB) capillary endothelial cells. Generated micelles include a high payload of xenon hosts that enable a strong and switchable impact on the bulk magnetization through hyper-CEST detection. Xe hyper-CEST MRI allows BBB endothelial cells to be distinguished from control aortic endothelial cells, and the small micelle volume allows preferred cell labeling with a minimally invasive volume (≈16,000-fold more efficient than ^{19}F cell labeling). Thus, these nanoscopic particles combine selectivity for human brain capillary endothelial cells with great sensitivity of Xe hyper-CEST MRI, and may enable novel MRI studies in brain diagnostics.

← FIG. 1
Novel Xe MRI contrast agents enable selective cell labeling at minimally invasive concentrations and are approx. 16,000-fold more efficient than established ^{19}F cell labeling agents.

SELECTED PUBLICATIONS

Kunth, M., Schröder, L. (2020) **Binding Site Exchange Kinetics Revealed through Efficient Spin-Spin Dephasing of Hyperpolarized ^{129}Xe.** Chem. Sci. (in print)

Schnurr, M., Volk, I., Nikolenko, H., Winkler, L., Dathe, M., Schröder, L. (2020) **Functionalized Lipopeptide Micelles as Highly Efficient NMR Depolarization Seed Points for Targeted Cell Labelling in Xenon MRI.** Advanced Biosystems 4 (3), 1900251.

Jayapaul, J., Schröder, L. (2020) **Probing Reversible Guest Binding with Hyperpolarized ^{129}Xe-NMR: Characteristics and Applications for Cucurbit[n]Urils.** Molecules 25 (4), 957.

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, "Multivalent Hosts for Hyperpolarized Xenon Enabling *in vivo* MRI Visualization of Tumor Cell Surface Glycans", Reinhart Koselleck funding (first of its kind for the Leibniz Association); 07/2017–06/2022; €1,525,000

International Human Frontier Science Program Organization, "Imaging cellular function non-invasively with genetically engineered reporters for hyperpolarized MRI", Program Grant, together with Mikhail Shapiro; 05/2016–04/2020; $750,000

Deutsche Forschungsgemeinschaft, Research Training Group "BIOQIC – Biophysical Quantitative Imaging Towards Clinical Diagnosis", managed by Charité – Universitätsmedizin Berlin; 04/2017–09/2021; €4,497,810

SPECIAL AWARDS/HONORS

Conference stipends for the 2020 ISMRM Annual Meeting (H.-A. Morik and P. Werner)

Magna cum laude award at the 2020 ISMRM Annual Meeting (P. Werner and P. Schünke)

Minerva Gentner Symposium stipend (H.-A. Morik)

Travel stipends from the ENC and the Suraj P. Manrao Science Foundation for contributions to the ENC conference (P. Werner and H.-A. Morik)

Travel stipend for the 2019 ISMRM Annual Meeting (P. Schünke)

Fulbright Fellowship (T. Fiala)

Certificate of Merit Award and selection to give Lightning Talk at an ESMRMB Meeting (P. Werner)

STRUCTURAL INTERACTOMICS

STRUKTURELLE INTERAKTOMIK

GROUP LEADER (at the FMP since 2017)
Prof. Dr. Fan Liu

GROUP MEMBERS
Dr. Michal Nadler-Holly, Dr. Boris Bogdanow, Dr. Cong Wang, Dr. Diogo Borges Lima, Ying Zhu, Siang-Wun Siao, Kerem Can Akkaya, Jahzerah Jahaziel, Immanuel Husic, Heike Stephanowitz, Marleen van Rossum

→ leibniz-fmp.de/liu

→ **BETTER UNDERSTANDING OF PROTEIN INTERACTIONS**

Nearly every process in the living cell is based on proteins. To precisely execute this plethora of tasks, proteins are highly organized in a variety of assemblies, ranging from stable protein complexes, well-regulated pathways, to extended protein interaction networks. Perturbation of these well-balanced systems is linked to many different physiological and pathological conditions. Our group is interested in developing and applying tools to characterize the complexity of protein interactions within the cell. Using state-of-the-art mass spectrometric technologies, in particular cross-linking mass spectrometry, we aim to gain a better understanding of protein interactomes in complex biological systems. These studies will offer enormous opportunities to elucidate the fundamental organization principles of proteins and discover previously unrecognized protein interactions in health and disease.

→ **WECHSELWIRKUNGEN VON PROTEINEN BESSER VERSTEHEN**

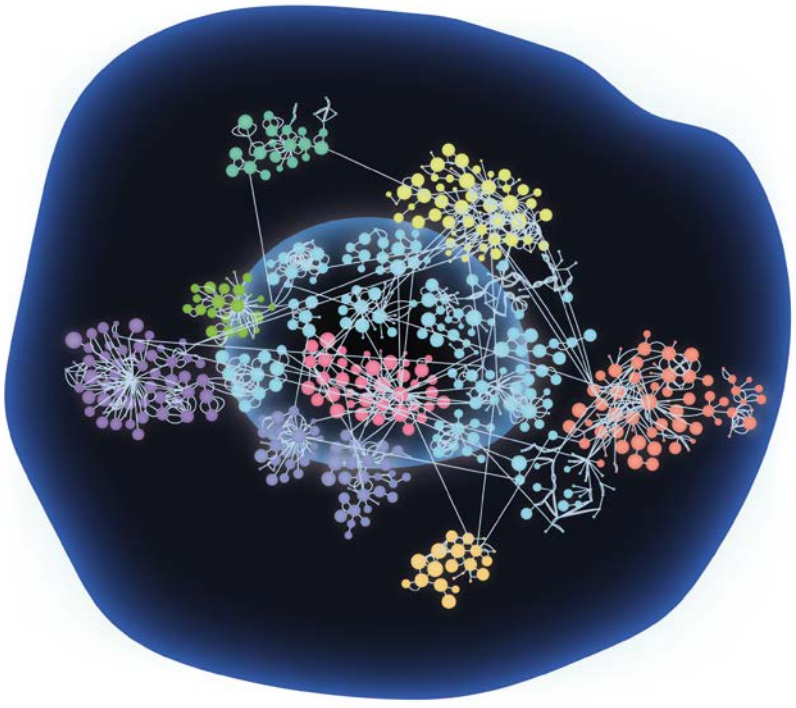
Eiweiße sind an nahezu jedem Prozess in der lebenden Zelle beteiligt. Um diese Fülle von Aufgaben präzise auszuführen, schließen sich die Eiweiße zu zahlreichen organisierten Komplexen zusammen und bilden so zum Beispiel gut regulierte Signalwege und weitreichende Protein-Interaktionsnetzwerke. Veränderungen oder Störungen dieser ausbalancierten Systeme haben Auswirkungen auf eine Vielzahl verschiedener physiologischer und pathologischer Zustände. Unsere Arbeitsgruppe forscht an der Entwicklung und Anwendung von Technologien, die es ermöglichen, die Komplexität dieser Proteinwechselwirkungen in der Zelle besser zu verstehen. Mithilfe modernster massenspektrometrischer Technologien, insbesondere der quervernetzenden Massenspektrometrie („Crosslinking-MS"), wollen wir die Wechselwirkungen von Proteinen in komplexen biologischen Systemen besser verstehen. Diese Untersuchungen bieten hervorragende Möglichkeiten, um die grundlegenden Prinzipien der Organisation von Proteinen aufzuklären und bisher nicht bekannte Proteinwechselwirkungen in der gesunden Zelle und bei Krankheiten aufzudecken.

DEVELOPING HIGH-THROUGHPUT PROTEOME-WIDE XL-MS STRATEGY

To comprehensively understand the protein interactome, our group has developed a novel XL-MS method to characterize the structures and interactions of various protein complexes in a high-throughput manner. This approach allows us to handle highly complex samples and simultaneously investigate stable and dynamic protein assemblies by capturing their residue–residue connectivities *in vivo*. In the future, we aim to unveil the full potential of this technique by designing novel cross-linkers, implementing creative approaches for cross-link enrichment, developing a cutting-edge data analysis pipeline, and applying state-of-the-art MS technology. We integrate expertise from synthetic chemistry, analytical chemistry, mass spectrometry and informatics, aiming to reach unprecedented analytical depth, complexity and precision in interactome profiling.

ESTABLISHING THE STRUCTURAL INTERACTOMES OF ORGANELLES

Organelles are specialized compartments within the cell, in which proteins are selectively imported to work cooperatively to conduct a variety of cellular functions. Although many organelles were discovered decades ago and found to play essential roles for the cell, questions regarding the extent to which protein complexes cooperate within and between organelles remain completely elusive. Our group studies the structural interactome of proteins in their organellular environment using the newly developed cross-linking mass spectrometry approach. We focus on two biological systems – neuronal synapses and mitochondria – the functions of which are linked to a wide variety of physiological and pathological conditions. Our aim is to obtain comprehensive protein interaction maps which will provide crucial insights into the interaction patterns, the binding interfaces, and the three-dimensional organization of protein complexes in their native cellular context.



← FIG. 1
Cellular functions are highly regulated through protein–protein interactions.

SELECTED PUBLICATIONS

Schnirch, L., Nadler-Holly, M., Siao, S., Frese, CK., Viner, R., and Liu, F. (2020) **Expanding the depth and sensitivity of cross-link identification by differential ion mobility using FAIMS.**
Anal Chem 92 (15),10495–10503.

Gonzalez-Lozano, MA., Koopmans, F., Sullivan, PF., Protze, J., Krause, G., Verhage, M., Li, KW.#, Liu, F.#, Smit, AB.# (2020) **Stitching the synapse: Cross-linking mass spectrometry into resolving synaptic protein interactions.**
Sci Adv 6 (8), eaax5783.

Liu, F., Lössl, P., Rabbitts, BM., Balaban, RS., Heck, AJR. (2018) **The interactome of intact mitochondria by cross-linking mass spectrometry provides evidence for coexisting respiratory supercomplexes.**
Mol Cell Proteomics. 17(2), 216–232.

SELECTED EXTERNAL FUNDING

Leibniz Association, Leibniz Programme for Women Professors (Leibniz Competition), "Cellular Interactomics in Health and Disease", 2020–2025, €808,055

ERC-2020-StG, "Revealing Synapse Architecture and Plasticity by Structural Interactomics (SynLink)", 2020–2025, €1,499,200

Deutsche Forschungsgemeinschaft, SFB 958 Z03, "Proteomics Platform for protein interaction mapping", 2019–2023, €245,464

COMPUTATIONAL CHEMISTRY / DRUG DESIGN

WIRKSTOFF-DESIGN

GROUP LEADER (at the FMP since 1993)
Dr. Ronald Kühne

GROUP MEMBERS
Dr. Bernd Rupp, Dr. Matthias Barone,
Dr. Matthias Müller, Dr. Michael Lisurek,
Raed Al-Yamori, Kathrin Motzny

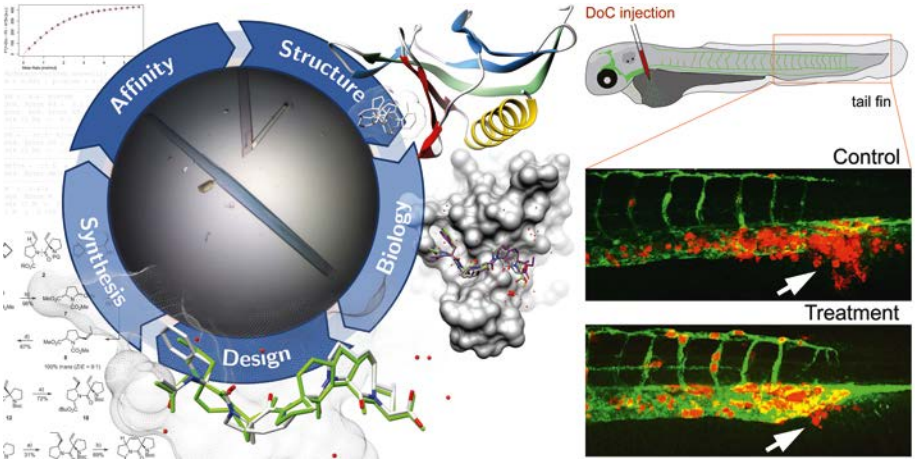
→ leibniz-fmp.de/kuehne

→ **DEVELOPING USEFUL SUBSTANCES AND SOFTWARE**

The major task of the Drug Design group is to develop chemical probes that bind to biologically important target proteins. Our drug design strategy involves in silico ligand design, structural biology (X-ray, NMR) and cell biology. In recent years, we have focused on targeting protein–protein interactions mediated by protein domains that specifically recognize proline-rich motifs. These domains are involved in many disease-relevant signal transduction cascades and in cytoskeleton remodeling. The design of chemical libraries for high-throughput screening is another focus of research in our group. Our library design software is directly linked to our regularly updated database of commercially available chemical compounds.

→ **NÜTZLICHE SUBSTANZEN UND SOFTWARE ENTWICKELN**

Unser zentrales Forschungsziel besteht darin, Substanzen zu entwickeln, die an biologisch wichtige Zielproteine binden. Dabei kommen in unserer Gruppe computergestütztes Ligandendesign, strukturbiologische Verfahren (Röntgenstrukturanalyse, NMR) und zellbiologische Methoden zur Anwendung. Wir wollen neuartige Inhibitoren von Protein–Protein-Wechselwirkungen entwickeln, die durch prolinreiche Motive vermittelt werden. Solche Wechselwirkungen finden sich in etlichen mit Krankheiten assoziierten Signalübermittlungswegen sowie in der strukturellen Organisation des Zytoskeletts. Einen weiteren Schwerpunkt unserer Arbeit bildet das Design chemischer Bibliotheken für das Hochdurchsatz-Screening. Die von uns entwickelte Software ist direkt mit unserer regelmäßig aktualisierten Datenbank kommerziell verfügbarer chemischer Verbindungen verknüpft.



← FIG. 1
Workflow of structure-guided drug design pursued by Ronald Kühne's group: High-resolution crystal structures serve as a basis to design scaffolds that mimic proline-rich segments. New synthesis routes are found by our collaborators. The substances are subsequently being tested *in vitro*, in a cellular and *in vivo* context, and scaffolds are being re-designed based on new complex structures.

→ DESCRIPTION OF PROJECTS

ENA/VASP EVH1 DOMAINS AS TARGETS TO INHIBIT CANCER CELL EXTRAVASATION

Metastasis is the major lethal attribute of cancer. Yet, the progress of metastasis-directed drug development efforts is limited, necessitating new approaches in drug design. We identified an unreported protein–protein interaction with the Ena/VASP EVH1 domain. Rendering the interaction non-functional by mutating the partner protein with CRISPR/Cas9 leads to a loss of cancer cell invasion in the Boyden chamber assay as well as extravasation of the knock-out cells in zebrafish xenograft. To address the protein–protein interaction identified, we use an integrated strategy of in silico design and X-ray crystallography to develop high-affinity inhibitors of the Ena/VASP EVH1 domain. Treatment of orthotopic mice xenografts using highly invasive triple-negative breast cancer cells and invasive pancreatic cancer cells with our unique chemical entities resulted in a significant reduction in tumor volumes.

LIBRARY DESIGN

Cheminformatics, bioinformatics and molecular modeling are important disciplines for supporting the rational design of chemical probes. In combination with experimental chemical biology, these in silico tools improve the probability of success for ligand development. We have established a wide range of methods, including library design, ligand optimization and the calculation of ADMET parameters. Our in-house library design toolbox utilizes an innovative fragment-based concept to select chemically diverse screening compounds with sufficient solubility, low toxicity and low chemical reactivity. Combined with our library design toolbox, our web-based database of commercially available compounds (DACS) enables us to rapidly design hit- or target-focused libraries, as well as new screening libraries.

SELECTED PUBLICATIONS

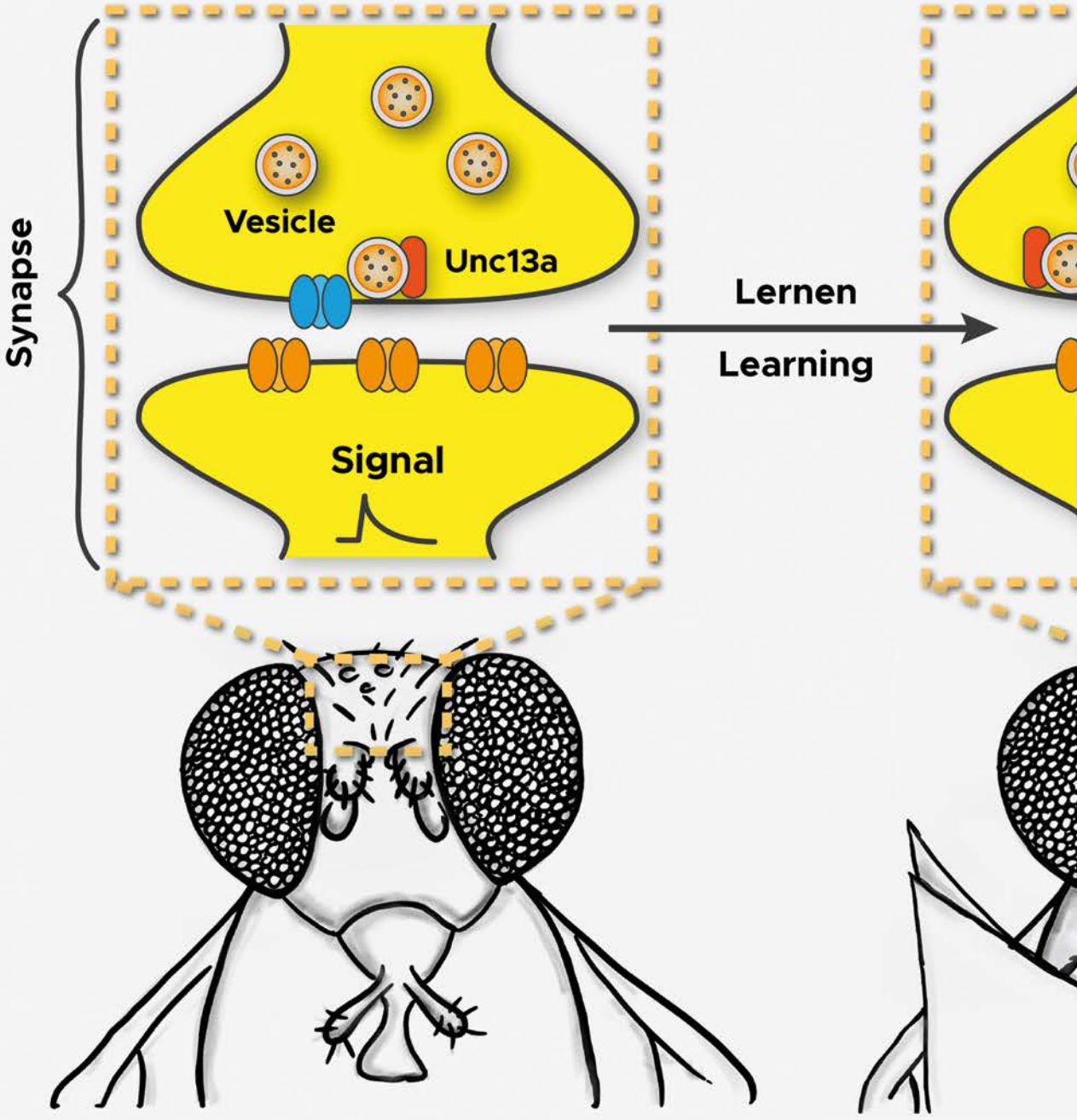
Barone, M., Müller, M., Chiha, S., Ren, J., Albat, D., Soicke, A., Dohmen, S., Klein, M., Bruns, J., van Dinther, M., Opitz, R., Lindemann, P., Beerbaum, M., Motzny, K., Roske, Y., Schmieder, P., Volkmer, R., Nazaré, M., Heinemann, U., Oschkinat, H., Ten Dijke, P., Schmalz, HG., Kühne, R. (2020) **Designed nanomolar small-molecule inhibitors of Ena/VASP EVH1 interaction impair invasion and extravasation of breast cancer cells.** Proc Natl Acad Sci U S A 117 (47), 29684–29690.

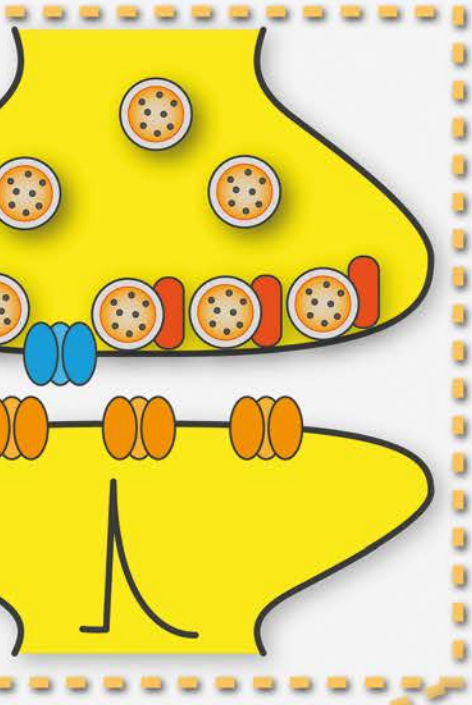
Maaßen, A., Gebauer, JM., Theres Abraham, E., Grimm, I., Neudörfl, JM., Kühne, R., Neundorf, I., Baumann, U., Schmalz, HG. (2020) **Triple-Helix-Stabilizing Effects in Collagen Model Peptides Containing PPII-Helix-Preorganized Diproline Modules.** Angew Chem Int Ed Engl 59 (14), 5747–5755.

Wong, EL., Nawrotzky, E., Arkona, C., Kim, BG., Beligny, S., Wang, X., Wagner, S., Lisurek, M., Carstanjen, D., Rademann, J. (2019) **The transcription factor STAT5 catalyzes Mannich ligation reactions yielding inhibitors of leukemic cell proliferation.** Nat Commun 10 (1), 66.

SELECTED EXTERNAL FUNDING

Validierung von Ena/VASP als Zielproteine zur Therapie metastasierender Krebserkrankungen (EnVision), BMBF framework program for Health Research, funding ID: 16GW0186K, MDC cooperation ageement Chemical Biology Platform


Synapse
Vesicle
Unc13a
Signal
Lernen
Learning



A PROTEIN FOR LEARNING

EIN PROTEIN FÜRS LERNEN

A protein called Unc13a is crucial for nerve cells to amplify the signal they send to downstream cells. The process of amplification is important for learning, but also to keep the nervous system functional after disturbances. This has been shown by researchers in team of Dr. Alexander Walter (FMP) and the FU Berlin in fruit flies *(Drosophila)*.
Böhme, MA. *et al.*, Nature Communications 2019

Image: Unc13a as a regulator of synaptic signal transmission. Simplified scheme of learning processes (from left to right) in which synaptic transmission strength changes. This happens, for example, when more Unc13a is accumulated at the synapse (right): It becomes stronger because more neurotransmitter vesicles can be released. Illustration: Mathias Bohme, Meida Jusyte, Alexander Walter

Ein Protein namens Unc13a ist entscheidend dafür, dass Nervenzellen das Signal verstärken können, welches sie an nachgeschaltete Zellen senden. Das haben Forscher um Dr. Alexander Walter (FMP) und der FU in Taufliegen *(Drosophila)* nachgewiesen. Wichtig ist, dass sowohl beim Lernen, als auch, um das System nach Störungen funktionsfähig zu halten.

Bild: Unc13a als Regulator der synaptischen Signalübertragung. Vereinfachtes Schema von Lernprozessen (von links nach rechts), bei denen sich synaptische Übertragungsstärken ändern. Dies geschieht beispielsweise wenn mehr Unc13a an der Synapse angereichert wird (rechts): Sie wird stärker, weil mehr Botenstoff-Bläschen freigesetzt werden können.

STRUCTURAL BIOINFORMATICS AND PROTEIN DESIGN

STRUKTUR-ORIENTIERTE BIOINFORMATIK UND PROTEINDESIGN

GROUP LEADER (at the FMP since 1998)
Dr. Gerd Krause

GROUP MEMBERS
Dr. Jonas Protze, Dr. Katrin M. Hinz,
Dr. Patrick Marcinkowski, Paul Becker,
Linda Vergili, Islam Masfaka

→ leibniz-fmp.de/gkrause

→ INVESTIGATING STRUCTURE AND FUNCTION OF MEMBRANE PROTEINS

Membrane proteins play an important role in several biological processes, such as transport of small molecules, establishing cell–cell contacts, and hormone recognition. Our group focuses on analyzing the relationship between the sequences and structures of membrane proteins and their potential interaction partners using structural bioinformatics, combined with experimental studies of altered protein sequences. One of our major activities is to develop bioinformatic tools to investigate these structure–function relationships. Another key activity is to verify our structure–function hypotheses by modeling guided site-directed mutagenesis of specific residues and analyzing their functional data. The main aims are to: (1) develop a detailed understanding of the intramolecular mechanisms of membrane proteins; (2) accelerate the rational discovery of molecular mechanisms and sites for protein–protein interactions, protein–ligand or protein–substrate interactions; and (3) predict small molecules or modifications of biosimilar molecules for potential pharmacological interventions.

→ STRUKTUR UND FUNKTION VON MEMBRANPROTEINEN

Wir beschäftigen uns mit der Frage, wie Sequenz und Struktur von Membranproteinen und deren potenzielle Interaktionspartner miteinander in Beziehung stehen. Dafür nutzen wir Methoden der strukturellen Bioinformatik in Kombination mit experimentellen Funktionsuntersuchungen gezielt veränderter Proteinsequenzen. Ferner entwickeln wir auch bioinformatische Werkzeuge und Datenbanken zur Untersuchung solcher Struktur-Funktionsbeziehungen. Die Hauptziele sind: (1) ein detailliertes Verständnis der intramolekularen Mechanismen von Membranproteinen zu entwickeln; (2) die rationale Entdeckung von molekularen Mechanismen und Stellen für Protein–Protein-Interaktionen, Protein–Ligand- oder Protein–Substrat-Interaktionen zu beschleunigen; und (3) kleine Moleküle oder Modifikationen von biologischen Molekülen für potenzielle pharmakologische Interventionen vorherzusagen.

→ DESCRIPTION OF PROJECTS

LIGAND BINDING TO THE ARYL HYDOCARBON RECEPTOR (AHR)

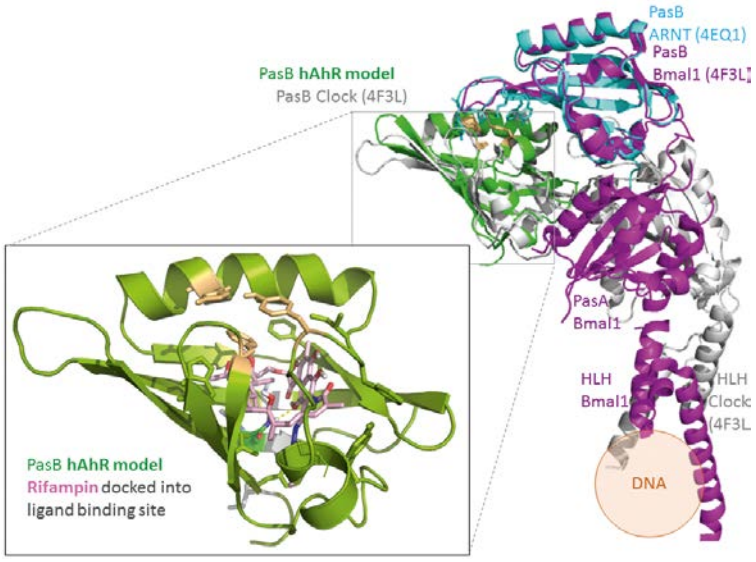
AhR binds phenazines, mediates their degradation, and regulates the expression of several host genes, including detoxifying enzymes, chemokines and cytokines. With our long-standing experience in biomolecular modeling and

biocomputing, we have successfully contributed to publications on the role of AhR in the immune defence system against bacteria (Lozza L *et al.* Sci Rep 2019; Puyskens A *et al.* Cell Host & Microbe 2020). Together with groups of the MPI IB Berlin, Oxford University and H. Oschkinat, we demonstrated that infected hosts show differential modulation of host AhR signaling over the course of P. aeruginosa infection in zebrafish, mice, and human cells. AhR signaling depended on the relative abundances of several classes of P. aeruginosa quorum sensing (QS) molecules. Since there is no crystal structure of AhR available, we generated a homologous structural model and predicted ligands that bind to the PasB domain of AhR (Figure 1) to interrogate whether and how these QS molecules from P. aeruginosa can be accommodated in the AhR-binding pocket. (Moura-Alves ***et al.*** Science 2019).

MODULATION OF MEMBRANE RECEPTORS

Pathogenic activation of the human thyroid-stimulating hormone receptor (TSHR), a G-protein coupled receptor (GPCR), by autoantibodies results in dysregulation of the thyroid hormone status. Blocking such pathogenic TSHR activation, we developed a negative allosteric small molecule modulator (NAM) S37a by i) high-throughput screening of the FMP compound library (in cooperation with Jens Peter von Kries), followed by ii) synthetic modifications (by Edgar Specker) and iii) functional characterization of potential value for the treatment of thyroid-associated ophtalmopathy (in cooperation with Ralf Schülein) (Marcinkowski, P. *et al.* Thyroid 2019). Moreover, we narrowed down a new allosteric binding site of S37a by mutagenesis and homology modeling (Marcinkowski, P. *et al.* Mol Pharmacology 2019). Ligand receptor interaction studies on a homologous GPCR, the luteinizing hormone receptor LHR, revealed small molecules as chaperones that rescued defects of pathogenic mutants in cell surface expression, binding and signaling (Newton, C. *et al.* Neuroendocrinology, 2020).

Membrane-embedded claudins, which are frequently overexpressed on the surface of cancer cells, are the receptors of *Clostridium perfringens* enterotoxin (CPE). Cancer treatment by wild-type CPE is restricted to carcinomas that express CPEwt-binding claudins (Cldn3, -4). We expanded the CPE-based oncoleaking strategy specifically for tumor types that overexpress claudins, which are not CPE receptors – such as Cldn1. We designed CPE mutants that target only Cldn1. This efficiently reduced tumor growth *in vitro* and *in vivo* in both papillary thyroid carcinoma (K1 cells) and lung NSCLC tumors (Piontek, A. *et al.* Mol Oncology 2020).



← FIG. 1
Homology model of the ligand binding PasB domain of the aryl hydrocarbon receptor (AhR) (green) with docked rifampin (pink). AhR consists of the DNA-binding HLH domain and the PasA and PasB domains. AhR forms a heterodimer with ARNT, consisting also of HLH, PasA and PasB. The homology model is assembled based on crystal structures such as PDB:4F3L, which represents a heterodimer of clock protein (gray) corresponding to AhR and of Bmal1 (magenta) corresponding to ARNT. The overlaid crystal structure of the PasB domain of ARNT (PDB:4EQ1 cyan) indicates that the PasB domain of ARNT interacts with particular residues (wheat) of AhR-PasB.

SELECTED PUBLICATIONS

Moura-Alves, P., Puyskens, A., Stinn, A., Klemm, M., Guhlich-Bornhof, U., Dorhoi, A., Furkert, J., Kreuchwig, A., Protze, J., Furkert, J., Lozza, L., Pei, G., Saikali, P., Perdomo, C., Mollenkopf, HJ., Hurwitz, R, Kirschhoefer, F., Brenner-Weiss, G., Weiner, J., Oschkinat, H., Kolbe, M., Krause, G., Kaufmann, SHE. (2019) **Host monitoring of and regulation by spying bacterial quorum sensing during Pseudomonas aeruginosa infection.** Science 366 (6472), eaaw1629.

Marcinkowski, P.*, Hoyer, I.*, Specker, E., Furkert, J., Rutz, C., Neuenschwander, M., Sobotka, S., Sun, H., Nazaré, M., Berchner Pfannschmidt, U., von Kries, J., Eckstein, A., Schuelein, R., Krause, G. (2019) **A new highly thyrotropin receptor-selective antagonist with potential for the treatment of Graves' orbitopathy.** Thyroid 29 (1), 111 – 123.

Piontek, A.*, Eichner, M.*, Zwanziger, D., Walther, W., Protze, J., Theurer, S., Beier, LS., Schmid, KW., Führer-Sakel, D., Piontek, J., Krause, G. (2020) **Cytotoxic targeting of claudin-overexpressing thyroid and lung cancer cells by modified Clostridium Perfringens Enterotoxin.** Mol Oncol 14 (2), 261 – 276.

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, New TSHR antagonists as a potential approach to bridge the therapeutic gap of Graves' ophthalmopathy, KR 1273/4-2, 10/2015 – 09/2019, €310,650

Deutsche Forschungsgemeinschaft, GRK 2318, Tight junction Train: Project A2, Piontek, J., Krause, G.

Deutsche Forschungsgemeinschaft, Searching for transport proteins for TRIAC or DITPA acting as T3/TH substitutes, KR 1273 9-1, PR1616/2-1, 12/2017 – 09/2021, €352,850

CORE FACILITY

NMR

NMR

GROUP LEADER (at the FMP since 1995)
Dr. Peter Schmieder

GROUP MEMBERS
Monika Beerbaum, Brigitte Schlegel,
Nils Trieloff

→ leibniz-fmp.de/nmr_facility

→ **NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY AT THE FMP**

The NMR facility maintains FMP's NMR spectrometers, enabling internal and external researchers to use both solid-state and solution-state NMR spectroscopy. NMR spectroscopy allows us to study the electronic environment of individual atoms and their interactions with neighboring atoms, for example to determine the structure and dynamics of molecules. Our facility provides the research groups with two open-access spectrometers (300 MHz and 600 MHz) for their own use. For more complex problems, we collaborate with the scientists using our NMR instruments equipped with cryoprobes. A probe suitable for 31P-NMR spectroscopy is of particular importance because the phosphorylation of different molecules is studied intensively in the Chemical Biology departments.

The solid-state spectrometers are primarily used by the Structural Biology departments to determine the structures of membrane proteins or larger aggregates. For this purpose, a wide range of field strengths and probes with different sample diameters is used. DNP (dynamic nuclear polarization) experiments can also be performed on two spectrometers. Furthermore, the facility receives requests from groups outside of the FMP, as well as from commercial companies located close to the institute. These requests are met in the form of collaborative activities or as an NMR service provided by the facility. The NMR facility also participates in the German DFG-funded G-NMR network of facilities, the iNEXT initiative, and worldwide NMR studies such as the Fab-NMR study by NIST.

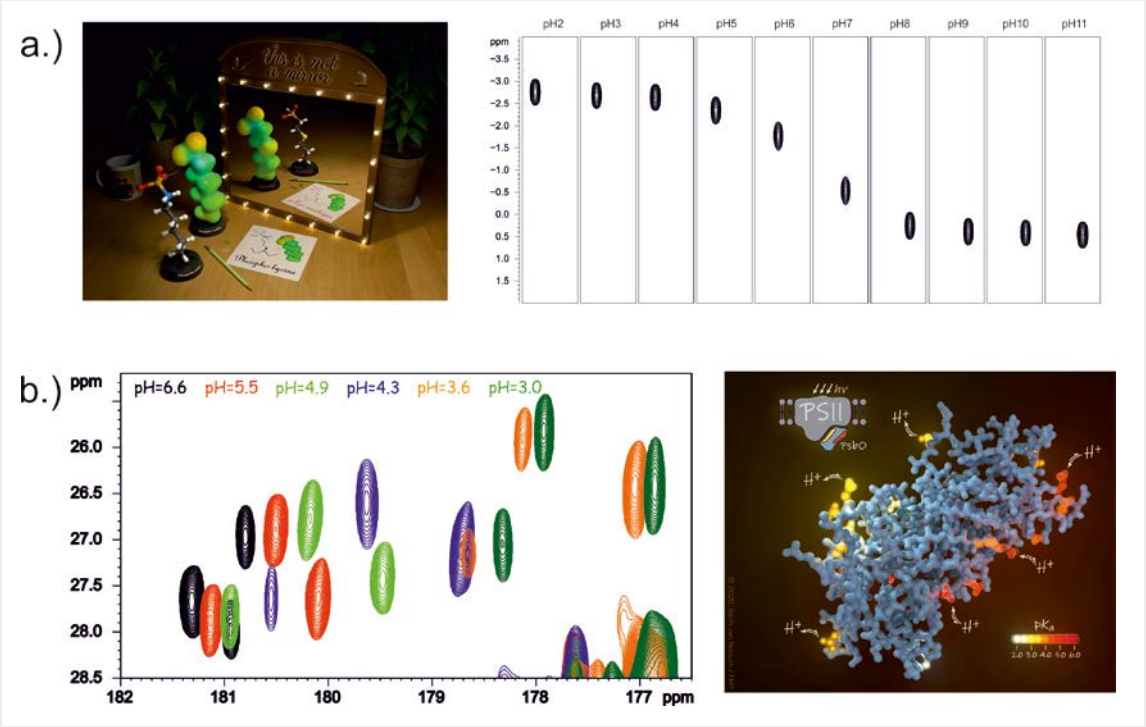
→ **KERNSPINRESONANZSPEKTROSKOPIE**

Wir betreuen die Kernspinresonanz- bzw. NMR-Spektrometer des FMP und unterstützen Forschende des FMP und anderer Institutionen bei der Nutzung der NMR-Spektroskopie – ob im Festkörper oder in Lösung. NMR-Spektroskopie macht es möglich, die elektronische Umgebung einzelner Atome und ihrer Wechselwirkungen mit Nachbaratomen zu untersuchen, etwa um Struktur und Dynamik von Molekülen zu bestimmen. Unsere Facility stellt den Forschungsgruppen zwei Open-Access-Spektrometer (300 MHz und 600 MHz) für die Eigennutzung zur Verfügung. Bei komplexeren Problemen arbeiten wir mit den Forschenden zusammen und setzen hierfür unsere mit Kryoköpfen ausgestatteten NMR-Geräte ein. Besonders von Bedeutung ist dabei ein für die 31P-NMR-Spektroskopie geeigneter Kopf, weil die Phosphorylierung von unterschiedlichen Molekülen in den Abteilungen für Chemische Biologie intensiv studiert wird.

Die Festkörper-Spektrometer werden vorrangig von den Abteilungen für Strukturbiologie genutzt, um Strukturen von Membranproteinen oder größeren Aggregaten zu bestimmen. Dazu setzen wir eine große Breite von Feldstärken und Probenköpfen mit unterschiedlichen Probendurchmessern ein. An zwei Spektrometern können zudem DNP-Experimente (Dynamische Kernpolarisation) durchgeführt werden. Daneben erhält die NMR-Facility viele Anfragen von anderen akademischen Gruppen oder von Firmen aus der Nähe des FMP. Diese Anfragen werden nach Möglichkeit entweder durch Kooperationen oder als NMR-Service beantwortet. Darüber hinaus sind wir Teil des von der DFG geförderten G-NMR-Facility-Netzwerks und an der iNEXT (infrastructure for NMR, EM and X-rays for Translational research)-Initiative sowie an weltweiten Ringversuchen beteiligt.

→ DESCRIPTION OF PROJECTS

Two related projects were realized as in-house collaborative activities. Together with the group of C. Hackenberger, the pKa values of analogs of phosphorylated lysine side chains were investigated using ^{31}P-NMR spectroscopy (Figure 1a). This was extended in collaboration with the group of H. Oschkinat, involving the determination of pKa values of aspartic acid and glutamic acid side chains of PsbO using triple-resonance experiments (Figure 1b). It is only possible to obtain such information with atomic resolution using NMR spectroscopy, helping to shed light on mechanistic aspects of biological processes.



↑ FIG. 1
(a) Determination of pKa values of analogs of phosphorylated lysine side chains using 1H,31P-HMBC spectra.
(b) Determination of the pKa values of aspartic acid and glutamic acid side chains in the protein PsbO using CBCACO spectra (utilizing carbon detection).
(Scientific Image: Barth van Rossum)

SELECTED PUBLICATIONS

Hauser, A., Poulou, E., Muller, F., Schmieder, P. , Hackenberger, C. (2020) **Synthesis and evaluation of non-hydrolyzable phospholysine peptide mimics.** Chemistry doi: 10.1002/chem.202003947. Online ahead of print.

Gerland, L., Friedrich, D., Hopf, L., Donovan, EJ., Wallmann, A., Erdmann, N., Diehl, A., Bommer, M., Buzar, K., Ibrahim, M., Schmieder, P., Dobbek, H., Zouni, A., Bondar, AN., Dau, H. , Oschkinat, H. (2020) **pH-Dependent Protonation of Surface Carboxylate Groups in PsbO Enables Local Buffering and Triggers Structural Changes.** Chembiochem 21, 1597–1604.

Harmel, RK., Puschmann, R., Nguyen Trung, M., Saiardi, A., Schmieder, P., Fiedler, D. (2019) **Harnessing (13)C-labeled myo-inositol to interrogate inositol phosphate messengers by NMR.** Chem Sci 10, 5267–5274.

ION CHANNEL VRAC ENHANCES IMMUNE RESPONSE AGAINST VIRUSES BY TRANSPORTING THE MESSENGER SUBSTANCE CGAMP FROM CELL TO CELL

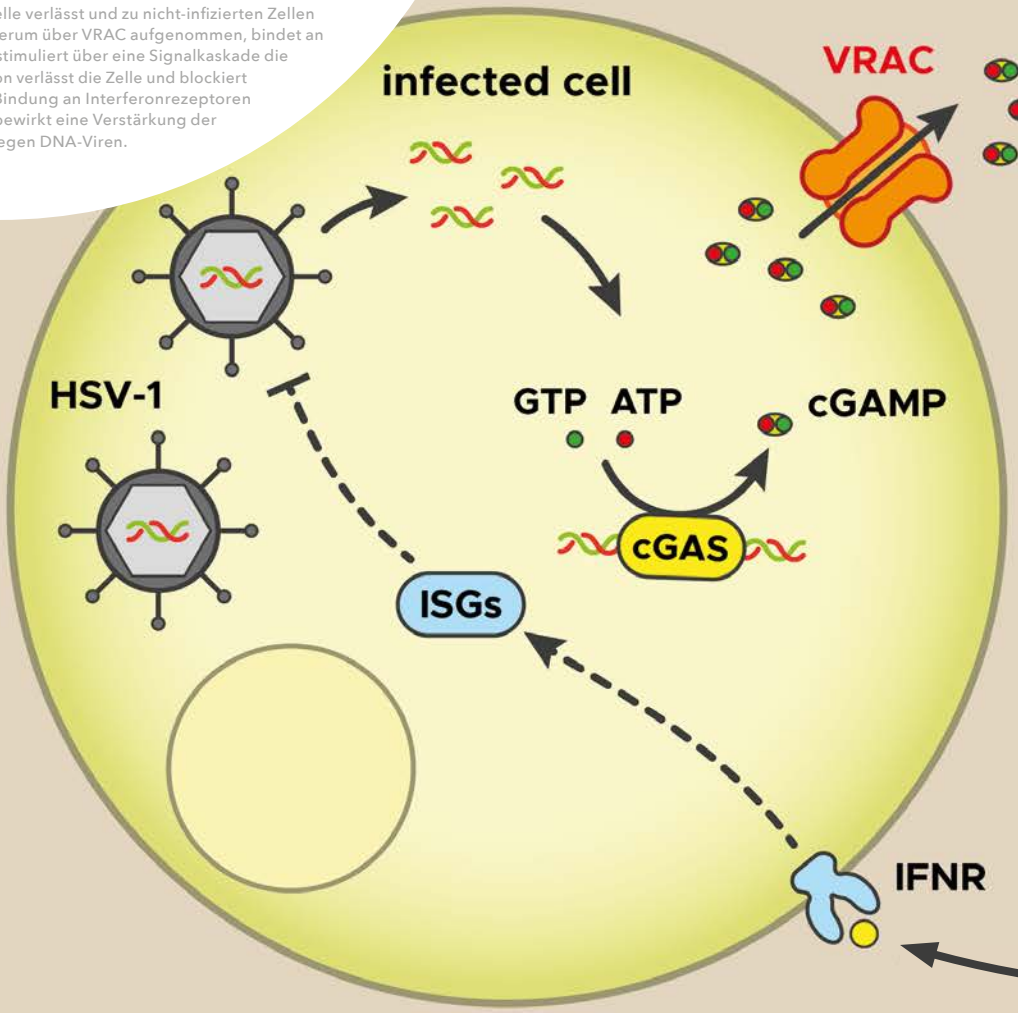
IONENKANAL VRAC VERSTÄRKT IMMUNANTWORT GEGEN VIREN DURCH TRANSPORT DES BOTENSTOFFS CGAMP VON ZELLE ZU ZELLE

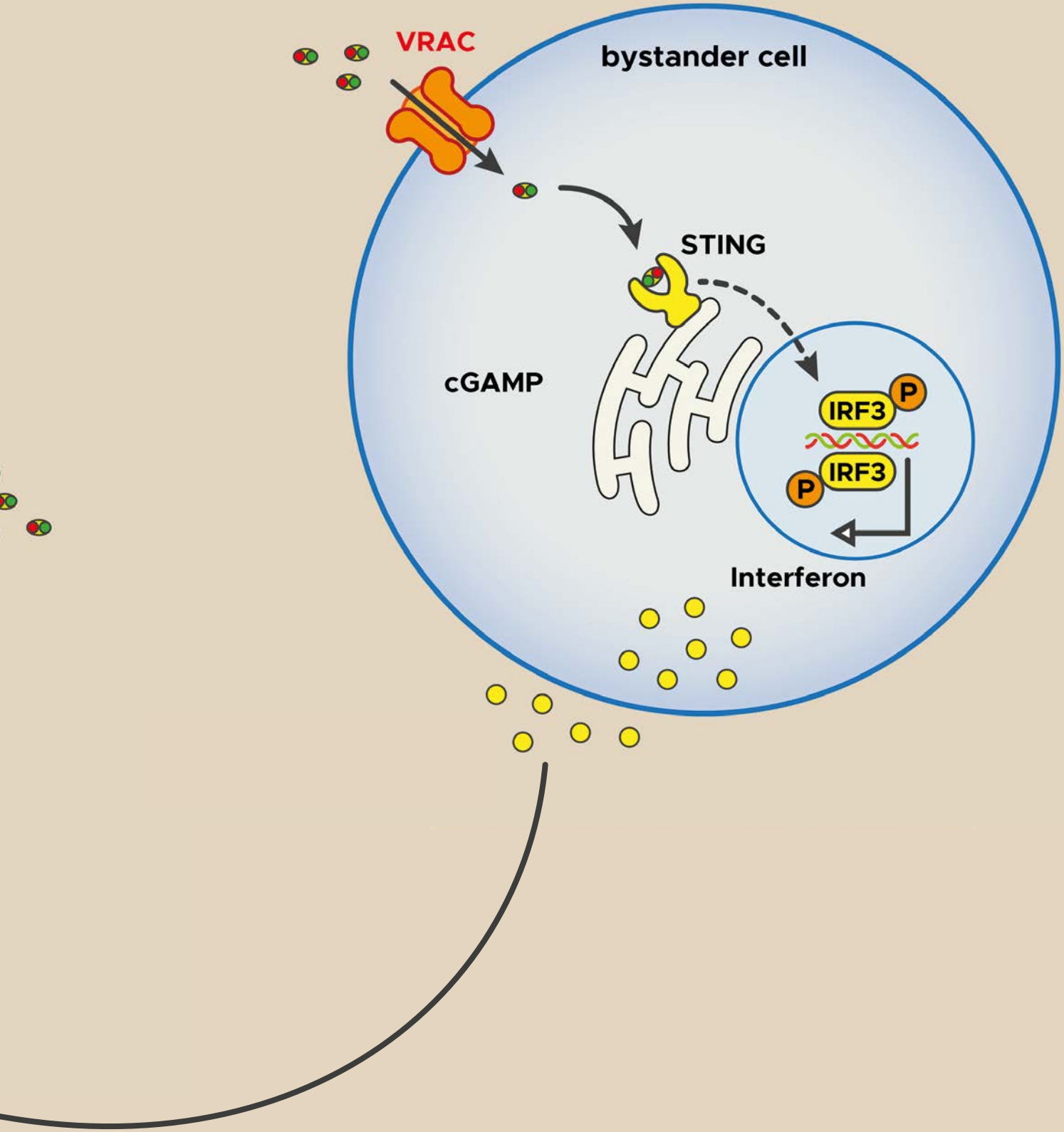
VRAC/LRRC8 chloride channels do not only play a decisive role in the transport of cytostatics, amino acids and neurotransmitters – they can also transport the important messenger substance cGAMP from cell to cell, strengthening the immune response to infections with DNA viruses. This has now been demonstrated by Professor Thomas Jentsch, who originally discovered LRRC8/VRAC channels, together with colleagues from Shanghai led by Professor Hui Xiao.
Zhou, C. *et al.*, Immunity 2020

Image: Upon infection of cells with a DNA virus (left), viral DNA binds to the enzyme cGAS, which then synthesizes the messenger molecule cGAMP. The present work shows that cGAMP can leave the cell through the anion channel VRAC and diffuses to non-infected cells in the vicinity. After entering the cell – again through VRAC – it binds to a receptor called STING, and indirectly stimulates the synthesis of interferon, which leaves the cell and, after binding to a receptor, suppresses the propagation of the virus (left cell). This provides a powerful amplification of the innate immune response against DNA viruses. Illustration: Rosa Planells-Cases, Barth van Rossum

VRAC/LRRC8-Chloridkanäle spielen nicht nur beim Transport von Zytostatika, Aminosäuren und Neurotransmittern eine entscheidende Rolle. Sie können auch den wichtigen Botenstoff cGAMP von Zelle zu Zelle transportieren und damit eine Immunantwort bei Infektionen mit DNA-Viren verstärken. Das hat jetzt der LRRC8/VRAC-Entdecker Prof. Thomas Jentsch zusammen mit Kolleg*innen um Prof. Hui Xiao aus Shanghai gezeigt.

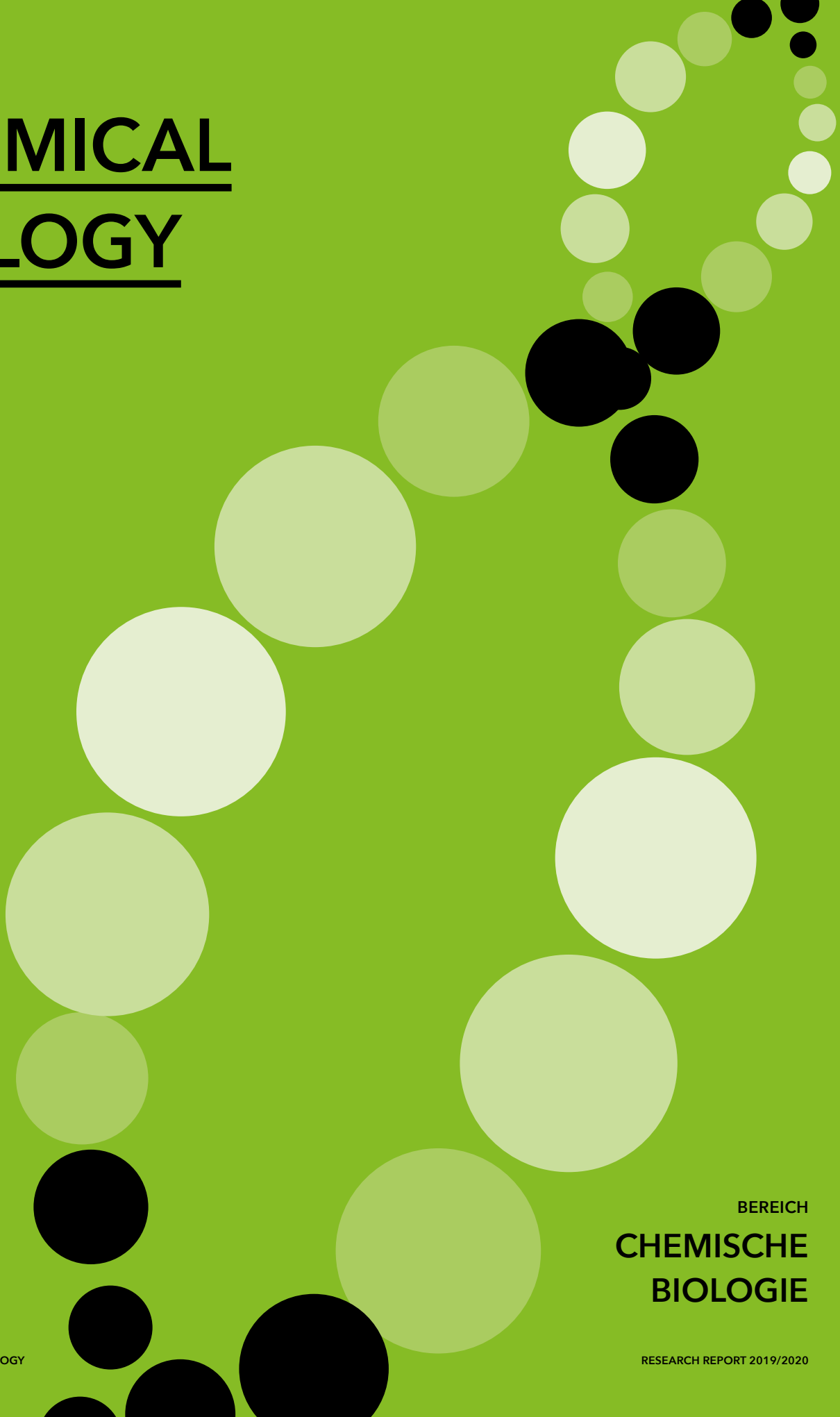
Bild: Wenn Zellen mit DNA-Viren infiziert werden (links), bindet freigesetzte virale DNA an das Enyzm cGAS. Dies führt zur Synthese des Botenstoffes cGAMP, der, wie in der Arbeit gezeigt, über den Ionenkanal VRAC die Zelle verlässt und zu nicht-infizierten Zellen (rechts) diffundiert. Dort wird cGAMP wiederum über VRAC aufgenommen, bindet an den Rezeptor STING in der Zelle, und stimuliert über eine Signalkaskade die Synthese von Interferon. Interferon verlässt die Zelle und blockiert die Vermehrung des Virus nach Bindung an Interferonrezeptoren (links). Dieser Mechanismus bewirkt eine Verstärkung der Immunantwort gegen DNA-Viren.




VRAC
bystander cell
STING
cGAMP
IRF3
P
IRF3
P
Interferon

SECTION

CHEMICAL BIOLOGY



BEREICH

CHEMISCHE BIOLOGIE

→ Chemical Biology utilizes chemical methods to advance the understanding and modulation of cellular function, especially in the context of pharmacological targets and the development of novel approaches in the medicinal sciences. Research projects in this Section are devoted to the synthesis and identification of novel bioactive small molecules and protein conjugates of high pharmacological potency, as well as the development of new chemical and analytical tools to study biologically relevant pathways. The two departments in this section, "Chemical Biology 1 and 2", headed by Dorothea Fiedler and Christian Hackenberger, have recently been supplemented by "ChemBioProbes", headed by junior group leader Johannes Broichhagen.

The Chemical Biology section provides the whole institute with important research and technologies. One central component is the "Chemical Biology Platform", which is devoted to the validation and chemical optimization of small molecule screening hits of pharmacological targets, thereby serving as an essential partner site in several institutional, national and international research networks. Within this platform, the "Screening Unit" core facility (Jens Peter von Kries) provides high-throughput RNAi and CRISPR-based screens in addition to using small molecules from the unique FMP compound library, which is managed in the "Compound Management" core facility (Edgar Specker). The "Medicinal Chemistry" group led by Marc Nazaré develops new chemical tools using strategies such as fragment growing, re-scaffolding approaches and structure-based design to chemically optimize initial screening hits. Han Sun heads the "Structural Chemistry and Computational Biophysics" group to support and develop this platform using theoretical methods.

→ Die Chemische Biologie nutzt chemische Methoden, um das Verständnis und die Modulation der Zellfunktion voranzutreiben, insbesondere im Zusammenhang mit pharmakologischen Zielen und der Entwicklung neuer Ansätze in den Medizinwissenschaften. Die Projekte der Abteilung widmen sich der Synthese und Identifizierung neuartiger bioaktiver kleiner Moleküle und Proteinkonjugate, die eine hohe pharmakologische Wirksamkeit aufweisen. Darüber hinaus entwickeln die Forschenden neue chemische und analytische Werkzeuge zur Untersuchung biologisch relevanter Signalwege. Neben den beiden Abteilungen „Chemische Biologie 1 und 2" unter der Leitung von Dorothea Fiedler und Christian Hackenberger hat Johannes Broichhagen als Nachwuchsgruppenleiter der Gruppe „ChemBioProbes" seine Arbeiten am FMP begonnen.

Innerhalb des Bereiches Chemische Biologie werden wichtige Forschung und Technologien für das gesamte Institut bereitgestellt. Ein zentraler Bestandteil ist dabei die „Chemische Biologie-Plattform", die sich der Validierung und chemischen Optimierung kleinmolekularer Screening-Treffer pharmakologischer Targets, sogenannter Hits, widmet. Dabei positioniert sich diese Einheit als unverzichtbarer Partnerstandort in mehreren nationalen und internationalen Forschungsnetzwerken, beispielsweise im EU-OPENSCREEN Netzwerk. Innerhalb dieser Plattform bietet die „Screening Unit" unter der Leitung von Jens Peter von Kries ein Hochdurchsatz-Screening von RNAi- und CRISPR-basierten Bibliotheken und kleinen Molekülen aus der einzigartigen FMP eigenen Wirkstoffbibliothek, die in der Technologieplattform „Compound Management" (Edgar Specker) verwaltet wird. Die von Marc Nazaré geführte Gruppe „Medizinische Chemie" erforscht neue chemische Werkzeuge, und nutzt hierbei Strategien wie Fragmentwachstum und strukturbasiertes Design, um die initialen Hits chemisch zu verbessern. Han Sun leitet die Gruppe „Strukturchemie und Computergestützte Biophysik", um die Plattform mit theoretischen Methoden zu unterstützen.

CHEMICAL BIOLOGY II

CHEMISCHE BIOLOGIE II

GROUP LEADER (at the FMP since 2012)
Prof. Dr. Christian P.R. Hackenberger

GROUP MEMBERS
Dr. Antoine Wallabregue, Dr. Philipp Ochtrop, Dr. Bingjia Yan, Dr. Reihaneh Safavi-Sohi, Dr. Dominik Schumacher, Marc-André Kasper, Sergej Schwagerus, Anett Hauser, Alice Baumann, Anselm Schneider, Lutz Adam, Alec Michels, Sebastián Florez Rueda, Don Shenal Munasinghe, Jacob Gorenflos, Christian Stieger, Eleftheria Poulou, Luise Franz, Benjamin Nava Höer, Dagmar Krause, Kristin Kemnitz-Hassanin, Beate Kindt, Ines Kretzschmar, Katrin Wittig, Jennifer Trümpler

→ leibniz-fmp.de/hackenbe
→ @PhosphorusFive

→ **HOW PROTEIN MODIFICATIONS CAN CHANGE FATE**

In the cell, protein modifications control many signaling pathways that support healthy functioning and that are disrupted in disease. Such modifications can act as "toggle switches" between health and disease. Chemical biologists want to control these protein modifications in the cell, both to study the biological role of such modifications and to decorate proteins with fluorescent moieties that permit their visualization. Our laboratory aims to identify new chemical approaches that allow the modification of peptides and proteins, both on isolated biomolecules as well as in living cells and organisms. Here, our main objective is to apply these highly selective bioconjugation reactions to study the functional consequences of natural protein modifications, as well as to generate novel pharmaceutical and medicinal applications, such as protein or antibody-drug conjugates (ADCs) against cancer or viral infections.

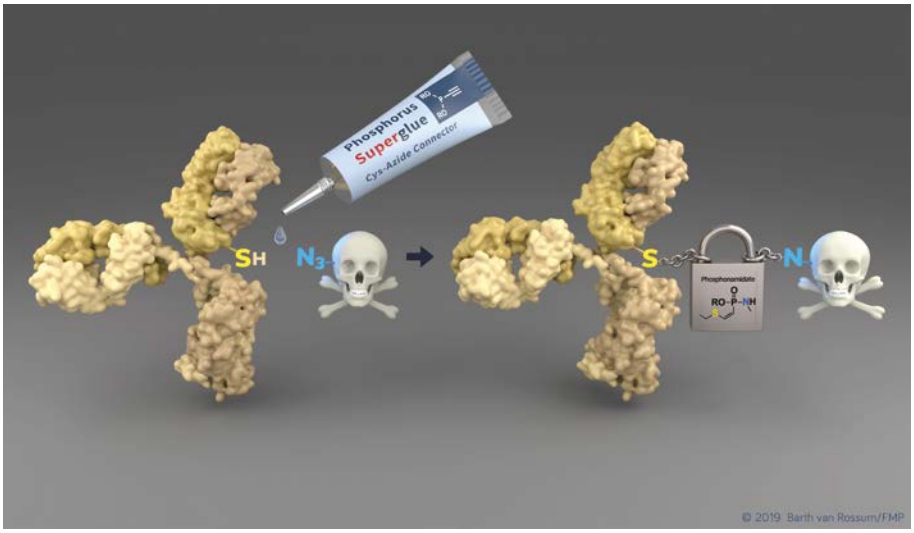
→ **WIE PROTEINMODIFIKATIONEN ALLES VERÄNDERN**

In der Zelle werden viele Signalwege, die normales Leben steuern und bei Krankheit gestört sind, durch Veränderungen an Proteinen reguliert. Solche Modifikationen können wie „Wechselschalter" zwischen Gesundheit und Krankheit wirken. Forschende in der Chemischen Biologie versuchen deshalb zunehmend, die Proteinmodifizierungen in der Zelle zu kontrollieren, um deren biologische Rolle zu erforschen oder bestimmte Proteine mit fluoreszierenden Gruppen zu versehen, die ihre Visualisierung ermöglichen. Wir haben uns zum Ziel gesetzt, neue chemische Verfahren zu entwickeln, mit denen sich Proteine und kleinere Moleküle sowohl in isolierter Form als auch in lebenden Zellen oder Organismen gezielt funktionalisieren, d. h. für bestimmte Aufgaben einsetzen lassen. Insbesondere wollen wir hochselektive, organisch-chemische Methoden für die Biokonjugation, also die Verknüpfung von einem Protein oder einem Antikörper mit einem synthetischen Molekül, entwickeln. Mit diesen Methoden können wir die Auswirkungen natürlich vorkommender Modifikationen auf die Proteinfunktion untersuchen, aber auch neue medizinische und pharmakologische Anwendungen ermöglichen, wie beispielsweise durch Protein- oder Antikörper-Wirkstoff-Konjugate gegen Krebs oder virale Infektionen gezeigt werden konnte.

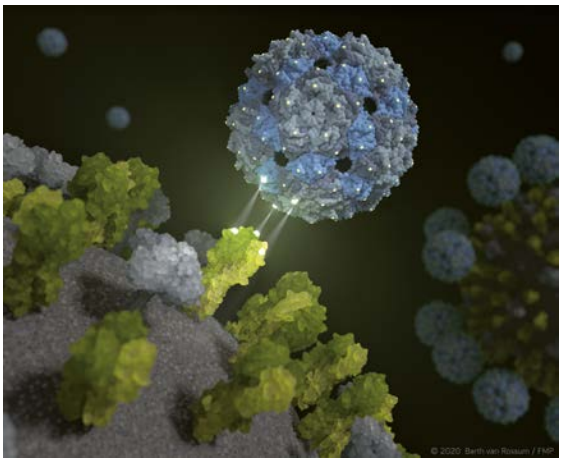
→ DESCRIPTION OF PROJECTS

Based on the discovery of a new chemoselective reaction for the modification of cystein residues in proteins and antibodies, we developed a new generation of antibody-drug conjugates (ADCs). These antibody conjugates are linked to cytotoxic drugs via phosphonamidate linkages, which outperformed a clinically approved drug against Hodgkin lymphoma. Furthermore, in collaboration with colleagues from LMU Munich, we engineered a chemoenzymatic protocol for the modular C-terminal modification of proteins by the tubulin tyrosine ligase. The combination of these technologies laid the foundation for the great success of the recently founded company Tubulis, which received €10.7 million in the first funding series.

Engineering novel therapeutics to fight influenza infection is one of the most challenging tasks in drug development due to the multivalent binding of a virus during infection. In order to break this multivalent interaction, we designed a structurally defined chemically glycosylated phage capsid, which showed nanomolar binding to the viral surface protein hemagglutinin and prevented influenza infections in living cells and *in vivo* against human and avian influenza viruses (Lauster, Klenk *et al.*, Nature Nanotech. 2020). This study, performed in close collaboration with the Herrmann group at the HU Berlin, offers a new approach to target viral infections by addressing multivalent binding sites in a structurally defined manner.



↑ FIG. 1
Next-generation antibody-drug conjugates (ADCs) with phosphonamidate-linked cytotoxic drugs.



← FIG. 2
Trivalent binding of glycosylated phage capsid against the viral surface protein hemagglutinin.

SELECTED PUBLICATIONS

Baumann, AL., Schwagerus, S., Broi, K., Kemnitz-Hassanin, K., Stieger, CE., Trieloff, N., Schmieder, P., Hackenberger, CPR. (2020) **Chemically induced vinylphosphonothiolate electrophiles for thiol-thiol bioconjugations.** JACS 142(20), 9544–9552.

Lauster, D., Klenk, S., Ludwig, K., Nojoumi, S., Behren, S., Adam, L., Stadtmüller, M., Saenger, S., Zimmler, S., Hönzke, K., Yao, L., Hoffmann, U., Bardua, M., Hamann, A., Witzenrath, M., Sander, LE., Wolff, T., Hocke, AC., Hippenstiel, S., DeCarlo, S., Neudecker, J., Osterrieder, K., Budisa, N., Netz, RR., Böttcher, C., Liese, S., Herrmann, A., Hackenberger, CPR. (2020) **Phage capsid nanoparticles with defined ligand arrangement block influenza virus entry.** Nat Nanotechnol 15 (5), 373–379.

Kasper, MA., Stengl, A., Ochtrop, P., Gerlach, M., Stoschek, T., Schumacher, D., Helma, J., Penkert, E. Krause, M., Leonhardt, H., Hackenberger, CPR. (2019) **Ethynylphosphoniamidates for the rapid and cysteine selective generation of efficacious Antibody-Drug Conjugates.** Angew. Chem. Int. Ed. 58(34), 11631–11636.

SELECTED EXTERNAL FUNDING

Deutsche Forschungsgemeinschaft, Priority Programme SPP 1623 "Chemoselective reactions for the synthesis and application of functional proteins":
- Funds for coordination of the Priority Programme, 2012–2019, €612,500
- Funds for joint project with H. Leonhardt (LMU Munich) and C. Cardoso (TU Darmstadt), "Site-specific functionalization of nanobodies: From labeling to cellular uptake", 2012–2019, €412,800
- Funds for joint project with J. Kirstein (FMP), "Chemoselective Staudinger-induced Michael-additions to antibodies to analyze protein homeostasis in C. elegans", 2016–2019, €217,150

SPP 1623 funding in total: €1,242,450

Leibniz Association, Senate Competition Committee (SAW), "Cystein-selective bioconjugation for next generation antibody drug conjugates", together with H. Leonhardt (LMU Munich), J. von Kries (FMP), C. Hertweck (HKI Jena) and L. Wessjohann (IPB Halle), 2018–2022, €864,183

Berlin University Alliance, "Corona Virus Pre-Exploration Project", together with A. Herrmann (HU Berlin), D. Brockmann (RKI), T. Wolff (RKI), 2020–2021, €436,437.50

SPECIAL AWARDS / HONORS

2020 Breakthrough of the Year Award (Life Sciences) by the Falling Walls Foundation
2019 Novartis Lecturer and Visiting Professor New York University (NYU)

CHEMICAL BIOLOGY I

CHEMISCHE BIOLOGIE I

GROUP LEADER (at the FMP since 2015)
Prof. Dr. Dorothea Fiedler

GROUP MEMBERS
David Furkert, Sandra Schlomach, Tim Kröber, Minh Nguyen Trung, Arif Celik, Leonie Kurz, Simon Bartsch, Annika Richter, Jeremy Morgan, Kathrin Motzny, Katy Franke, Jennifer Trümpler

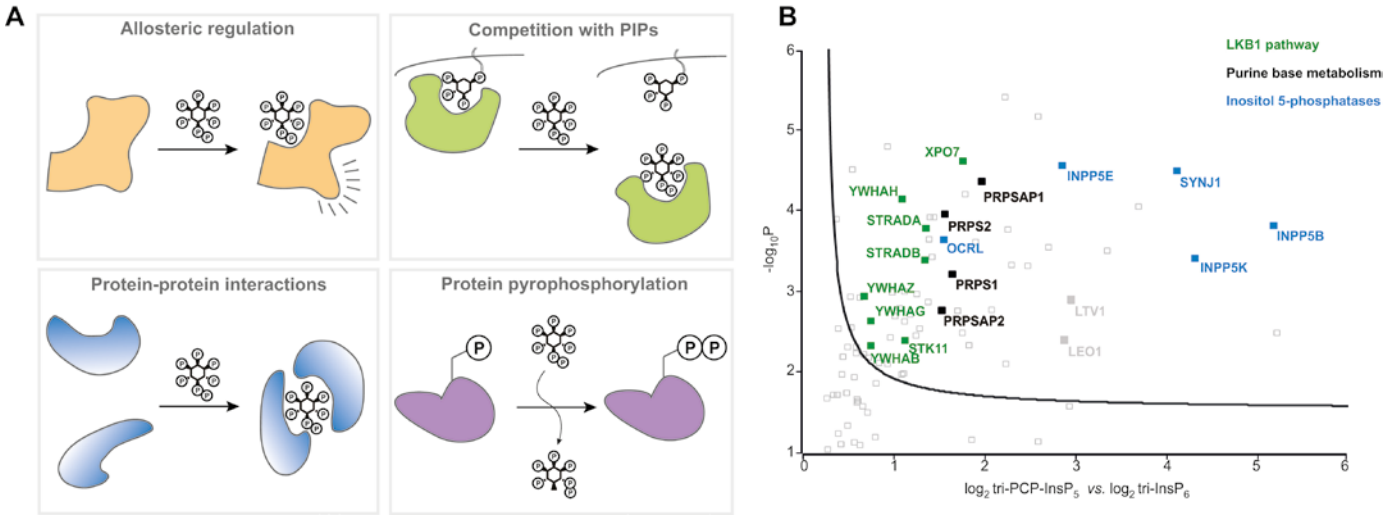
→ leibniz-fmp.de/d_fiedler
→ @FiedlerLab

→ **ELUCIDATING AND CONTROLLING THE FUNCTION OF MESSENGER MOLECULES IN SIGNALING PROCESSES**

Cells are able to constantly process information about their environment and their internal status via highly regulated signaling networks. Since deregulation of cellular information transfer is associated with a wide range of diseases, a detailed annotation of signaling events in healthy and diseased states can highlight new avenues for therapeutic intervention. One group of messengers of particular interest to our group are inositol pyrophosphates (PP-InsPs). These molecules have emerged as central regulators of cell homeostasis, and genetic studies in mice and humans implicate PP-InsPs in a host of processes, including weight gain, fertility, longevity, and tumor metastasis. However, it is not well understood how these molecules exert their effects at the molecular level. Using a multi-disciplinary approach involving techniques from organic chemistry, chemical genetics and genetics, molecular biology, and proteomics, our goal is to decipher the concrete signaling functions of PP-InsPs and ultimately guide the development of new therapeutic strategies against cancer, diabetes and obesity.

→ **DIE ROLLE VON BOTENSTOFFEN IN SIGNALPROZESSEN AUFKLÄREN UND BEEINFLUSSEN**

Mit hochvernetzten Signalketten sind Zellen in der Lage, Informationen aus ihrer Umgebung und über ihren internen Zustand zu übermitteln. Ist der Informationstransfer in Zellen gestört, kommt es zu einer Vielzahl von Krankheiten. Wir wollen Signalereignisse in gesunden und kranken Zuständen ausführlich aufklären und so dazu beitragen, neue therapeutische Ansätze zu entwickeln. Von besonderem Interesse ist eine Gruppe von Botenstoffen, die Inositolpyrophosphate (PP-InsPs). Diese Moleküle sind als zentrale Regulatoren der Zellhomöostase bekannt. Genetische Untersuchungen an Mäusen und Menschen zeigen, dass PP-InsPs an einer Vielzahl von Prozessen beteiligt sind, darunter Gewichtszunahme, Fruchtbarkeit, Langlebigkeit und Tumormetastase. Doch wie diese Moleküle ihre Wirkung auf molekularer Ebene ausüben, ist nur ansatzweise zu erahnen. Mit einem multidisziplinären Ansatz, der Techniken aus der organischen Chemie, der chemischen Genetik und der Genetik, der Molekularbiologie und der Proteomik einsetzt, wollen wir die konkreten Signalfunktionen von PP-InsPs entschlüsseln und letztlich die Entwicklung neuer therapeutischer Strategien gegen Krebs, Diabetes und Fettleibigkeit ermöglichen.



↑ FIG. 1
A) PP-InsPs are thought to access a variety of mechanisms of action to transmit information. Common to these mechanisms is an interaction of the PP-InsP with the protein targets.
B) Several proteins preferentially interact with 5PCP-InsP5 over InsP6, illustrated by a Volcano plot depicting LFQ values of 5PCP-InsP5 against InsP6. Components of the LKB1 pathway (green), inositol 5-phosphatases (blue) and purine base metabolism (black) are highlighted.

→ DESCRIPTION OF PROJECTS

MEASURING INOSITOL (PYRO)PHOSPHATE LEVELS IN COMPLEX MIXTURES

To elucidate the functions of InsPs and PP-InsPs, robust techniques for the characterization of inositol phosphate metabolism are required, at both the biochemical and cellular level. Our group developed a new detection method that employs uniformly 13C-labeled compounds in combination with NMR spectroscopy. This approach permits the biochemical characterization of inositol kinases at physiological substrate concentrations. In addition, 13C-labeled inositol facilitates metabolic labeling of mammalian cells, followed by detection of the generated InsP and PP-InsP species, without the need for separation or enrichment. In all, the method greatly facilitates the analysis of this otherwise spectroscopically silent group of molecules, and holds great promise for the analysis of inositol-based signaling molecules under normal and pathological conditions.

CHARACTERIZATION OF THE MAMMALIAN INOSITOL PYROPHOSPHATE INTERACTOME

PP-InsPs are thought to function via binding to protein targets, but only a few PP-InsP-interacting proteins are known to date. To create a more mechanistic picture, we sought to annotate the mammalian interactome of the most abundant inositol pyrophosphate, 5PP-InsP5. To do so, reagents were developed in which a metabolically stable PP-InsP analog was immobilized in three different ways. Application of these reagents to mammalian lysates identified between 300-400 putative interacting proteins. These interactomes revealed connections between 5PP-InsP5 and central cellular regulators, such as lipid phosphatases and GTPases, and identified protein domains commonly targeted by 5PP-InsP5. By expanding this approach to other organisms, we expect to produce molecular details on how PP-InsPs can mediate such a wide range of cellular responses.

SELECTED PUBLICATIONS

Furkert, D., Hostachy, S., Nadler-Holly, M., Fiedler, D. (2020). **Triplexed Affinity Reagents to Sample the Mammalian Inositol Pyrophosphate Interactome.** Cell Chem Biol. 27 (8), 1097–1108.

Li, M., Puschmann, R., Herdlitschka, A., Fiedler, D., Wennemers H (2020). **Delivery of myo-Inositol Hexakisphosphate to the Cell Nucleus with a Proline-Based Cell-Penetrating Peptide.** Angew. Chem. Int. Ed., 59 (36), 15586–15589.

Harmel, RK., Puschmann, R., Trung, MN., Saiardi, A., Schmieder, P., Fiedler, D (2019). **Harnessing 13C-labeled myo-inositol to interrogate inositol phosphate messengers by NMR.** Chem Sci. 10 (20), 5267–5274.

SELECTED EXTERNAL FUNDING

Swiss National Science Foundation, Sinergia. Together with A. Mayer, S. Hiller, M. Hothorn. "Discovery and mechanistic dissection of novel signaling pathways controlling phosphate homeostasis in eukaryotes", 2016–2021, CHF 2,405,000

Leibniz Association, Leibniz Competition. Together with H. Oschkinat, V. Haucke. "Systems-level analysis of inositol messengers in nutrient signaling", 2017–2020, €1,063,000

Deutsche Forschungsgemeinschaft, DFG Excellence Initiative, EXC UniSysCat. "Controlling cellular pools of inositol phosphate messengers with light", 2019–2022, €330,000


hyper fuel
PFCE
40 M
65 %
vol
P-CrA-
A2
2.5 mM
5,5 %
vol

NEW CONTRAST AGENT AIMING AT EARLY DETECTION OF BRAIN METASTASES

NEUES KONTRASTMITTEL FÜR DIE FRÜHDIAGNOSE VON METASTASEN IM GEHIRN

Leif Schröder's group has found a way to detect metastases of certain types of cancer in the brain in the future at an early stage and using little contrast agent. The team uses a synthetic molecule to detect the formation of new blood vessels and visualize them in a more differentiated way than with conventional diagnostic methods. The results could be used to improve the diagnosis of cancer types such as breast cancer.
Schnurr, M. *et al.*, Advanced Biosystems 2020

Image: Dr. Margitta Dathe, Dr. Leif Schröder and co-workers demonstrate an MRI contrast agent that uses the available magnetization in a highly efficient way to enable selective cell labeling at minimally invasive concentrations. Visualization: Barth van Rossum, FMP.

Die Gruppe von Dr. Leif Schröder hat einen Weg gefunden, wie sich Metastasen bestimmter Krebsarten im Gehirn in Zukunft frühzeitig und mit möglichst wenig Kontrastmittel auffinden lassen. Das Team setzt ein synthetisches Molekül ein, um die Neubildung von Blutgefäßen aufzuspüren und differenzierter darzustellen als mit herkömmlichen Diagnosemethoden. Die Ergebnisse könnten zur besseren Diagnose etwa bei Brustkrebs eingesetzt werden.

Bild: Margitta Dathe, Leif Schröder und Mitarbeiter*innen demonstrieren ein MRT-Kontrastmittel, das die verfügbare Magnetisierung auf höchst effiziente Weise nutzt, um eine selektive Zellmarkierung bei minimalinvasiven Konzentrationen zu ermöglichen.

MEDICINAL CHEMISTRY

MEDIZINISCHE CHEMIE

GROUP LEADER (at the FMP since 2013)
Dr. Marc Nazaré

GROUP MEMBERS
Benjamin Brennecke, Dr. Davide Cirillo, Thais Gazzi, Dr. Monica Guberman, Axel Hentsch, Dr. Peter Lindemann, Leonard Mach, Keven Mallow, Sandra Miksche, Jérôme Paul, Dr. Lioudmila Perepelittchenko, Dr. Carolina Vinagreiro, Dr. Malgorzata Wasinska-Kalwa

→ leibniz-fmp.de/nazare

→ **DESIGN AND SYNTHESIS OF CHEMICAL PROBES FOR THE PHARMACOLOGICAL INVESTIGATION OF BIOLOGICAL SYSTEMS**

Small molecules can be used as research tools to investigate protein functions and elucidate molecular mechanisms or to influence signal transduction pathways. They can also be employed to validate hypotheses from genetic studies such as knock-down and loss-of-function approaches. Moreover, these substances can serve as starting points for new therapeutic approaches and new drugs. The goal of our research is to discover and develop highly active, selective chemical tools for the specific modulation of protein–ligand or protein–protein interactions. Taking advantage of these optimized tools, and going a step further, we also investigate the tailored development of fluorescently labeled probes as well as DOTAM-based sensors for imaging and proximity labeling in chemical biology and biomarker applications.

→ **DESIGN UND SYNTHESE VON CHEMISCHEN WERKZEUGEN ZUR PHARMAKOLOGISCHEN UNTERSUCHUNG BIOLOGISCHER SYSTEME**

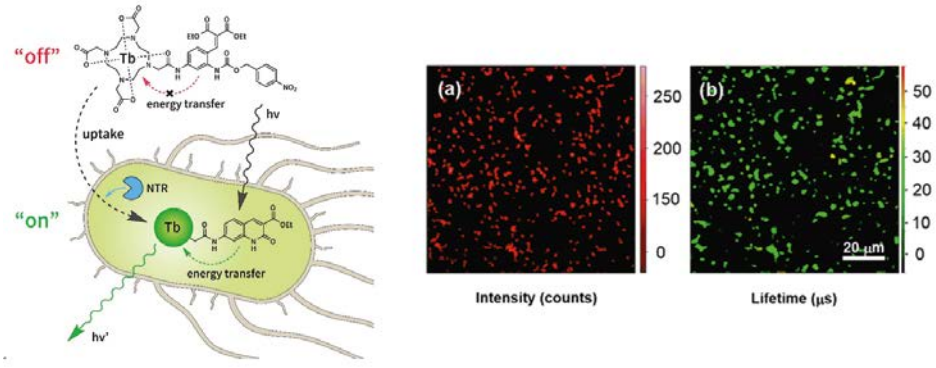
Kleine Moleküle lassen sich als Forschungswerkzeuge nutzen, um damit Proteinfunktionen zu untersuchen und molekulare Mechanismen aufzuklären oder ganze Signaltransduktionswege mithilfe dieser Substanzen zu beeinflussen. Zudem können sie genutzt werden, um Hypothesen aus genetischen Studien zu validieren, die aus Knock-Down- oder Loss-of-Function-Ansätzen gewonnen wurden. Oft dienen die Substanzen als Vorläufer von Pharmaka oder sind gar ein Startpunkt für neuartige Therapien. Ziel unserer Forschung ist die Entdeckung und Entwicklung hochaktiver, selektiver chemischer Sonden für eine spezifische Modulation von Protein–Liganden- oder Protein–Protein-Wechselwirkungen. Unter Einsatz dieser optimierten Werkzeuge untersuchen wir in einem weiteren Schritt die maßgeschneiderte Entwicklung von fluoreszenzmarkierten Sonden sowie von DOTAM-basierten Sensoren für die Bildgebung und Näherungsmarkierung für Anwendungen in der chemischen Biologie und für die Biomarkerentwicklung.

DEVELOPMENT OF SPECIFIC INHIBITORS OF THE TYROSINE PHOSPHATASE SHP-2

In stark contrast to their validated significance in signal transduction and disease pathology, phosphatases are notoriously difficult to inhibit using small molecules. The protein tyrosine phosphatase Shp-2 plays a critical role in growth factor-mediated processes, primarily by promoting the activation of the RAS/ERK signaling pathway. Aberrant gain-of-function mutations are associated with several metastatic cancers, and were recently linked to drug resistance against cancer medications such as MEK and BRAF inhibitors. In collaboration with Walter Birchmeier (MDC), a re-scaffolding approach that involves replacing the former framework of a tyrosine phosphatase Shp-2 inhibitor led to the discovery of novel structural classes and eliminated several chemical liabilities, i.e. unfavorable structural features. These novel compounds are not only active in a nanomolar range in the Shp-2-enzyme assay, but are also effective in the low micromolar range in cell lines that are resistant to cancer drugs and hepatocyte growth factor (HGF)-stimulated canine MDCK-C cells, as well as human pancreatic tumor cells for epithelial-mesenchymal transition (EMT), which are hallmarks of malignant cancer cell dissemination.

DEVELOPMENT OF AN ACTIVATABLE LANTHANIDE LUMINESCENT PROBE FOR TIME-GATED DETECTION OF NITROREDUCTASE IN LIVE BACTERIA

Infections caused by multidrug-resistant (MDR) Gram-negative bacteria result in a dramatic increase in mortality and morbidity worldwide. Still, diagnostics rely on cultivation approaches in clinical microbiology laboratories, which are time-consuming and require a high level of technical skills. Novel non-invasive methods to detect infections at sites that are unknown during the early stage or that are inaccessible for sampling are urgently needed. Such methods would enable timely interventions before local manifestations (e.g., through biofilm formation) or the systemic spread of the infection can occur. Nitroreductases (NTRs) are a family of bacterial enzymes that are able to reduce nitro-functional groups. The occurrence of NTRs in multi-resistant strains escaping standard antibiotics treatments makes this enzyme family a highly relevant diagnostic target for the detection of bacterial infections. We have developed a DOTAM-based activatable lanthanide luminescent probe for the detection of NTR in bacteria. Due to its effective intracellular enrichment, our probe enables the simple detection and imaging of nitroreductase activity in live bacteria comprising clinically relevant MDR strains. This resulted in the first use of fluorescence lifetime imaging (FLIM) to trace enzymatic activity in live bacteria using lanthanide luminescent probes (Figure 1). These features illustrate that this type of probe concept is an attractive option for future analytical applications in medical diagnostics.



← FIG. 1
Structure and activation principle of the DOTAM-based lanthanide luminescent probe. Fluorescence lifetime imaging of live E. coli bacteria incubated with the probe. (a) Fluorescence intensity image; (b) lifetime map.

SELECTED PUBLICATIONS

Mostinski, Y., Heynen, GJJE., López-Alberca, MP., Paul, J., Miksche, S., Radetzki, S., Schaller, D., Shanina, E., Seyffarth, C.,Kolomeets, Y., Ziebart, N., de Schryver, J., Oestreich, S., Neuenschwander, M., Roske, Y., Heinemann, U., Rademacher, C., Volkamer, A., von Kries, JP., Birchmeier, W., Nazaré, M. (2020) **From Pyrazolones to Azaindoles: Evolution of Active-Site SHP2 Inhibitors Based on Scaffold Hopping and Bioisosteric Replacement.** J Med Chem 63 (23),14780–14804.

Schoene, J., Gazzi, T., Lindemann, P., Christmann, M., Volkamer, A., Nazaré, M. (2019) **Probing 2H-Indazoles as Templates for SGK1, Tie2, and SRC Kinase Inhibitors.** ChemMedChem 14, 1514–1527.

Brennecke, B., Wang, Q., Zhang, Q., Hu, H.-Y., Nazaré, M. (2020) **An Activatable Lanthanide Luminescent Probe for Time-Gated Detection of Nitroreductase in Live Bacteria.** Angew Chem Int Ed Engl 59 (22), 8512–8516.

SELECTED EXTERNAL FUNDING

EU-OPENSCREEN DRIVE, EU Horizon 2020 823893, 2019–2022, €258,200

Philipp Schwartz Initiative of the Alexander von Humboldt Foundation "Development of Novel Transition Metal Catalyzed Strategies to Access 2H-Azaindazoles and 2H-Indazoles as Privileged Heterocyclic Scaffolds", 2017–2020, €108,000

Deutsche Forschungsgemeinschaft, Sino-German Center for Research Promotion (DFG), GZ 1271, "Tumor-targeting SMART Imaging Agents", together with Prof. Haiyu-Hu, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China. 2016–2019, €207,845

CORE FACILITY

SCREENING UNIT

SCREENING UNIT

GROUP LEADER (at the FMP since 2003)
Dr. Jens Peter von Kries

GROUP MEMBERS
Dr. Katina Lazarow, Dr. Silke Radetzki, Dr. Martin Neuenschwander, Dr. Christopher Wolff, M.Sc. Marc Wippich (–2018), Sabrina Kleissle, Carola Seyffarth, Astrid Mühl, Romy Leu (–2018), Andreas Oder, Felix Hansen

→ leibniz-fmp.de/screening_unit

→ **HIGH-THROUGHPUT TESTING OF COMPOUNDS AND IDENTIFICATION & VALIDATION OF NOVEL TARGETS**

The Screening Unit serves as an open-access technology platform for automated screening, using either compound libraries or genome-wide RNAi libraries. The platform's primary aim is to enable the systematic use of drugs in academic research as tools for analysis of molecular mechanisms in disease and development. Besides supporting assay development, process automation, screening and automated data analysis, the Unit engages in the identification of novel screening technologies. The Unit supports screening projects in assay development and optimization of high-throughput compound screening (HTS, Silke Radetzki), as well as automated data documentation and analysis (Martin Neuenschwander). Genome-wide RNAi and CRISPR-CAS screening (HTS, Katina Lazarow) has been added for the identification and validation of novel cellular targets in disease. In 2019, we started applying 3D analysis with a confocal microscope and morphological pattern analysis to profile drug effects in cell culture systems (Christopher Wolff).

→ **SUBSTANZEN FINDEN UND NEUE „TARGETS" IDENTIFIZIEREN**

Die Screening Unit ist eine frei zugängliche Technologieplattform für automatisierte Serienuntersuchungen. Wir verwenden entweder Substanzbibliotheken oder genomweite RNA-Interferenz (RNAi), die spezifische RNA-Moleküle zur Hemmung der Übersetzung jedes einzelnen Gens in sein entsprechendes Protein enthalten. Wir unterstützen Forschende des FMP und anderer, kooperierender Institutionen bei der Testentwicklung, Prozessautomatisierung, beim Screening und bei der automatischen Datenanalyse. Darüber hinaus identifizieren wir neue Screening-Techniken und implementieren diese für den Einsatz. Derzeit unterstützen wir Screening-Projekte bei der Entwicklung und Optimierung von Testverfahren zum Hochdurchsatz-Screening (Silke Radetzki), und bei der automatisierten Datendokumentation und Analyse (Martin Neuenschwander). Zudem haben wir in unserer Unit das genomweite RNAi- und CRISPR-CAS-Screening (Katina Lazarow) etabliert, um neue zelluläre Zielstrukturen („Targets") für die pharmakologische Interferenz in Krankheiten zu identifizieren. Seit 2019 etablieren wir 3D-Analysen mit konfokalen Mikroskopen, um in der Tradition von Rudolf Virchow (Zelluläre Pathologie) morphologische Muster in der Reaktion von Zellen auf toxische Substanzen zu identifizieren (Christopher Wolff).

COMPUTER-AIDED PATTERN RECOGNITION

About 160 years ago, Rudolf Virchow realized that human diseases are often reflected in an aberrant cellular morphology (Cellular Pathology). Virchow employed chemists and physicians to set up diagnostic procedures for human diseases. We want to expand this by state-of-the-art computing and robotic HTS technologies.

We decided to select for profiling of toxic reference compounds with known cellular targets and molecular mechanisms to generate specific morphological fingerprints for each kind of mechanism and compound. For this purpose, we used fluorescent dyes to stain and visualize cellular components such as nuclei, mitochondria or actin filaments and membranes. More than 1,000 parameters per individual cell were analyzed and compared in the process of computer-aided image and cell structure recognition (Figure 1). The reference-validated painting process will be used to profile the toxic potential of the EU-OPENSCREEN and FMP compound libraries. This approach may feed into novel diagnostics, advancing Virchow's work from 160 years ago.

SELECTED PUBLICATIONS

Kircher, T., Pantsar, T., Oder, A., von Kries, JP., Juchum, M., Pfaffenrot, B., Kloevekorn, P., Albrecht, W., Selig, R. and Laufer, S. (2020) **Design and synthesis of novel fluorescently labeled analogs of vemurafenib targeting MKK4.**
Eur J Med Chem 209, 112901.

Dema, A., Faust, D., Lazarow, K., Wippich, M., Neuenschwander, M., Zühlke, K., Geelhaar, A., Pallien, T., Hallscheidt, E., Eichhorst, J. , Wiesner, B., Cernecka, H., Popp, O., Mertins, P., Dittmar, G., von Kries, JP. and Klussmann, E. (2020) **Cyclin-Dependent Kinase 18 Controls Trafficking of Aquaporin-2 and Its Abundance through Ubiquitin Ligase STUB1, which Functions as an AKAP.**
Cells 9 (3), 673.

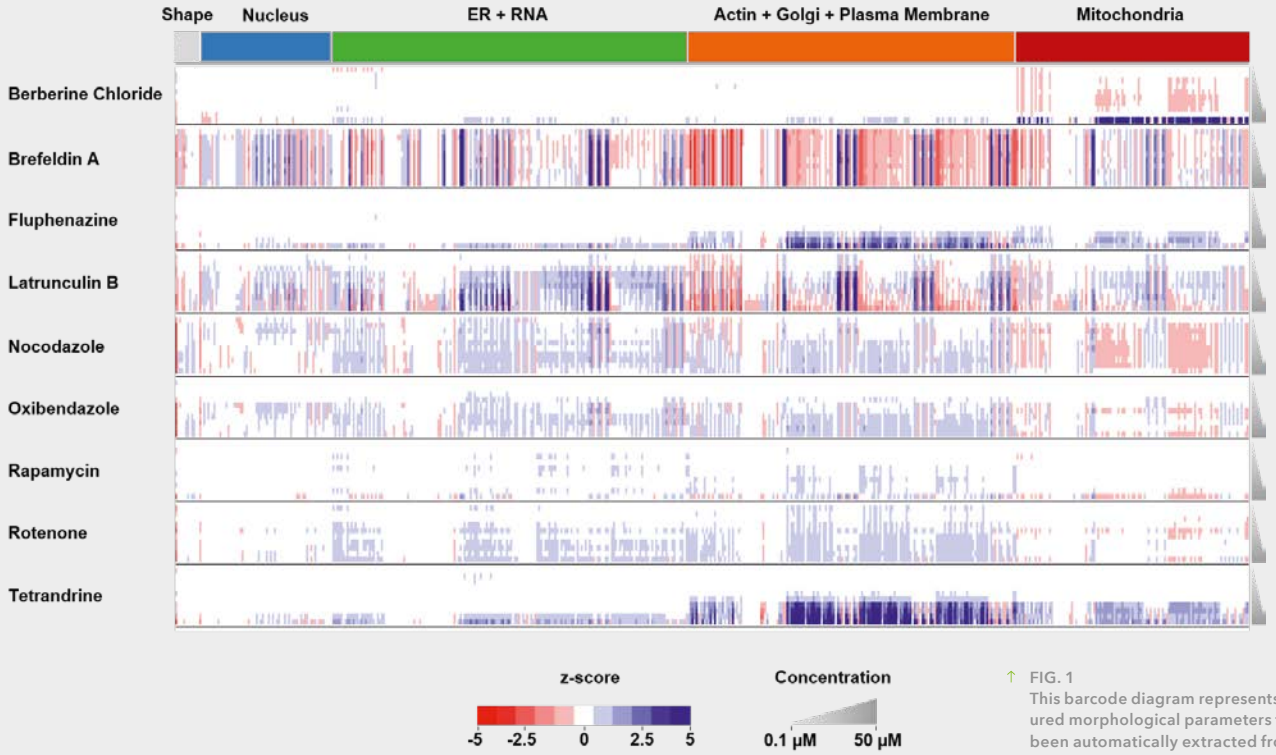
Merkert , S., Schubert, M., Olmer, R., Engels, L., Radetzki, S., Veltman, M., Scholte, BJ., Zöllner, J., Pedemonte, N., Galietta, LJV., von Kries, JP., Martin, U. (2019) **High-Throughput Screening for Modulators of CFTR Activity Based on Genetically Engineered Cystic Fibrosis Disease-Specific iPSCs.**
Stem Cell Rep 12, 1389–1403.

SELECTED EXTERNAL FUNDING

BMBF, EU-OPENSCREEN, from 09/2019, approx. € 1,400,000 (investment)

BMBF, Helmholtz Drug Research Initiative, from 09/2011, € 1,632,000

BMBF, CCMCURE, E-RARE 2014, 06/2015 – 05/2018, € 102,040.80



↑ FIG. 1
This barcode diagram represents 500 measured morphological parameters that have been automatically extracted from images. The red and blue bars show decreased and increased values in relation to different compound concentrations.

DISCOVERY OF A NEW MECHANISM IN THE RARE GENETIC DISEASE ALKAPTONURIA

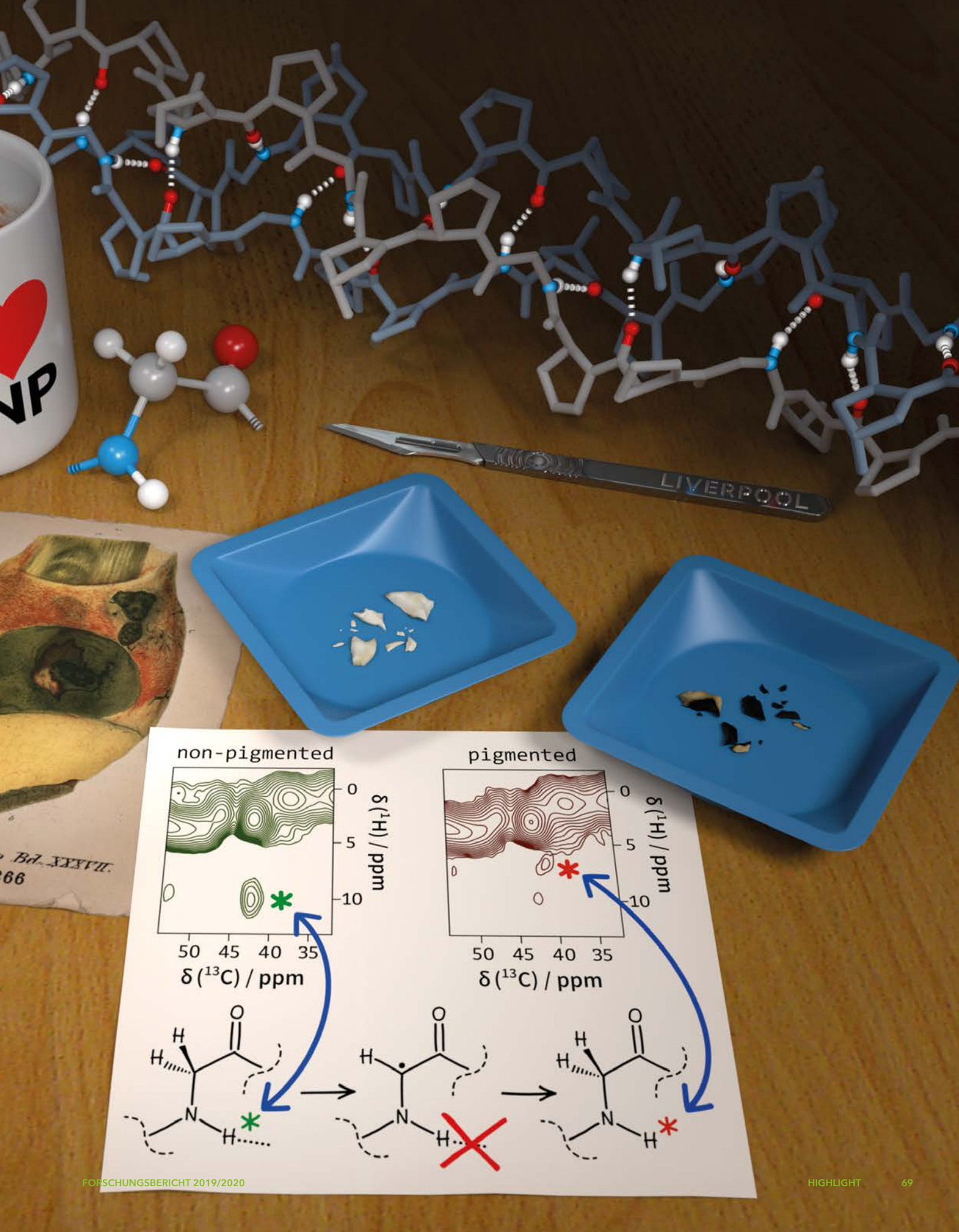
NEUER MECHANISMUS DER SELTENEN ERBKRANKHEIT ALKAPTONURIE ENTDECKT

Alkaptonuria is a rare genetic disease characterized by high levels of homogentisic acid (HGA) and unusual tissue pigmentation, leading to cartilage degradation and severe joint pain, which is why young adults with this disease often need a joint replacement. A team led by Professor Hartmut Oschkinat showed that transient glycyl radicals play a major role in the destruction of collagen, one of the main building blocks of cartilage tissue. The work contributes to a better understanding of this rare disease, and may enable patients to access promising medication more quickly.
Chow, WY. *et al.*, Angewandte Chemie Int. Ed. Engl. 2020

Image: Using DNP-enhanced solid-state NMR and EPR spectroscopy, the scientists demonstrate that semiquinone radicals play a role in the chemistry of the pigmentation process. Visualization by Barth van Rossum

Alkaptonurie ist eine seltene erbliche Erkrankung, die durch eine hohe Anreicherung von Homogentisinsäure (HGA) und eine ungewöhnliche Gewebepigmentierung gekennzeichnet ist. Knorpelabbau und Gelenkbeschwerden sind die Folge und bereits junge Erwachsene benötigen einen Gelenkersatz. Ein Team um Prof. Hartmut Oschkinat zeigte, dass flüchtige Glycylradikale eine maßgebliche Rolle bei der Zerstörung des Kollagens spielen, welches das Grundgerüst von Knorpeln bildet. Die Arbeit trägt zu einem besseren Verständnis der seltenen Erbkrankheit bei und könnte möglicherweise Betroffenen schneller zu einem vielversprechenden Medikament verhelfen.

Bild: Durch Anwendung von DNP-verstärkter Festkörper-NMR und EPR-Spektroskopie weisen die Wissenschaftler*innen auf eine Rolle von Semichinonradikalen in der Chemie des Pigmentierungsprozesses hin.


non-pigmented
pigmented
δ(¹H) / ppm
δ(¹³C) / ppm
0
5
10
50 45 40 35
LIVERPOOL

NEW GROUPS AT THE FMP

NEUE GRUPPEN AM FMP

GROUP LEADER (at the FMP since 1997, Core Facility since 2020)
Prof. Dr. Ralf Schülein

GROUP MEMBERS
Dr. Claudia Rutz, Bettina Kahlich, Marie Bieck

CORE FACILITY

CELL ENGINEERING

CELL ENGINEERING

→ The Cell Engineering Facility uses state-of-the-art CRISPR/Cas techniques to generate gene knock-outs and knock-ins in target cells. By using the resulting cell clones, the function of specific genes and proteins can be studied in detail within the cellular context. Gene knock-out means that the function of a specific gene, and consequently that of its encoded protein, is disrupted by a specific mutation. Gene knock-in means that the specific target gene and its protein gain a new function because of an engineered mutation.

→ Die Cell Engineering Facility setzt CRISPR/Cas-Techniken ein, um Gen-Knock-Outs und Knock-Ins in Zielzellen zu erzeugen. Mithilfe der entstandenen Zellklone kann die Funktion spezifischer Gene und Proteine im zellulären Kontext detailliert untersucht werden. Gen-Knock-Out bedeutet, dass die Funktion eines bestimmten Gens und folglich die seines kodierten Proteins durch eine eingeführte Mutation zerstört werden. Gen-Knock-In bedeutet, dass das spezifische Zielgen und sein Protein aufgrund der eingeführten Mutation eine neue Funktion erhalten.

GROUP LEADER (at the FMP since 2020)
Dr. Noa Lipstein

GROUP MEMBERS
Currently being recruited

→ @LipsteinNoa

SYNAPSE BIOLOGY

BIOLOGIE DER SYNAPSEN

→ The Synapse Biology group focuses on elucidating the contribution of synaptic proteins to neuronal function and plasticity, and on deciphering synaptic disease mechanisms in brain disorders. We combine genetic manipulations in mouse models with electrophysiological and cell type-specific biochemical analysis to study the molecular composition and organization of synapses, with the aim of understanding how these define synaptic function and dysfunction.

→ Die Forschungsgruppe „Biologie der Synapsen“ erforscht den Einfluss von synaptischen Proteinen auf die neuronale Funktion und Plastizität sowie die Entschlüsselung synaptischer Krankheitsmechanismen bei Erkrankungen des Gehirns. Wir kombinieren genetische Manipulationen in Mausmodellen mit elektrophysiologischen und zelltypspezifischen, biochemischen Analysen zur Untersuchung der molekularen Zusammensetzung und Organisation der Synapsen, um schließlich zu verstehen, wie diese die synaptische Funktion und Dysfunktion beeinflussen.

STRUCTURE AND MECHANISM OF MICROBIOME-DRIVEN DISEASES

STRUKTUR UND MECHANISMUS MIKROBIOM-BEDINGTER KRANKHEITEN

GROUP LEADER (at the FMP since 2020)
Dr. Daniel Roderer

GROUP MEMBERS
Uwe Fink, Alina Roderer, 2 PhD students are currently being recruited

→ @daniel_roderer

→ We are interested in understanding the molecular mechanism of host–microbiome interactions with key roles in the development of colorectal cancer. Using cryo-EM, we solve the structures of protein complexes that facilitate the adhesion of microorganisms to epithelial cells. This high-resolution structural information show us mechanistic details which are prerequisites for structure-based drug design. Moreover, we apply different screening methods to identify further as-yet undescribed interactions with high relevance in carcinogenesis.

→ Wir untersuchen molekulare Mechanismen von Wirt–Mikrobiom-Interaktionen, die bei der Entstehung von Darmkrebs eine entscheidende Rolle spielen. Mittels Kryo-EM lösen wir die Strukturen von Proteinkomplexen, welche die Adhäsion von Mikroorganismen an Epithelzellen ermöglichen. Diese hochaufgelösten strukturellen Informationen tragen maßgeblich zum Verständnis mechanistischer Details bei und sind die Voraussetzung für strukturbasierte Wirkstoffentwicklung. Weiterhin wenden wir verschiedene Screening-Methoden an, um weitere, noch unbekannte Wirt–Mikrobiom-Interaktionen mit karzinogener Relevanz zu

CHEMBIOPROBES

CHEMBIOPROBES

GROUP LEADER (at the FMP since 2020)
Dr. Johannes Broichhagen

GROUP MEMBERS
Ramona Birke, Jahaziel Jahzerah, Kilian Roßmann, Christiane Huhn, Abha Valavalkar, Tristan Reif

→ @BroichhagenJ

→ Our mission is to put the spotlight on the invisible to see more in fundamental research. Our expertise lies in the development of synthetic, custom-tailored fluorescent substrates for use in microscopy. As such, we employ modern organic chemistry to bring our designs to light, and then evaluate them spectroscopically at great depth for critical parameters. We think in unconventional ways, and pursue the novel approaches in the design and synthesis of fluorophores and markers for high-definition imaging in living cells.

→ Unser Ziel ist es, das bisher Unsichtbare zum Leuchten zu bringen, um es für die Grundlagenforschung sichtbar zu machen. Unsere Expertise ist die Entwicklung von synthetischen, perfekt angepassten, leuchtenden Fluoreszenzfarbstoffen für die Mikroskopie. Um unser Design zu verwirklichen, verwenden wir moderne organische Chemie und untersuchen unsere Substanzen genau in Hinsicht auf kritische Parameter. Wir denken in und verfolgen unkonventionelle(n) Wege(n) in Design und Synthese von Farbstoffen und Markern für „High-Definition"-Bildaufnahmen in lebenden Zellen.

GROUP LEADER (at the FMP since 2020)
Dr. Han Sun

GROUP MEMBERS
Saed Abdolvand (co-supervision with Prof. Andrew Plested), Johann Biedermann (co-supervision with Prof. Andrew Plested), Florian Heiser (co-supervision with Prof. Andrew Plested), Songhwan Hwang, Xiaolu Li, Berke Türkaydin, Dr. Tillmann Utesch. From 01/2021: Raed Al-Yamori, Dr. Michael Lisurek, Dr. Bernd Rupp

STRUCTURAL CHEMISTRY AND COMPUTATIONAL BIOPHYSICS

STRUKTURCHEMIE UND COMPUTERGESTÜTZTE BIOPHYSIK

→ Our research interests are the development and application of molecular modeling and molecular dynamics simulations together with other cheminformatic and bioinformatic tools with the aim of designing novel bioactive molecules and characterizing their interactions with biological targets. Furthermore, we seek to develop a better understanding of the biophysical principles of membrane proteins, with a special focus on ion channels.

→ Unsere Forschungsschwerpunkte liegen in der Entwicklung und Anwendung von molekularer Modellierung und Moleküldynamiksimulationen in Verbindung mit anderen chemo- und bioinformatischen Werkzeugen, um neue bioaktive Moleküle zu designen und deren Wechselwirkungen mit ihren biologischen Zielen zu charakterisieren. Des Weiteren erforschen wir biophysikalische Prinzipien von Membranproteinen, mit einem Schwerpunkt auf Ionenkanäle.

GROUP LEADER (at the FMP since 2020)
Dr. Edgar Specker

COMPOUND MANAGEMENT

COMPOUND MANAGEMENT (SUBSTANZSAMMLUNG)

→ The goal of the core facility is to provide screening plates to the Screening Unit and to prepare hitpicking plates to conduct the concentration-dependent validations of hits. The Facility performs QC controls and helps users to prioritize hit lists. The Facility manages a diversity library of 43,000 compounds enriched with 4,000 fragments, an academic library of 8,000 compounds and 20,000 natural product-derived compounds.

→ Die Aufgabe ist die Anfertigung von Screening-Platten für die Screening Unit und die Bereitstellung von Hitpicking-Platten für die konzentrationsabhängige Validierung der Hits. Es führt die Reinheitskontrolle per LC-MS durch und hilft den Nutzer*innen bei der Priorisierung der Hitlisten. Die Bibliothek enthält 43.000 strukturell diverse Substanzen, 4.000 Fragmente, eine akademische Sammlung von 8.000 Substanzen und eine aus 20.000 Naturstoffen abgeleitete Bibliothek.

ALL RESEARCH GROUPS

ALLE FORSCHUNGSGRUPPEN

MOLECULAR PHYSIOLOGY AND CELL BIOLOGY

- → **PHYSIOLOGY AND PATHOLOGY OF ION TRANSPORT**
  Thomas J. Jentsch
- → **MOLECULAR PHARMACOLOGY AND CELL BIOLOGY**
  Volker Haucke
- → **MOLECULAR NEUROSCIENCE AND BIOPHYSICS**
  Andrew Plested
  Heisenberg Guest Group
- → **SYNAPSE BIOLOGY**
  Noa Lipstein (from 10/2020)
  Junior Research Group
- → **MOLECULAR AND THEORETICAL NEUROSCIENCES**
  Alexander Walter
  Emmy Noether Junior Research Group
- → **MEMBRANE TRAFFIC AND CELL MOTILITY**
  Tanja Maritzen (until 09/2020)
  Junior Research Group
- → **PROTEOSTASIS IN AGING AND DISEASE**
  Janine Kirstein (until 07/2019)
  Junior Research Group
- → CORE FACILITY: **CELLULAR IMAGING**
  Martin Lehmann
- → CORE FACILITY: **CELL ENGINEERING**
  Ralf Schülein (from 01/2020)
- → CORE FACILITY: **ANIMAL FACILITY**
  Natali Wisbrun

STRUCTURAL BIOLOGY

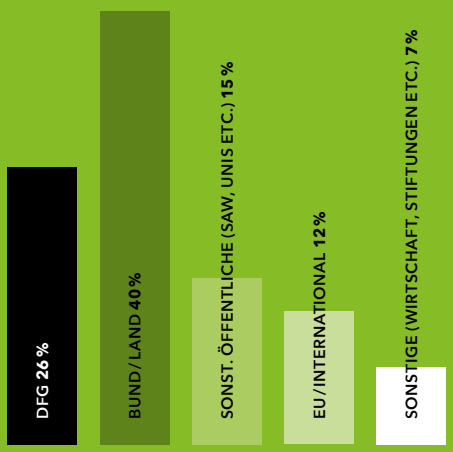
- → **MOLECULAR BIOPHYSICS**
  Adam Lange
- → **NMR-SUPPORTED STRUCTURAL BIOLOGY**
  Hartmut Oschkinat
- → **MOLECULAR IMAGING**
  Leif Schröder
  Junior Research Group
- → **STRUCTURE AND MECHANISM OF MICROBIOME-DRIVEN DISEASES**
  Daniel Roderer (from 11/2020)
  Junior Research Group
- → **STRUCTURAL INTERACTOMICS**
  Fan Liu
- → **COMPUTATIONAL CHEMISTRY/ DRUG DESIGN**
  Ronald Kühne
- → **STRUCTURAL BIOINFORMATICS AND PROTEIN DESIGN**
  Gerd Krause
- → CORE FACILITY: **NMR**
  Hartmut Oschkinat/
  Peter Schmieder
- → CORE FACILITY:
  MASS SPECTROMETRY
  Fan Liu

CHEMICAL BIOLOGY

- → **CHEMICAL BIOLOGY II**
  Christian Hackenberger
- → **CHEMICAL BIOLOGY I**
  Dorothea Fiedler
- → **MEDICINAL CHEMISTRY**
  Marc Nazaré
- → **STRUCTURAL CHEMISTRY AND COMPUTATIONAL BIOPHYSICS**
  Han Sun (from 10/2020)
- → **CHEMBIOPROBES**
  Johannes Broichhagen
  (from 03/2020)
  Junior Research Group
- → CORE FACILITY:
  SCREENING UNIT
  Jens Peter von Kries
- → CORE FACILITY:
  PEPTIDE CHEMISTRY
  Christian Hackenberger
- → CORE FACILITY:
  COMPOUND MANAGEMENT
  Edgar Specker (from 01/2020)

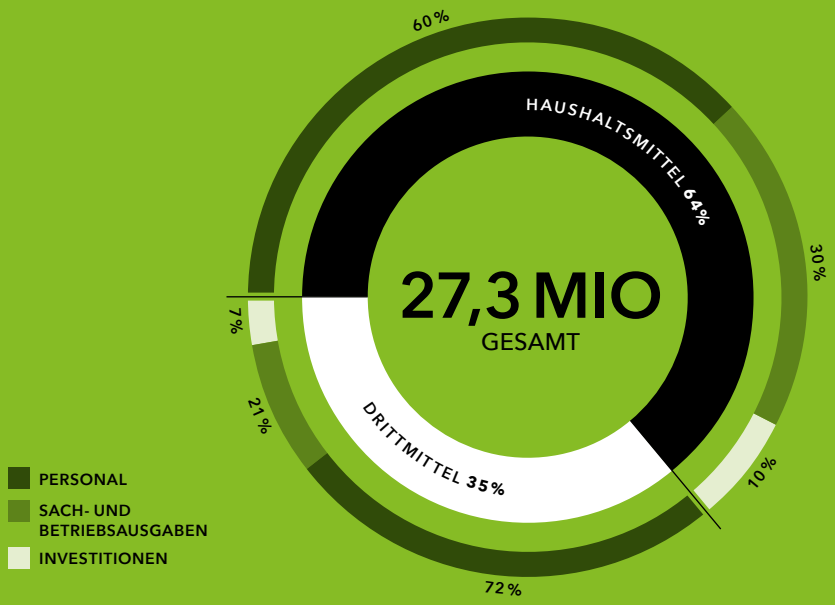
FACTS AND FIGURES

DRITTMITTEL 2020
IN PROZENT



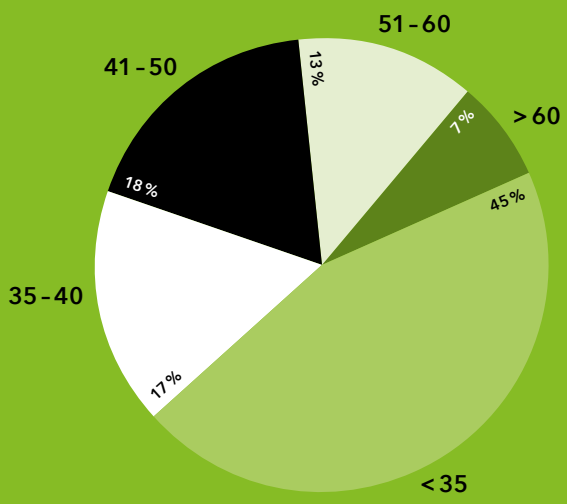
9,8 MIO
GESAMT

AUSGABEN 2020
IN PROZENT

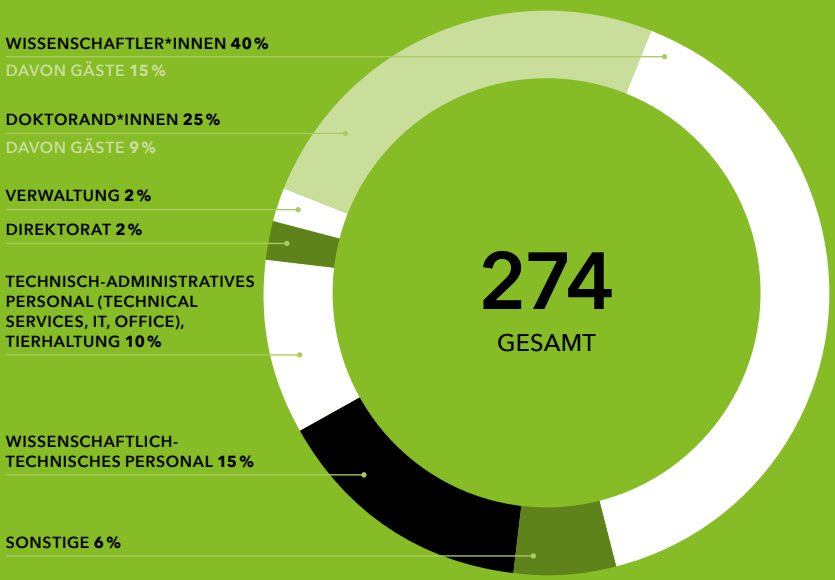


FRAUEN / MÄNNER

ALTERSSTRUKTUR
IN JAHREN



MITARBEITER*INNENSTRUKTUR
IN PROZENT



NATIONALITÄTEN

ARGENTINIEN (1), BELGIEN (1), BRASILIEN (1), CHINA (7), DEUTSCHLAND (201), FRANKREICH (2), GEORGIEN (1), GRIECHENLAND (1), GROSSBRITANNIEN (1), INDIEN (2), IRAN (1), ISRAEL (2), ITALIEN (10), KAMERUN (1), KANADA (1), KOLUMBIEN (2), KOREA (2), LITAUEN (1), MEXIKO (1), NIEDERLANDE (6), ÖSTERREICH (5), POLEN (2), PORTUGAL (1), RUMÄNIEN (1), RUSSISCHE FÖDERATION (4), SCHWEDEN (1), SCHWEIZ (1), SERBIEN (1), SPANIEN (4), SYRIEN (1), TÜRKEI (4), UKRAINE (1), VEREINIGTE STAATEN (2), ZYPERN (1)

TECHNOLOGY TRANSFER

TECHNOLOGIE-TRANSFER

HEAD/LEITUNG
Dr. Birgit Oppmann

Technology transfer at the FMP supports scientists in translating their research results into applications. This can be done, for example, by licensing out patent families to industrial partners or by facilitating spin-off projects. The following spin-offs have been established recently:

TUBULIS GMBH
As part of a scientific cooperation between the laboratories of Christian Hackenberger (FMP) and Heinrich Leonhardt (Ludwig Maximilian University Munich), two processes were developed to provide proteins with site-specific functionalities. These can be active agents, fluorophores, tracers, small chemical molecules, proteins or peptides. The so-called Tub-tag® and P5 technologies form the basis for the spin-off Tubulis GmbH, founded in 2019 by Leonhardt and Hackenberger (advisors) and their (former) employees Jonas Helma-Smets (CSO) and Dominik Schumacher (CEO). The spin-off aims to market technologies for the production of diagnostic and therapeutic protein conjugates and to use these technologies to produce its own diagnostic and therapeutic products. In July 2020, the company raised € 10.7 million series A funding to advance the development of a new generation of antibody drug candidates (ADC). In December 2020, Tubulis entered into a strategic partnership with WuXi Biologics and WuXi STA to move their ADC towards clinical evaluation.

PROSION GMBH
The foundations for the PROSION spin-off project were laid over several years of cooperation between the laboratories of Ronald Kühne (FMP) and Hans-Günther Schmalz (Department of Chemistry, University of Cologne). The spin-off was established in 2020 by four co-founders (CEO Slim Chiha, CSO Mutlu Yönel, and advisors R. Kühne and H.-G. Schmalz). The company's business will initially focus on the development, manufacture and marketing of novel secondary structure mimetic building blocks, as well as chemical libraries derived from them for use in drug research.

Der Technologietransfer am FMP unterstützt Wissenschaftler*innen darin, ihre Forschungsergebnisse in die Anwendung zu bringen. Das kann etwa durch Auslizensierung von Patentfamilien an Industriepartner geschehen oder durch Unterstützung von Ausgründungsvorhaben. Vor Kurzem wurden folgende Firmen ausgegründet:

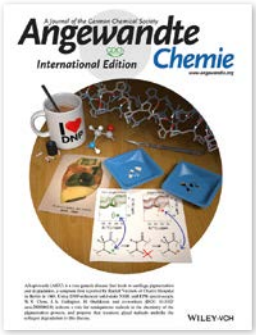
TUBULIS GMBH
Im Rahmen einer wissenschaftlichen Kooperation der Labore von Christian Hackenberger (FMP) und Heinrich Leonhardt (Ludwig-Maximilians-Universität München) wurden Verfahren entwickelt, um Proteine ortsspezifisch mit Funktionalitäten auszustatten. Dies können etwa Wirkstoffe, Fluorophore, Tracer, kleine chemische Moleküle, Proteine und Peptide sein. Die sogenannten Tub-tag®- und P5-Technologien bilden die Grundlage für die Ausgründung der Tubulis GmbH, welche von den AG-Leitern Leonhardt und Hackenberger (Berater) sowie deren (ehemaligen) Mitarbeitern Jonas Helma-Smets (CSO) und Dominik Schumacher (CEO) 2019 gegründet wurde. Die Ausgründung hat das Ziel, Technologien für die Herstellung von diagnostischen und therapeutischen Proteinkonjugaten zu vermarkten und mit diesen Technologien eigene diagnostische und therapeutische Produkte herzustellen. Im Juli 2020 erhielt das Unternehmen eine Serie-A-Finanzierung in Höhe von 10,7 Millionen Euro, um die Entwicklung einer neuen Generation von Antikörper-Wirkstoff-Konjugaten (ADC) voranzutreiben. Im Dezember 2020 ging Tubulis eine strategische Partnerschaft mit WuXi Biologics und WuXi STA ein, um ihre ADC in Richtung klinische Evaluierung weiterzuentwickeln.

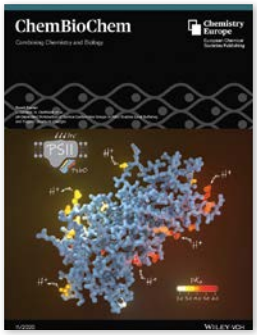
PROSION GMBH
Die Grundlagen für die in 2020 gegründete Firma wurden in einer langjährigen Zusammenarbeit zwischen den Laboren von Ronald Kühne (FMP) und Hans-Günther Schmalz (Department für Chemie, Universität zu Köln) geschaffen. Die vier Gründer sind CEO Slim Chiha, CFO Mutlu Yönel und die Berater R. Kühne und H.-G. Schmalz. Das Geschäftsfeld der Firma wird zunächst die Entwicklung, Herstellung und Vermarktung neuartiger Sekundärstruktur-mimetischer Bausteine umfassen sowie davon abgeleitete chemische Bibliotheken zum Einsatz in der Wirkstoffforschung.

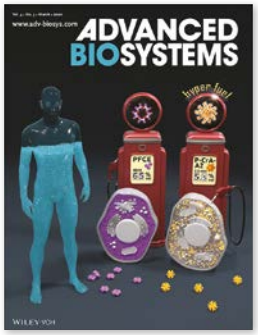
VISUALIZING SCIENCE

WISSENSCHAFT VISUALISIEREN

HEAD/LEITUNG
Dr. Barth van Rossum







Visuals to communicate scientific results are increasingly gaining in importance. Good scientific visuals can raise the visibility and impact of research and help to reach a broader audience. Recent years have seen a rise of scientific visualization in all fields of science, often driven by the need to merge and contextualize data obtained with different methodologies. This clearly places a demand on scientists, who are now often required to act as graphic designers.

Since 2019, Barth van Rossum has been dedicating half of his time to promoting outreach and scientific visualization for the entire institute. Various examples of his work can be found throughout this report. His work covers, among other things, the design and/or improvement of scientifically accurate illustrations for publications, presentations and grant proposals; the transformation of scientific results into visual stories for cover illustrations, graphical abstracts, press releases, conference posters and social media.

Visuelle Darstellungen für die Kommunikation wissenschaftlicher Ergebnisse gewinnen zunehmend an Bedeutung. Gute wissenschaftliche Visualisierungen können die Sichtbarkeit und Wirkung von Forschung erhöhen und helfen, ein breiteres Publikum zu erreichen. In den letzten Jahren hat die wissenschaftliche Visualisierung in allen Bereichen der Wissenschaft zugenommen, oft angetrieben durch die Notwendigkeit, Daten, die mit verschiedenen Methoden gewonnen wurden, zusammenzuführen und zu kontextualisieren. Dies stellt eindeutig eine Anforderung an Forschende, die nun oft als Grafikdesigner*innen agieren müssen.

Seit 2019 widmet Barth van Rossum die Hälfte seiner Zeit dem Outreach und der wissenschaftlichen Visualisierung für das gesamte Institut. Verschiedene Beispiele seiner Arbeit sind in diesem Bericht zu finden. Sie umfassen unter anderem das Design und/oder die Verbesserung von wissenschaftlich korrekten Illustrationen für Publikationen, Präsentationen und Förderanträge; die Umwandlung von wissenschaftlichen Ergebnissen in visuelle Geschichten für Cover-Illustrationen, grafische Abstracts, Pressemitteilungen, Konferenzposter und soziale Medien.

PUBLIC RELATIONS

ÖFFENT-LICHKEITS-ARBEIT

HEAD/LEITUNG
Silke Oßwald, M.A., M.Sc.

PUBLIC RELATIONS ACTIVITIES COVER MANY ASPECTS, INCLUDING BROCHURES, FLYERS AND AN INTERNAL NEWSLETTER (FMP INTERVIEW) AS WELL AS PRESS RELEASES, WEBSITES AND SOCIAL MEDIA. EVERY YEAR WE WELCOME VISITORS ON CAMPUS BERLIN-BUCH AND ORGANIZE SEVERAL EVENTS IN THE CITY:

DIE ÖFFENTLICHKEITSARBEIT UMFASST VIELE ASPEKTE, ZU NENNEN WÄREN BROSCHÜREN, NEWSLETTER (FMP INTERVIEW) SOWIE PRESSEMITTEILUNGEN, WEBSITES UND SOCIAL MEDIA. JEDES JAHR EMPFANGEN WIR BESUCHER*INNEN AUF DEM CAMPUS BERLIN-BUCH ODER NEHMEN AN EVENTS IN GANZ BERLIN TEIL:

LONG NIGHT OF THE SCIENCES

Every year, thousands of visitors come to the Campus Berlin-Buch to experience the latest in research, watching shows, listening to lectures or taking part in laboratory tours. More than 100 program items attract visitors to the institutes.

Visits in 2019 (6,912); 2020 (event cancelled due to the coronavirus)

LANGE NACHT DER WISSENSCHAFTEN

Jedes Jahr nehmen Tausende von Besucher*innen am großen Experimentieren auf dem Campus Berlin-Buch teil und erleben in Shows, Vorlesungen oder Laborführungen Aktuelles aus der Forschung. Mehr als 100 Programmpunkte wecken das Interesse der Besucher.

Besuche 2019 (6912); 2020 (wegen der Corona-Krise ausgefallen)

FMP CHEMLAB

The ChemLab is the student laboratory at the FMP. Scientists have been teaching chemistry methods in a vivid and unconventional way there since 2010. The following courses are available: caffeine, dyes, plastics, fragrances and proteins. A total of 2,745 students attended the ChemLab in 2019 and 2020.

FMP-CHEMLAB

Das ChemLab ist das Schülerlabor des FMP. Hier vermitteln seit 2010 Wissenschaftler*innen Methoden der Chemie anschaulich und unkonventionell. Zur Wahl stehen diese Kurse: Koffein, Farbstoffe, Kunststoffe, Duftstoffe und Proteine. 2019 und 2020 besuchten insgesamt 2745 Schüler*innen das ChemLab.

GIRLS' DAY
Schoolgirls from different grades are guests in the research groups at the FMP every year. Over the space of a day, they can look over the researchers' shoulders and try out small experiments themselves.

GIRLS' DAY
Schülerinnen aus unterschiedlichen Klassenstufen sind jährlich in den Arbeitsgruppen am FMP zu Gast und dürfen für einen Tag den Forschenden über die Schulter schauen und kleine Experimente selber ausprobieren.

BERLIN SCIENCE WEEK
It has been possible to explore Berlin as a "Brain City" at Berlin Science Week since 2016. For ten days, Berlin is transformed into a showcase for science. The most important attraction is the Falling Walls Conference. Scientists from all over the world present their most outstanding projects and are honored on November 9, the day the Berlin Wall came down peacefully in 1989. Christian Hackenberger received the "Breakthrough of the Year" award in the Life Sciences category in 2020.

BERLIN SCIENCE WEEK
Berlin als „Brain City" zu erkunden, ist seit 2016 während der Berlin Science Week möglich. Für zehn Tage wird die Hauptstadt in ein Schaufenster der Wissenschaft verwandelt. Wichtigste Attraktion ist die Falling-Walls-Konferenz. Wissenschaftler*innen aus aller Welt stellen ihre herausragendsten Projekte vor und werden am 9. November, dem Tag des friedlichen Falls der Berliner Mauer 1989, gekürt. Christian Hackenberger erhielt 2020 den „Breakthrough of the Year"-Preis in der Kategorie Lebenswissenschaften.

EDUCATION AND TRAINING

AUSBILDUNG

SHARING KNOWLEDGE. THE PROMOTION OF YOUNG, TALENTED PEOPLE IS A CENTRAL CONCERN AT THE FMP.

WISSEN WEITERGEBEN! DIE FÖRDERUNG JUNGER, TALENTIERTER MENSCHEN IST EIN ZENTRALES ANLIEGEN AM FMP.

INDEPENDENT PROJECT

WIRKSTOFFRADIO (EPISODES IN GERMAN ONLY)

Wherever Bernd Rupp meets scientists – whether in his own living room or in a laboratory – the topics always focus on active substances of drugs. With great enthusiasm for science, research and a lot of curiosity, new episodes are produced for the "Wirkstoffradio" podcast. Feel free to listen in and to subscribe via the usual "Podcatcher" or directly via the wirkstoffradio.de website.

EIGENSTÄNDIGES PROJEKT

FORSCHENDEN ZUHÖREN – DAS WIRKSTOFFRADIO

Egal, wo sich Bernd Rupp mit Wissenschaftler*innen trifft, ob in Bernds Wohnzimmer oder in einem Labor eines Forschungsinstituts – die Themen drehen sich immer um Wirkstoffe. Mit großer Begeisterung für die Wissenschaft, eigener Recherche und einer Portion Neugier entstehen neue Folgen für den Podcast „Wirkstoffradio", den man über die üblichen „Podcatcher" sowie direkt über die Website wirkstoffradio.de anhören und abonnieren kann.

STUDENT LABORATORY FMP-CHEMLAB

In the ChemLab, located in the Gläsernes Labor, students from upper and secondary schools slip into the role of chemists and carry out experiments that are impossible to implement in school laboratories. The following courses are available: caffeine, dyes, plastics, fragrances and proteins.

SCHÜLERLABOR FMP-CHEMLAB

Im ChemLab, im Gläsernen Labor, schlüpfen Schüler*innen der Ober- und Sekundarstufe in die Rolle von Chemiker*innen und führen Experimente durch, wie sie in Schullaboren nicht umsetzbar sind. Zur Wahl stehen die Kurse: Koffein, Farbstoffe, Kunststoffe, Duftstoffe und Proteine.

APPRENTICESHIPS

From school desk to lab bench. Our apprentices training to become animal keepers or biology laboratory assistants can look forward to a comprehensive program in the working groups at the FMP. Training is supplemented by courses in the MDC learning laboratory, which are held together with trainees from the Campus Berlin-Buch. Theoretical training takes place in the vocational schools Lise-Meitner Schule (for biology laboratory assistants) and Peter-Lenné-Schule (for animal keepers).

AUSBILDUNGSBERUFE

Von der Schulbank zur „Lab Bench"! Unsere Auszubildenden zum/zur Tierpfleger*in oder Biologielaborant*in erwartet ein umfassendes Programm in den Arbeitsgruppen am FMP. Ergänzt wird die Ausbildung durch Kurse im MDC-Lernlabor, die gemeinsam mit den Auszubildenden des Campus Berlin-Buch stattfinden. Die theoretische Ausbildung erfolgt in den Berufsschulen Lise-Meitner-Schule (für Biologielaborant*innen) und Peter-Lenné-Schule (für Tierpfleger*innen).

ACADEMIC STUDIES

Students are welcome to do the experimental work for their Bachelor or Master's theses at our institute. We offer courses as an introduction to working here, e.g.:

- Seminar and practical course on Molecular Pharmacology and Cellular Signal Transduction (Ralf Schülein, Volker Haucke)
- Biological NMR Spectroscopy (Hartmut Oschkinat)
- NMR Spectroscopy and Imaging (Hartmut Oschkinat)
- NMR School (Peter Schmieder), NMR Spectroscopy (Adam Lange)
- Chemical Biology: Protein Synthesis, Labeling and Function (Dorothea Fiedler and Christian Hackenberger)

STUDIUM

Studierende können bei uns die Experimente für ihre Bachelor-/Masterarbeit durchführen. Als Einstieg in die Arbeiten in unserem Institut bieten wir Kurse an, z. B.:

Seminar und Praktikum „Molekulare Pharmakologie und zelluläre Signaltransduktion" (Ralf Schülein, Volker Haucke)

- Biologische NMR-Spektroskopie (Hartmut Oschkinat)
- NMR-Spektroskopie und Imaging (Hartmut Oschkinat)
- NMR-School (Peter Schmieder)
- NMR-Spektroskopie (Adam Lange)
- Chemische Biologie: Proteinsynthese, Labeling und Funktion (Dorothea Fiedler und Christian Hackenberger)

PHD – THE FMP GRADUATE SCHOOL

Working towards a successful PhD involves doctoral students being well supervised in their project as well as their ability to familiarize themselves with the research questions and methods of other groups, and ultimately to build networks. In order to guarantee the best possible support for the education of doctoral students at the FMP, doctoral students and their supervisors sign a supervision agreement that defines the rights and obligations of all parties involved. The FMP Graduate School additionally offers all doctoral students various formats to facilitate exchange and professional development. For example, doctoral students meet every two years at the FMP Winter School, where they can attend career lectures and visit the laboratories of other research groups. In addition to the education program of the FMP Graduate School, doctoral students can also take advantage of the wide range of courses offered by the Humboldt Graduate School. This facility is headed by Christian Hackenberger and managed by Katrin Wittig.

PROMOTION – DIE FMP GRADUATE SCHOOL

Für eine erfolgreiche Promotion sollten Doktorand*innen nicht nur in ihrem Projekt gut betreut werden, sondern auch die Fragestellungen und Methoden anderer Gruppen kennenlernen und Netzwerke bilden können. Um die Ausbildung der Doktorand*innen am FMP bestmöglich zu garantieren, unterzeichnen Doktorand*innen und ihre Betreuer*innen eine Betreuungsvereinbarung, die Rechte und Pflichten aller Beteiligten festlegt. Die FMP Graduate School bietet zudem allen Doktorand*innen verschiedene Formate für Austausch und Fortbildung. So kommen die Doktorand*innen z. B. alle zwei Jahre in der FMP Winter School zusammen, wo sie neben Karrierevorträgen auch die Labore der anderen Arbeitsgruppen besuchen können. Zusätzlich zu eigenen Fortbildungsangeboten steht den Doktorand*innen auch das breitgefächerte Angebot der Humboldt Graduate School zur Verfügung. Geleitet wird die Graduiertenschule von Christian Hackenberger, die Verwaltung liegt in den Händen von Katrin Wittig.

NETWORKING ON CAMPUS BERLIN-BUCH

During the doctoral period, the Graduate School will hold a joint annual retreat with the Max Delbrück Center for Molecular Medicine (MDC) as well as postdoctoral retreats, which are jointly organized by the two institutes.

VERNETZUNG AUF DEM CAMPUS BERLIN-BUCH

Während der Promotion findet im Rahmen der Graduate School ein gemeinsames jährliches Retreat mit dem Max-Delbrück-Centrum für Molekulare Medizin (MDC) statt sowie auch Post-Doc-Retreats, die beide Institute gemeinsam veranstalten.

ADMINISTRATIVE AND TECHNICAL SERVICES

ADMINISTRATIVE UND TECHNISCHE DIENSTLEISTUNGEN

STAND DEZEMBER 2020

DIRECTORS

Prof. Dr. Volker Haucke
Managing Director

Prof. Dr. Dorothea Fiedler

SCIENTIFIC ADMINISTRATION

Dr. Henning Otto, Dr. Franziska Ringleb, Dr. Maria Jäpel
Scientific Coordinators

Silke Oßwald
Public Relations

Dr. Barth van Rossum
Scientific Visualization

Dr. Birgit Oppmann
Technology Transfer

Katrin Wittig
PhD Program Coordinator

GENERAL ADMINISTRATION

Frank Schilling
Head of Administration

Marina Spors
Human Resources

Claudia Messing
General Administration

Dennis Bischoff
General Administration

Daniela Schwidlinsky
General Administration

Gabriele Schumacher
Secretary

DEPARTMENT OFFICES

Alexandra Chylla, Susan Kunze Juliane Langner
Department of Molecular Pharmacology and Cell Biology

Dr. Norma Nitschke, Dr. Hülya Kaplan
Scientific Coordinators
Department of Physiology and Pathology of Ion Transport

Stefanie Schneider
Department of Molecular Biophysics

Andrea Steuer
Department of NMR-Supported Structural Biology

Jennifer Trümpler
Department of Chemical Biology I and II

COMPUTER SERVICES (IT)

Ronald Jäckel
Chief Information Officer (CIO), System Administration

Marco Rentz
System Administration

Silvio Rönick
System Administration

Ingo Breng
Service Engineer

Alexander Heyne
Service Technician

TECHNICAL SERVICES

Marco Niepraschk (Head), Hajo Mussehl, Marco Mussehl, Holger Panzer, Stephanie Wendt, Pascal Schulz, Bernd-Uwe Wagner, Roy Wolschke, Beatrix Kaping

ANIMAL CARE OFFICER

Dr. Nadjeschda Heinrich

WORKPLACE SAFETY

Dr. Oxana Krylova

LASER SAFETY OFFICER

Dr. Martin Lehmann

WORKS COUNCIL

Dr. Peter Schmieder

EQUAL OPPORTUNITIES OFFICER

Silke Zillmann

OMBUDSPERSON

Dr. Dmytro Puchkov

GENETIC ENGINEERING / BIOLOGICAL SAFETY

Prof. Dr. Ralf Schülein

IMPRINT

IMPRESSUM

LEIBNIZ-FORSCHUNGSINSTITUT FÜR MOLEKULARE PHARMAKOLOGIE (FMP) IM FORSCHUNGSVERBUND BERLIN e. V.

Campus Berlin-Buch
Robert-Rössle-Str. 10
13125 Berlin
Germany

Phone + 49 30 947 93 104
Fax + 49 30 947 93 109
E-mail osswald@fmp-berlin.de

www.leibniz-fmp.de

RESEARCH REPORT 2019/2020

Editorial Board
Dorothea Fiedler, Christian Hackenberger, Volker Haucke, Thomas Jentsch, Adam Lange, Hartmut Oschkinat

Coordination
Silke Oßwald

Authors
Volker Haucke, Beatrice Hamberger, Silke Oßwald

Editing
Teresa Gehrs & Stephanie Brouwers

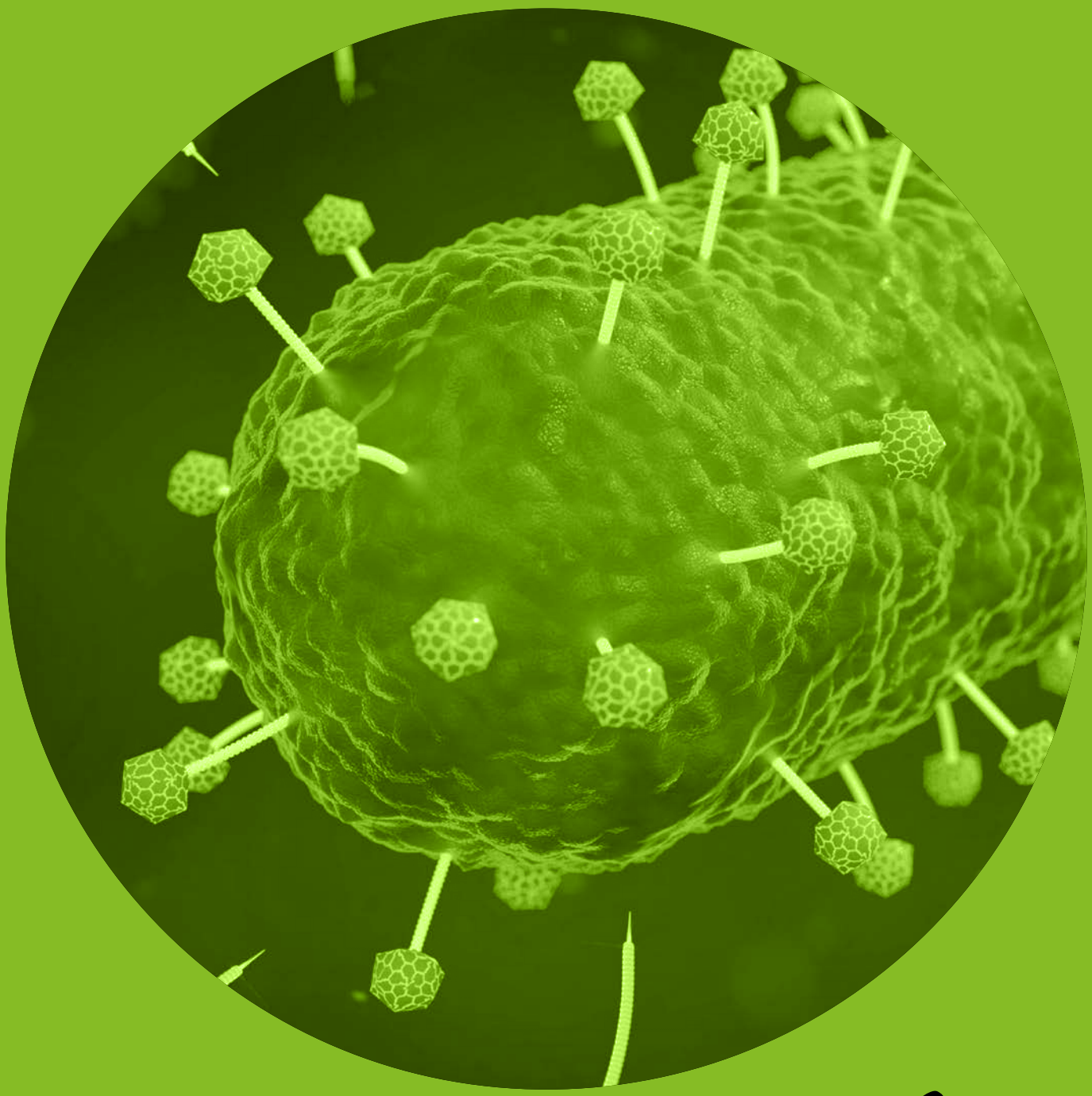
Photography
Silke Oßwald

Further Photography
p. 12: Stefan Jentsch, p. 16: Andrew Plested (private), p. 36: Adam Lange (private), p. 38: Maj Britt Hansen, p. 70: Jan Ficner, p. 72: David Ausserhofer, p. 78/79: Anyess von Bock/Peter Himsel

3-D Illustration
Barth van Rossum

Design and Layout
KRAUT & KONFETTI, Berlin

Berlin, January 2021



LEIBNIZ
FORSCHUNGSINSTITUT
FÜR MOLEKULARE
PHARMAKOLOGIE

Leibniz-Gemeinschaft