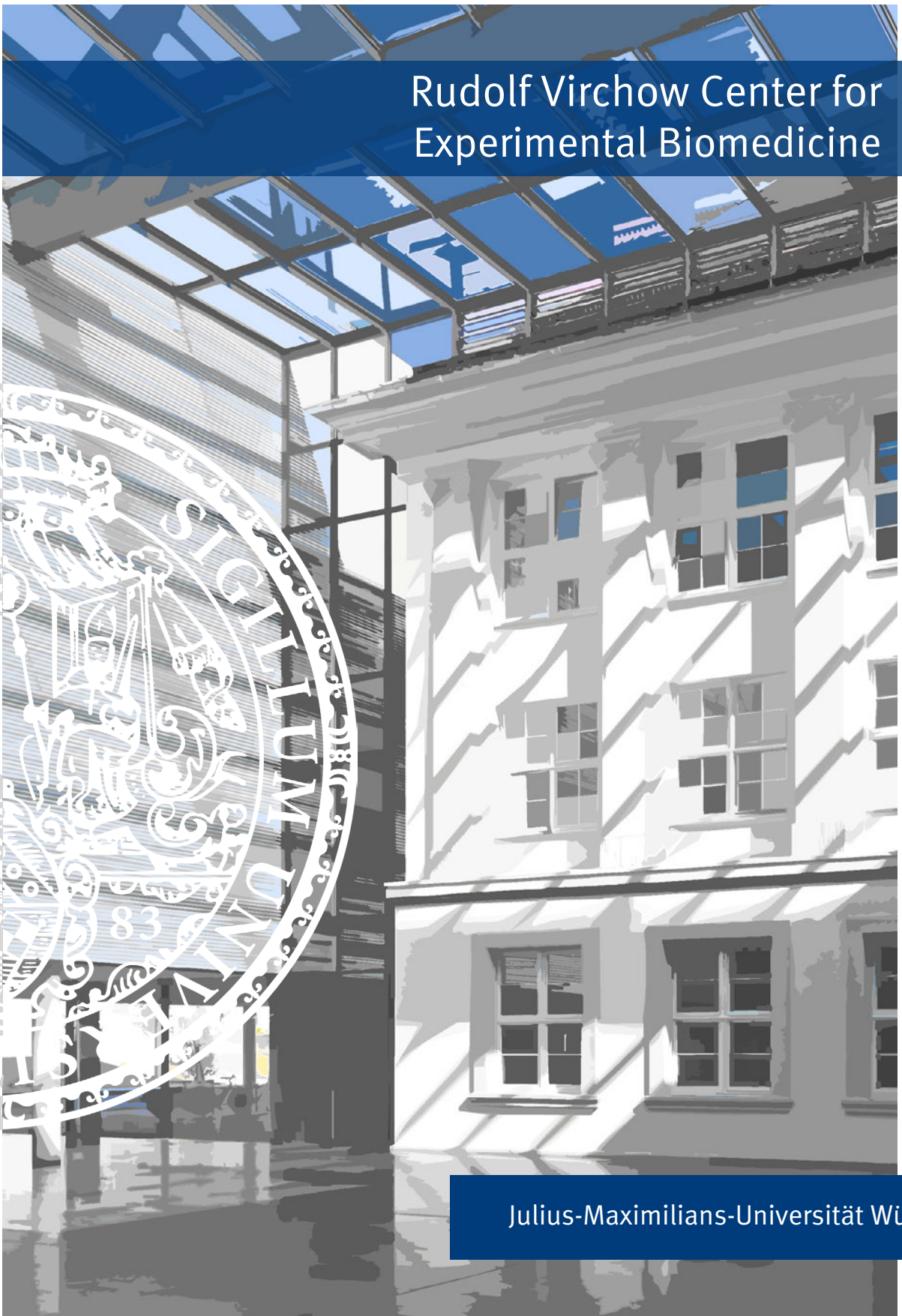
# ANNUAL REPORT

# 2017-2018

RUDOLF VIRCHOW ZENTRUM

UNI WÜ

## Rudolf Virchow Center for Experimental Biomedicine



Julius-Maximilians-Universität Würzburg

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# CONTENT

# ABOUT THE RUDOLF VIRCHOW CENTER FOR EXPERIMENTAL BIOMEDICINE

In the summer of 2001 the German Research Foundation (DFG) approved funding for the first of three DFG Research Centers. The successful proposal of the University of Würzburg to establish the Rudolf Virchow Center envisioned a biomedical research institution that uses state-of-the-art technologies to investigate the causes of human diseases at the molecular level.

In October 2009 the Rudolf Virchow Center moved into its present building on the medical campus of the University of Würzburg and thus closer to its medical collaboration partners. This proximity promotes interdisciplinary collaboration across disciplines.

In 2013 the Rudolf Virchow Center was transfered from DFG to funding by the State of Bavaria and has since been a central institution of the University of Würzburg.

# EDITORIAL

The Rudolf Virchow Center for Experimental Biomedicine (RVZ) is a key element of the biomedical research enterprise at the Julius Maximilians University of Würzburg (JMU).
The Center derives its name from the eminent 19th century German pathologist Rudolf Virchow, who was the first to map the causes of diseases at the level of individual cells.

Since Virchow's concept of cellular pathology, modern life sciences have taken huge strides and have moved on to the molecular and even atomic level to probe the causes of diseases. Scientists at the Rudolf Virchow Center focus on so-called target proteins, central regulatory biomolecules derived from diverse cell types with a causal connection to human health.
When target proteins are dysfunctional or misregulated, this may lead to pathophysiological states, and eventually, to a diseased organism. Given their pivotal role in the cell, target proteins are therefore of prime importance (as targets) for therapeutic interventions.

The importance of target proteins, both from the viewpoint of basic science and for translational approaches to developing novel therapeutic compounds and strategies, translates into the structural importance of the Rudolf Virchow Center for the biomedical campus in Würzburg. With its research projects at the interface of basic and translational science, the Center serves as a link between basic life sciences research activities at the University of Würzburg and clinical research centers such as the Comprehensive Heart Failure Center (DZHI) and the Comprehensive Cancer Center (CCC). Numerous ties and successful collaborations exist between researchers at the Rudolf Virchow Center and colleagues in these and other research institutions at the University of Würzburg and the University Hospital.

The last two years have been marked by substantial changes for the Rudolf Virchow Center. A few highlights will be presented in more detail in the following pages, together with snapshots of ongoing research projects of all research groups at the Center, the activities of the Public Science Center, the Center's study program Biomedicine as well as its interactions with the Graduate School of Life Sciences at the University of Würzburg.

The Rudolf Virchow Center has attracted two new junior research group leaders, who both started their research groups on January 1st, 2018. Dr. Pedro Friedmann-Angeli, a Brazilian cell biologist, has been recruited from the Helmholtz Center München/German Research Center for Environmental Health and works on ferroptosis, a novel mechanism of controlled cell death.

Dr. Hans Maric, a chemist by training, joined us from the Department of Drug Design and Pharmacology at the University of Copenhagen. Hans has been setting up a microarray-based platform for the synthesis of peptide-

derived, universally applicable high-affinity binders. Hans' recruitment was achieved through a joint effort with Prof. Markus Sauer's group from the Department of Biotechnology and Biophysics and has served to create new ties between the Rudolf Virchow Center and the Biocenter.

In addition to these new group leaders, Prof. Katrin Heinze has received a professorship for Molecular Microscopy, which illustrates the importance of imaging technologies at the Rudolf Virchow Center.

The Rudolf Virchow Center and the Institute of Experimental Biomedicine of the University Hospital have been the major drivers in the successful application for a DFG-funded Collaborative Research Center/ Transregio. The new SFB/TR 240 on platelets will continue the successful tradition of cardiovascular research at the Rudolf Virchow Center in the years to come.

With respect to research infrastructure, the Rudolf Virchow Center has become home to one of the most advanced cryo electron microscopes (EM) currently available. In a joint effort with the Department of Biochemistry, Prof. Bettina Böttcher was recruited to the University of Würzburg and has set up a state-of-the-art cryo EM facility at the Rudolf Virchow Center.

PROF. CAROLINE KISKER
Director of the Rudolf Virchow Center

PROF. BERNHARD NIESWANDT
Director of the Rudolf Virchow Center

TODAY

# RUDOLF VIRCHOW CENTER

## FOR EXPERIMENAL BIOMEDICINE

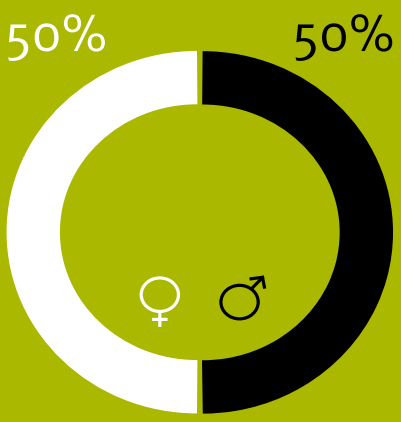
About 100 scientists work at the Rudolf Virchow Center in the field of target proteins. Target proteins fulfil important physiological tasks. Our research groups investigate the structure and function of these proteins to understand the causes of diseases.

Structural biology, molecular microscopy, proteomics and mass spectrometry are just some of the key technologies established in our research groups.

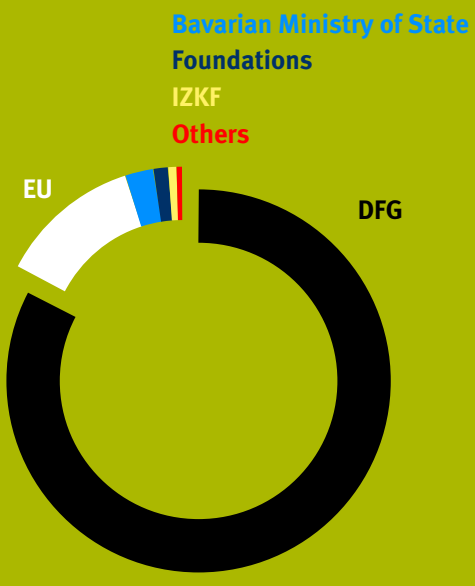
# FACTS & NUMBERS

159
STAFF AT THE RVZ
(Nov 2018)

21
PHD GRADUATIONS




RVZ GROUP LEADERS
(Nov 2018)




EXTERNAL FUNDING
2017 & 2018

## INTERNATIONAL DIVERSITY OF RVZ STAFF

- India (11)
- China (5)
- Brazil (3)
- France (2)
- USA (2)
- Great Britian (2)
- Azerbaijan (1)
- Columbia (1)
- Cuba (1)
- Georgia (1)
- Iran (1)
- Israel (1)
- Lebanon (1)
- Mexico (1)
- Poland (1)
- Russia (1)
- Taiwan (1)
- Turkey (1)
- Ukraine (1)
- Zimbabwe (1)

## INDIVIDUAL GRANTS

14x DFG Research Grants
2x DFG Emmy Noether Groups
1x European Regional Development Fund
1x European Research Grant
(ERC Starting Grant)
1x Sander Stiftung
1x Bayerische Forschungsallianz
1x EMBO Young Investigator

## COLLABORATIVE GRANTS

2x EU Innovative Training Network
4x DFG Collaborative Research Centers
(including 2 RVZ coordination)
1x DFG Research Training Group
1x Elite Network of Bavaria
1x IZKF Clinician Scientist Program
Graduate School of Life Sciences (GSLS)

# DEVELOPMENT

During the past two years exciting developments have taken place at the Rudolf Virchow Center. New researchers have joined the Center, some have left, prizes and awards have been won, new research projects granted and new technologies installed. The following pages summarize some of these developments.

## NEW GROUP LEADERS

Pedro Friedmann Angeli and Hans Maric started their junior research groups.

## NEW PROFESSOR

Katrin Heinze was appointed Professor for Molecular Microscopy.

## NEW TECHNOLOGIES

In a joint effort with the Department of Biochemistry, a top-notch cryo electron microscope was set up.

## FAREWELL

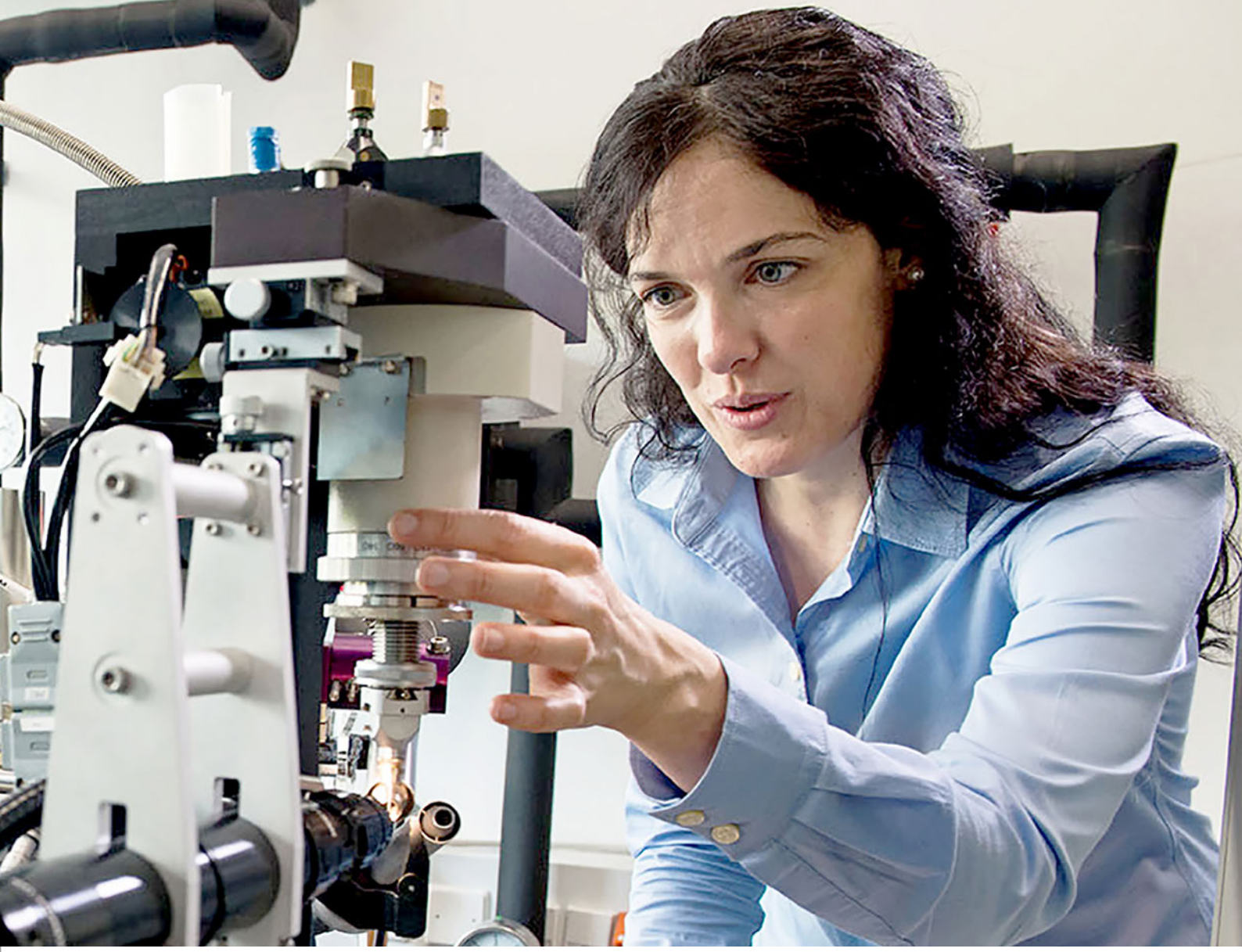
Martin Heisenberg, a renowned neurobiologist and senior professor, retired.

SUMARA'S DIOSCURI CENTRE

# DR. GRZEGORZ SUMARA

In October 2018, group leader Dr. Grzegorz Sumara received an offer to lead one of the first Dioscuri Centres in Warsaw, Poland. He competed against 45 applicants from all over the world.

The Dioscuri Programme was initiated by the Max Planck Society, is jointly managed with the Polish National Science Centre (NCN), and aims to establish internationally competitive research groups in Poland. The Dioscuri Centre is planned to be located at the Nencki Institute, where Grzegorz will continue his research focus on the elucidation of signaling pathways that play a role in metabolic diseases.



EMBO YOUNG INVESTIGATOR

# DR. SONJA LORENZ

In October 2017, Dr. Sonja Lorenz was accepted into the prestigious young scientist support scheme of the European Molecular Biology Organization (EMBO) acknowledging her outstanding research work.

As one of the 28 new EMBO Young Investigators, selected from the 11 EMBO member states as well as India and Singapore, Sonja and her research group will receive a range of benefits, including financial support, access to technical infrastructure, and exceptional training, mentoring, and networking opportunities.

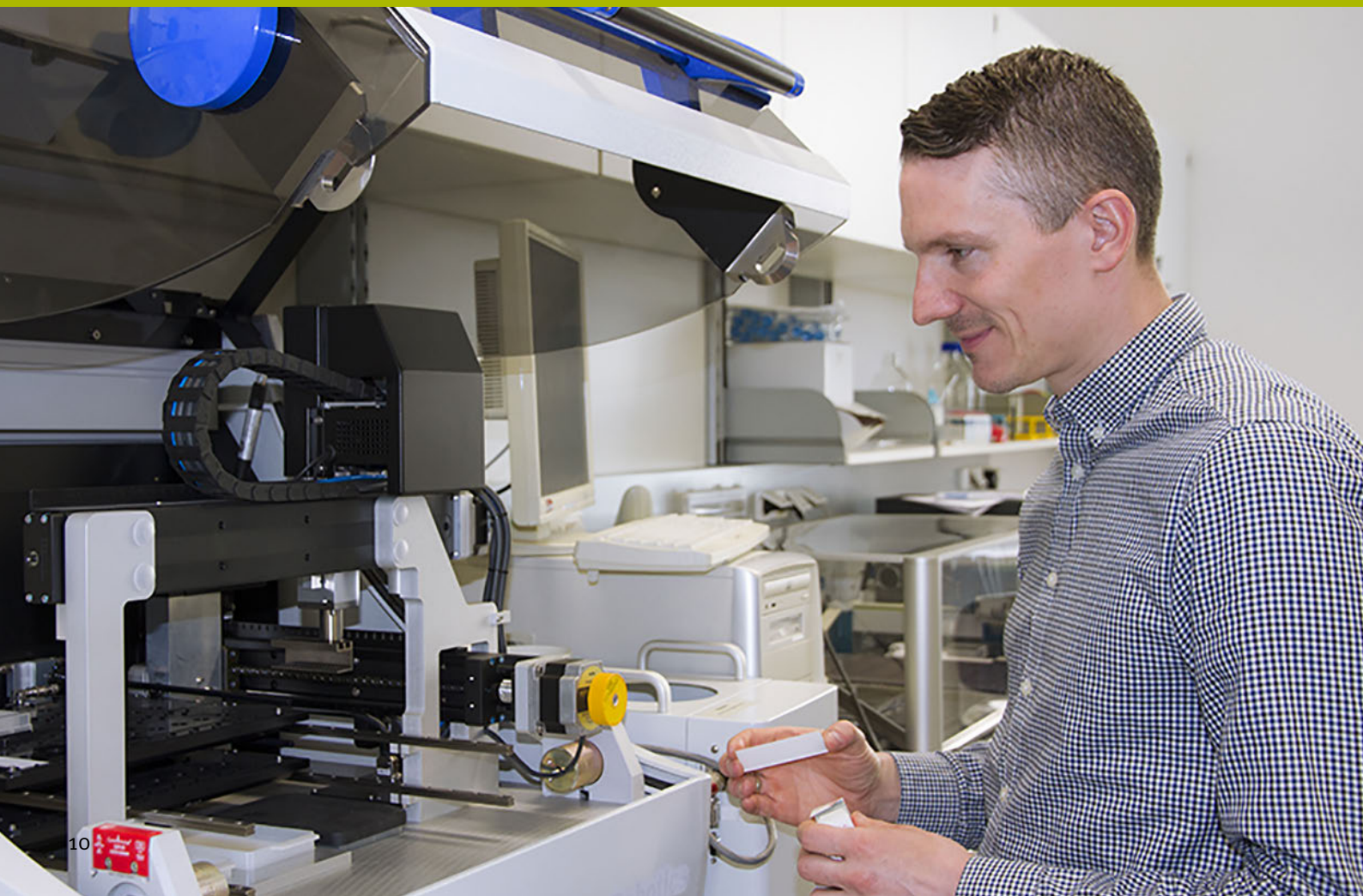
NEW GROUP LEADER

# DR. HANS MARIC

Fascinated by microarray technology, Dr. Hans Maric accepted a position as an assistant professor at the newly founded Center for Biopharmaceuticals in Copenhagen in 2015. With the help of the Hoerslev, the Brødrene Hartmanns and the Frimodts Foundation he succeeded in building a unique microarray platform.

Since January 2018, Hans has been a new group leader at the Rudolf Virchow Center. Among other things, he wants to develop a fundamentally new class of biomolecules, so-called “Protein Superbinders”. “At first, I worked with simple fragments of a protein binding partner, which I then further improved in an iterative process. Now I am also working with starting molecules that were predicted *in silico*”, explains Hans. His methodological focus is on organic synthesis and protein chemistry as well as on biophysical protein and protein interaction analysis methods. In addition, Hans brings a new expertise to Würzburg: the quantification of protein-protein interactions in high throughput and the production of selected peptide drug candidates on a gram scale.

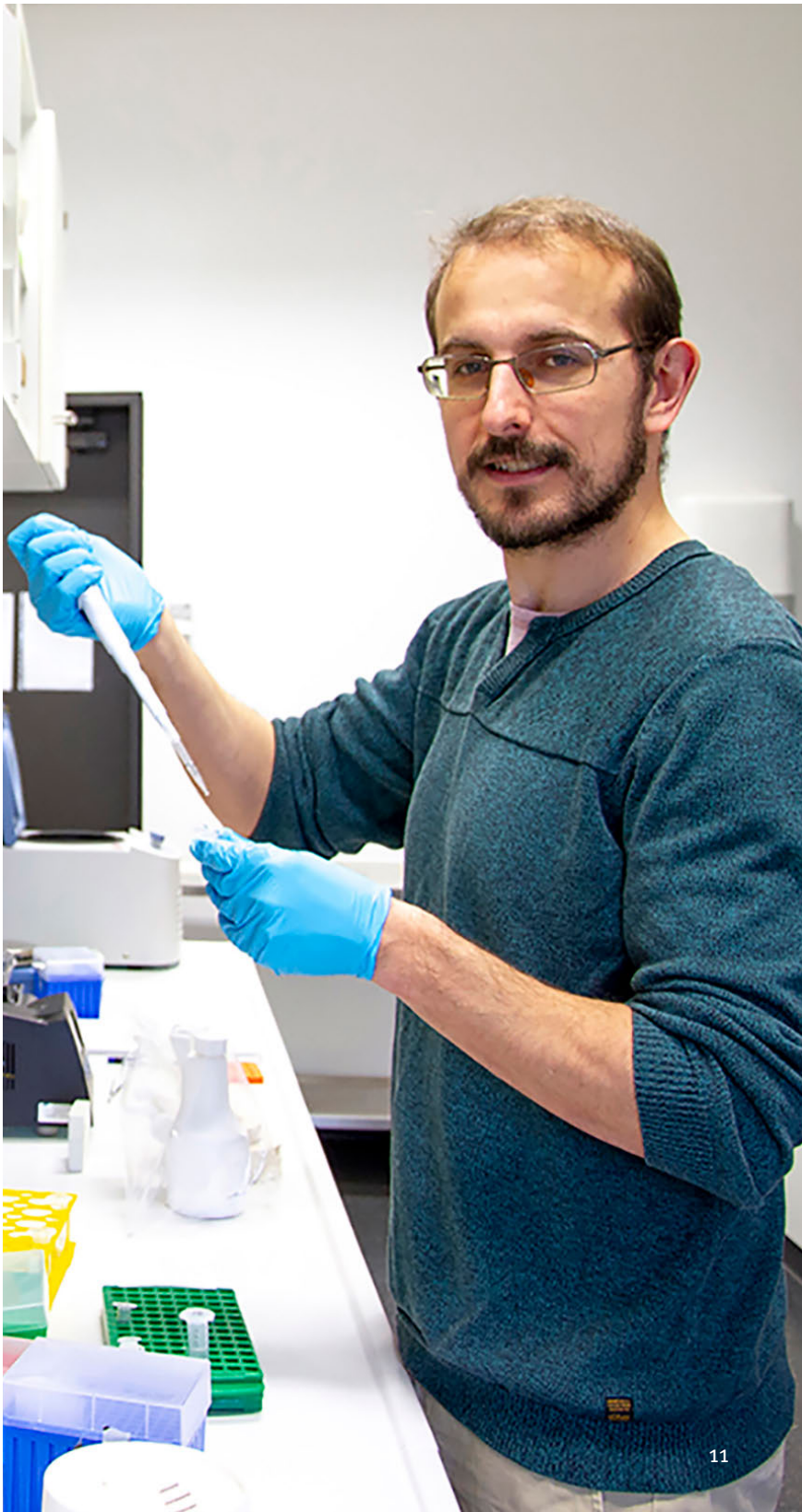
His research group is supported by the program “Excellent Ideas” of the JMU.



NEW GROUP LEADER

# DR. JOSÉ PEDRO FRIEDMANN ANGELI

During his PhD at the University of Sao Paolo, Dr. José Pedro Friedmann Angeli studied the toxic effect of lipid oxidation products, which are common metabolites found in pathological conditions. Given his interest in their role in more physiological settings, Pedro decided to move to the German Helmholtz Center Munich supported by a two year postdoctoral fellowship offered by the Humboldt foundation. He was introduced to the field of mouse genetics and genetic engineering, enabling him to study the effects of lipid oxidation in physiologically relevant settings. Pedro has provided the first piece of evidence that lipid oxidation drives a specific form of cell death called ferroptosis and has defined its relevance *in vivo*. This work provided the basis for a project supported by the Human Frontier Science Program (HFSP). Since his start at the Rudolf Virchow Center in January 2018, Pedro has continued his work aiming to characterize and dissect mechanisms that control ferroptosis sensitivity, as well as to understand its pathological implications.



APPOINTMENT

# PROF. KATRIN HEINZE

In May 2017, Dr. Katrin Heinze was appointed Professor for Molecular Microscopy at the Rudolf Virchow Center. Katrin is a physicist by training. She develops and applies highly advanced light microscopy methods to investigate biomolecules, cells and entire organs. Using state-of-the-art and often custom-built microscopy technologies, Katrin and her group contribute essential imaging expertise to many biomedical research projects at the Rudolf Virchow Center and the University of Würzburg.

BAVARIAN ACADEMY

# PROF. CAROLINE KISKER

In spring 2017, the plenum of the Bavarian Academy of Sciences and Humanities elected Prof. Caroline Kisker as one of its new members.

Founded in 1759, the Bavarian Academy of Sciences and Humanities is among the largest and oldest academies in Germany. It has been committed to its tasks as a learned society, a non-university research institution and a place of lively scientific dialogue with society and politics for more than 250 years.

Caroline Kisker has been the Head of the Department of Structural Biology at the Rudolf Virchow Center since 2006 and Dean of the Graduate School of Life Sciences at the University of Würzburg since 2009. She is also a member of the Academy of Sciences Leopoldina and Deputy Chair of the Scientific Advisory Committee at the Helmholtz Center for Infection Research in Braunschweig.


FUNDING

# PROF. BERNHARD NIESWANDT

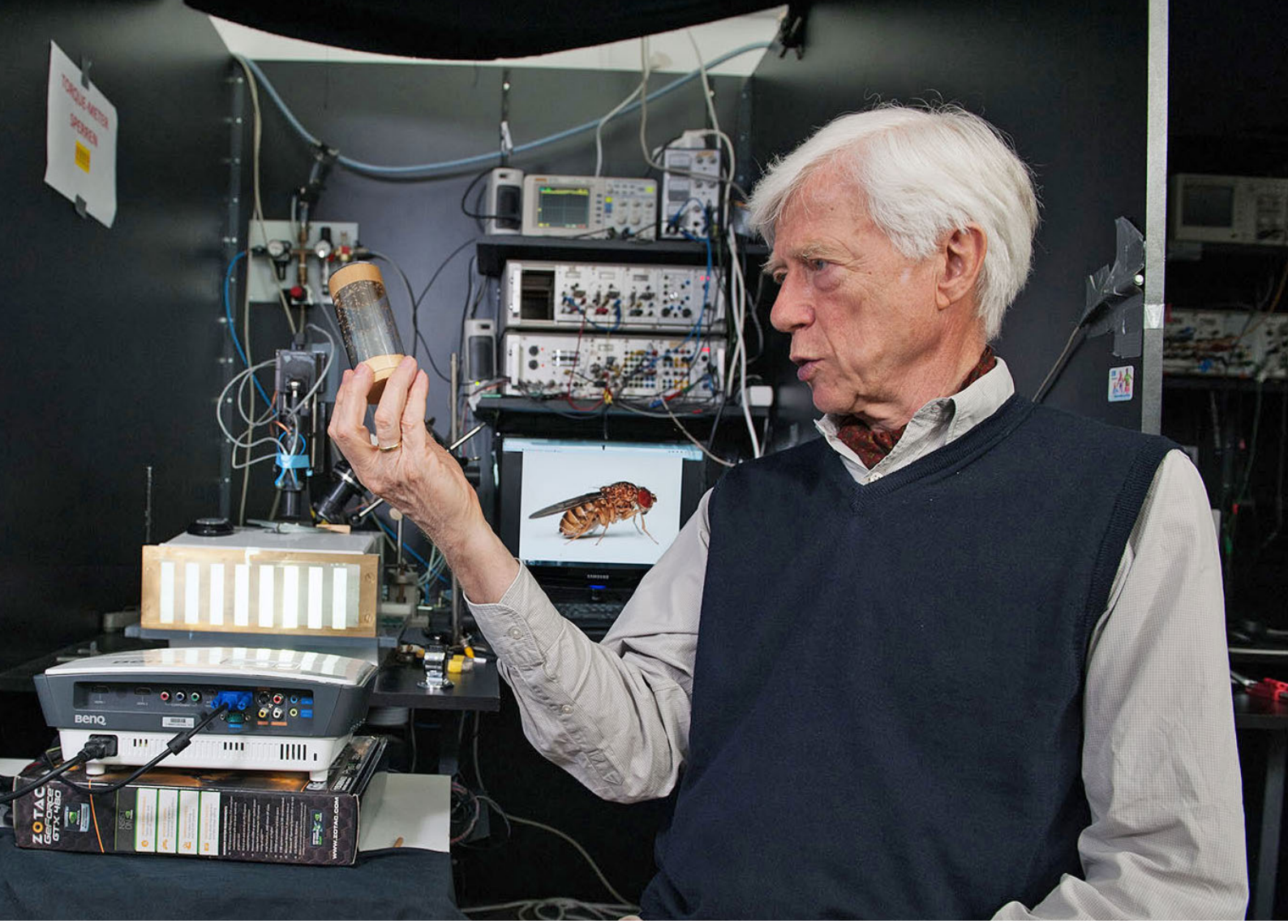
In July 2018, a new Collaborative Research Center started with a total funding of nearly 14 million Euro, headed by the Institute for Experimental Biomedicine in Würzburg. The DFG approved the Collaborative Research Center Transregio (SFB / TR 240) “Platelets – Molecular, cellular and systemic functions in health and disease”.

The aim is to decode the complex and insufficiently understood functions of platelets. The scientists involved hope to gain new insights into the biology of platelets, a prerequisite for better treatment of conditions such as heart attack, stroke, acute lung failure and cancer. Professor Bernhard Nieswandt, one of the Directors of the Rudolf Virchow Center, is also Director of the Institute for Experimental Biomedicine, supported by the University Hospital Würzburg and the Rudolf Virchow Center of the University of Würzburg.

TECHNOLOGY

# PROF. BETTINA BÖTTCHER

In 2018 one of the world's most powerful electron microscopes was installed at the Rudolf Virchow Center, providing images of biological molecules of unparalleled quality.
Bettina Böttcher is responsible for the microscope and her methodological focus is cryo electron microscopy. She has been a professor at the Department of Biochemistry of the University of Würzburg since August 2016.
"The device allows us to automatically record high-resolution data during several days of non-stop operation. Depending on the specimen, the microscope yields structural data of two to four ångström," Professor Bettina Böttcher explains.
In 2017 the German Research Foundation approved the application and released 3.8 million Euro for the purchase. In addition to researchers from Würzburg, the microscope will also allow scientists from the universities of Bayreuth, Erlangen and Regensburg to take structural images of biological samples smaller than one millionth of a millimetre.




FAREWELL

# PROF. MARTIN HEISENBERG

Prof. Dr. Dr. h.c. Martin Heisenberg is a German neurobiologist and geneticist. Prior to his retirement in 2008, he held the Chair for Genetics and Neurobiology at the Biocenter of the University of Würzburg. Since then, he continued his research until 2018 with a senior professorship at the Rudolf Virchow Center of the University of Würzburg.

Martin Heisenberg studied chemistry and molecular biology in Munich, Tübingen and Pasadena. In 1975 he became Professor of Genetics and Neurobiology at the University of Würzburg. Heisenberg's work has focused on the neurogenetics of Drosophila (the fruit fly), with the aim of investigating the genetic foundations of the Drosophila brain by studying the effect of genetic mutations on brain function. In addition, Heisenberg has published a number of essays on topics of universal importance such as science in society, perception, as well as the freedom of will.

Martin Heisenberg was elected a member of the Leopoldina in 1989.

# GROUP LEADERS

The Rudolf Virchow Center hosts several research groups each run by independent group leaders. Some of them are long-term groups headed by established scientists as professors, others are temporary and provide opportunities for talented junior research leaders to pursue their own projects and to qualify for professorial or other leadership positions.

GROUP LEADERS
at the Rudolf Virchow Center

# Dr. José Pedro Friedmann Angeli

## GOAL

Our overall goal is to understand how cells cope with and adapt to oxidatively induced damage to their phospholipid membranes. Particularly, how metabolic conditions predispose a cell for premature oxidation and ultimately cell death - a cellular event that is at the root of a series of degenerative diseases. Ultimately, understanding these molecular events could lead us to propose strategies to extend or shorten the cell “life-span”.

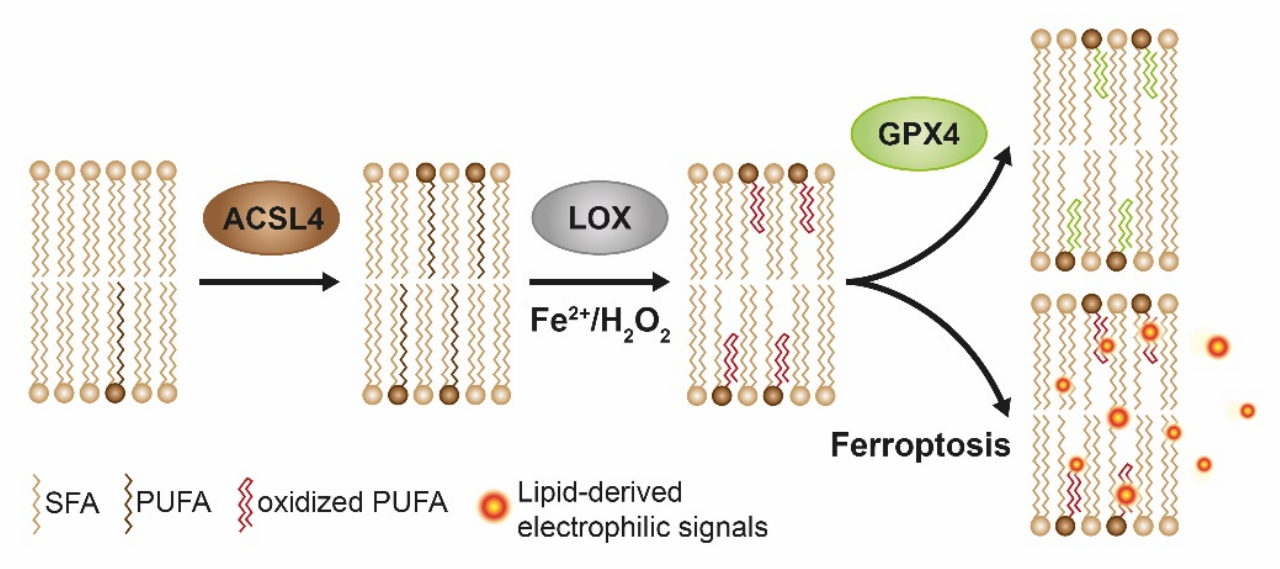
## RESEARCH BACKGROUND

Ferroptosis is a novel form of cell death that has received considerable attention over the last years due to its potential implication in a wide array of pathological conditions such as neurodegeneration and ischaemia reperfusion injury. Almost five years ago we showed that ferroptosis is regulated by the selenoprotein GPX4.
This enzyme was shown to be required to repair oxidized phospholipid and prevent the associated premature cell death. Therefore it is now accepted that the oxidative modification of phospholipid is essential to drive a specific cell death modality.

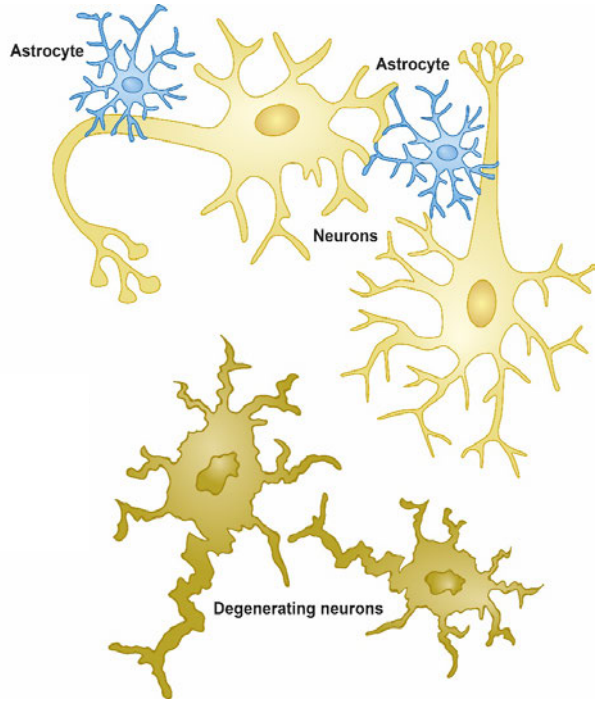
## RESEARCH HIGHLIGHTS

Lipid metabolism determines ferroptosis sensitivity:
To understand factors that regulate sensitivity to ferroptosis we have used a CRISPR-based, genome wide loss-of-function screen to identify genes that are required for ferroptosis execution. This study allowed us to identify Acyl-CoA long chain family member 4 (ACSL4) as a critical regulator of this pathway (Doll et al., Nat Chem Biol 2017). We have also shown that pharmacological inhibition of this node is possible using thiazolinediones, suggesting that the decrease in dementia risk in people taking such medication could be related to ferroptosis inhibition.

Ferroptosis as an evolutionary pressure to retain selenoproteins?
The ferroptosis regulator GPX4 is a selenoprotein. Selenoproteins are proteins that contain the rare amino acid selenocysteine. Incorporation of selenocysteine into proteins is an energetically costly process of unknown importance. We were able to show that, unlike cysteine, selenocysteine is resistant to enzyme inactivation (Ingold et al., Cell 2017). This appears to be critical in the central nervous system, since mutant mice die shortly after birth. Our work suggests that the complex lipid composition was only possible due to the presence of a selenoprotein containing GPX4.




Ferroptosis contributs to premature (neuronal) cell death.




## FUTURE PLANS

Our current plans are to characterize novel regulatory nodes of this complex pathway. This knowledge will be fundamental for understanding under which conditions ferroptosis can be prematurely triggered or chronically suppressed. This knowledge will prove instrumental in understanding pathological conditions where ferroptosis is believed to play role, such as neurodegenerative conditions (e.g. dementia and amyotrophic lateral sclerosis). Moreover, we are also developing novel ways to trigger this pathway in order to eradicate tumor entities resistant to standard chemotherapeutics.

## SELECTED PUBLICATIONS

Ingold I, Berndt C, Schmitt S, Doll S, Poschmann G, Buday K, Roveri A, Peng X, Porto Freitas F, Seibt T, Mehr L, Aichler M, Walch A, Lamp D, Jastroch M, Miyamoto S, Wurst W, Ursini F, Arnér ESJ, Fradejas-Villar N, Schweizer U, Zischka H, Friedmann Angeli JP, Conrad M. Selenium Utilization by GPX4 Is Required to Prevent Hydroperoxide-Induced Ferroptosis. Cell. (2017) pii: S0092-8674(17)31438-1. doi: 10.1016/j.cell.2017.11.048.

Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, Irmler M, Beckers J, Aichler M, Walch A, Prokisch H, Trümbach D, Mao G, Qu F, Bayir H, Füllekrug J, Scheel CH, Wurst W, Schick JA, Kagan VE, Friedmann Angeli JP*, Conrad M*. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol. (2017) 13(1):91-98. doi: 10.1038/nchembio.2239.

# Prof. Bettina Böttcher

## GOAL

The goal of our research is to understand the structural basis of how biological complexes utilize modular architectures to fulfill their diverse functions and how structural dynamics enhance this functionality. For this we use electron cryo microscopy and image processing, which we develop to fulfill our specific needs.

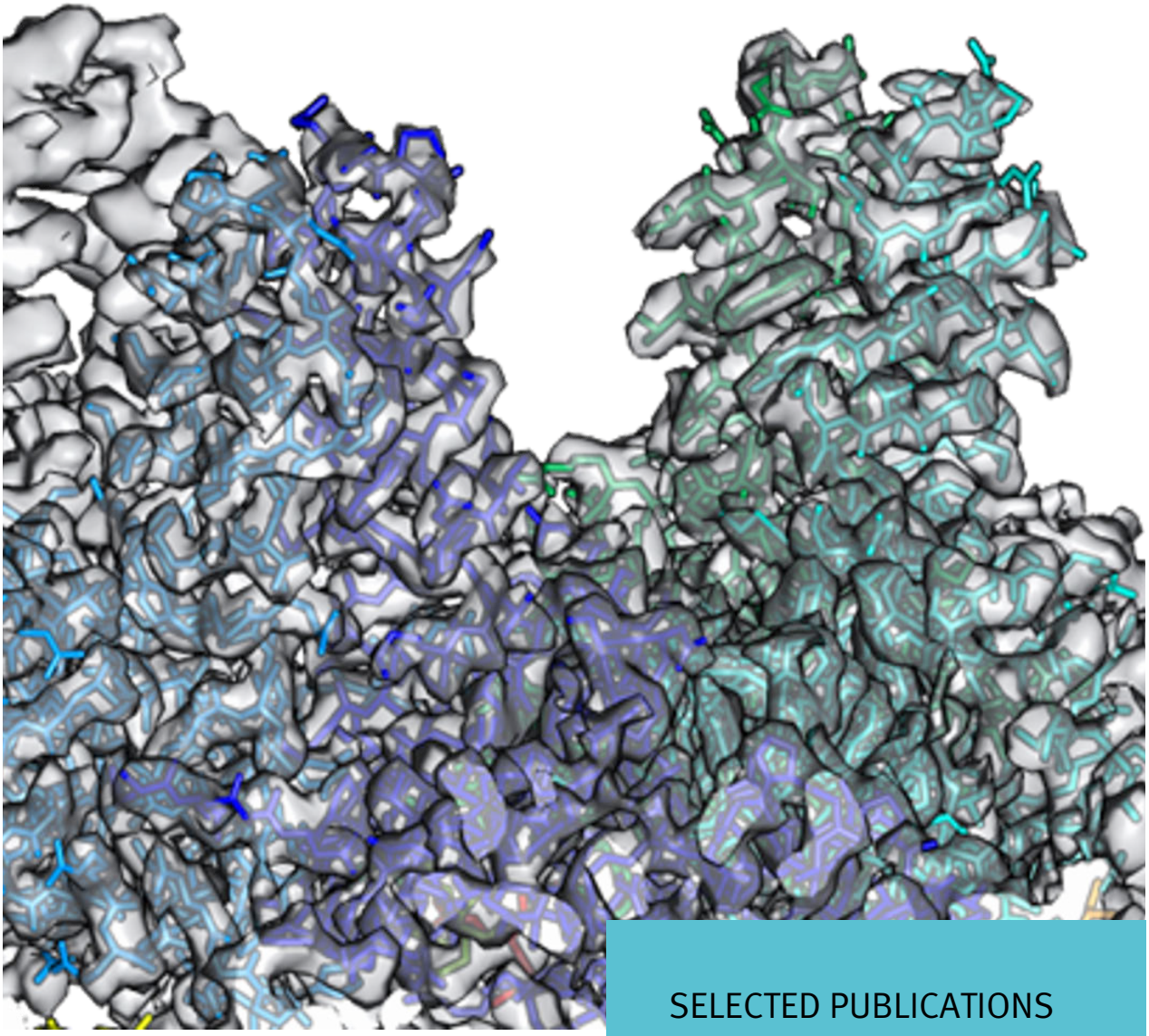
## RESEARCH BACKGROUND

Proteins catalyse reactions in living organisms by supplying reactive groups and binding surfaces that specifically recognize and orient reaction partners. Several proteins together assemble into larger complexes. Such higher order organization of individual components adds extra functionality that goes far beyond catalysis and includes scaffolding, provision of protective environments, and control of multi-step reaction pathways. To understand how higher-order organization enhances functionality we require high resolution structural information that we obtain by electron cryo microscopy.

## RESEARCH HIGHLIGHTS

We have investigated the structure of African cassava mosaic virus (ACMV), which affects cassava, an essential carbohydrate source for hundreds of millions of people. The virus forms an unusual twin particle, in which two incomplete icosahedra are joined at a five-fold vertex. We have determined the structure of ACMV at 3.6 Å resolution. It reveals that the inter-capsomer contacts are mediated by the N-termini of the capsid protein, which adopt a different fold in general parts of the icosahedron than at the twin interface. Furthermore, we discovered a new pocket for possible DNA binding, which segregates large parts of the genome at the inner surface of the capsid at a suitable position for fast release.

In a second project, we have investigated the structure of capsids formed by a premature envelopment mutant of Hepatitis B virus, which is a major human pathogen with 250 million carriers worldwide. They have an increased risk of liver cancer and liver cirrhosis. Our structure at 2.4 Å resolution shows that the mutation increases the size of a pocket in the center of the spikes by rearrangement of the adjacent side chains. This increased pocket provides an enhanced binding platform for factors facilitating envelopment. The pocket binds small molecules, suggesting that it is a suitable target for potential drugs that interfere with viral maturation.



Close-up of Hepatitis B core protein capsids of the premature envelopment mutant.

## FUTURE PLANS

In 2018, we installed a Titan-Krios electron microscope for high-resolution imaging. To take full advantage of the system, optimization of acquisition and processing with a variety test objects is required. The outcome will inform future experiments on what is important for obtaining sub- 3 Å resolution maps. This resolution is essential for reliable *de novo* model building.

We have started the investigation of mechanosensitive channels of small conductance. Here, we want to understand how these channels shape their membrane environment and how the interplay of membrane and protein enables mechano-sensation. This will address a so far largely neglected aspect of membrane protein function that is based on the contribution and arrangement of lipid molecules in the immediate environment of the protein.

## SELECTED PUBLICATIONS


Hipp K, Grimm C, Jeske H, Böttcher B. Near-Atomic Resolution Structure of a Plant Geminivirus Determined by Electron Cryomicroscopy. Structure (2017) 25: 1303-1309 e3

Nassal M & Böttcher B. Structure of Mutant Hepatitis B Core Protein Capsids with Premature Secretion Phenotype J. Mol. Biol in press (2018) https://doi.org/10.1016/j.

# Prof. Davide Calebiro

## GOAL

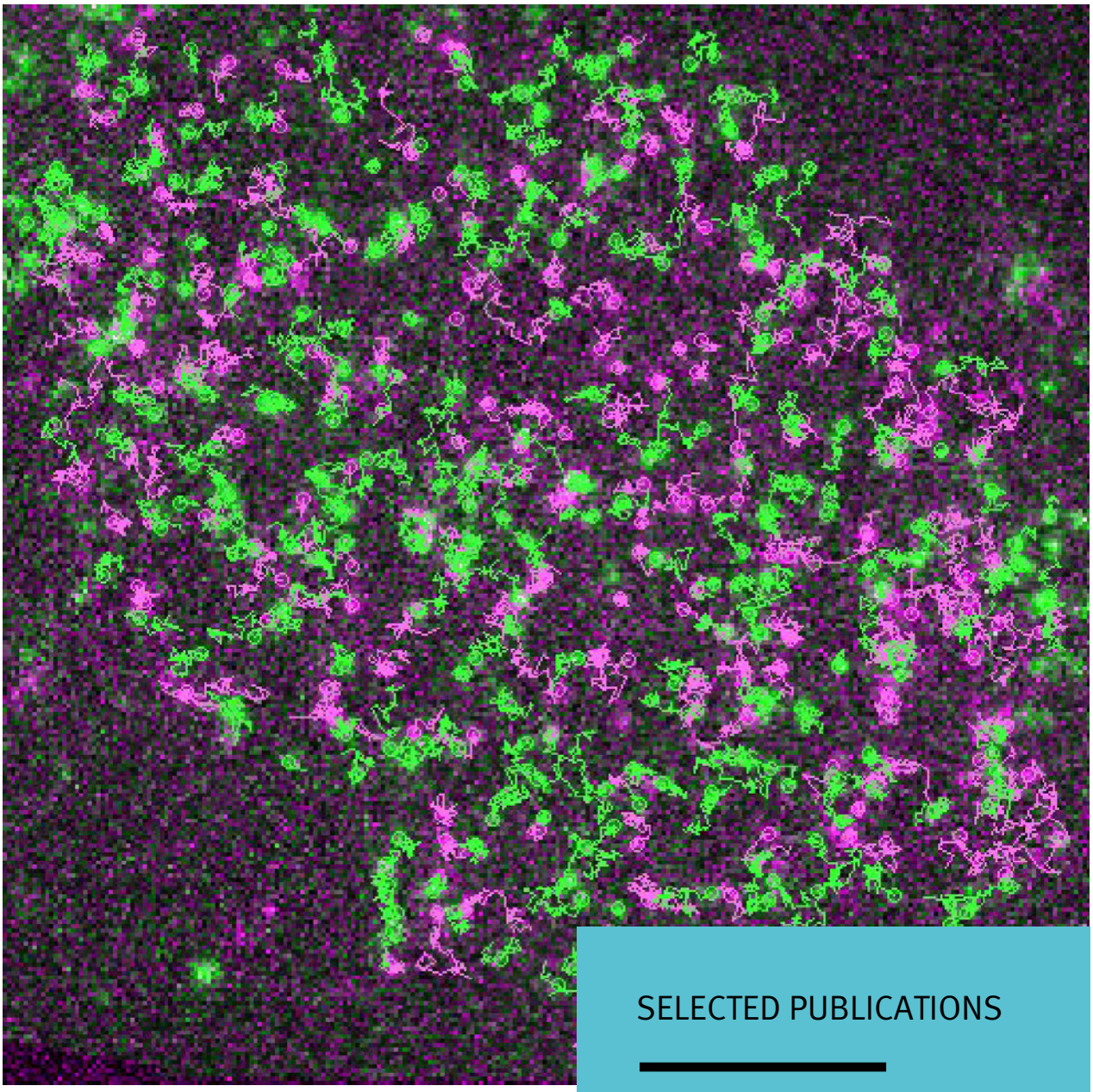
Cells communicate with each other and sense the extracellular environment via receptors located on their surface. G protein-coupled receptors (GPCRs) constitute the largest family of cell receptors and serve as major pharmacological targets. In our laboratory, we investigate the basic mechanisms of GPCR signaling and their alterations in endocrine and metabolic diseases. To do this, we develop and use innovative microscopy methods to directly visualize signaling events in living cells with very high spatiotemporal resolution.

## RESEARCH BACKGROUND

GPCRs mediate the effects of a large number of extracellular cues, including light, odorants, hormones and neurotransmitters. Whereas the main biochemical steps involved in GPCR signaling are well-known in detail, how these receptors function in the complexity of a living cell or organism to produce rapid and specific effects remains poorly understood. This is largely because the standard methods used to investigate GPCRs require cell disruption and possess insufficient spatiotemporal resolution. My group develops, and uses advanced optical methods, such as FRET and single-molecule microscopy, which allow us to investigate GPCRs and the signals produced by their activation directly in living cells. With these methods we achieve a resolution of up to 10 ms and 10 nm, i.e. about 20 times better than with confocal microscopy.

## RESEARCH HIGHLIGHTS

One previous key finding of our group was that GPCRs can continue signalling on intracellular membranes after their internalization (Calebiro et al., PLoS Biology 2009).
Over the last two years, we demonstrated for the first time that this occurs via retrograde trafficking of the internalized receptors to the trans-Golgi network (TGN), where they are able to induce local cAMP signals (Godbole et al., Nat Commun 2017). These findings have major implications for drug discovery and might provide the basis for developing new drugs with improved efficacy and tolerability.
In parallel, we discovered several new gene mutations and genetic alterations in GPCR signalling that cause endocrine diseases. Moreover, we have developed an innovative single-molecule microscopy approach to investigate receptor interactions on the plasma membrane with unprecedented spatiotemporal resolution. Using this approach, we have succeeded for the first time in directly visualizing individual receptors and G proteins as they diffuse, interact and signal on the surface of living cells (Sungkaworn et al. Nature 2017). This has revealed nanometer-sized “hot spots” on the plasma membrane, where receptors and G proteins accumulate and interact to induce local signals. We hypothesise that these mechanisms are crucial to confer the high speed and specificity observed in GPCR signaling.



Individual receptors (green) and G proteins (magenta) imaged as they diffuse and interact on the surface of a living cell.

## FUTURE PLANS

In the future, we will further develop our multidisciplinary approach to study the spatio-temporal dynamics of GPCR signaling in living cells with unprecedented spatio-temporal resolution. We will use these innovative methods to investigate fundamental and still unresolved questions about the function of these important receptors, with the ultimate goal of developing novel therapeutic strategies for common diseases such as diabetes or heart failure.

## SELECTED PUBLICATIONS


Sungkaworn T, Jobin ML, Burnecki K, Weron A, Lohse MJ, Calebiro D. Single-molecule imaging reveals receptor-G protein interactions at cell surface hot spots. Nature (2017) 550, 543-547

Godbole A, Lyga S, Lohse MJ, Calebiro D. Internalized TSH receptors en route to the TGN induce local Gs-protein signaling and gene transcription. Nature Communications (2017) 8, 443

Calebiro D, Sungkaworn T. Single-Molecule Imaging of GPCR Interactions. Trends in Pharmacological Sciences (2017) 39, 75-89

GROUP LEADERS
at the Rudolf Virchow Center

# Prof. Katrin Heinze

## GOAL

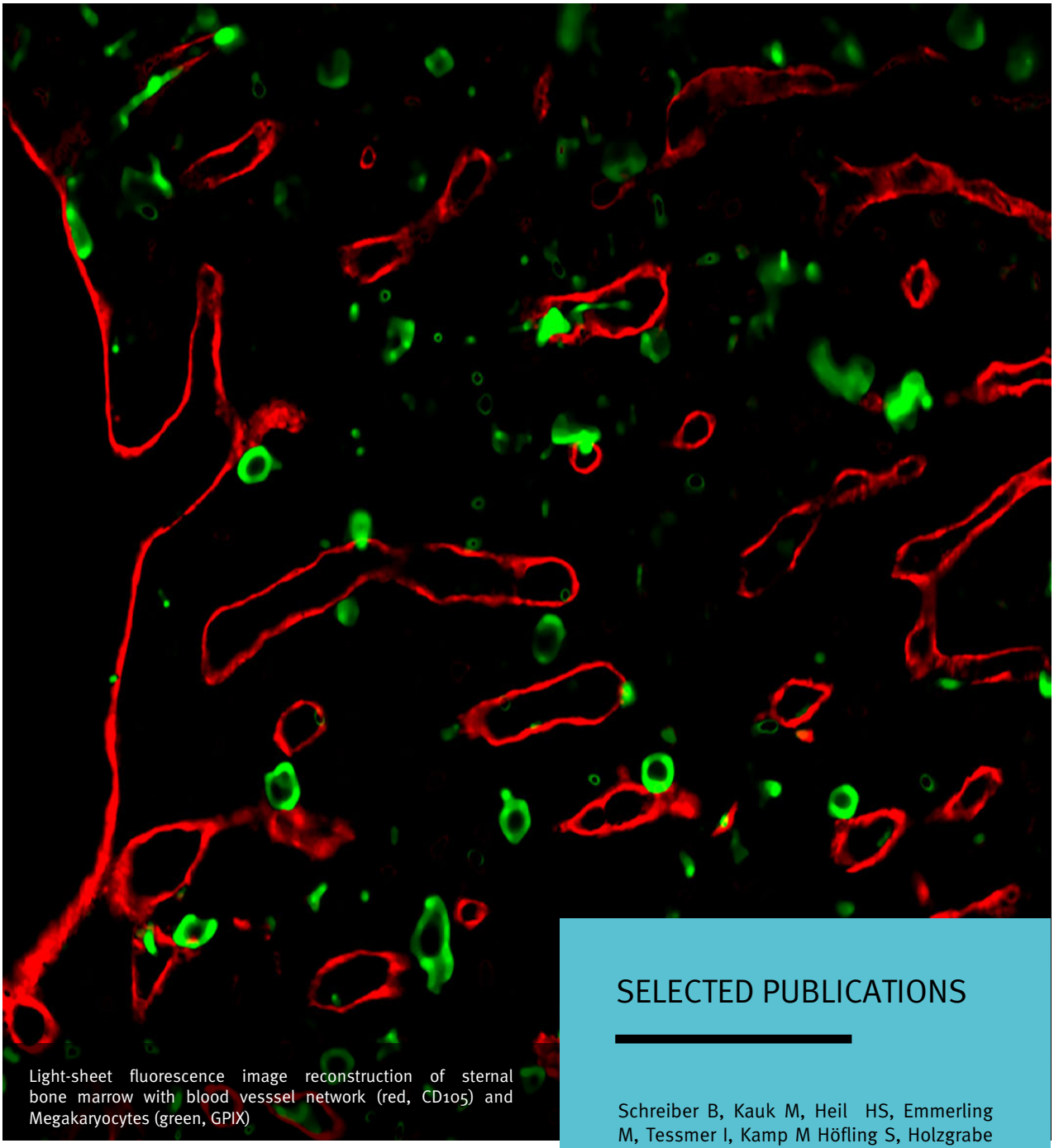
Discoveries in medicine and biosciences are frequently stimulated by the invention of new scientific tools. In our laboratory, we develop 3D fluorescence microscopy and spectroscopy techniques that allow either spatio-temporal super-resolution or whole organ imaging with subcellular details.

## RESEARCH BACKGROUND

In biomedical research, the imaging method that everyone dreams of is able to non-invasively and selectively visualize subcellular compositions of a whole body in a single snapshot. Unfortunately, this 'ideal' method where very fine details can be captured in no time over a large field-of-view has not yet been invented. We tackle this problem by complementary approaches using advanced intravital and light sheet fluorescence microscopy with tweaks, as well as specially designed nano-coatings for live cell super-resolution. This imaging tool box spans scales from single molecules to whole organs.

## RESEARCH HIGHLIGHTS

On small scales down to single molecules, optoplasmonic tools can provide unrevaled axial resolution, the Achilles heel in modern microscopy. Our tailored biocompatible nano-coatings enable axial super-resolution by interference and surface plasmon effects near the structure surface. Moreover, we showed that such nano-coatings can operate as a 'booster' for already established microscopy techniques such as direct Stochastic Optical Reconstruction Microscopy, Fluorescence Correlation Spectroscopy and Fluorescence Resonance Energy Transfer (ACS Photonics 2018). Besides maximizing resolution and spatial selectivity, spanning scales is often desired, however difficult to achieve: It is still impossible to image a millimeter scale tissue sample with nanometer resolution without cutting the sample into very small pieces. However, complementary approaches can help to tackle this problem and complete the puzzle of spatio-temporal information of cell-cell or cell-vessel interactions within a large tissue context. Here, Light Sheet Fluorescence Microscopy (LSFM) together with computational methods has pushed the limits. In close collaboration with Dr. David Stegner we recently obtained fascinating 3D-insights into the bone marrow and successfully elucidated new details of the process of thrombocyte generation (Nat Commun 2017).



Light-sheet fluorescence image reconstruction of sternal bone marrow with blood vesssel network (red, CD105) and Megakaryocytes (green, GPIX)

## FUTURE PLANS

In the future, we will refine the booster properties of the metal-dielectric layers by optimizing their design, complexity, and material choice. In parallel, we will combine this super-resolution approach with hyperspectral analysis to maximize aquisition speed and axial resolution without compromising lateral resolution. In the context of whole organ imaging, we will refine machine learning tools to recognize “textures” as functional units of the organ without the need of a separate color channel.

## SELECTED PUBLICATIONS


Schreiber B, Kauk M, Heil HS, Emmerling M, Tessmer I, Kamp M Höfling S, Holzgrabe U, Hoffmann C, Heinze KG. Enhanced fluorescence resonance energy transfer in G protein-coupled receptor probes by nano-coated microscopy coverslips. ACS Photonics. (2018) 5(6): 2225-2233 doi: 10.1021/acsphotonics.8b00072

Stegner D, van Eeuwijk J, Angay O, Gorelashvili M, Semeniak D, Pinnecker J, Schmithausen P, Meyer I, Friedrich M, Brede C, Beilhack A, Schulze H, Nieswandt B, and Heinze KG. Thrombopoiesis is spatially regulated by the bone marrow vasculature, Nat Commun. (2017) 8(1):127. doi: 10.1038/s41467-017-00201-7.

# Prof. Carsten Hoffmann

## GOAL

Combining high spatial and high kinetic resolution of signaling events in an imaging processes is a complicated task. Our group aims to improve genetically encoded tools to monitor receptors and signaling mechanisms “at work“ and in living cells.

## RESEARCH BACKGROUND

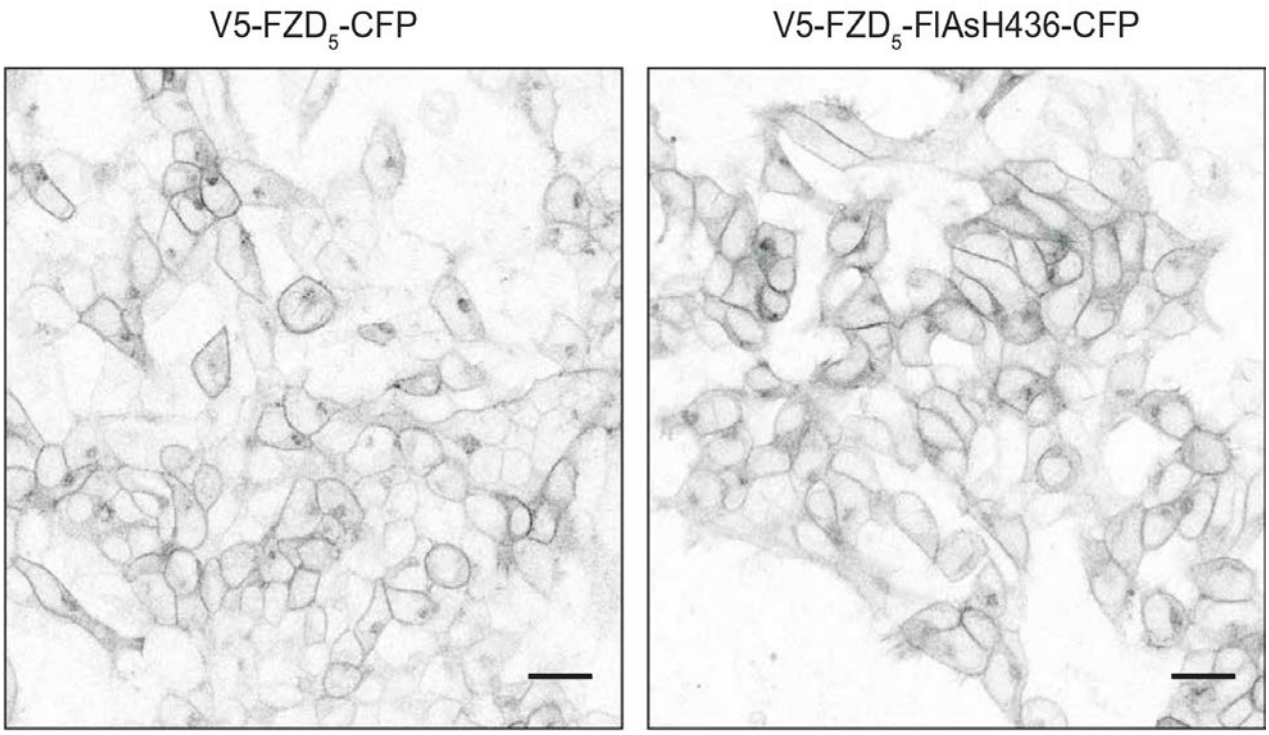
Communication between cells occurs through signaling molecules such as hormones or neurotransmitters that are recognized by specific receptors, which constitute the primary class of drug targets. We investigate their function and regulation in various model systems to explore general mechanisms and functional principles. Over the last few years, we have developed a variety of techniques to visualize receptor activation, inactivation, and the resulting signals by means of new sensors and fluorescence microscopy methods. This allows us to directly observe receptors and signaling mechanisms “at work” and enables us to analyze the speed and localization of receptor signaling in isolated cells and *in vivo*.

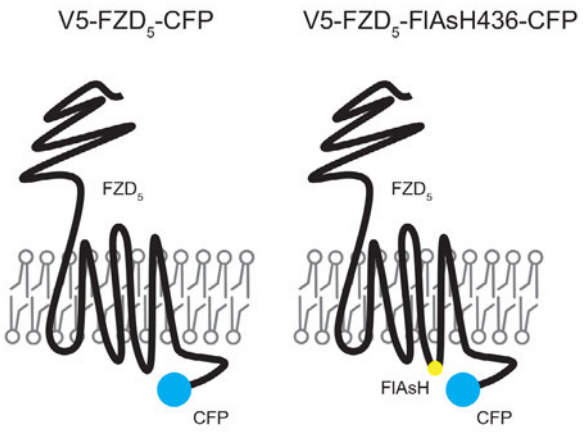
## RESEARCH HIGHLIGHTS

In 2017, together with two groups of pharmaceutical chemists lead by Prof. Ulrike Holzgrabe and Prof. Michael Decker, we were able to describe the first M1 selective muscarinic receptor ligand that can be isomerized by light between an agonist or antagonist. Such ligands are called photoswitchable ligands. They offer a new way to control receptor activity by light, and open a new field of photopharmacology. Such ligands will be helpful to study the underlying mechanisms of Alzheimer disease at a new level of precision.

In 2018, we were able to demonstrate the similarity of the molecular activation mechanisms between class A GPCRs, which mostly bind small molecules as receptor agonists and the Frizzled receptors. Frizzled receptors belong to the class of F GPCRs, and by binding “wnt” as their ligands, mediate important signaling cascades for development and cell polarity, and are also involved in cancer development. We provided detailed evidence for regular G protein coupling of Frizzled 5 receptors, and that the main activation feature of an outward movement of Transmembrane 6 is maintained in the Frizzled receptor family (Science Signaling 2018).

Together with the group of Prof. Katrin Heinze we have demonstrated that specific nano-coatings can operate as a ‘booster’ for already established microscopy techniques such as Fluorescence Resonance Energy Transfer (ACS Photonics 2018).




Top: Illustration depicting FZD5 constructs used in FRET experiments.
Bottom: Representative confocal images showing CFP fluorescence in HEK293 cells expressing FZD5-CFP or FZD5-FlAsH436-CFP. Scale bar 25 µm

## FUTURE PLANS

In 2017, Prof. Carsten Hoffmann was appointed Head of the Institute of Molecular Cell Biology in Jena. The institute aims to contribute to the understanding of the complex functioning of signaling proteins. Using biochemical, high-end microscopic approaches and techniques of cell biology or physiology, the research groups within the institute investigate molecular reactions of selected signaling proteins in correlation with the concomitant functional pattern of cells and organisms. Understanding the pathological relevance of signaling reactions is an important focus of the institute. Cellular and mice models allow insights into the molecular pathology of selected diseases. The results of these studies contribute to the development of therapeutic approaches against these diseases.

## SELECTED PUBLICATIONS

Agnetta L, Kauk M, Alonso Cañizal MC, Messerer R, Holzgrabe U, Hoffmann* C, Decker M. A photoswitchable dualsteric ligand controlling receptor efficacy. Angewandte Chemie International Edition (2017) 56 (25): 7282-7287; doi: 10.1002/anie-201701524
(*co-corresponding author)

Wright SC, Alonso Cañizal MC, Benkel T, Simon K, Le Gouill C, Matricon P, Namkung Y, Lukasheva V, König GM, Laporte SA, Carlsson J, Kostenis E, Bouvier M, Schulte G, Hoffmann C. FZD5 is a G q-coupled receptor exhibiting the functional hallmarks of prototypical GPCRs. Science Signaling (2018) 11, issue 559, eaar5536; doi: 10.1126/scisignal.aar5536

GROUP LEADERS
at the Rudolf Virchow Center

# Prof. Caroline Kisker

## GOAL

Our laboratory uses high resolution structural biology in combination with state-of-the-art biochemical and biophysical analyses to address fundamental questions in DNA repair mechanisms, the maintenance of genomic integrity, and de-ubiquitination cascades. We utilize this approach to exploit new targets for structure-based drug design to combat specific diseases.

## RESEARCH BACKGROUND

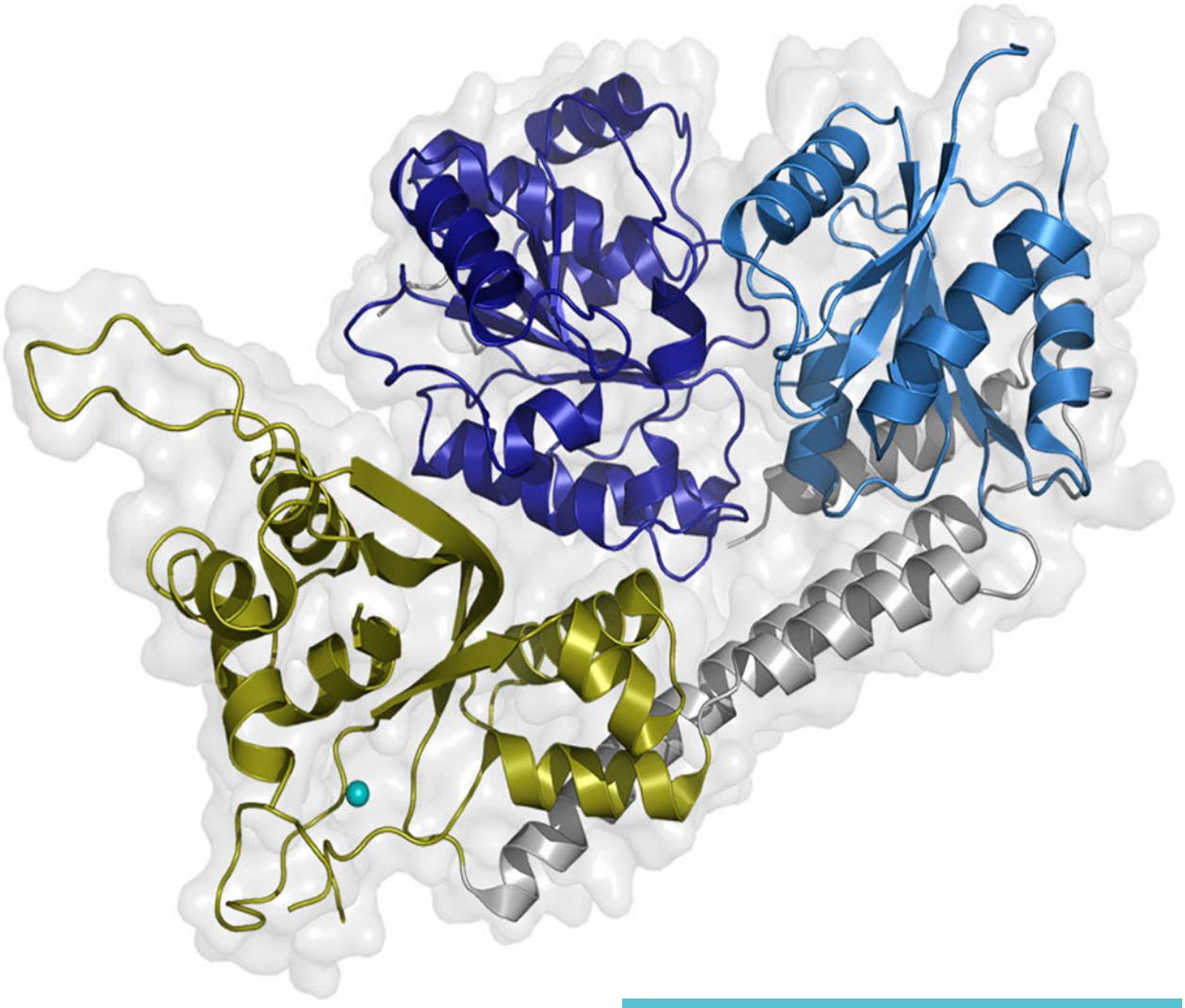
DNA is constantly damaged by endogenous and exogenous sources and it has been shown that 80 to 90% of all human cancers are ultimately due to DNA damage. Organisms thus require efficient DNA repair systems to maintain their genomes in a functional state. Nucleotide excision repair (NER) recognizes structurally highly diverse damages, and it is our goal to obtain a general understanding of the sequential process of this repair pathway and exploit its role in cancer therapy. RecQ helicases assume key functions to maintain genomic integrity and are frequently upregulated in many cancers. We investigate the intricate molecular network of RecQ4 to decipher its function and to assess it as a target for cancer therapy.

## RESEARCH HIGHLIGHTS

One major player in the NER cascade is the general transcription factor TFIIH.

TFIIH is a multiprotein complex consisting of ten subunits. We solved structures of a complex formed by the p34 N-terminal vWA and p44 C-terminal zinc binding domains. Our data reveal the presence of a redundant interaction network within core-TFIIH, which may serve to minimize the susceptibility to mutational impairment. This analysis provides first insights into why so far no mutations in the p34 or p44 core-TFIIH subunits have been identified that lead to the hallmark nucleotide excision repair syndromes xeroderma pigmentosum or trichothiodystrophy.

RecQ4 is one of five human RecQ helicases that are fundamental for genome maintenance. We solved the structure of the core RecQ4 helicase unit, revealing unique structural domains that are absent in other RecQ proteins. Combined with our functional analysis, we suggest that RecQ4 may employ a helicase mechanism that is different from that of all other human RecQ family members. Our results set the stage to examine the molecular basis of unique RecQ4 genome maintenance functions and analyse the structure-function relationship of patient mutations leading to RecQ4 associated human diseases.



Human RecQ4 helicase structure (amino acids 449-1111): Depicted in blue are the two helicase domains, hallmark structural elements that mediate ATP-driven DNA translocation. In contrast to all other RecQ family members, RecQ4 features a unique domain, the RecQ4-zinc-bidning domain (in yellow).

## FUTURE PLANS

The concepts that we have already and will continue to unveil by tackling basic research questions that elucidate mechanisms of DNA repair and maintaining genomic integrity will guide our approach towards translational aspects of these processes. We will develop pipelines for the development of new inhibitors that target specific steps in the analysed pathways. Our analysis will not only provide insights at the atomic level, but will also lead to their evaluation in appropriate animal models. Consequently, we will follow a more wholistic approach to maximize our knowledge about the important translational implications fostered by our basic research.

## SELECTED PUBLICATIONS


Radu L, Schoenwetter E, Braun C, Marcoux J, Koelmel W, Schmitt D, Kuper J, Cianférani S, Egly J-M, Poterszman A, Kisker C. The intricate network between the p34 and p44 subunits is central to the activity of the transcription/ DNA repair factor TFIIH. Nucleic Acids Res. (2017) 13;45(18):10872–83.

Kaiser S, Sauer F, Kisker C. The structural and functional characterization of human RecQ4 reveals insights into its helicase mechanism. (2017) Nat. Commun. 8, 15907.

GROUP LEADERS
at the Rudolf Virchow Center

# Dr. Sonja Lorenz

## GOAL

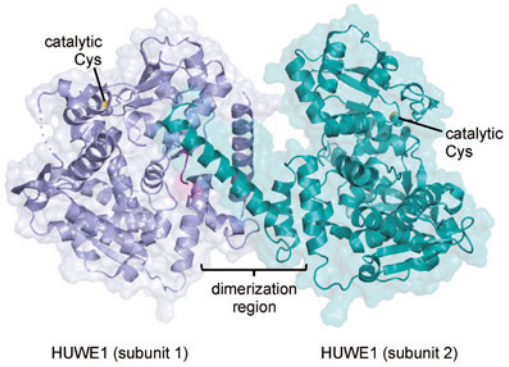
Our research group aims to decipher how ubiquitin – a single, small protein – achieves specificity in regulating all aspects of eukaryotic cell biology. We will utilize our insights to devise novel avenues towards targeting the ubiquitin system for cancer therapy.

## RESEARCH BACKGROUND

With around 1000 members in the human proteome, ubiquitin ligases are the most diverse class of ubiquitination enzymes, and provide critical specificity determinants in ubiquitin signaling. The immense potential of ubiquitin ligases as pharmacological targets is illustrated by the clinical efficacy of thalidomide and derivatives in the treatment of hematological malignancies. However, progress towards rationally manipulating ubiquitin ligases has been impeded largely by our insufficient understanding of their structural underpinnings and functional integration into cellular pathways.

## RESEARCH HIGHLIGHTS

Over the last two years our group has made significant progress in unraveling the structural basis of a particular class of ubiquitin ligases, known as HECT ligases, by interrogating their conformational dynamics, macromolecular interactions, and regulation mechanisms. A major line of our research focuses on HUWE1, a key player in diverse signaling pathways, such as cell death, proliferation, genome stability, protein quality control, and tumorigenesis. How HUWE1 accomplishes these complex physiological roles is poorly understood.
Our group described for the first time a structural mechanism of HUWE1 regulation (eLife, 2017). We discovered that HUWE1 undergoes conformational switching between an active, monomeric and an auto-inhibited, dimeric state, regulated by a sophisticated balance of intra- and intermolecular interactions. Strikingly, our studies also suggest that the tumor suppressor p14ARF stabilizes the auto-inhibited state of HUWE1, thereby providing a molecular mechanism for its inhibitory action on this ligase. Taken together, our work has important ramifications for predicting the effects of disease-associated mutations in HUWE1 and the design of pharmacological strategies targeting this ligase.
A particular personal highlight in 2017 was my acceptance into the EMBO Young Investigator Program.




Conformational switching of HUWE1, illustrated metaphorically (above) Katharina Beer (PhD student, RVZ). Crystal structure of the auto-inhibited dimeric state of the ubiquitin ligase HUWE1 (below).

## FUTURE PLANS

While the importance of allosteric mechanisms has been illustrated for multi-component RING-type ubiquitin ligases, the field of HECT ligases has lagged behind, not least because these large, single-chain enzymes are part of more dynamic macromolecular assemblies.

Our lab aims to fill this gap by systematically identifying and characterizing macromolecular complexes of HECT ligases by integrated proteomic, structural, and functional approaches. We envision these studies will transform our rather descriptive knowledge of HECT ligase functions into a 'global', mechanistic understanding of how these enzymes integrate diverse cellular signals and respond to them during homeostasis and disease.

## SELECTED PUBLICATIONS

Sander B, Xu W, Eilers M, Popov N, Lorenz S. A conformational switch regulates the ubiquitin ligase HUWE1. (2017). eLife 2017;6:e21036

Lorenz S. Structural mechanisms of HECT-type ubiquitin ligases. (2017) Biol Chem 399(2):127-145

GROUP LEADERS
at the Rudolf Virchow Center

# Dr. Hans Maric

## GOAL

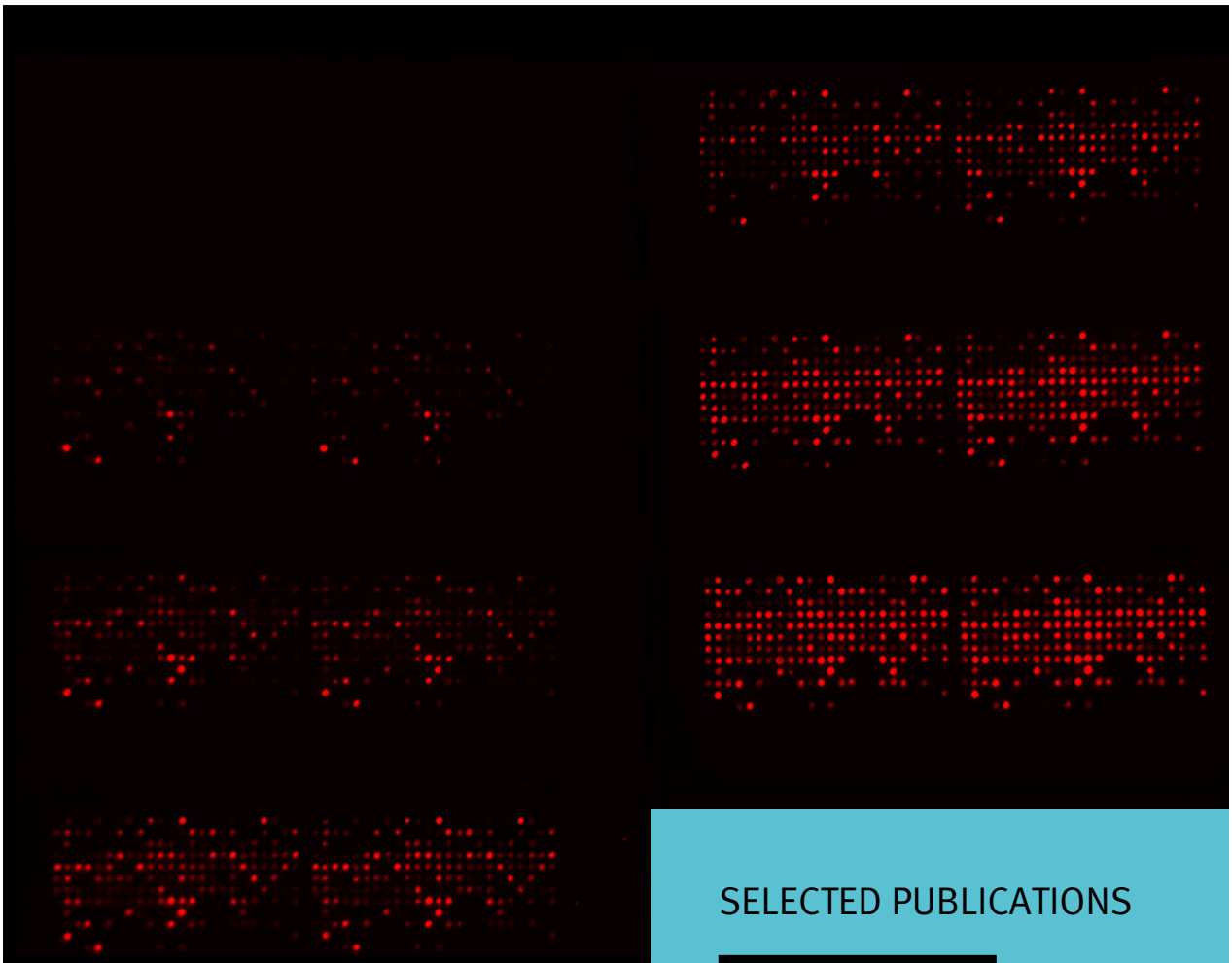
In 2018 we established a highly advanced technology setup to study the molecular action of proteins with highest throughput. Our goal is to create compact high affinity protein binders with optimal selectivity profiles, we call “Protein Super Binders” – molecules useful to uncover novel therapeutic principles and visualize healthy and pathogenic processes with molecular resolution.

## RESEARCH BACKGROUND

Proteins translate the 2D information of DNA into the 3D space of life. We decided to tackle the enormous challenge to understand their interplay on the basis of peptide microarrays that are produced by robotic systems. This technology gives us molecular-level insight into protein-protein interactions that are of fundamental importance for diverse physiological and pathological processes in the human body, such as blood coagulation, the function of the human brain, or the onset of cancer.

## RESEARCH HIGHLIGHTS

New protein targets for epilepsy treatment:
We have identified and characterized the specific interaction of two protein components of the inhibitory synapse. The corresponding mouse model of our collaborator Prof. Moss (AstraZeneca Lab, Tufts, Boston) highlighted the relevance of this interaction for the pathogenesis and treatment of epilepsy (Nature Communications 2018).
Novel fluorescent probes for high-end microscopy:
The application of conventional protein labels to high-end microscopy methods is severely limited by their comparably large size. We have shown that compact, microarray-maturated fluorescent peptides can display binding efficiencies ideal for super-resolution microscopy (Nature Chemical Biology 2017).
New strategies to target Myc for cancer therapy:
Myc proteins are transcription factors that are implicated in over half of all human cancers. Possibly due to their disordered nature, only a few of the known Myc interactors could be studied at the molecular level. We have recently described the efficient microarray-based screening and characterization of Myc interactions (Cell Reports 2018). We will use this approach to facilitate the design of first-in-class Myc-derived protein inhibitors that hold promise of revealing alternative cancer treatments.



Dose-dependent protein binding to peptide microarrays visualized by fluorescence.

## FUTURE PLANS

A distinct subgroup of protein regions function as protein binding hubs, which are of central importance in a multitude of protein-protein interaction networks, including transcriptional regulation and synapse function. These regions hold enormous and previously untapped potential for elucidating fundamental biological processes, with direct implications for human health. We will use our microarray setup to identify and evolve such functionally enriched protein regions into compact molecules with picomolar binding affinities. These molecules will have great potential as molecular probes for developing novel therapeutics, and as imaging modalities in super-resolution microscopy.

## SELECTED PUBLICATIONS


Hines R, Maric H, Hines D, Modgil A, Panzanelli P, Nakamura Y, Nathanson A, Cross A, Deeb T, Brandon N, Davies P, Fritschy J-M, Schindelin H, Moss S. Developmental seizures and mortality result from reducing GABAA Receptor 2 subunit interaction with collybistin. Nature Communications (2018) doi: 10.1038/s41467-018-05481-1

Maric* H, Hausrat T, Neubert F, Dalby O, Doose S, Sauer M, Kneussel M, Strømgaard K. Gephyrin-Binding Peptides Visualize Post-Synaptic Sites and Modulate Neurotransmission, Nature Chemical Biology (2017) doi: 10.1038/nchembio.2246
(*First authorship and shared corresponding authorship)

GROUP LEADERS
at the Rudolf Virchow Center

# Prof. Bernhard Nieswandt

## GOAL

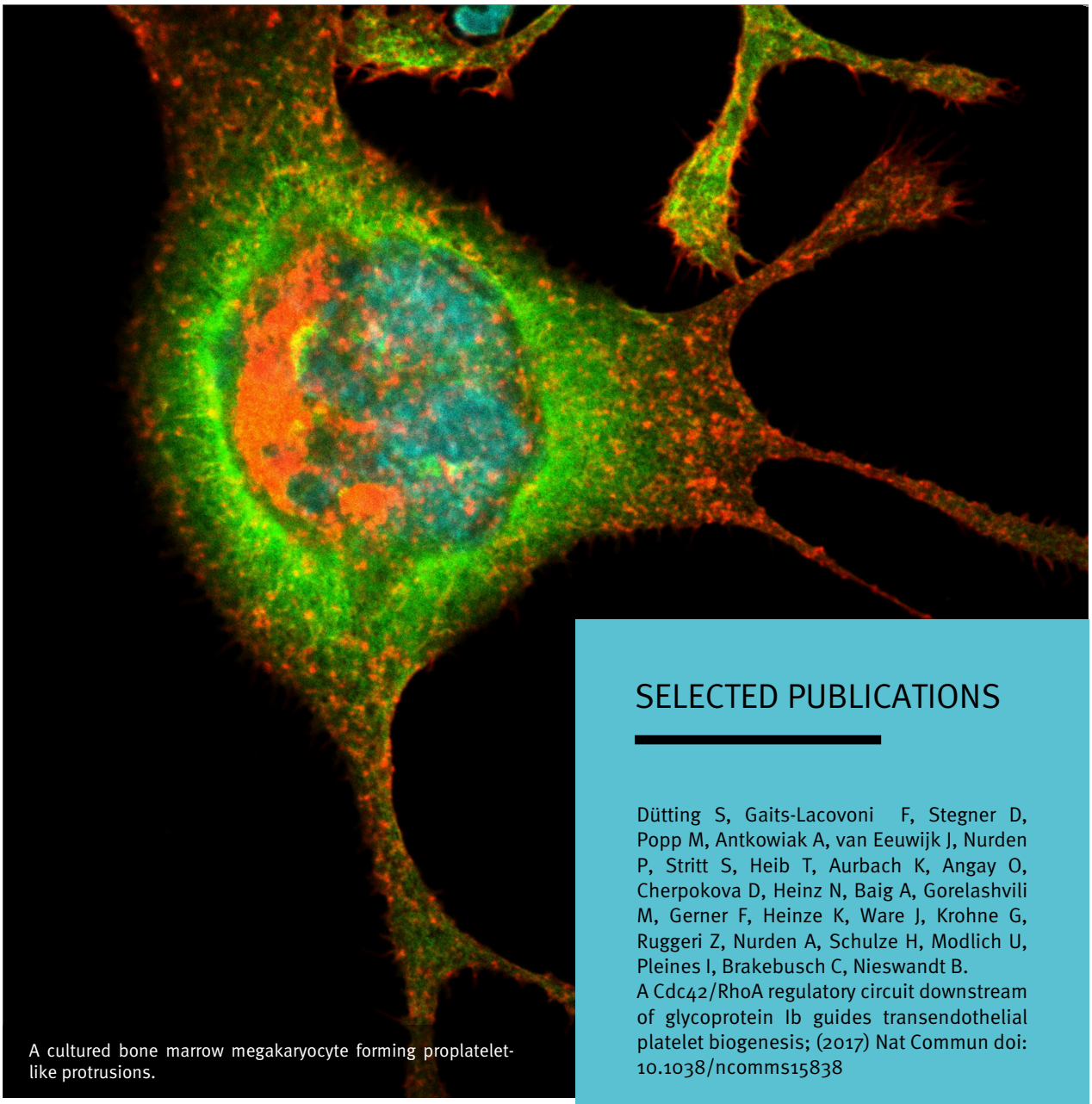
Our research focuses on the process of platelet biogenesis and the role of platelets in thrombotic and thrombo-inflammatory diseases with the aim to identify novel therapeutic targets for cardiovascular diseases. For this, we employ a combination of transgenic mouse models, cell culture systems and advanced *in vitro* and *in vivo* imaging.

## RESEARCH BACKGROUND

Platelets are produced by the megakaryocytes (MKs) in the bone marrow (BM) and are essential for hemostasis and maintenance of vascular integrity. Platelet activation at sites of vascular injury leads to the formation of a hemostatic plug, but may also result in pathological thrombus formation in diseased vessels. Inherited or acquired defects in platelet biogenesis or function can cause thrombocytopenia and bleeding. Moreover, the interaction of platelets with cells of the immune system plays a major role in systemic inflammatory reactions developing particularly under ischemic conditions.

## RESEARCH HIGHLIGHTS

Within the past two years we have obtained new insights into the complex process of platelet biogenesis. MK maturation was long thought to involve migration from a vessel-distant niche to the vessel within the BM. We could show that the niche concept is highly unlikely since, due to limited intervascular space, MKs are always in close contact with blood vessels (Nat Commun 2017a).
Mature MKs extend cytoplasmic fragments (“proplatelets”) into the blood vessel, where final platelets are shed. In another study, we investigated the mechanisms that limit transendothelial crossing of proplatelets. Our findings revealed that the small GTPases Cdc42 and RhoA act as a regulatory circuit to coordinate transendothelial platelet biogenesis *in vivo* (Nat Commun 2017b).
Finally, we arrived at novel insights into the mechanisms preventing activation of MKs. At sites of vascular injury, exposed subendothelial collagens normally trigger rapid platelet activation. We showed that newly formed platelets exhibit a selective collagen activation defect, indicating that platelet reactivity towards collagen is induced in the circulation (Blood 2018).
Our findings are of relevance not only for the *in vitro* production of platelets for transfusion medicine, but also for the treatment of inherited platelet disorders.



A cultured bone marrow megakaryocyte forming proplatelet-like protrusions.

## SELECTED PUBLICATIONS


Dütting S, Gaits-Lacovoni F, Stegner D, Popp M, Antkowiak A, van Eeuwijk J, Nurden P, Stritt S, Heib T, Aurbach K, Angay O, Cherpokova D, Heinz N, Baig A, Gorelashvili M, Gerner F, Heinze K, Ware J, Krohne G, Ruggeri Z, Nurden A, Schulze H, Modlich U, Pleines I, Brakebusch C, Nieswandt B.
A Cdc42/RhoA regulatory circuit downstream of glycoprotein Ib guides transendothelial platelet biogenesis; (2017) Nat Commun doi: 10.1038/ncomms15838

Gupta S, Cherpokova D, Spindler M, Morowski M, Bender M, Nieswandt B.
GPVI signaling is compromised in newly formed platelets after acute thrombocytopenia in mice; (2018) Blood doi: 10.1182/blood-2017-08-800136WW


## FUTURE PLANS

Led by our institute and together with the University Hospital Tübingen, the “ISAS” Dortmund, and the University of Greifswald, we established the new Collaborative Research Center (CRC/TR 240 “Platelets – molecular, cellular and systemic functions in health and disease”). The CRC/TR started its work in July 2018 with a total funding of 13.7 million Euro from the DFG.
The strength of this network is the pronounced translational character that unites cutting edge basic, translational and clinical research. The CRC will focus on mechanisms of platelet biogenesis and the role of platelets in (patho)physiological conditions beyond thrombosis and hemostasis, such as thrombo-inflammation, tissue remodelling and cancer, with the aim of developing novel treatment concepts.

GROUP LEADERS
at the Rudolf Virchow Center

# Prof. Hermann Schindelin

## GOAL

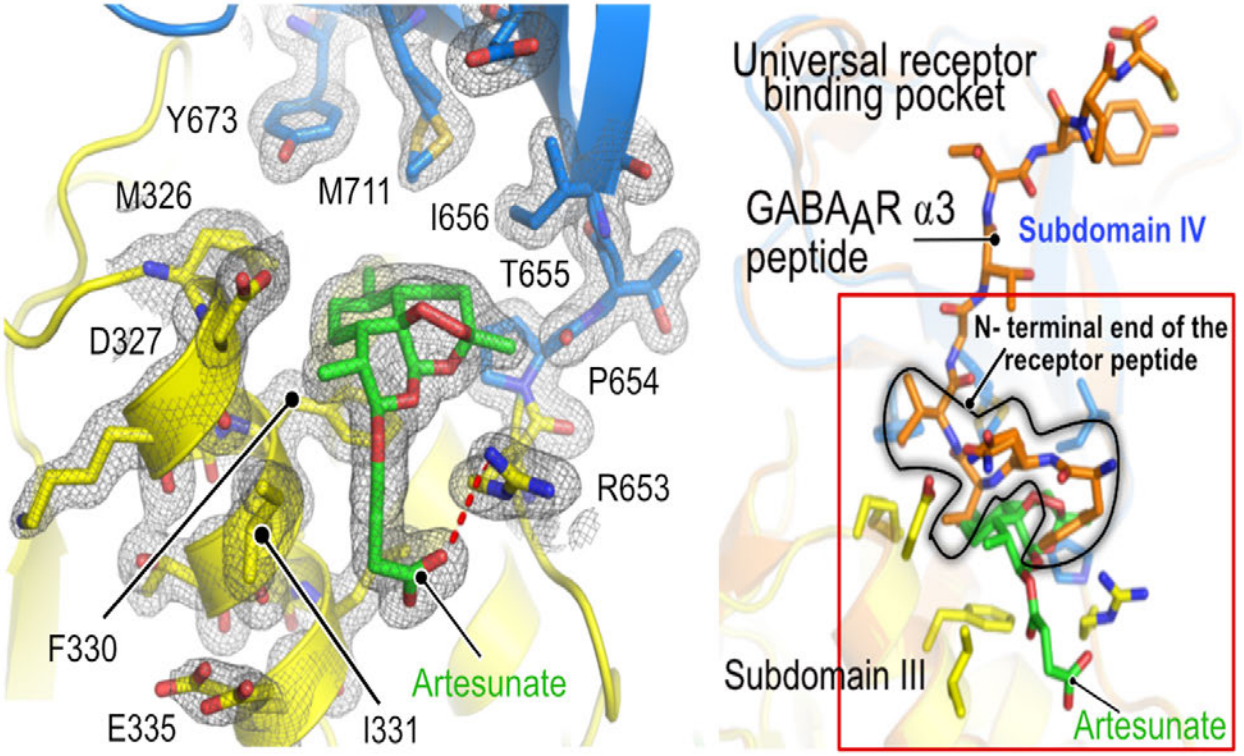
The key principle of structural biology, namely that knowledge about the three-dimensional structure of biological macromolecules provides important insights into their functions, provides the rationale for our research efforts. Our structural studies are augmented with biochemical, biophysical and cell-based experiments to derive fundamental structure-function relationships.

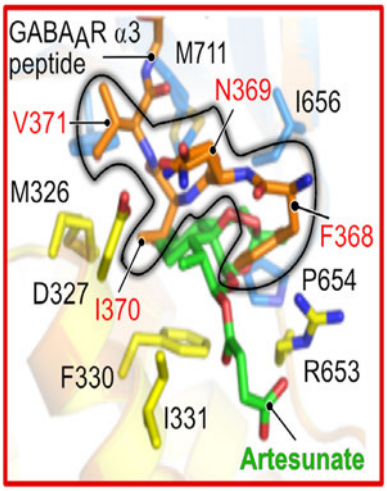
## RESEARCH BACKGROUND

Proteins carry out the vast majority of cellular functions, and a detailed mechanistic understanding of their properties is a prerequisite for understanding the molecular basis of life. Our research efforts are concentrated in two areas: (1) The modification of proteins with ubiquitin or ubiquitin-like modifiers with a focus on the activating enzymes and selected ubiquitin ligases. (2) Neuronal signal transmission via inhibitory neurotransmitter receptors such as the glycine and $GABA_A$ receptors as well as anchoring and transport of these receptors.

## RESEARCH HIGHLIGHTS

Artemisinins are traditional anti-malarial drugs and artemisinin-based combination therapies constitute state-of-the-art antimalarial drug regimens. In mammalian systems, artemisinins have also been implicated in the modulation of various cellular processes including potential anti-cancer treatments. Despite their documented and suggested therapeutic benefits, the molecular mechanism of action of these compounds has so far remained elusive. Recently, the inhibitory neurotransmitter receptor anchoring protein gephyrin was discovered to be a prime mammalian target of artemisinins prompting us to investigate this interaction in detail. Initial differential scanning calorimetry studies revealed a stabilization of the C-terminal domain of gephyrin by these molecules. High resolution crystal structures of this domain in complex with two artemisinin derivatives, artesunate and artemether, mapped the interaction at near atomic resolution. These structures present the first crystal structure of any artemisinin derivative in complex with a target protein. Interestingly, the binding pocket partially overlaps with the glycine and $GABA_A$ receptor-binding cleft in the C-terminal domain of gephyrin; hence we investigated whether artemisinins modulate inhibitory neurotransmission.




Crystal structure of the neurotransmitter-anchoring protein gephyrin in complex with the antimalarial drug artesunate.

Displacement titration calorimetry data confirmed a drug-receptor competition and electrophysiology experiments demonstrated a decrease in glycinergic neurotransmission with an obligatory dependence on gephyrin. Furthermore, confocal microscopy revealed a time-dependent regulation of receptor-gephyrin clustering in the presence of artemisinins. Thus, these data provide a comprehensive model for the regulation of inhibitory neurotransmission by artemisinins. As dysfunctional inhibitory neurotransmission contributes to severe neurological disorders such as autism, epilepsy, and also schizophrenia, these studies provide an excellent starting point for future structure-based drug discovery efforts that aim to develop novel treatment concepts (Neuron, in press).

## SELECTED PUBLICATIONS

Misra M, Kuhn M, Löbel M, An H, Statsyuk AV, Sotriffer C, Schindelin H. Dissecting the Specificity of Adenosyl Sulfamate Inhibitors Targeting the Ubiquitin-Activating Enzyme. (2017) Structure 25, 1120-1129.

Hines RM, Maric HM, Hines DJ, Modgil A, Panzanelli P, Nakamura Y, Nathanson AJ, Cross A, Deeb T, Brandon NJ, Davies P, Fritschy J-M, Schindelin H, Moss SJ. Developmental seizures and mortality result from reducing GABAA receptor 2-subunit interaction with collybistin. (2018) Nature Communications 9(1), 3130.

GROUP LEADERS
at the Rudolf Virchow Center

# Dr. Andreas Schlosser

## GOAL

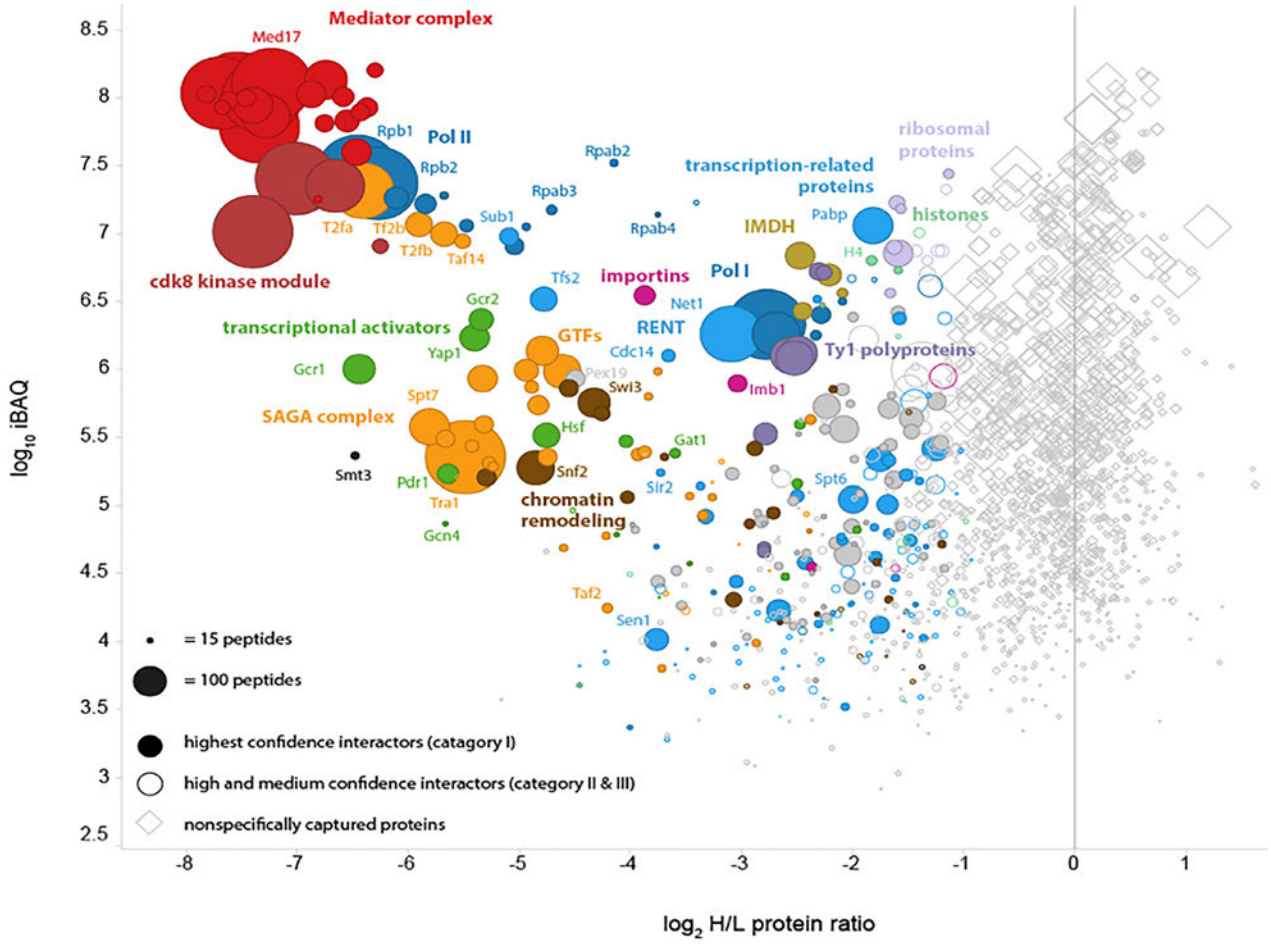
We use mass spectrometry to study protein-protein interactions, protein posttranslational modifications (PTMs), as well as neuropeptides and peptides presented to the immune system by the major histocompatibility complex (MHC peptides).

## RESEARCH BACKGROUND

Proteins typically do not act as isolated entities. In order to fulfill their cellular functions they extensively interact with other proteins, either by forming stable protein complexes and molecular machines with distinct cellular functions, such as ribosomes for translation, or by transient interactions with other proteins and protein complexes. PTMs, such as phosphorylation, acetylation, or ubiquitination, represent another important cellular way to regulate protein functions. Mass spectrometry is a versatile and powerful tool to study both protein-protein interactions and PTMs.

## RESEARCH HIGHLIGHTS

Regulation of transcription is one the most fundamental and important cellular tasks, and the Mediator complex plays a central role in transcription regulation. Its major function is to communicate regulatory signals from gene-specific transcription factors to the RNA polymerase II machinery. Since Mediator has a variety of different functions during all stages of transcription, its interactome is highly dynamic and transient. However, studying transient interactions is a major challenge, because transient protein complexes can easily dissociate during CoIP (Co-Immunoprecipitation).
We carefully optimized all steps of CoIP in order to preserve labile protein complexes during isolation. To this end, we applied cell lysis with cryogenic grinding in liquid nitrogen in a planetary ball mill, and used optimized CoIP buffer conditions with particularly low detergent concentrations. This finally allowed us to detect extraordinarily large numbers of transient interaction partners of the yeast Mediator complex, and to present the most comprehensive analysis of the yeast Mediator complex interactome to date. Our data provide clear evidence that Mediator interacts not only with RNA polymerase II, but also with RNA polymerases I, and indicates that the Mediator complex plays a functional role in rRNA processing and ribosome biogenesis.




The yeast Mediator complex transiently interacts with a large number of proteins. Besides RNA-Pol II, transcriptional activators, general transcription factor and chromatin remodeling complexes, we were able for the first time to identify RNA-Pol I as an interactor of Mediator (Figure from Uthe et al. 2017).

## FUTURE PLANS

Our group plans to perform mass spectrometry-based interactome analyses for a number of protein complexes, such as RNA Pol II, Myc, transcription elongation factors, CCR4 NOT complex, p97 and others more. In particular, we want to study how these interactomes change under different cellular conditions, e.g. different types of stress conditions. In addition, we want to compare interactomes of wild type protein and proteins bearing disease-relevant mutations, e.g. for Myc and p97. We expect that this will provide us new insights into how disease-relevant mutations lead to cellular malfunctions.

## SELECTED PUBLICATIONS


Bach M, Lehmann A, Brünnert D, Vanselow JT, Hartung A, Bargou RC, Holzgrabe U, Schlosser A, Chatterjee M. Ugi Reaction-Derived α-Acyl Aminocarboxamides Bind to Phosphatidylinositol 3-Kinase-Related Kinases, Inhibit HSF1-Dependent Heat Shock Response, and Induce Apoptosis in Multiple Myeloma Cells. J Med Chem (2017) 60:4147-4160.

Uthe H, Vanselow JT, Schlosser A. Proteomic Analysis of the Mediator Complex Interactome in Saccharomyces cerevisiae. (2017) Sci Rep. 7:43584.

# Dr. Grzegorz Sumara

## GOAL

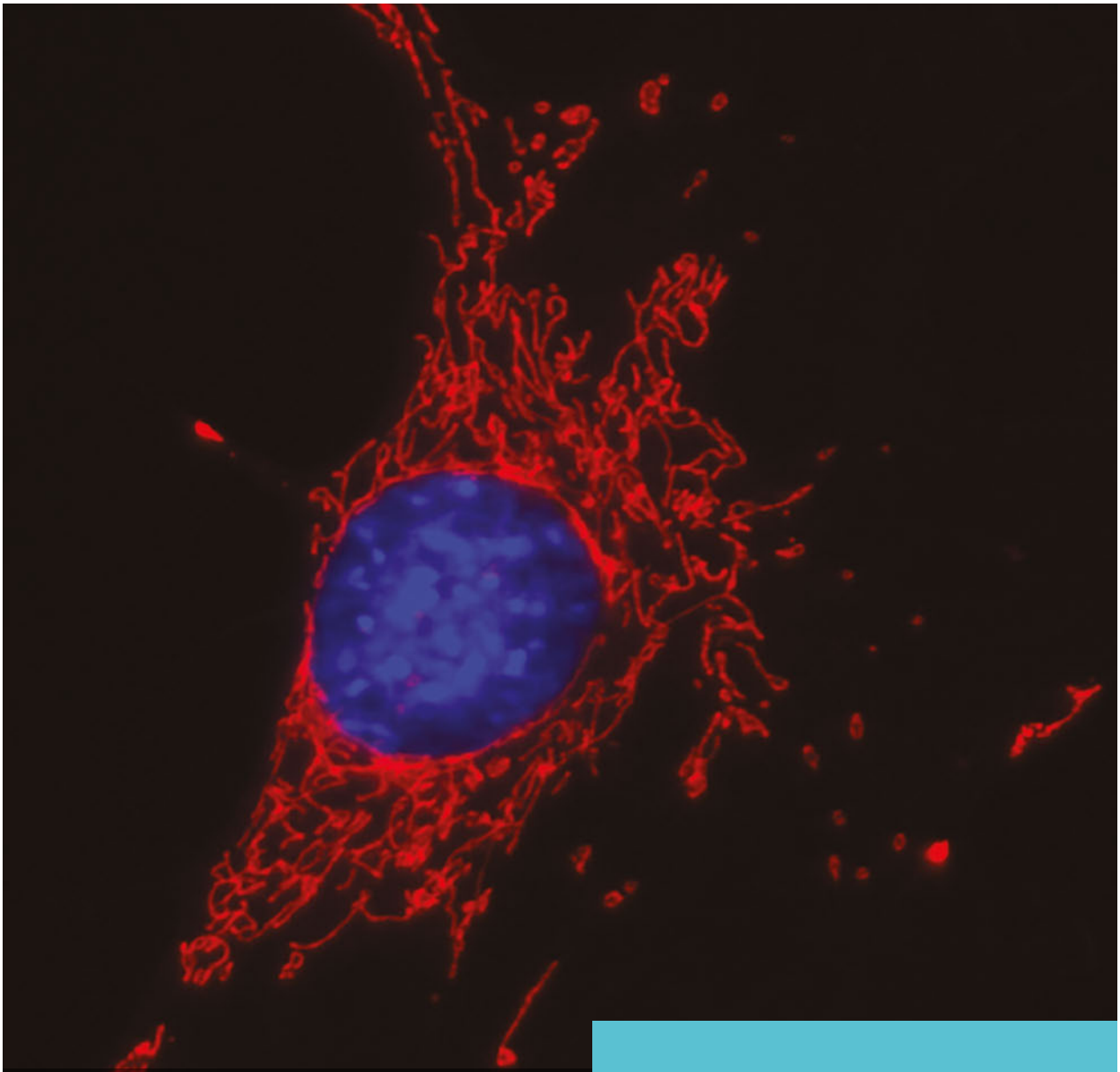
Our group aims to understand how signaling cascades regulating basic cellular processes in adipocytes and hepatocytes (lipogenesis, lipolysis, as well as nutrient utilization) contribute to the development of the spectrum of metabolic diseases such as obesity, type 2 diabetes and non-alcoholic fatty liver disease.

## RESEARCH BACKGROUND

Perturbations in signaling cascades regulating basic metabolic processes in adipocytes and hepatocytes often result in metabolic imbalance and metabolic diseases. Increased lipogenesis and lipolysis in adipocytes in combination with reduced energy dissipation are the hallmarks of obesity and type 2 diabetes (T2D). Elevated lipogenesis also contributes to the development of non-alcoholic fatty liver disease (NAFLD). My research group aims to understand the complex signaling network regulating such basic metabolic processes.

## RESEARCH HIGHLIGHTS

Nutrient overload in combination with decreased energy dissipation promotes obesity, T2D and NAFLD. Obesity results in the accumulation of diacylglycerol (DAG) in multiple organs. Members of the Protein kinase D (Pkd) family, comprising three isoforms (Pkd1, Pkd2 and Pkd3), are DAG and protein kinase C effectors that integrate multiple nutritional and hormonal inputs. We identified Pkd1 as a crucial factor promoting accumulation of lipids in adipocytes and the development of obesity and diabetes. We showed that Pkd1 promotes lipogenesis by inhibiting AMPK activity. Moreover, Pkd1 suppresses the expression of thermogenic genes as well as mitochondrial content and dynamics to reduce energy dissipation (M. Loeffler et al., EMBO J, 2018). We also demonstrated that ablation of Pkd2 in mice results in resistance to obesity and T2D. Our recent results indicate that Pkd2 drives lipid absorption in the intestine. Therefore, we hypothesize that these two closely related kinases can serve as drug targets for the treatment of obesity and obesity-related diseases. Our data indicate that the expression of Pkd3 is largely restricted to the liver. Pkd3 suppresses AKT and mTOR-dependent lipogenesis in hepatocytes and therefore protects mice from the development of NAFLD. Altogether, we showed that Pkd isoforms are central players in the development of obesity, T2D and NAFLD.



Staining for mitochondrial marker in adipocytes expressing active form of PKD1.

## FUTURE PLANS

In the future, we will combine targeted and high-throughput approaches to investigate classical (phosphorylation) and non-canonical routes (ubiquitination) of signal transduction in the regulation of lipid and glucose metabolism in adipose tissue and liver. We will also test the impact of identified signaling molecules on the development of obesity and T2D. Our research will hopefully establish new classes of molecules as potential targets for generationing anti-obesity and anti-diabetic drugs. In the long-term perspective, we plan to establish industrial collaborations around the novel drug targets identified by our research.

## SELECTED PUBLICATIONS


Löffler MC, Mayer AE, Trujillo Viera J, Loza Valdes A, El-Merahbi R, Ade CP, Karwen T, Schmitz W, Slotta A, Erk M, Janaki-Raman S, Matesanz N, Torres JT, Marcos M, Sabio G, Eilers M, Schulze A, and Sumara G. Protein kinase D1 (PKD1) deletion in adipocytes enhances energy dissipation and protects against adiposity. EMBO Journal (2018) ahead of print

Cai K, El-Merahbi R, Löffler M, Mayer A, Sumara G. Ndrg1 promotes adipocytes differentiation and sustains their function. Scientific Reports (2017) 7(1):7191. doi: 10.1038/s41598-017-07497-x

ASSOCIATED GROUP LEADER
at the Rudolf Virchow Center

# Dr. Ingrid Tessmer

## GOAL

Our goal is to elucidate the mechanisms of DNA processing systems. We study protein-protein and protein-DNA interactions involved in DNA repair and replication processes using single molecule atomic force microscopy.

## RESEARCH BACKGROUND

Our work aims at understanding general and specific features of DNA damage recognition strategies in different DNA repair systems and different kingdoms of life. In our studies, we use single molecule imaging by atomic force microscopy (AFM) imaging combined with other biophysical and biochemical approaches. In collaborations, we also study protein interactions involved in DNA replication initiation to gain insights into the mechanistic regulation of eukaryotic DNA replication.

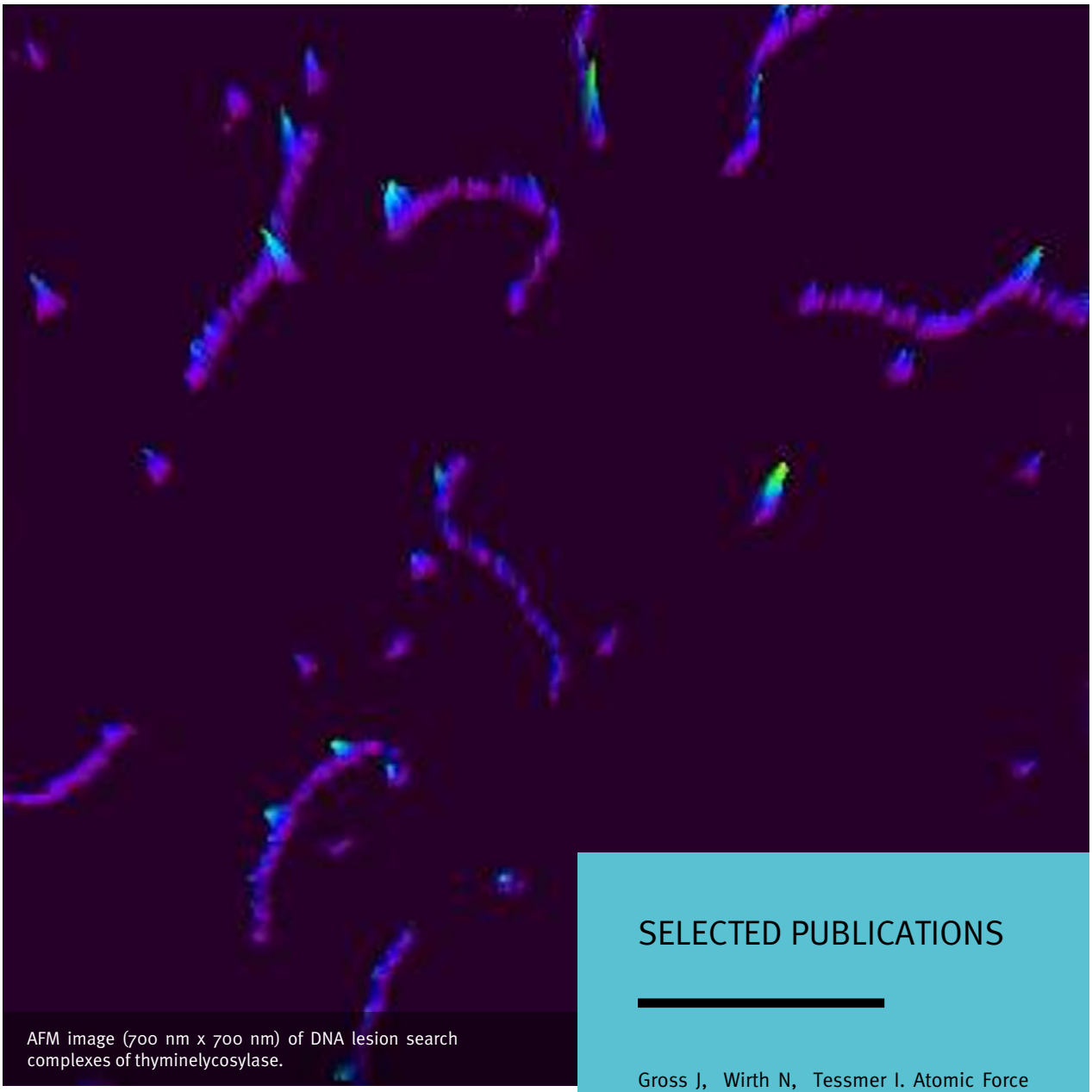
## RESEARCH HIGHLIGHTS

In recent work, we were able to characterize target site recognition strategies of the eukaryotic nucleotide excision repair (NER) helicase XPD and to establish important differences between XPD and its bacterial homolog UvrB.

In collaboration with Prof. F. Grosse's laboratory at the Leibniz Institute on Aging in Jena, we investigated the loading of single stranded DNA (ssDNA) binding protein RPA by Cdc45 in human replication.

Simian virus 40 (SV40) provides a simplified model for eukaryotic replication. We started an exciting new collaboration with Prof. H.P. Nasheuer's laboratory at the University of Galway, Ireland, to study RPA interactions with the SV40 large T antigen replication helicase.
We also recently established a highly interesting collaboration with the laboratory of Dr. Reinhard Kalb at the University of Würzburg on structural and functional aspects of disease-relevant mutations in RPA.

In addition, we were able to secure new funding from the DFG for a period of three years.



AFM image (700 nm x 700 nm) of DNA lesion search complexes of thyminelycosylase.

## FUTURE PLANS

O6-alkyl-guanine DNA alkyltransferase (AGT) repairs alkyl lesions in DNA. AGT homologs, the alkyltransferase-like proteins (ATLs), exist in many organisms. Based on their high structural similarity, it is interesting to compare lesion search and recognition by AGT and ATL. Based on our work on the glycosylases TDG and hOGG1, we have previously proposed an initial lesion sensing mechanism for glycosylases To test the general applicability of this initial lesion-sensing step in base excision repair, we will investigate and compare DNA conformations at target lesions in the absence of protein, and within the relevant glycosylase complex for a range of diverse BER lesions and glycosylases, using AFM and FRET.

## SELECTED PUBLICATIONS


Gross J, Wirth N, Tessmer I. Atomic Force Microscopy Investigations of DNA Lesion Recognition in Nucleotide Excision Repair; J Vis Exp. (2017) doi: 10.3791/55501

Szambowska A, Tessmer I, Prus P, Schlott B, Pospiech H, Grosse F. Cdc45-induced loading of human RPA onto single-stranded DNA; Nucleic Acids Research (April 2017) doi: 10.1093/nar/gkw1364

ASSOCIATED GROUP LEADERS
at the Rudolf Virchow Center

# Dr. Ann Wehman

## GOAL

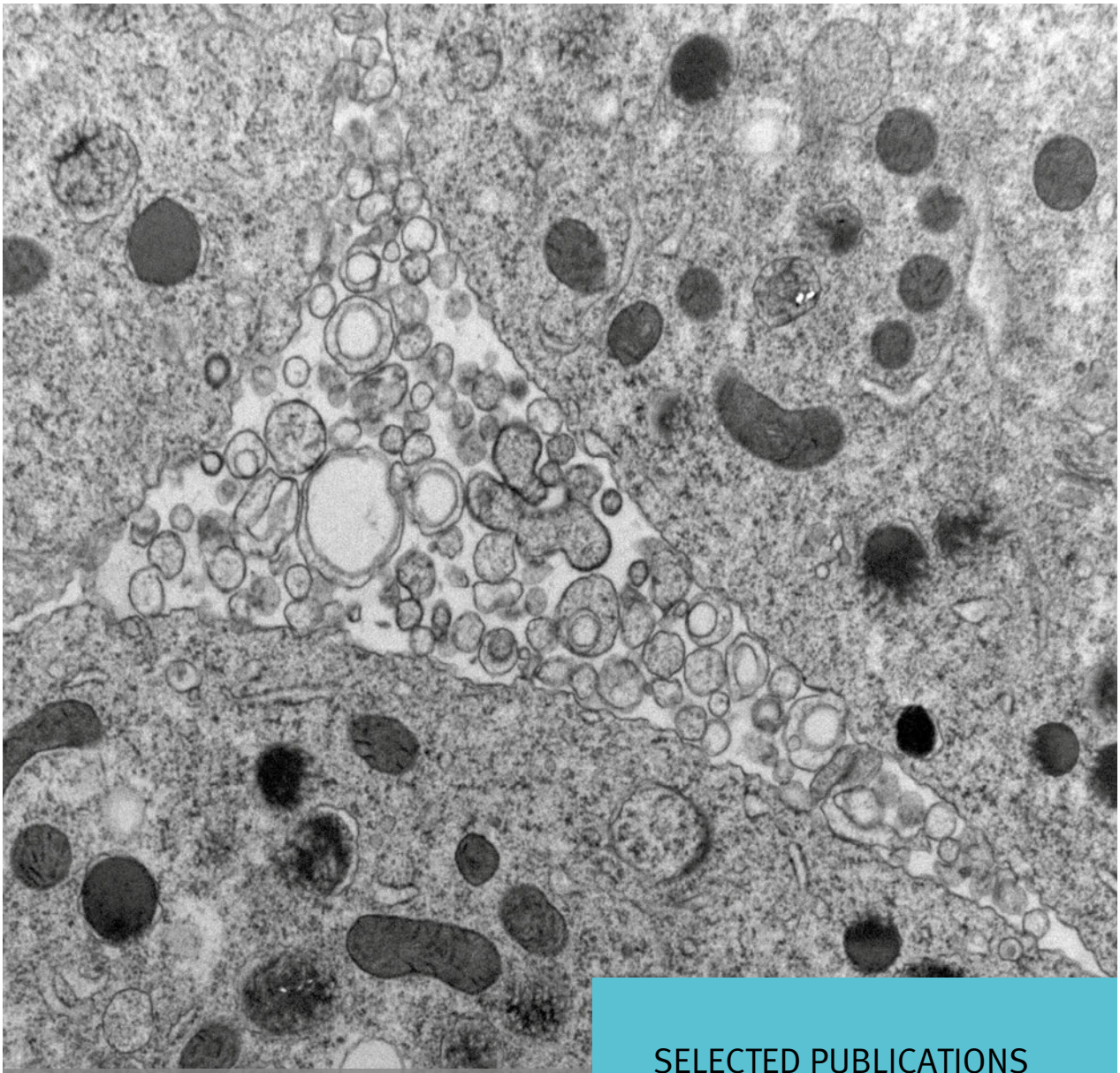
Extracellular vesicles are membrane-wrapped fragments of cells that contribute to disease as well as to normal development and homeostasis. Our lab uses genetic and imaging approaches to understand how extracellular vesicles are released, how they signal to neighboring cells, and how they are cleared from the cellular environment.

## RESEARCH BACKGROUND

Extracellular vesicles are released by all cells, from bacteria to humans. They remodel cell membranes after injury and send signals between cells. Extracellular vesicles in body fluids provide biomarkers and these vesicles can be used for drug delivery. Despite their many roles, the mechanisms underlying their formation, function, and clearance are unclear. We established a model for plasma membrane budding to release extracellular vesicles centered around the phospholipid flippase TAT-5. Our lab also discovered that extracellular vesicles are cleared by LC3-associated phagocytosis.

## RESEARCH HIGHLIGHTS

To define how extracellular vesicles are released, we developed degron-based reporters to label extracellular vesicles, since no existing markers distinguished them from cells. Degron tags cause proteins in the cytosol to be degraded, while proteins released in extracellular vesicles are protected from degradation. Using degron reporters, we discovered new regulators of extracellular vesicle release, many of which help traffic TAT-5 to the plasma membrane. The novel PAD-1 protein is required for TAT-5 lipid flippase activity (PNAS 2018). This work uncovered redundant intracellular trafficking pathways and pinpointed TAT-5 as a key regulator of plasma membrane budding.
Our lab also revealed novel insights into phagosome maturation during extracellular vesicle clearance (Comm Int Biol 2017) and phagosome resolution during necrotic corpse clearance (Cell Reports 2018). Using degron reporters, we discovered that the autophagy protein LC3 expedites degradation of the corpse membrane inside the phagolysosome. We also revealed that corpse degradation is facilitated by mTOR-dependent tubulation of phagolysosomes into smaller vesicles. These insights into LC3-associated phagocytosis are important to understand and avoid autoimmune reactions to cell debris.



Extracellular vesicles released between *C. elegans* cells (TEM)

## FUTURE PLANS

Our lab is developing new degron reporters to facilitate further studies on extracellular vesicle release and the clearance of cell debris. We are determining the mechanisms of TAT-5 trafficking and extracellular vesicle release. We are also testing the role of extracellular vesicle release during cell division, which would establish a critical function for vesicle budding during development and homeostasis. Finally, we are determining the mechanisms of programmed necrosis and the role of lipid asymmetry in phagocytosis.

## SELECTED PUBLICATIONS


Beer K, Rivas-Castillo J, Kuhn K, Fazeli G, Karmann B, Nance J, Stigloher Ch, Wehman A. Extracellular vesicle budding is inhibited by redundant regulators of TAT-5 flippase localization and phospholipid asymmetry; Proc Natl Acad Sci U S A (2018) doi: 10.1073/pnas.1714085115

Fazeli G, Stetter M, Lisack J, Wehman A. C. elegans blastomeres clear the corpse of the second polar body by LC3-associated phagocytosis; Cell Reports (2018) doi: 10.1016/j.celrep.2018.04.043


INFRASTRUCTURE

# STATE-OF-THE-ART

Key research infrastructures established in our research groups include a wealth of technologies for structural biology, as well as for imaging in the life sciences. Here is an overview of the research technologies available at the Rudolf Virchow Center.

## STRUCTURAL BIOLOGY

### Böttcher, Kisker & Schindelin Group

The structural biology research groups at the RVZ use state-of-the-art X-ray crystallographic technologies to determine the three-dimensional structures of biological macromolecules. Another approach to arrive at three-dimensional models of biological macromolecules is the application of cryo electron microscopy, for which an extremely powerful cryo EM has recently become available.

## IMAGING

### Heinze Group

The Heinze group develops and advances fluorescence microscopy from macro to nano, from single molecule to whole organ imaging. This includes fluorescence enhancement for super-resolution imaging by optoplasmonics and biocompatible nanocoatings, as well as light-sheet and computational approaches for quantitative imaging.

## MOUSE TECHNOLOGIES

### Nieswandt, Sumara & Friedmann Angeli Group

The use of mouse models is an indispensable tool to validate the physiological and pathophysiological role of proteins under normal and disease conditions. The RVZ mouse facility uses state-of-the-art transgenic mouse technologies in accordance with the highest animal welfare standards to enable translational approaches in biomedicine. Animal models are used in research projects of scientists at the RVZ on cardiovascular and metabolic diseases, as well as on controlled cell death.

## MASS SPECTROMETRY

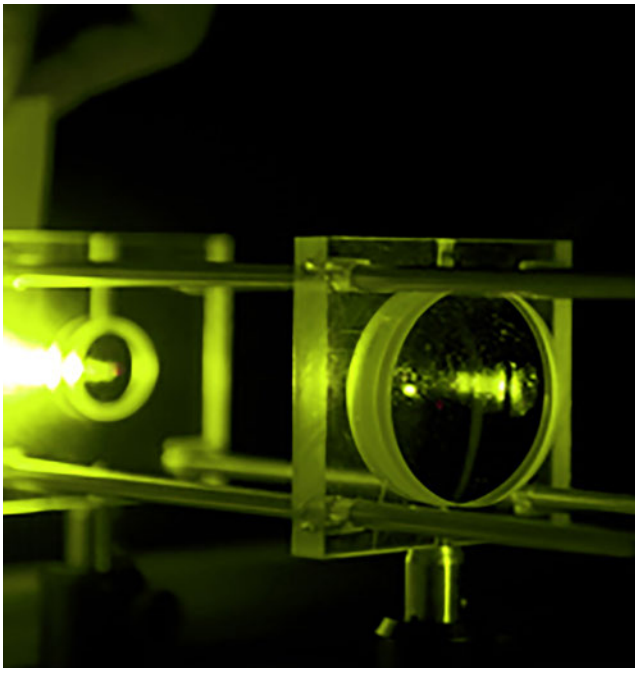
### Schlosser Group

The Schlosser group develops new and improved methods for the analysis of peptides and proteins. This research group is focused on the analysis of posttranslational modifications (PTMs), such as phosphorylation, ubiquitylation or acetylation, the analysis of protein interactomes as well as the analysis of neuropeptides and MHC peptides.

## PEPTIDE SYNTHESIS AND MICROARRAYS

### Maric Group

Hans Maric has been setting up a high throughput pipeline for the parallel synthesis and purification of up to 1536 small proteins, peptides and peptidic compounds, in nanogram to gram scales. Chemical modifications of the synthesized molecules with functional groups make them highly versatile tools for numerous applications including imaging and immobilization. The peptides and expressed proteins are immobilized in a femtomolar scale on solid surfaces using automated printers. These libraries are used to screen, identify or quantify protein-protein interactions in high throughput assays with low sample consumption.



INFRASTRUCTURE

# SUPPORT

The research infrastructure at the Rudolf Virchow Center is also available to researchers outside the Center. The Rudolf Virchow Center contributes to life on campus by providing space, infrastructure and personnel for the organization of major scientific events* such as symposia, on-site evaluations of new research initiatives and festivities, as well as space and technical support for the end-of-term exams in the medical study program.



*Selected major scientific events on page 66 (Appendices)

## LARGE SCALE PROTEIN EXPRESSION

The recombinant protein expression facility provides support regarding the production of specific target proteins, especially if they cannot be produced in the standard expression system *E. coli*. Services include cloning into appropriate expression vectors, expression in the desired system, analysis of the expression and optionally purification of the protein. Several expression systems and methods are available.

11
EXTERNAL USERS

62
EXTERNAL RUNS

4400
HOURS USED

## IMAGING

The RVZ imaging unit run by Katrin Heinze offers advanced light microscopy approaches ranging from superresolution to whole organ imaging. Besides STED, two-photon and light sheet microscopy, these include video and confocal fluorescence microscopy, as well as all state-of-the-art fluorescence techniques such as FRET, FLIM, FRET and FCS.

36
EXTERNAL USERS

1480
EXTERNAL RUNS

3709
HOURS USED

## MASS SPECTROMETRY

The technology platform mass spectrometry and proteomics, headed by Andreas Schlosser, offers a wide range of methods to all institutes of the University of Würzburg. Major applications are the identification of protein interactions and of cellular drug targets, the analysis of posttranslational modifications, such as acetylation, ubiquitylation or phosphorylation, as well as the identification of neuropeptides and MHC peptides. The technology platform is equipped with two state-of-the-art nanoLC-coupled Orbitrap mass spectrometers.

25
EXTERNAL USERS

8000
EXTERNAL RUNS

16000
HOURS USED

ANNUAL EVENT

# RVZ RETREAT

The annual RVZ retreat has always been among the most important joint activities of all research groups at the Rudolf Virchow Center. The retreat is an ideal opportunity for new group leaders and their doctoral students to introduce themselves and their research projects in an informal way outside the regular RVZ setting. It also encourages all attending scientists to take a step back from their daily routine and immediate needs of the projects they are involved in to appreciate the broader framework of research going on at the Rudolf Virchow Center. Being together as a group and physically away from the Center, even only for one or two days, has always been a scientifically and socially rewarding experience with many new ideas for ongoing and future research projects and new collaborations.

# SELECTION OF ACHIEVEMENTS IN 2017 & 2018
of RVZ lab members

## LORENZ LAB

**Anna Liess*** won a poster prize @ EMBO meeting "Modularity of signaling proteins and networks" 2018
**Rahul Nair*** received a Youth Travel Award from FEBS
**Lena Ries*** was awarded the Kekule PhD fellowship by the Fonds der Chemischen Industrie (2014-2017)
**Barbara Orth*** was selected for the EMBO YIP PhD Course in Heidelberg (2018)

## WEHMAN LAB

**Gholamreza Fazeli**** was awarded a DFG grant in collaboration with Christian Stigloher at Biocenter (2018-2021)
**Katharina Beer*** received a talk award at the RVZ retreat 2018
**Alida Melse**° won a scholarship from the DAAD RISE program (Summer 2018)
**Jaime Lisack**° was awarded a scholarship from the Fulbright program (2016-2017)

## SUMARA LAB

**Alexander E Mayer*** Best oral presentation Award at 3rd Central European Biomedical Congress
**Jonathan Trujillo Viera*** Best oral presentation Award at 3rd Central European Biomedical Congress
**Jonathan Trujillo Viera*** 1st prize for the best PhD talk during the RVZ retreat 2018
**Till Karwen*** 3rd prize for the best poster during the RVZ retreat 2018

## SCHINDELIN LAB

**Philipp Mostosi**°° received a GdCH 'Analytical Chemistry' travel stipend
**Andrea Thorn**** organized the first European Crystallographic Computing Forum in Mieres, Spain and was invited to give the keynote lecture for this year's Gordon Research Seminar in Diffraction Methods
**Anabel Pacios Michelena*** & **Aparna Pottikkadavath*** were awarded the PhD Fellowships of the GSLS

## NIESWANDT LAB

**Isabelle Becker*, Julia Volz*** and **Vanessa Klaus*** were awarded PhD Fellowships from the GSLS
**Katja Aurbach*** won the poster prize at the SFB 688/DZHI Joint Symposium in Würzburg (October 2017)
**Vanessa Klaus*** won the 1st poster prize at the EUREKA Symposium 2018 in Würzburg (October 2018)
**Sarah Beck*, Inga Scheller*** and **Katja Aurbach***, were awarded in total four GSLS Travel Fellowships
**Inga Scheller*** received a fellowship for the course "Navigate your career! CG-UNICA Joint Training Workshop for PhD candidates" from the GSLS (October 2017)
**Isabelle Becker*, Sarah Beck*, Inga Scheller*, Julia Volz*** and **Markus Spindler*** received Young Investigator Awards at the 2017 ISTH-International Society on Thrombosis and Haemostasis Congress in Berlin
**Julia Volz*** and **Yvonne Schurr*** received Young Investigator Award at the ECTH - European Congress on Thrombosis and Haemostasis in Marseille (October 2018)

## HEINZE LAB

**Hannah Heil*** won a poster prize in 2018 and "best student talk" prize at the RVZ retreat 2017 & 2018

## KISKER LAB

**Dr. Daniel Grabarczyk**** was awarded a DFG grant to support his own research work
**Theresa Klemm*** received a poster award at the RVZ Retreat 2018

° Bachelor Intern; °° MSc student; * PhD student; ** Postdoc

VIRCHOWLAB

# 10TH ANNIVERSARY

When the Rudolf Virchow Center welcomed 30 tenth graders for the first time in its laboratories in July 2008, nobody assumed that this would be the first chapter of a remarkable success story. Since then, 5,592 students from 33 schools have taken the opportunity to gain an insight in research topics of biology, biochemistry and biomedicine. The focus of the Virchowlab has always been on practical experience: After a half-hour introduction to the topic and a short safety instruction, pupils go straight to the lab to carry out experiments until the afternoon. At the end of the day they present their results and discuss them in the group. The concept was initiated by the Public Science Center to inspire young people about science. The organizers also see their commitment as an investment in the future, as life sciences are currently developing rapidly. One example is the CRISPR/Cas method. Anyone who wants to have a say and to be able to correctly assess the opportunities and risks of such trends, should do so with sufficient background knowledge. The Virchowlab provides a realistic insight into such crucial topics of the future.

# SCIENCE FOR SOCIETY

The Public Science Center (PSC) is an independent division at the Rudolf Virchow Center. It fosters dialog between science and society by sharing the research work of the Rudolf Virchow Center with the public.
A variety of public activities are offered for childreen and adults throughout the year.
Since 2008 school kids can visit Rudis Forschercamp or/and Virchowlab to conduct experiments in the teaching laboratoy. Rudis Forschercamp is designed for the age group 8 to 12 years, and offers exciting hands-on experiments in biology, medicine, chemistry and physics on weekday afternoons. Due to the high demand the waiting list is long and currently requires a reservation one and a half years in advance. By now, Rudis has attracted well over 1000 school children since its start in 2004.
The Virchowlab aims at high school students and celebrated its 10th anniversary in July 2018 (more on page 52).
The PSC is also engaged in public outreach by communicating with the media and organising public events. The latest research results are regularly published in press releases on the website, in various social media channels and via an extensive network of journalists.
The Center is also involved in external scientific communication, for example related to the visit of guest speakers and events.

## HIGHLIGHTS

After completing the “Web-Refresh” project by the University of Würzburg, it was time to move the 10 year old RVZ website to the University page. In June 2018 the launch of the new website was announced: www.uni-wuerzburg.de/rvz. The new website now offers comprehensive information about the Rudolf Virchow Center and its current research activites. The PSC page lists all activities that are happening throughout the year and offers various materials to download. To attract highly qualified applicants, the job offer page has been renamed “Jobs and Career” and provides an overview of the infrastructure at the RVZ and the University.
On October 3rd 2018 the PSC encouraged conversations about biomedical sciences by opening the doors to the public as part of the ”Sendung mit der Maus WDR Türöffner-Tag”. School children had the chance to see and perform experiments in our labs. Their parents took the opportunity to visit the labs and ask our scientists many questions about their research. A similar interaction was also offered as part of the “Rudis Ferien-Forschercamp” (Rudis summer holiday camp) in early August 2017 and 2018.
The Public Science Center published 16 press releases about new research findings (publications) and developments at the RVZ.


UNIVERSITÄT WÜRZBURG
WELTOFFEN.
INNOVATIV.
LEISTUNGSSTARK
AUS TRADITION.
10th Anniversary 2016


Rudolf Virchow Center
for Experimental Biomedicine
UNIVERSITÄT WÜRZBURG
WELTOFFEN.
INNOVATIV.
LEISTUNGSSTARK
AUS TRADITION.
10th Anniversary 2016
Graduate Schools
Life Sciences
Humanities
Science & Technology
>1100 Doctoral Researchers
>1600 Peer Reviewed Publications
>600 Current Projects
>600 Dissertations
>40 Nationalities


Rudolf Virchow Cente
for Experimental Biomedi

# An exceptional panel discussion with and for young researchers

Opening speech from the JMU president Prof. Alfred Forchel

## 15 YEARS RUDOLF VIRCHOW CENTER

A quarter of a century of science was celebrated on October 14th, 2016 at the Rudolf Virchow Center: 15 years of the Research Center for Experimental Biomedicine and 10 years of the University of Würzburg Graduate Schools (UWGS).

The Rudolf Virchow Center and the UWGS both have a keen focus on young scientists and their professional development. Against this backdrop a slightly unusual discussion with the title “Future Science?!” took place, in addition to several scientific lectures and keynote speeches.

Unlike in normal disussions, where young researchers typically raise their questions from the back rows of the auditorium, this time they moved to center stage and got the chance to sit next to experts on the podium. Politicians of the Bavarian State Parliament (Oliver Jörg, Verena Osgyan and Georg Rosenthal) and decision makers from various types of universities and other institutions in society (Prof. Robert Grebner, Prof. Andrea Szczesny, Prof. Reinhard Jahn and Max-Martin Deinhard) responded to their questions. Moderator Prof. Enrico Schleiff (University of Frankfurt/Main) was on the spot to intervene or rephrase questions in case some of the experts answered evasively - or he spontaneously asked knowledgeable people in the auditorium for their expert assessment.

The audience was keen to hear honest and clear answers to some of the most pressing questions of young people in academia: Is the shortage of permanent positions in the German academic system perceived by decision makers? And do they consider this a problem? Is the strict separation between universities and non-university institutions sustainable? Or: How to prevent the brain drain at German universities?

Using Twitter #WissZu2016, about 250 listeners in the audience were also able to raise their questions during the discussion, with moderator Schleiff immediately passing them on to the panel of experts.

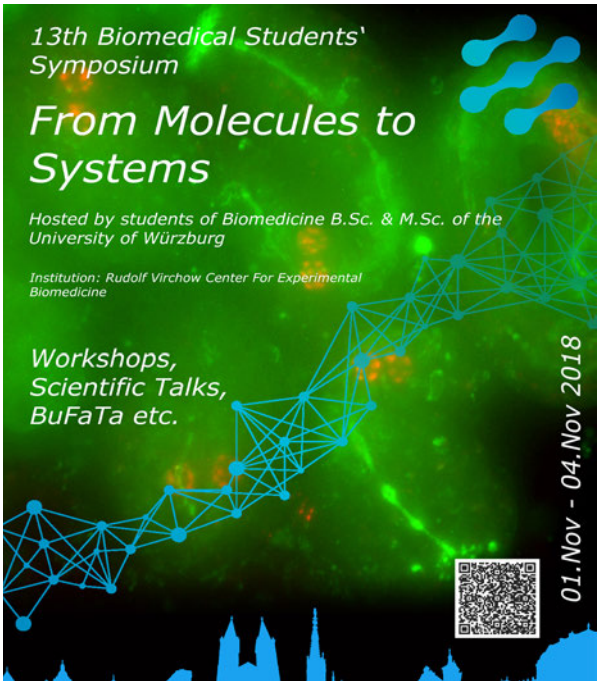
“Young scientists need to abandon their perception of having only junior status and actively advocate their interests at the universities as well as in politics,” recommended Professor Sibylle Baumbach (University of Innsbruck) at the end of her keynote speech.

# BSc / MSc programs in Biomedical Sciences

## BACKGROUND

The Faculty of Medicine and the Faculty of Biology of the University of Würzburg offer a joint program in Biomedicine, where students are trained at the interface between classical natural sciences and clinical research.
The program was initiated as part of the aim of the RVZ to foster the training of future generations of scientists. Several RVZ groups still provide key teaching modules.
The core curriculum consists of research-oriented training with intensive laboratory courses in small groups and early immersion in current research topics. Additional internships in individual work groups guarantee efficient and productive projects that conclude with the final Bachelor or Master thesis.
While the Bachelor curriculum is tightly structured, students are rather free to set their own priorities in the Master program, which includes a comprehensive course on model organisms throughout the first semester. A special feature of the Biomedicine program is the high number of students who choose practical courses abroad, sometimes for several months. Students use this opportunity to widen their scientific and personal horizons.

Dean of Studies Professor Manfred Gessler (second from left) with students




## HIGHLIGHTS

The students have established a very active student representation that closely interacts with local and national student bodies.
They organized the participation in the international iGEM (international Genetically Engineered Machine) contest and coordinated several local student activities. Supported by the Dean of Studies, Professor Manfred Gessler (Chair of Developmental Biochemistry), they also hosted the 13th Biomedical Students' Symposium at the beginning of November 2018 with several talks and 21 workshops attracting over 200 participants.
There is a great demand for the 35 study places in the BSc program as well as the 16 places in the MSc program. Most of the graduates opt for further scientific qualifications through a PhD degree, about 40% of them in Würzburg, while the remaining graduates chose other institutions in Germany or abroad.
There are additional programs in Biochemistry (BSc/MSc) and Translational Medicine (degree courses and MSc within the Elite Network of Bavaria) with contributions from several groups at the RVZ. These studies focus either on the molecular and functional understanding of basic processes of life, or the transition between basic research and clinical studies and application.

# Graduate School of Life Sciences

## BACKGROUND

The Graduate School of Life Sciences (GSLS) is a joint initiative of the Faculties of Biology, Medicine, Chemistry & Pharmacy, Physics and Human Sciences (Psychology). The school was founded in 2003 and operates under the umbrella of the University of Würzburg Graduate Schools (UWGS). The school's concept won support from the Excellence Initiative of the German Federal and State Governments in 2006 and 2012.

The GSLS is an interdisciplinary research training platform, comprises five thematic sections (Biomedicine, Clinical Sciences, Infection & Immunity, Integrative Biology, Neuroscience) and offers a three-year doctoral study program. Currently, more than 600 doctoral researchers from 46 countries and more than 250 principal investigators contribute to the interdisciplinary and international spirit of the GSLS. A core element of structured doctoral training in the GSLS is the three-person thesis committee that identifies individual elements of training ("prescription") depending on the doctoral student's background and goals. Each participant can choose from a wide spectrum of seminars, lectures, scientific training and transferable skills courses, all taught in English.

The Doctoral Students' Symposium "EUREKA 2018" in the Rudolf Virchow Center

New GSLS building between Campus Hubland North and South

For medical students, the GSLS offers a structured and research-oriented doctorate to foster closer integration of basic medical research and patient care. In the MD/PhD program, candidates who have already obtained a medical degree can obtain a doctoral degree in the natural sciences (Dr. rer. nat). Among the research institutions contributing to the GSLS doctoral progam is the Rudolf Virchow Center with its Virchow Graduate Program. The central element of the Virchow Graduate Program is the doctoral students' afternoon at the annual Rudolf Virchow Center retreat where all new doctoral students introduce themselves and their projects. Historically, the Virchow Graduate Program was the nucleus of the GSLS and served as a role model for the entire graduate school training concept.

## HIGHLIGHTS

After several years in the RVZ/IMIB building on the medical campus, the GSLS has moved into a new building on the northern part of Campus Hubland. Funding for the new building was granted by the Federal State of Bavaria after the successful proposal of the GSLS in the second round of the Excellence Initative (2012).

One of the most prominent GSLS activities is the annual Doctoral Students' Symposium entirely organized by the GSLS doctoral students themselves. This 2-day event comprises talks by distinguished national and international speakers, talks by student speakers, a poster session as well as an image and essay writing contest. In 2017 and 2018, the symposium took place again with more than 200 participants. As in the years before, the venue of the symposium was the Rudolf Virchow Center, highlighting the close collaboration between the Center and the GSLS.

RVZ ANIMAL FACILITY

# INSIGHT INTO ANIMAL RESEARCH

The Rudolf Virchow Center focusses on basic and translational research, combining structural biology, mouse models, advanced imaging techniques, systems biology, and clinical research expertise.

The RVZ research group for Vascular Biology, for example, uses genetically modified mouse strains with defined changes in surface receptors and adaptor proteins to study platelet adhesion and activation processes. This group aims to develop novel treatment concepts for thrombo-inflammatory and malignant disorders.

By being more open about our animal research, we want to ensure that the layperson has accurate and up-to-date information about what animal research involves. We particularly want to explain the role animal research plays in the overall process of scientific discovery and the development of novel treatments for major public health issues such as cardiovascular disorders and diabetes.

Guided by our Animal Facility Manager, the Rudolf Virchow Center now offers regular tours through the animal research facility (picture right). Visitors get first-hand information about how research involving animals is regulated in Germany and the EU, and what our researchers and animal caretakers do to promote animal care and welfare in the Rudolf Virchow Center.

Visitors in the RVZ animal facility (2018)

# APPENDICES
## Annual Report 2017 & 2018

## RVZ GUEST SPEAKERS

| | | |
|---|---|---|
| 12.01.2017 | Prof. Dr. Oliver Daumke,<br>MDC Berlin | "Structure, function and mechanisms of dynamin superfamily proteins." |
| 26.01.2017 | Prof. Dr. Volker Doetsch,<br>BMLS Frankfurt | "2 Inactive 4 Destruction - Quality Control in Oocytes by p63" |
| 09.02.2017 | Prof. Dr. Ralf Seidel,<br>Universität Leipzig | "Insight into protein mechanisms - one molecule at a time" |
| 13.04.2017 | Dr. Rose E. Goodchild,<br>VIB-KU Leuven Center | "Torsins link an evolutionary conserved mode of lipid regulation with neurological disease" |
| 08.06.2017 | Prof. Emile van Schaftingen,<br>Institute de Duve, Brüssel | "Metabolite repair, a neglected but essential aspect of intermediary metabolism" |
| 22.06.2017 | Dr. Helmut Pospiech<br>Leibniz-Institut für Alternsforschung | "Understanding tumourigenesis of hereditary breast cancer" |
| 06.07.2017 | Prof. Florence Niedergang,<br>Institut Cochin Paris | "Macrophages under normal or virus-infected conditions, emergence of opportunistic bacterial infections" |
| 21.09.2017 | Dr. Santiago Costantino,<br>Université Montréal | "Optical labeling and manipulation of live single cells" |
| 02.11.2017 | Dr. Martin Oheim,<br>Université Paris Descartes | "The heat is on: Shorter pulses and lower average laser power reduce photodamage during two-photon imaging ..." |
| 23.11.2017 | Prof. Thomas Schmidt,<br>Leiden University | "Mechano-chemical coupling in pancreatic ductal adenocarcinoma" |
| 18.01.2018 | Dr. Christoph Müller,<br>EMBL Heidelberg | "Molecular mechanisms of RNA polymerase I and III transcription" |
| 25.01.2018 | Prof. Juri Rappsilber,<br>TU Berlin | "Structural systems biology by cross-linking/mass spectrometry - emerging prospects" |
| 01.02.2018 | Prof. George Garinis,<br>University of Crete | "DNA damaging responses in aging" |
| 22.03.2018 | Prof. Sander Kersten,<br>Wageningen University | "Molecular regulation of metabolism by fatty acids" |
| 12.04.2018 | Prof. Ivan Dikic,<br>Goethe University Frankfurt | "Ubiquitin and Autophagy Networks in Health and Disease" |
| 19.04.2018 | Dr. Coen Paulusma,<br>Academic Medical Center, Amsterdam | "Contribution of P4-ATPases to the inflammatory response and degra dation of pathogens" |
| 26.04.2018 | Dr. Bernardo Franklin,<br>University of Bonn | "Regulation of inflammasome activity by platelets" |
| 11.06.2018 | Dr. Simona Polo,<br>University of Milan | "Insights into HECT Ub ligases: catalysis, regulation and inhibition" |
| 21.06.2018 | Dr. Stefan Kubicek,<br>Austrian Academy of Sciences | "Targeting cell identity with small molecules" |
| 28.06.2018 | Prof. Matthias Weiss,<br>University of Bayreuth | "Exploring cellular dynamics from molecules to embryos" |
| 09.07.2018 | Prof. Michael Rape,<br>UC Berkeley | "The other code: roles of ubiquitin in neuronal development and neurodegeneration" |
| 12.07.2018 | Prof. Pete Cullen,<br>University of Bristol | "Mechanistic insight into endocytic cargo recycling: implications for human disease" |
| 27.08.2018 | Prof. Natalia Jura,<br>University of California, USA | "Multimerization and allostery in control of phosphorylation" |
| 08.11.2017 | Prof. Simon Tuck,<br>UCMM Schweden | "Phospholipid translocase function in ciliated neurons" |
| 06.12.2018 | Dr. Alexandros Vegiopoulos,<br>Deutsches Krebsforschungszentrum | "Metabolic stem cell responses and the plasticity of fat" |
| 13.12.2018 | Prof. Margaret Stratton,<br>University of Massachusetts USA | "Understanding the molecular determinants of memory formation" |

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## SELECTED MAJOR SCIENTIFIC EVENTS IN THE BUILDING WITH RVZ SUPPORT (2017 & 2018)

- On-site evaluation SFB-TR 124 pathogenic fungi (Feb. 2017)
- GSLS welcome week (Apr. 2017, March 2018)
- Status meeting clinical research group „Sphingolipids“ (Jun. 2017)
- 94. Annual congress of the „Vereinigung der Bayerischen Chirurgen“ (19.-21.7.2017)
- On-site evaluation SFB-TR 255 Biofabrication (Sept. 2017)
- SFB 688/DZHI joint symposium (4.-6.10.2017)
- GSLS symposium EUREKA (10.-12.10.2017/2.-4.10.2018)
- GSLS interview days (Nov. 2017)
- On-site evaluation SFB/TR 240 platelets (27.-28.02.2018)
- On-site evaluation FOR XYZ Prof. Dölken (16.11.2018)
- Forum medical dissertation projects (21.6.2018, 22.11.2018)
- Forum practical year for medical students (18.10.2018)
- 40 years anniversary chair child and adolescent psychiatry (Oct. 2018)
- Exhibition on construction work on medical campus (23.-26.11.2018)

## MAJOR COLLABORATIVE RESARCH GRANTS

European Regional Development Fund (Europäischer Fond für Regionale Entwicklung (EFRE)): Translational Network For Research In Thrombo-Inflammatory Diseases

Marie Sklodowska-Curie Innovative Training Network (ITN): Targeting Platelet Adhesion Receptors in Thrombosis (TAPAS)

DFG Research Training Group (GRK) UBI 2243: Understanding Ubiquitylation: From Molecular Mechanisms To Disease

DFG Collaborative Research Centre (Sonderforschungsbereich) Transregio 240: Platelets – Molecular, Cellular and Systemic Functions in Health and Disease

DFG Collaborative Research Centre (Sonderforschungsbereich) Transregio 166: High-end Light Microscopy Elucidates Membrane Receptor Function - Receptor Light

DFG Collaborative Research Centre (Sonderforschungsbereich) Transregio 124: Pathogenic Fungi and their Human Host: Networks of Interaction - FungiNet

# RVZ (PUBLIC SCIENCE CENTER) PRESS RELEASES

**2017**

Ubiquitous and influential [02/15/2017]

Cellular waste management: how animal cells protect themselves against dangerous goods [03/20/2017]

Regulation of blood coagulation: Molecular switches guide blood forming cells [06/15/2017]

Guardian of the genome: Structure of key enzyme decoded [07/05/2017]

The dense vessel network regulates formation of thrombocytes in the bone marrow [07/25/2017]

Herz-Kreislauf-Erkrankungen besser verstehen und versorgen [10/12/2017]

Besondere Auszeichnung für Sonja Lorenz [10/24/2017]

Professor Harald Schulze erhält Preis für herausragende Hämophilie-Forschung [11/14/2017]

**2018**

Correspondence between cells is strictly regulated [02/02/2018]

Protein controls clumping of platelets during thrombosis and stroke [03/19/2018]

New research group at the Rudolf Virchow Center [04/04/2018]

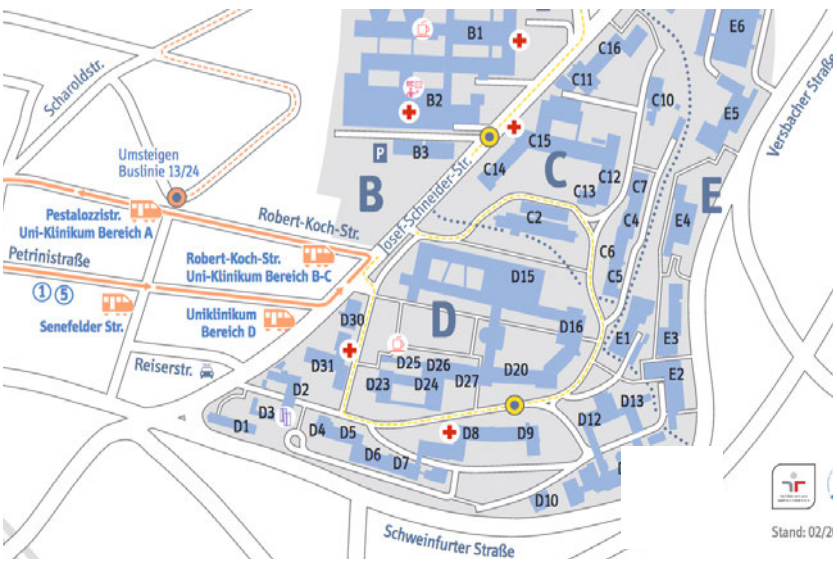
Forbidden FRET situations on wafer-thin gold [04/09/2018]

Young embryo devours dangerous cell [05/16/2018]

Targeting platelets [05/24/2018]

The school laboratory as a success story [08/13/2018]

# LOCATION

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