ANNUAL REPORT
2019-2020

RUDOLF VIRCHOW CENTER

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Rudolf Virchow Center for Integrative and Translational Bioimaging

Julius-Maximilians-Universität Würzburg

CONTENT

ABOUT THE RUDOLF VIRCHOW CENTER

FOR INTEGRATIVE AND TRANSLATIONAL BIOIMAGING

In 2001 the German Research Foundation (DFG) started funding for the first three Centers of Excellence. The University of Würzburg was successful with its application to establish the Rudolf Virchow Center (RVZ) as a biomedical research institution that uses state-of-the-art technologies to investigate the causes of human diseases at the molecular level.

To meet growing requirements for office and laboratory space, in October 2009 the RVZ 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.

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

In 2020 the name of the RVZ was modified to reflect a development in the Center's overall scientific focus. The Rudolf Virchow Center for Experimental Biomedicine became the Rudolf Virchow Center for Integrative and Translational Bioimaging. The Center combines the development and improvement of imaging techniques with the investigation of biomedical problems over a wide range of complexity and scale — from individual atoms up to entire organ systems.

EDITORIAL

The Rudolf Virchow Center for Integrative and Translational Bioimaging (RVZ) is a central player in the biomedical research community 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, life sciences have progressed enormously, both conceptually and with respect to applied technologies. State-of-the-art imaging now offers unprecedented insights at the molecular and even atomic level to explore the causes of disease.

Scientists at the Rudolf Virchow Center use a broad spectrum of methods to investigate biomolecules that are causally related to human health and disease at different levels of organization.

Continuing along the lines of Rudolf Virchow's visionary ideas, research at the RVZ is guided by the principle that malformation of single structures or misregulation of interactions between biomolecules can lead to pathophysiological conditions and finally to a diseased organism. Therefore, knowledge about protein function and structure is the basis for developing therapeutic interventions.

RVZ research focuses on mechanistic functions of key biomolecules, both from a basic research perspective and for translational approaches to develop novel therapeutic compounds and strategies, accounting for the significance 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 these areas 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 at these and other research institutions at the University of Würzburg and the University Hospital.

The last two years have been full of exciting developments for the Center. Some highlights will be presented in more detail below, together with snapshots of ongoing research projects of all the research groups of the Center, the activities of the Public Science Center, the Biomedicine study program associated with the Center, and the interactions with the Graduate School of Life Sciences at the University of Würzburg.

Above all, the RVZ has re-defined its overall orientation and has moved biomedical imaging with all its facets into the center stage. This is reflected in the new name "Center for Integrative and Translational Bioimaging". In May 2020, the University officially passed and announced the new bylaws for the Rudolf Virchow Center.

As part of this realignment, a new executive board was elected. The current members of the RVZ Executive Board are Caroline Kisker, Bernhard Nieswandt and Markus Sauer. With the executive board member Markus Sauer, who also chairs the Department of Biotechnology and Biophysics at the campus Hubland, even closer ties between the RVZ and the Biocenter have been established.

The Rudolf Virchow Center recruited a new junior research group leader in June 2020. Dr. Tamara Girbl, an Austrian molecular biologist, joined us from the Institute of Science and Technology Austria. Tamara works on the interactions between immune cells and blood vessels to better understand autoimmune diseases, myocardial infarction, and stroke.

In addition, Katrin Heinze was promoted to a W3 professor in Molecular Microscopy, stressing the importance of imaging technologies at the Rudolf Virchow Center.

At this point, we would also like to express our gratitude to all the RVZ staff whose great commitment has made it possible to maintain research activities even under difficult pandemic conditions.

PROF. CAROLINE KISKER
Director and speaker of the
Rudolf Virchow Center

PROF. BERNHARD NIESWANDT
Director of the
Rudolf Virchow Center

PROF. MARKUS SAUER
Director of the
Rudolf Virchow Center

TODAY

RUDOLF VIRCHOW CENTER

FOR INTEGRATIVE AND TRANSLATIONAL BIOIMAGING

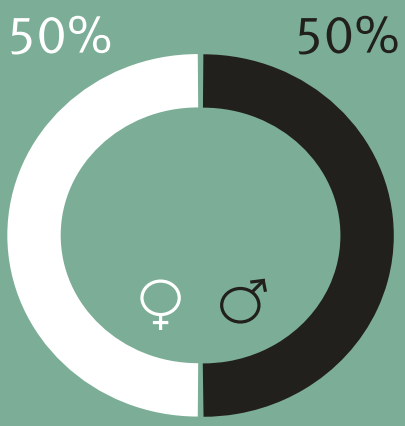
About 160 scientists work at the Rudolf Virchow Center. Our research groups use a wide range of visualization technologies to pinpoint the causes of disease by deciphering disease mechanisms at the molecular and cellular level.

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

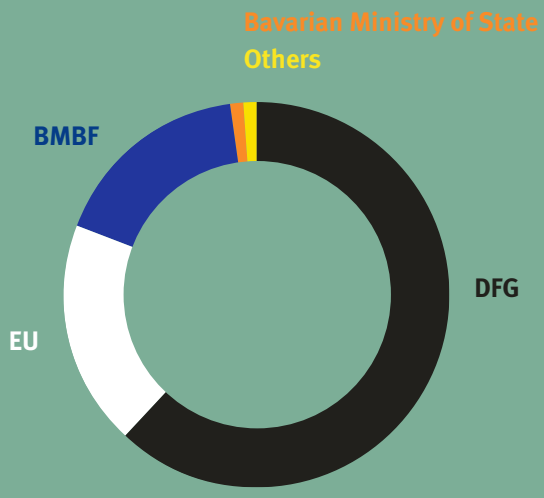
FACTS & NUMBERS

169
STAFF AT THE RVZ
(DEC 2020)

20
PHD GRADUATIONS



RVZ GROUP LEADERS
(Dec 2020)



EXTERNAL FUNDING
2019 & 2020

INTERNATIONAL DIVERSITY OF RVZ STAFF

- India (9)
- China (6)
- Brazil (4)
- Great Britain (3)
- Poland (3)
- Bulgaria (2)
- Italy (2)
- Austria (1)
- Colombia (1)
- Cuba (1)
- France (1)
- Greece (1)
- Hungary (1)
- Iran (1)
- Israel (1)
- Kazakhstan (1)
- Lebanon (1)
- Mexico (1)
- New Zealand (1)
- Russia (1)
- Switzerland (1)
- Taiwan (1)
- USA (1)
- Zimbabwe (1)

INDIVIDUAL GRANTS

19x DFG Research Grants
2x DFG Emmy Noether Groups
1x European Regional Development Fund
1x European Research Grant
(ERC Starting Grant)
1x EMBO young investigator
1x BMBF Grant

COLLABORATIVE GRANTS

1x EU Innovative Training Network
3x DFG Collaborative Research Centers
(including 1 RVZ coordination)
1x DFG Research Training Group
1x Elite Network of Bavaria

DEVELOPMENTS

Exciting developments have taken place at the Rudolf Virchow Center in the last two years. The RVZ has developed into the Center for Integrative and Translational Bioimaging. New scientists have joined the Center and new research projects have started. The following pages summarize some of these developments.

NEW GROUP LEADER

Tamara Girbl started her junior research group.

NEW W3 PROFESSOR

Katrin Heinze was appointed Professor for Molecular Microscopy.

NEW RVZ BOARD MEMBER

Markus Sauer joined the RVZ Executive Board.

NEW DFG PRIORITY PROGRAM

Pedro Friedmann Angeli and others established a new DFG Priority Program.

THE RUDOLF VIRCHOW CENTER (RVZ)
for Integrative and Translational Bioimaging

The RVZ is an interdisciplinary research center at the University of Würzburg (JMU) and focuses on the visualization of biomedical scenarios from the subnano to the macro scale. Researchers at the RVZ work together to solve the puzzle presented in health and disease. Thus, we target protein structures, their biomolecular functions and their impact in the cellular and organismic setting to elucidate disease-relevant states as the essential starting point of any therapeutic intervention.

Research groups at the RVZ collaborate closely with JMU researchers from the natural sciences departments and researchers at the Medical Faculty and the University Hospital Würzburg.

Imaging technologies are essential to reach our goals, and can be understood as a direct continuation of the scientific vision of Rudolf Virchow, the eminent 19th century pathologist who introduced the concept of cellular pathology in 1855. Virchow's idea that cells are the smallest functional entities of living matter, yet also the origin of disease, was a major stepping stone in groundbreaking biomedical insights. Virchow's success also relied on technological inventions and rapid progress in constructing and manufacturing microscopes, which enabled the visualization of tissues and individual cells.

Biomedical sciences have progressed tremendously since the pioneering work of Rudolf Virchow, and nowadays we can investigate biomedical problems over a wide range of complexity and scale — from entire organ systems down to individual atoms.

The 21st century view of live processes, in both healthy and diseased states, requires advanced visualization and quantification techniques at all levels: atomic, molecular, cellular, tissue and organismic. In particular, the development and improvement of low-invasive fluorescence imaging techniques in recent years has revolutionized our understanding of cellular processes. Modern high-end fluorescence microscopy methods offer whole-organ imaging at subcellular resolution and routinely go beyond the classic resolution limit. These refined imaging technologies provide insights into the molecular architecture of cells and the dynamics of molecular assemblies and their interactions.

At the same time, the resolution revolution in electron cryomicroscopy (cryo-EM) has paved the way to visualize complex molecular machines with unprecedented atomic or near atomic detail.

The RVZ is "integrative" in its approach of visualizing elementary processes across scales, thereby embracing many different imaging and spectroscopic methods, which can be combined or used complementarily (see Fig. 1). The RVZ with its broad, well-balanced biomedically and technologically driven research groups is an ideal place for such endeavors, where scientists from different disciplines

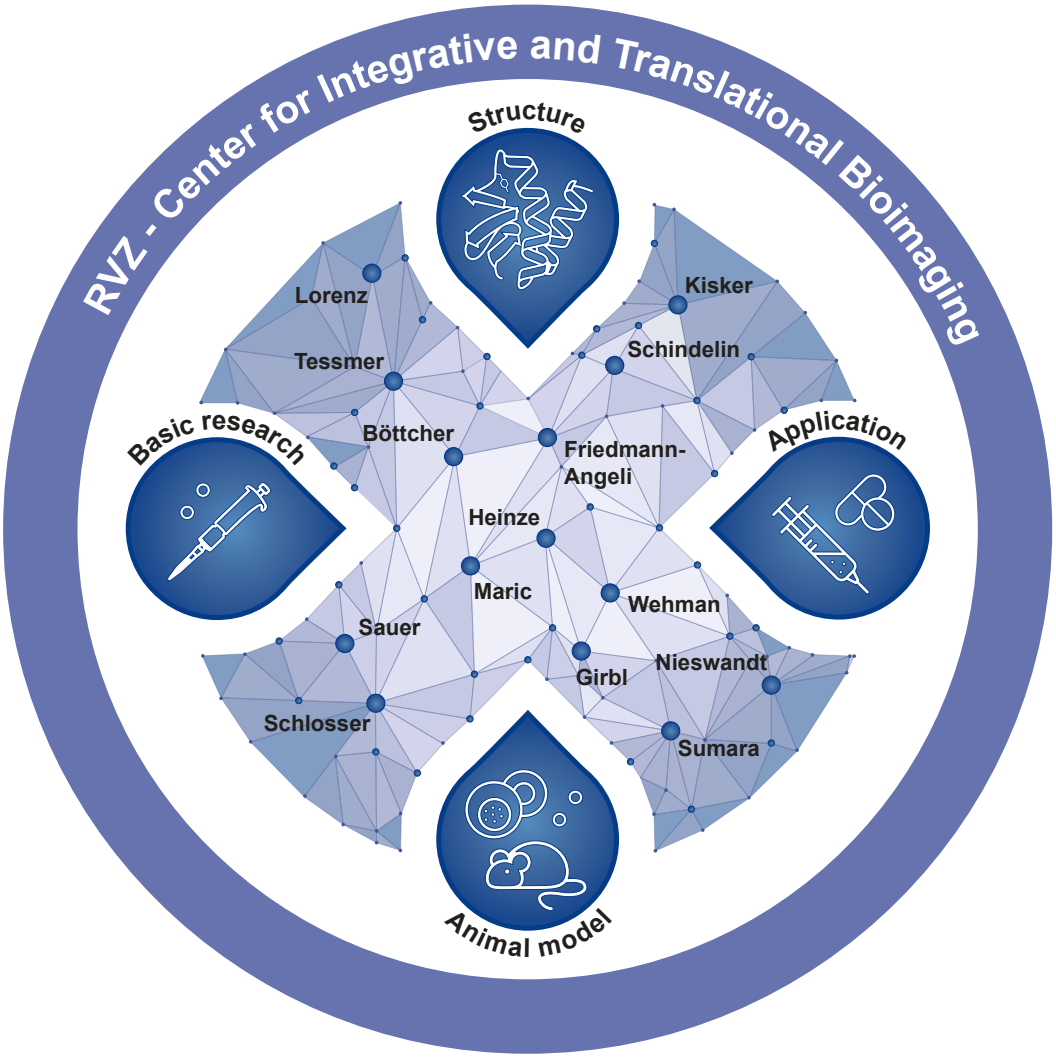


Figure 1: The RVZ network with its research groups focusing on different research areas.

join efforts to understand the chain reactions underlying disease, from the smallest to the largest units of life.

An excellent example of these collaborations is how dedicated microscopists and technology developers in the team of Katrin Heinze interact with vascular biologists in Bernhard Nieswandt's research group interested in thrombo-inflammatory diseases and the cellular players involved. Jointly, the two groups visualized the bone marrow of an intact bone in 3D and discovered important patterns in the distribution of megakaryocytes and the vasculature *in vitro* and *in silico,* as well as the shedding of platelets, potential thrombus-causing agents, into the blood stream *in vivo*. This feat was only possible with the arsenal of tailored microscopes and image analysis pipelines exclusively available at the RVZ.

Another success story is the close collaboration between chemical biologists in the group of Hans Maric and structural biologists in Hermann Schindelin's team. Maric's group uses high throughput peptide array technologies to identify super binders of proteins involved in inhibitory synaptic transmission; Schindelin's team visualizes these

Visualizing life, learning about its structures and functions from the single target protein to its hosting organ, is the motto of the RVZ.

ligands at atomic resolution by X-ray crystallography and characterizes the thermodynamic and kinetic principles of these interactions by biophysical means. The overarching goal of this collaboration is to develop novel neuropharmacological therapeutics.

Combining mass spectrometry, biochemistry and structural biology, the groups of Andreas Schlosser and Caroline Kisker teamed up to successfully elucidate the structure-function relationships in an important kinase complex which is a major drug target in cancer therapy. This powerful teamwork provided insights into the activation mechanism and substrate specificity of this key molecular complex.

The RVZ is "translational" in its focus on processes with major health and disease implications, addressing primarily cancer, cardiovascular and neurological diseases. Translational research at the RVZ covers the entire spectrum from basic to clinical research. Several projects make it all the way from research results to clinical applications. The team of Markus Sauer, for example, recently visualized the distribution of tumor-associated antigens on healthy and tumor cells, and provided absolute expression profiles based on single-molecule localization microscopy by *d*STORM, which he pioneered and has continuously advanced over many years. This methodological breakthrough is key to developing novel, personalized forms of immunologic anti-cancer treatments with tumor-specific antibodies and CAR T-cells; it allows imaging of the receptome of tumor cells and their interaction with genetically engineered T-cells with so far unmatched spatial resolution.

Within the overall framework of employing imaging technologies to gain a mechanistic understanding of the pathophysiology of diseases, research groups at the RVZ address different levels of biological organization. The

research activities of RVZ research groups thus span the entire spectrum from molecular-mechanistic to cellular/tissue/organ system-level approaches (see Fig. 2).

In May 2020, the University officially passed and announced the new bylaws for the Rudolf Virchow Center as a Center for Integrative and Translational Bioimaging. Now, the RVZ is ready for an exciting future! The RVZ team, with newly appointed RVZ scientists and board members, unifies a critical mass of biomedical expertise and infrastructure. This has sparked the transformation of the RVZ into a research center that uses a wide range of visualization technologies to pinpoint the causes of disease by deciphering disease mechanisms at the molecular and cellular level.

A fundamental biological principle that guides many of the research projects at the RVZ is that knowledge about the structure of a cellular component – be it a single protein, a complex multimeric molecular assembly or an entire organelle – holds the key to understanding its function. Conversely, protein structure deviations associated with a loss of function may explain why "larger units" such as cells and organs or organisms are driven into pathophysiological states of severe illness or lethal organ failure.

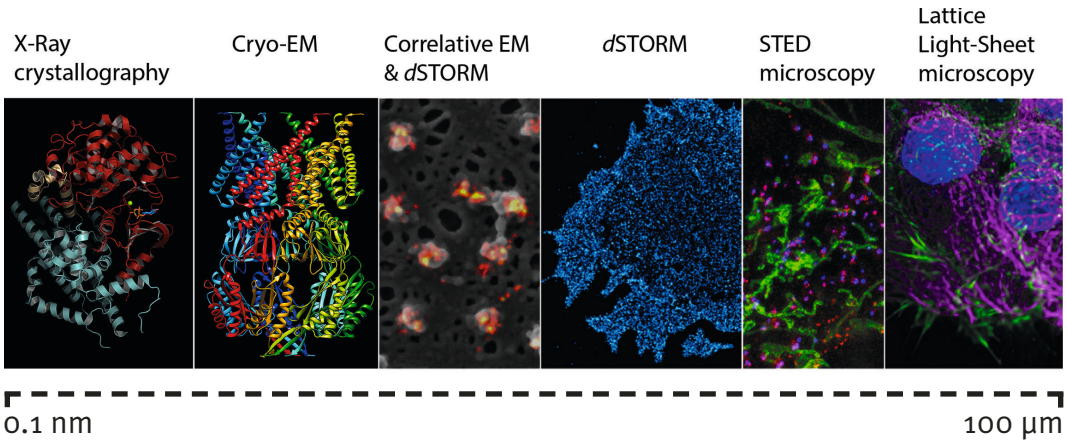


Figure 2: The entire spectrum of the RVZ imaging technologies.

PROF. CAROLINE KISKER

In 2020, the International Institute of Molecular and Cell Biology (IIMCB) in Warsaw appointed Prof. Caroline Kisker as new member of their International Advisory Board (IAB). The Institute is one of the most modern research institutes in its field in Poland. Research topics at the IIMCB cover the areas of structural biology, bioinformatics, computer modeling, molecular and cell biology, among others. The main goals of the IIMCB are to carry out high-quality research in molecular biomedicine, and create the best possible conditions for ambitious, motivated group leaders whose work is assessed by the IAB on a regular basis.

Since 2020 Caroline Kisker has been a member of the DFG Review Board, which evaluates proposals to fund research projects and advises on issues concerning the further development and organization of the DFG funding programs. Caroline Kisker has also been the Chair of the Academic Senate of the University of Würzburg since 2019 and Speaker of the Rudolf Virchow Center since 2020.

NEW RVZ BOARD MEMBER

PROF. MARKUS SAUER

Coinciding with the renaming of the RVZ as Center for Integrative and Translational Bioimaging, Prof. Markus Sauer joined the RVZ in 2020 to strengthen its expertise in bioimaging.

A chemist by training, Markus Sauer started to focus his research at an early stage of his academic career on single-molecule spectroscopy and imaging with particular emphasis on the development of sophisticated super-resolution microscopy techniques and their use in biomedical applications. After spending six years at the University of Bielefeld (2003-2009) as Chair of Laser Physics and Laser Spectroscopy he was appointed as Professor for Biotechnology and Biophysics at the University of Würzburg.

Since then he has been constantly improving single-molecule localization microscopy by *d*STORM and has combined it with electron and expansion microscopy to overcome current limitations of super-resolution fluorescence imaging.

Recently, Markus Sauer demonstrated for the first time the successful application of *d*STORM in immunotherapy on primary cells together with the University Hospital Würzburg. Furthermore, Markus Sauer coordinates several national immunotherapy projects. Very recently he received an ERC Synergy Grant (ULTRARESOLUTION) together with Silvio Rizzoli (Göttingen) and Ed Boyden (MIT) to develop super-resolution microscopy methods with true molecular resolution.

“I hope that the redefinition and further strengthening of our research focus will help us establish the RVZ among the internationally visible centers for bioimaging,” explains Markus Sauer.

APPOINTMENT

PROF. KATRIN HEINZE

In March 2020, Professor Katrin Heinze was officially appointed to the new “Chair of Molecular Microscopy” at the Medical Faculty of the University of Würzburg. With her widely applicable microscopy and image analysis methods she visualizes the “functional units of biomedicine” from molecular complexes in living cells to the architecture of whole organs. The activities and new projects of the new Chair of Molecular Microscopy with extended premises and additional investment funds will strengthen and expand biomedical microscopy at the Rudolf Virchow Center.

DFG PRIORITY PROGRAM

DR. JOSÉ PEDRO FRIEDMANN ANGELI

In July 2020, Dr. José Pedro Friedmann Angeli, together with others, shaped and spearheaded the successful establishment of a new DFG Priority Program “SPP2306: Ferroptosis: from molecular basics to clinical application”. Ferroptosis is a pervasive and disease-relevant form of cell death characterized by specific metabolic constraints and triggered by excessive damage to cellular phospholipids. Within the SPP several different aspects of ferroptosis will be explored, which should help to define not only its underlying molecular mechanism but also define pathologies and intervention strategies that target this pathway. To achieve this goal, the DFG within the SPP framework has funded twenty-six projects for the next six years focusing on different aspects of ferroptosis. Pedro Friedmann Angeli and his group aim to understand specific metabolic pathways that support the functioning of key enzymes suppressing ferroptosis. This knowledge, he believes, could be harnessed to specifically trigger this form of cell death in cancer cells reported to be markedly sensitive to ferroptosis, including B-Cell malignancies and neuroblastoma.

NEW GROUP LEADER

DR. TAMARA GIRBL

During her PhD project at the University Clinics of Salzburg, Austria, Dr. Tamara Girbl studied the adhesion and migration patterns of lymphocytes in chronic lymphocytic leukemia. In order to pursue her interest in the basic principles of immune cell trafficking, Tamara Girbl undertook her postdoctoral research at the William Harvey Research Institute, Queen Mary University of London, UK. Supported by generous fellowships from the British Heart Foundation and the Marie Curie Co-Fund program she gained proficiency in advanced confocal intravital microscopy methods. Her main work described how local guiding cues (chemokines) instruct circulating neutrophils to breach the different layers of blood vessel walls *in vivo*. During a short postdoctoral research project at the Institute of Science and Technology, Austria, she extended her technical repertoire to mechanistic single cell analyses using live cell imaging approaches.

Tamara Girbl joined the Rudolf Virchow Center in June 2020, where she is now investigating leukocyte interactions with blood vessel walls and their implications in inflammatory diseases.

GROUP LEADERS

The Rudolf Virchow Center comprises a mixture of permanent and junior group leaders, the latter with an appointment for six years and a generous package to permit a jump-start into their research topics.

GROUP LEADER
at the Rudolf Virchow Center

Dr. José Pedro Friedmann Angeli

GOAL

Our overall goal is to understand how cells cope and adapt to oxidatively induced damage to phospholipids. Specifically, we aim to understand the metabolic conditions predisposing to premature oxidation and ultimately cell death. Understanding these events and developing strategies that modulate these events will allow us to extend or shorten a cell "lifespan" for therapeutic benefit.

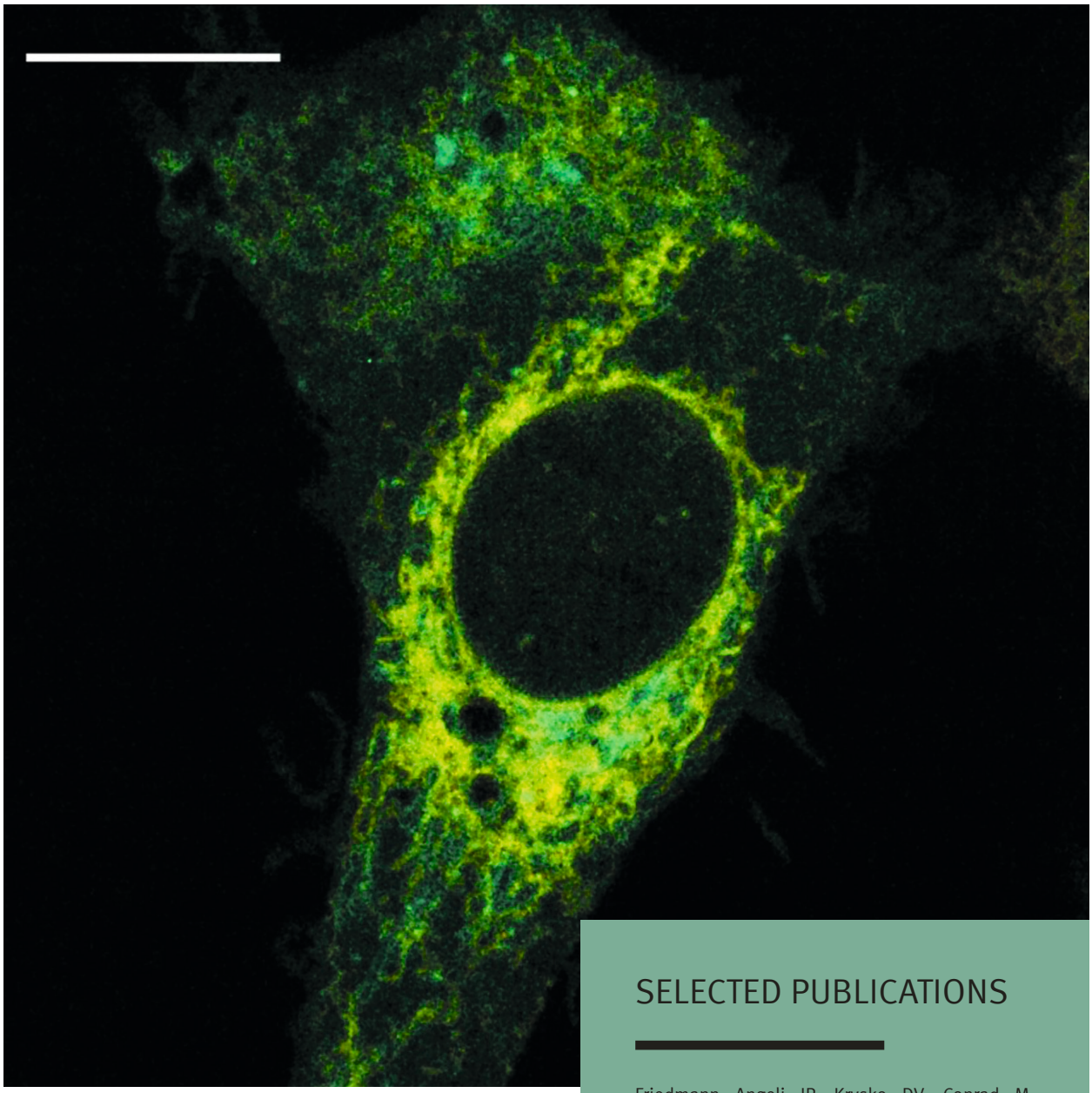
RESEARCH BACKGROUND

Six 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. Landmark studies have recently demonstrated that cancer cell refractory to therapy, due to lineage-specific or non-mutational mechanisms, acquire a marked dependence on GPX4 for survival. This has now spurred a growing interest in developing strategies to trigger ferroptosis and understand the mechanisms that regulate sensitivity to this process.

RESEARCH HIGHLIGHTS

Discovery of ferroptosis suppressor protein 1 (FSP1) as a key regulator of ferroptosis. We have used a genome wide cDNA overexpression screen in order to identify genes that complement the genetic loss of GPX4. These studies demonstrated that oxidoreductase FSP1 can complement the loss of GPX4 and act as an important enzymatic system regenerating intracellular antioxidants associated with phospholipid. Our group has demonstrated that it is associated with membranes via its myristoyl chain, which allows it to efficiently reduce the metabolite ubiquinone (Doll, Freitas et al., Nature 2019). Pharmacologically targeting this pathway led to a remarkable sensitivity to ferroptosis, and now allows us to develop improved strategies to target this pathway.

Conceptualization and establishment of a DFG priority program (Ferroptosis: from Molecular Basics to Clinical Applications" (SPP 2306). This program will specifically support the ferroptosis-related project during the years of 2021-2027, and will catalyze an important step towards the translation of ferroptosis strategies to the clinic.



Enhanced resolution confocal microscopy of HT1080 cells (FSP1–GFP) or overexpressing mCherry-Sec61ß (endoplasmic reticulum localization). GFP is displayed in green; mCherry fluorescence is pseudo-coloured in yellow. Scale bar, 10 µm (top). Credit for the image: Andreas Kurz (Chair of Biotechnology and Biophysics).

FUTURE PLANS

Our group is currently dedicated to understanding the mechanisms that regulate ferroptosis sensitivity. Specifically, we are now focusing on characterizing the contribution of specific metabolic pathways, including lipid and specific amino acids, to the sensitivity to ferroptosis. This knowledge will prove instrumental not only for understanding pathological conditions but also to develop pharmacological strategies that can be used to selectively kill tumors refractory to therapy.

SELECTED PUBLICATIONS

Friedmann Angeli JP, Krysko DV, Conrad M. Ferroptosis at the crossroads of cancer-acquired drug resistance and immune evasion. Nat Rev Cancer. (2019); 19(7):405-414.
doi: 10.1038/s41568-019-0149-1

Doll S, Freitas FP, Shah R, Aldrovandi M, da Silva MC, Ingold I, Goya Grocin A, Xavier da Silva TN, Panzilius E, Scheel CH, Mourão A, Buday K, Sato M, Wanninger J, Vignane T, Mohana V, Rehberg M, Flatley A, Schepers A, Kurz A, White D, Sauer M, Sattler M, Tate EW, Schmitz W, Schulze A, O'Donnell V, Proneth B, Popowicz GM, Pratt DA, Angeli JPF, Conrad M. FSP1 is a glutathione-independent ferroptosis suppressor. Nature (2019); 575(7784):693-698.
doi: 10.1038/s41586-019-1707-0

GROUP LEADER
at the Rudolf Virchow Center

Prof. Bettina Böttcher

GOAL

The goal of our research is to understand how biological complexes work from a structural viewpoint. For this we use electron cryomicroscopy and image processing, which we develop to match our specific needs.

RESEARCH BACKGROUND

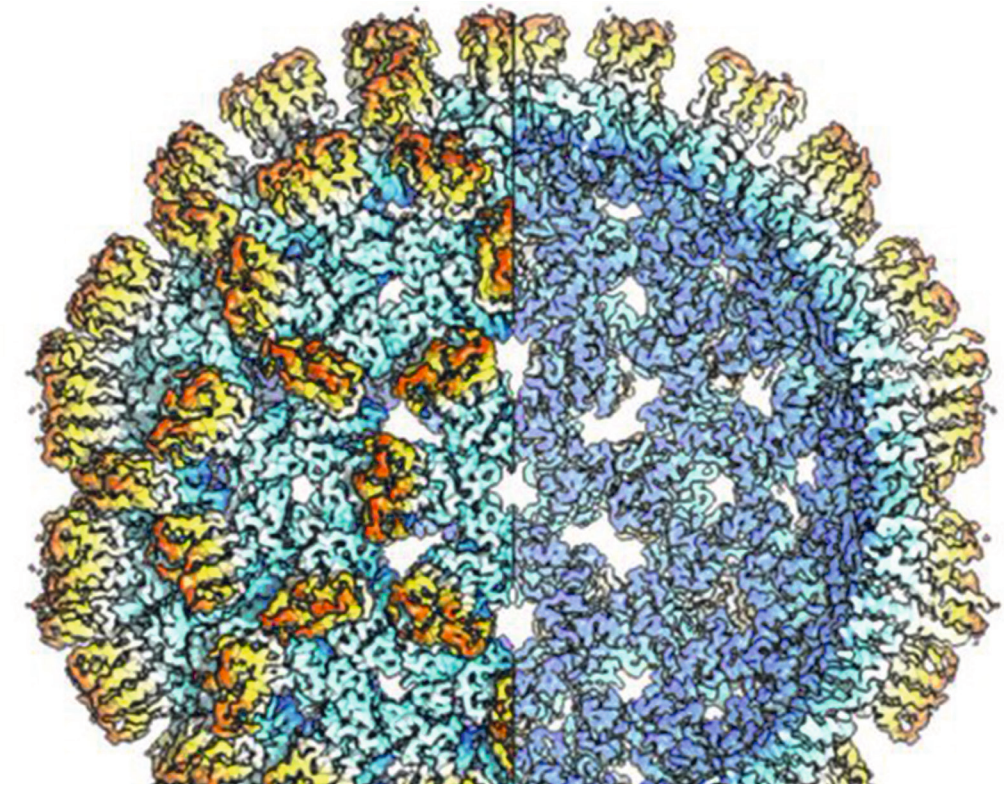
Electron cryomicroscopy is a powerful tool for the routine structural determination of biological assemblies that are larger than ca. 100 kDa. The method is particularly effective for membrane proteins. These can be reconstituted into close to native, membranous nano-environments where structurally coordinated lipids can be resolved and interpretated with respect to the protein and the membrane. Furthermore, sophisticated analysis allows us to map the conformational space that is adopted by the individual building blocks of an assembly, providing insights into cooperativity and plasticity.

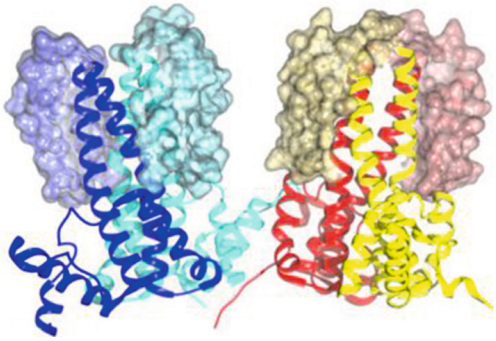
RESEARCH HIGHLIGHTS

Mechanosensitive channels of small conductance (MscS) protect bacteria against osmotic down-shock and increase survival fitness in adverse environments. Gating depends on changes in pressure in the surrounding membrane. We have resolved several lipids in MscS-like channels, that are stabilized by the surrounding protein in unusual positions. Co-ordination of these lipids fine-tunes the pressure threshold and gatingcharacteristics of MscS-like channels.

Bacterial cytochrome bd oxidases are terminal reductases of the respiratory chain and couple the oxidation of ubiquinol or menaquinol with the reduction of dioxygen to water. Together with Friedrich's group we have resolved the structure of the *E.coli* bd-oxidase at 3.3 Å resolution. The structure reveals an unexpected new subunit, CdY, which blocks the dioxygen entry side.

Human hepatitis B virus and duck hepatitis B virus are prototypic representatives of two branches of the phylogenetic tree of Hepadnaviridae. We have determined the structure of capsids of the duck hepatitis B capsid protein (DHBc). It differs from the human variant by a large, proline-rich insertion domain that broadens the tips of the capsidspikes. The insertion domain is essential for supporting viral replication and folds only slowly in the absence of a peptidyl-prolyl-cis-trans-isomerase.





Duck hepatitis B core protein capsids and subunits of the asymmetric unit.

FUTURE PLANS

Structure determination of membrane proteins depends on their efficient structural stabilization. We want to find generally applicable strategies for how to best stabilize membrane proteins for structure determination by electron cryomicroscopy. We will use this knowledge to determine the structures of larger MscS-like channels.

Structure determination by electron cryomicroscopy becomes increasingly difficult with decreasing molecular weight. Although structure determination of assemblies in the 50-100 kDa range is possible, it often requires several image acquisition attempts before the problem can be solved. We want to improve the success rate and develop predictive tools that indicate whether determining the structure of a particular small assembly is likely to be productive.

SELECTED PUBLICATIONS

Makbul C, Nassal M and Bottcher B (2020). Slowly folding surface extension in the prototypic avian hepatitis B virus capsid governs stability. Elife 9.

Thesseling A, Rasmussen T, Burschel S, Wohlwend D, Kagi J, Müller R, Böttcher B* and Friedrich T* (2019). Homologous bd oxidases share the same architecture but differ in mechanism. Nat Commun 10(1): 5138.

GROUP LEADER
at the Rudolf Virchow Center

Dr. Tamara Girbl

GOAL

Efficient immune cell trafficking into inflamed tissues is essential for a functional immune system. Our overall goal is to determine the role of venular pericytes in controlling leukocyte entry into tissues during physiological immune responses, and how leukocyte-pericyte interactions contribute to the development of inflammatory disorders.

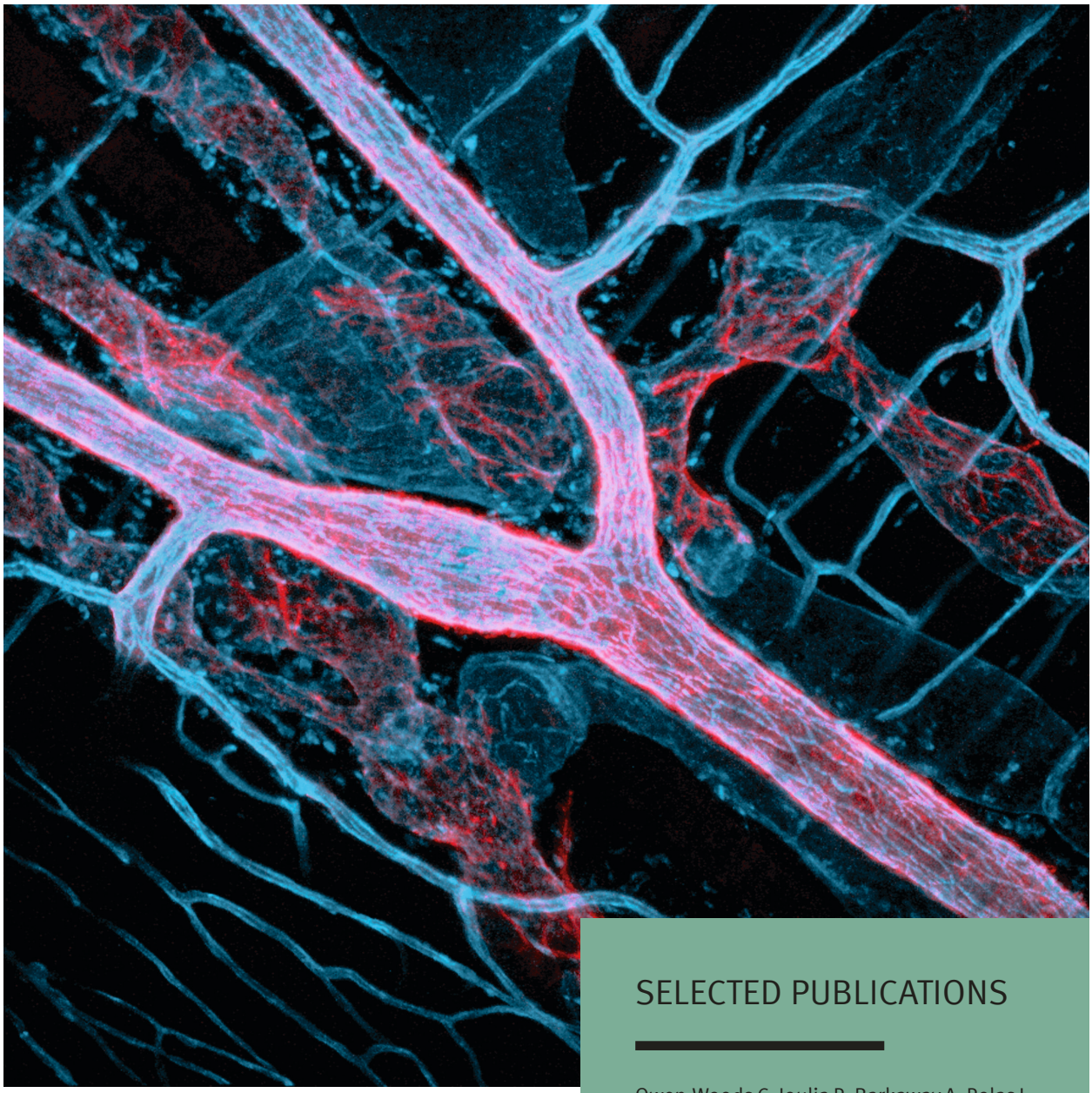
RESEARCH BACKGROUND

In order to enter sites of inflammation, circulating leukocytes need to pass two different cellular layers of blood vessel walls: i) endothelial cells, and ii) the pericyte sheath. While leukocyte migration through the endothelium has been extensively studied, little is known about their subsequent migration through the pericyte layer. Our previous research demonstrated that pericytes play a decisive role in mediating neutrophil breaching of venular walls and suggested that pericytes act as 'vascular checkpoints' controlling leukocyte entry into tissues (Girbl and Nourshargh et al., Immunity 2018).

RESEARCH HIGHLIGHTS

Our recent study showed that transmigrating neutrophils that have passed the endothelial cell layer, receive local guidance cues from venular pericytes via the chemokine CXCL1, which is required for full neutrophil exit from venular walls (Girbl and Nourshargh et al. Immunity 2018). While these results indicate an important role of pericyte-derived chemokines in innate immunity, almost nothing is currently known about the contribution of venular pericytes to adaptive immune responses. Over the last year we have performed pilot studies, which showed that T lymphocytes engage in intense physical interactions with pericytes during their transmigration during dermal inflammation *in vivo*. These key results provide a strong basis for further investigations that our new group will undertake at the RVZ.

Furthermore, I have engaged in a postdoctoral study at the Institute of Science and Technology Austria (lab of Prof. Michael Sixt), where I developed novel techniques to study the relationship between leukocyte migration and intracellular energy metabolism, which I will apply to my future work.



The confocal microscopy image shows immunofluorescently stained blood and lymphatic vessels in the murine cremaster muscle (endothelial cells shown in blue, pericytes and smooth muscle cells shown in red).

SELECTED PUBLICATIONS

Owen-Woods C, Joulia R, Barkaway A, Rolas L, Ma B, Nottebaum AF, Arkill K, Stein M, Girbl T, Golding M, Bates DO, Vestweber D, Voisin MB, Nourshargh S, Local microvascular leakage promotes trafficking of activated neutrophils to remote organs. J Clin Invest, May 2020,
doi: 10.1172/JCI133661.

FUTURE PLANS

We will investigate the interaction between pericytes and adaptive immune cells during physiological immune responses and in multiple inflammatory disease models. These studies aim to dissect the molecular mechanisms mediating lymphocyte passage through the pericyte network and show how the cross-talk between both cell types regulates adaptive immune responses.
We will use state-of-the-art techniques including intravital microscopy, genetically modified mouse models and RNA sequencing. Our results will very likely advance our basic understanding of leukocyte trafficking and have a strong potential to identify novel therapeutic strategies aimed at regulating leukocyte responses for the treatment of inflammatory disorders, such as autoimmune diseases, myocardial infarction and stroke.

GROUP LEADER
at the Rudolf Virchow Center

Prof. Katrin Heinze

GOAL

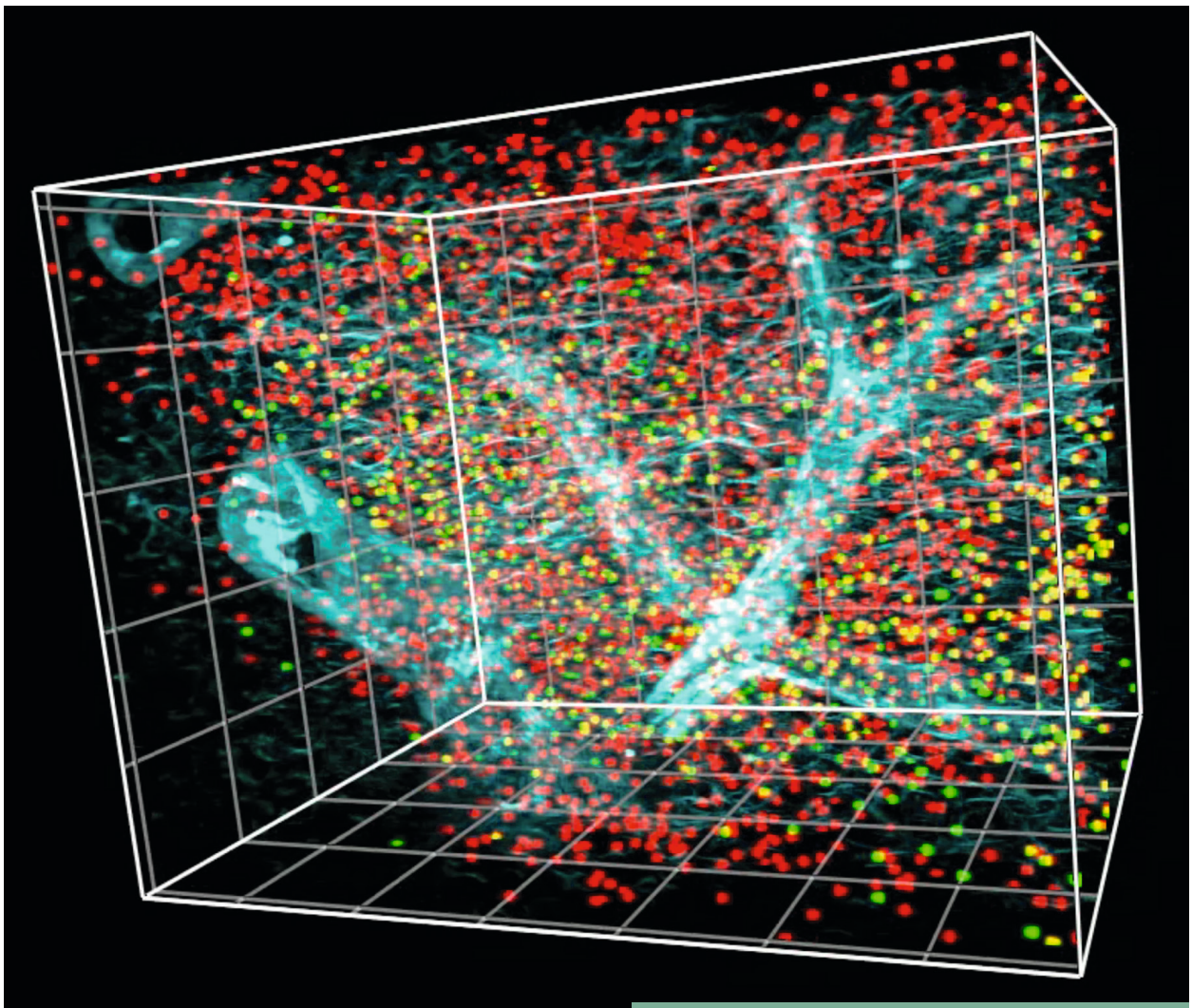
How can fluorescence sharpen our view of biomedical processes? In my lab, we develop 3D fluorescence techniques that can catch very sharp details on rapid cellular processes or zoom into an entire organ to see subcellular details.

RESEARCH BACKGROUND

Discoveries in medicine and biosciences are frequently stimulated by the invention of new methods. The imaging method that everyone dreams of is a non-invasive, highly selective tool to visualize subcellular compositions of a whole body in a single snapshot. Unfortunately, this 'perfect' method where very fine details can be captured in no time over a large field-of-view has not been invented yet. We tackle this problem by complementary approaches using advanced intravital and light sheet fluorescence microscopy with tweaks, and push superresolution imaging to its limits by specially designed nano-coatings. Our imaging toolbox therefore covers a wide range from single molecules to whole organs.

RESEARCH HIGHLIGHTS

Recently, we decided to pursue new avenues and use large 3D images and objects from whole-organ light-sheet fluorescence microscopy as biological templates to run physiologically relevant simulations of complex scenarios that are hardly assessible experimentally. In close collaboration with Dr. David Stegner we recently obtained fascinating 3D-insights into the bone marrow and its cellular interplay. With many images of megacaryocytes and bone vasculature at hand, we found that megakaryocytes act as 'bouncers' restraining migration of other cells in the bone marrow. Thus, megakaryocytes play an important role in cell migration even if not migrating themselves. The large megakaryocytes represent passive obstacles, and thus significantly influence migration of other cells such as hematopoietic stem cells and neutrophils in the bone marrow (Haematologica 2020). In close collaboration with Prof. Andreas Beilhack we even pushed high resolution whole imaging further to describe fungal growth and the local immune response in whole lungs at cellular resolution within its anatomical context, to eventually dissect local host-immune Aspergillus fumigatus interactions (mBio 2020).



Light sheet fluorescence microscopy (LSFM) maps the three-dimensional structural microarchitecture of intact lungs and depicts immune cell subpopulations at cellular resolution.

FUTURE PLANS

In the future, we will refine super-resolution imaging by combining correlation strategies and enhancing coatings with tailored biophotonics features. However, for extremely dense, highly abundant membrane receptors even this advanced approach may fail. Therefore, we have started establishing Expansion Microscopy for quantitative platelet receptor studies where the platelet is physically expanded in a hydrogel approach to maximize the resolution gain. On the opposite scale, in the context of whole organ imaging, we will make use of machine learning tools to recognize “textures” and shapes as functional units of the organ without the need for a separate color channel.

SELECTED PUBLICATIONS

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Gorelashvili MG, Angay O, Hemmen K, Klaus V, Stegner D, Heinze KG. Megakaryocyte volume modulates bone marrow niche properties and cell migration dynamics. Haematologica. (2020);105(4):895-904. doi:10.3324/haematol.2018.202010. Epub 2019 Jun 27.PMID: 31248970

GROUP LEADER
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 use this approach to exploit novel targets for structure-based drug design to combat specific diseases.

RESEARCH BACKGROUND

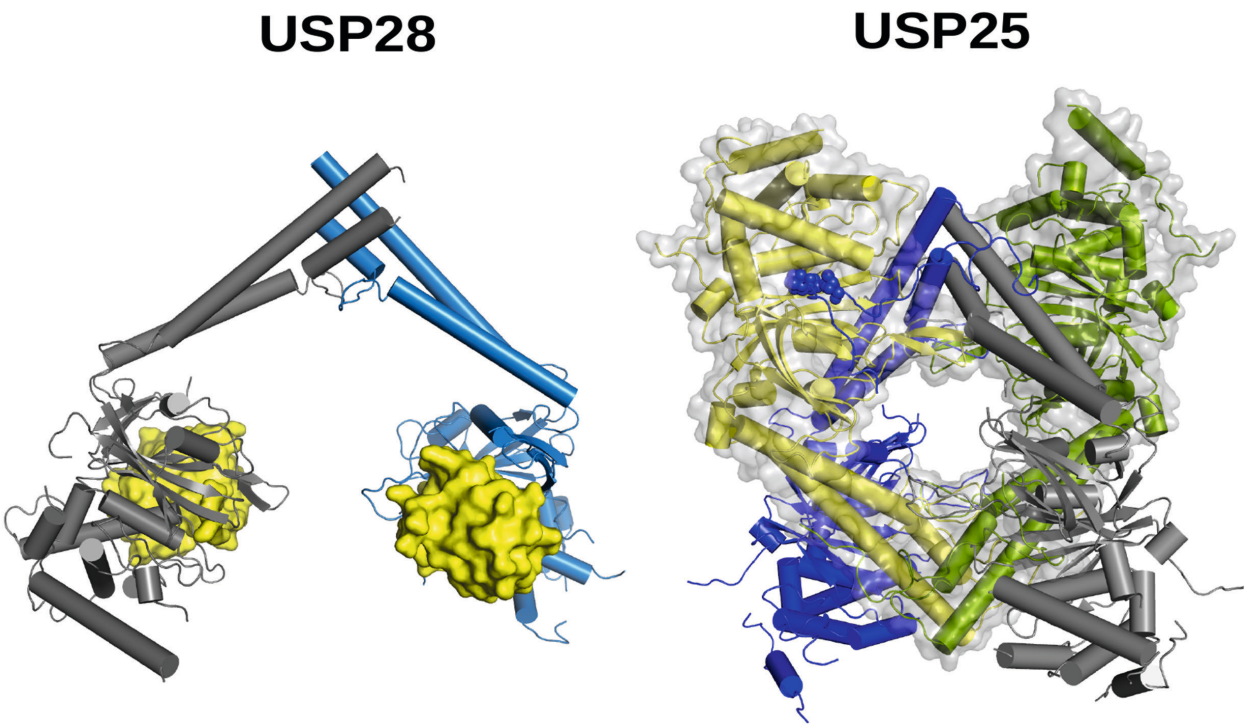
Numerous endogenous and exogenous agents damage our DNA and within a single human cell approx. 10^4 to 10^6 damages are encountered per day. Organisms thus require efficient DNA repair systems to maintain their genomes in a functional state. Nucleotide excision repair (NER) recognizes structurally highly diverse DNA 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.

The increasing awareness that deubiquitylases (DUBs) are involved in multiple pathways associated with malignant transformation or cancer progression has moved these enzymes also into the focus as promising therapeutic targets. Our goal is to understand the two closely related human DUBs USP28 and USP25 and to develop inhibitors that specifically address the individual enzymes.

RESEARCH HIGHLIGHTS

The general transcription factor IIH (TFIIH) is a multiprotein complex that plays essential roles in transcription and DNA repair. TFIIH harbors three enzymatic activities mediated by the XPB and XPD helicases, and the CDK7 kinase. All activities are tightly controlled by the other subunits within the complex. Our data revealed how the activity of the XPD helicase is tightly controlled by its interaction partners MAT1, p44 and p62. We could show in addition that p62 assumes an important novel role in the damage verification process. The XPB helicase can be activated either by DNA or by the interaction with the TFIIH subunits p52 and p8. Importantly, we show that p52 and p8 act as the master regulators of XPB as activators and speed limiters at the same time. Finally, we solved the long-awaited structure of active CDK7 in a complex with its interaction partners MAT1 and Cyclin H, which provides a structural basis for the mechanism of CDK7 activation and its activity regulation.

The two deubiquitinases USP25 and USP28 share high sequence similarity but assume different cellular functions. Whereas USP28 is a target for the treatment of varying tumor entities, USP25 acts as a regulator of the innate immune system, but was recently also shown to play a role in tumorigenesis. Our data revealed that USP28 exists as a constitutively active dimer, while USP25 is an auto-inhibited tetramer which requires dissociation into the dimeric state to be active.



Crystal structures of the constitutively active dimeric USP28 (bound to its substrate ubiquitin) and auto-inhibited USP25 catalytic domains.

FUTURE PLANS

A basic understanding of the NER pathway or the functionalities of the deubiquitinases permits a glimpse towards possible intervention strategies in cancer therapy. However, advances in inhibitor development can only be achieved when the interplay between the different players in their respective pathways has been deciphered, which then leads to a clear understanding where intervention may cause the desired result. We will develop pipelines for the development of new inhibitors to target specific steps in the pathways analyzed. 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 the gain of knowledge about the important translational implications fostered by our basic research.

SELECTED PUBLICATIONS

Sauer F, Klemm T, Kollampally RB, Tessmer I, Nair RK, Popov N, Kisker C. Differential Oligomerization of the Deubiquitinases USP25 and USP28 Regulates Their Activities. Mol Cell. 2019 May 2;74(3):421-435.e10. doi: 10.1016/j.molcel.2019.02.029.

Peissert S, Sauer F, Grabarczyk DB, Braun C, Sander G, Poterszman A, Egly JM, Kuper J, Kisker C. In TFIIH the Arch domain of XPD is mechanistically essential for transcription and DNA repair. Nat Commun. 2020 Apr 3;11(1):1667. doi: 10.1038/s41467-020-15241-9.

GROUP LEADER
at the Rudolf Virchow Center

Dr. Sonja Lorenz

GOAL

My research group aims to decipher how ubiquitin, a single, small protein, achieves specificity in regulating all aspects of eukaryotic cell biology. We use our insights to devise novel avenues towards targeting the ubiquitin system for therapeutic benefit.

RESEARCH BACKGROUND

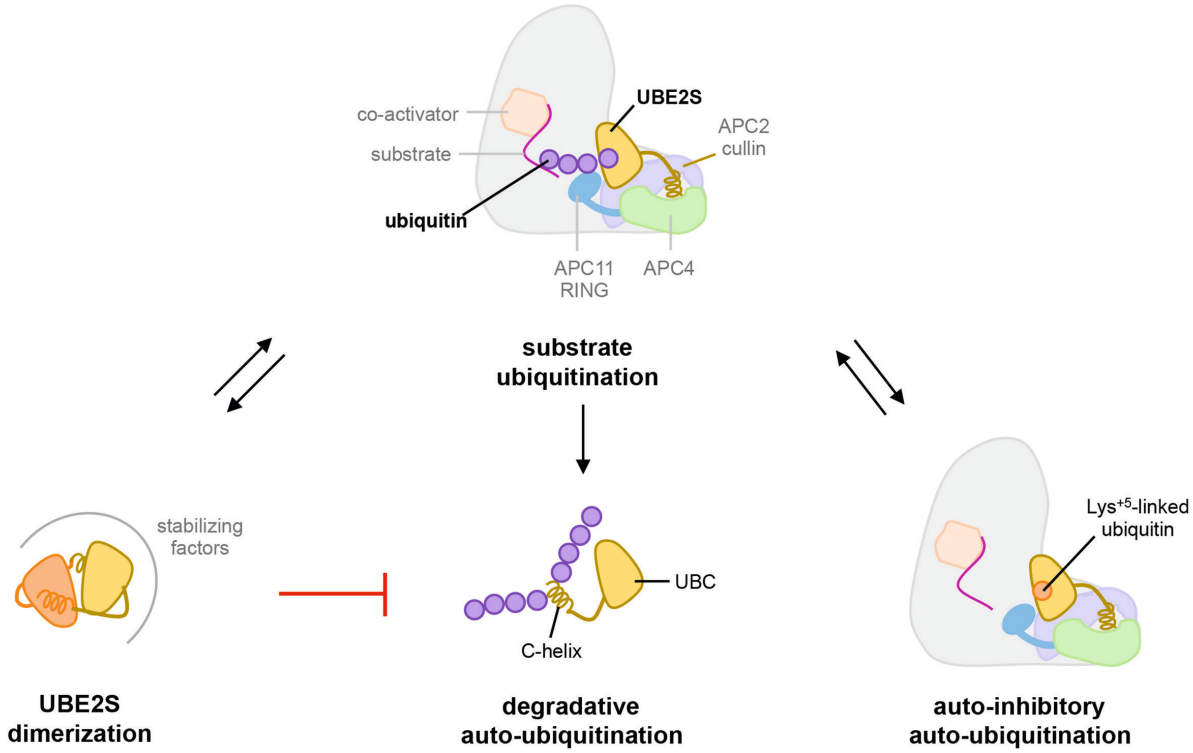
With around 1000 members in the human proteome, ubiquitin ligases (E3 enzymes) are the most diverse class of ubiquitination enzymes and provide critical specificity determinants in ubiquitin signaling. The immense potential of these enzymes as pharmacological targets is illustrated by the clinical efficacy 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

My group has made substantial progress in understanding the catalytic mechanisms and specificities of ubiquitination enzymes by interrogating their conformational dynamics and macromolecular interactions at a structural level. A major line of our research has focused on substrate and ubiquitin recognition by key ligases in tumorigenesis, such as HUWE1 and E6AP, defining basic determinants of their specificities.

Moreover, my group discovered two distinct mechanisms of regulation in ubiquitin-conjugating (E2) enzymes, which deliver ubiquitin to E3 enzymes. Using the human anaphase-promoting complex (APC/C)-associated E2 UBE2S as a model system, we demonstrated that the catalytic activity of E2s can be auto-inhibited through auto-ubiquitination of a conserved site. We further discovered that UBE2S is controlled by dimerization, which confers a “safe-lock” to the E2, thus providing a reservoir of molecules protected from auto-ubiquitination-driven degradation.

Expanding on my previous efforts in shaping the ubiquitin-related research landscape in Würzburg, I co-defended the Mildred-Scheel Nachwuchszentrum, now founded by the Deutsche Krebshilfe, and participated in the preliminary steering committee of a planned, transregional ubiquitin initiative, and as a co-speaker of the DFG-funded GRK 2243 “Understanding ubiquitination:



Model of the conformational regulation of the APC/C-associated ubiquitin-conjugating enzyme UBE2S, a key regulator of human cell proliferation, as described in Liess et al. 2019, and Liess et al. 2020.

from molecular mechanisms to disease". Finally, I was granted extended funding by the DFG Emmy Noether Program for my research group, which will relocate to the Max Planck Institute for Biophysical Chemistry in Göttingen in March 2021.

FUTURE PLANS

While the importance of allosteric mechanisms in determining the specificity of ubiquitination 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. My lab aims to fill this gap by systematically identifying and characterizing macromolecular complexes of HECT ligases using integrated proteomic, structural, and functional approaches. We envision these studies will transform our rather descriptive knowledge of HECT ligase functions into a mechanistic understanding of how these enzymes integrate diverse cellular signals and elicit specific signaling responses during homeostasis and disease.

SELECTED PUBLICATIONS

Liess AKL#, Kucerova A#, Schweimer K, Yu L, Roumeliotis TI, Diebold M, Dybkov O, Sotriffer C, Urlaub H, Choudhary JS, Mansfeld J*, Lorenz S*. Structure. Autoinhibition Mechanism of the Ubiquitin-Conjugating Enzyme UBE2S by Autoubiquitination. 2019 Structure 27:1195-1210.
Featured in Bodrug T, Brown NG (2019). UBE2S learns self control. Structure 27:11185-1187.

Liess AKL#, Kucerova A#, Schweimer K, Schlesinger D, Dybkov O, Urlaub H, Mansfeld J*, and Lorenz S*. Dimerization regulates the human APC/C-associated ubiquitin-conjugating enzyme UBE2S. 2020
Sci Signal. 13:eaba8280.
Featured in: Bremm A. (2020) Hug and hold tight: Dimerization controls the turnover of the ubiquitin-conjugating enzyme UBE2S. Sci Signal 13:eabd9892.

GROUP LEADER
at the Rudolf Virchow Center

Dr. Hans Maric

GOAL

Our laboratory focusses on the high-throughput molecular analysis and quantification of protein-protein interactions. Mapped protein interfaces are used as starting points for developing conceptually new tools for the precise localization, quantification and manipulation of key proteins in live cells und tissue.

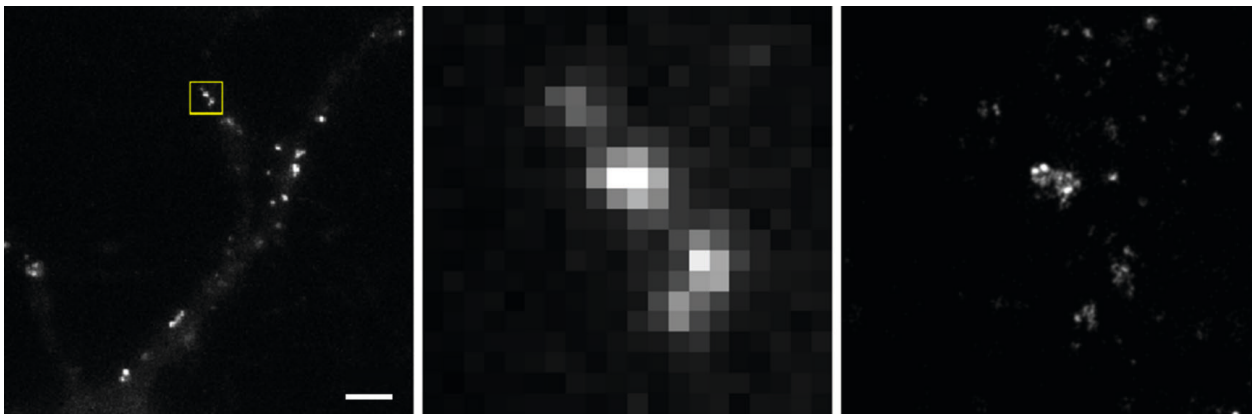
RESEARCH BACKGROUND

Protein-protein interactions play critical roles in virtually all physiological processes and their visualization, molecular characterization and quantification continues to transform biology and medicine. We combine chemical synthesis with advanced readouts to study protein interactions in the highest throughput, and develop peptides with relevance for neurological diseases, epigenetic targets, cancer, and other life threatening conditions. We also develop peptide-based chemical tools and probes for investigating of disease-relevant mechanisms *in vitro* and *in vivo* with nanometer resolution.

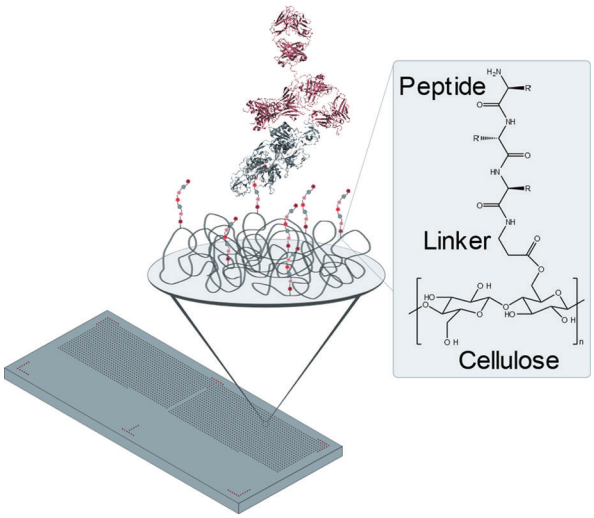
RESEARCH HIGHLIGHTS

State-of-the-art protein interaction quantification methods are limited by the requirement for labeling or immobilizing the studied ligands. Exploiting a phenomenon called Temperature Related Intensity Change (TRIC), we recently achieved sensitive in-solution quantification of protein interactions using unmodified ligand libraries in unprecedented throughput (iScience 2020). Advanced miniaturization and automatization further enabled us to answer fundamental questions related to transcription and cancer (Nat Genet 2019, Mol Cell 2019, PLoS Genet 2020, EMBO Mol Med 2020). Using our technology setup in an iterative way allowed us to tailor chemo proteomic tools and design novel neuronal modulators, which revealed new therapeutic strategies (Neuron 2019, Front Mol Neurosci 2019; J Med Chem 2020, J Neurosci 2020, J Am Chem Soc 2020).

Class I histone deacetylase (HDAC) enzymes are major epigenetic effectors and promising targets for cancer therapy. Until now, conventional methods could not effectively resolve the fast and transient interactions of HDACs. We addressed this limitation by providing a conceptional new microarray type and demonstrated its use to resolve the molecular action of HDACs isozymes and develop a new class of cellularly active and highly isozyme-selective HDAC inhibitors (Nat Commun 2020).



Inhibitory synapses of a cortical neuron visualized by direct stochastical optical reconstruction microscopy (*d*STORM) using our newly developed fluorescent small molecule probe. Scale bar 5 µm.



Left: Scheme of a peptide microarray produced in our lab. Up to 1536 peptides are synthesized and printed as cellulose-conjugates in microarray format to obtain hundreds of library copies.

FUTURE PLANS

In contrast to compounds that allosterically affect neurotransmitter receptors across the brain, targeting the receptor-associated proteins has the potential to adjust brain activity with circuit precision, thereby potentially overcoming the severe side-effects of conventional drugs, and addressing unmet clinical needs. We will apply novel proteomic approaches to systematicaly identify neurotransmitter receptor-associated proteins and study their functions in cells and tissues using the first examples of a new class of super-resolution compatible fluorescent probes.

In a subgroup of autoimmune neuropathies the neutralization or removal of autoantibodies can lead to immediate patient recovery. So far, however, only a few autoantibodies have been identified. Supported by the IZKF, we will address this limitation in diagnostic and therapeutic options by identifying and characterizing new autoantigens.

SELECTED PUBLICATIONS

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High-throughput Quantification of Protein Interactions using Nanomolar Scaled and Unmodified Peptide Libraries. iScience, 24 (2020) 101898.
doi: 10.1016/j.isci.2020.101898.

Moreno-Yruela C, Bæk M, Vrsanova AE, Schulte C, Maric HM*, Olsen CA*. Hydroxamic Acid-Modified Peptide Microarrays for Profiling Isozyme-Selective Interactions and Inhibition of Histone Deacetylases. Nature Communications, 12 (2020) 62.
doi: 10.1038/s41467-020-20250-9.
*corresponding authors

GROUP LEADER
at the Rudolf Virchow Center

Prof. Bernhard Nieswandt

GOAL

We are interested in the molecular mechanisms underlying platelet biogenesis and function in normal physiology and the pathogenesis of thrombo-inflammatory diseases. Our major goal is to identify novel therapeutic targets for these diseases. We are working with transgenic mouse models, cell culture systems and advanced *in vitro* and *in vivo* imaging techniques.

RESEARCH BACKGROUND

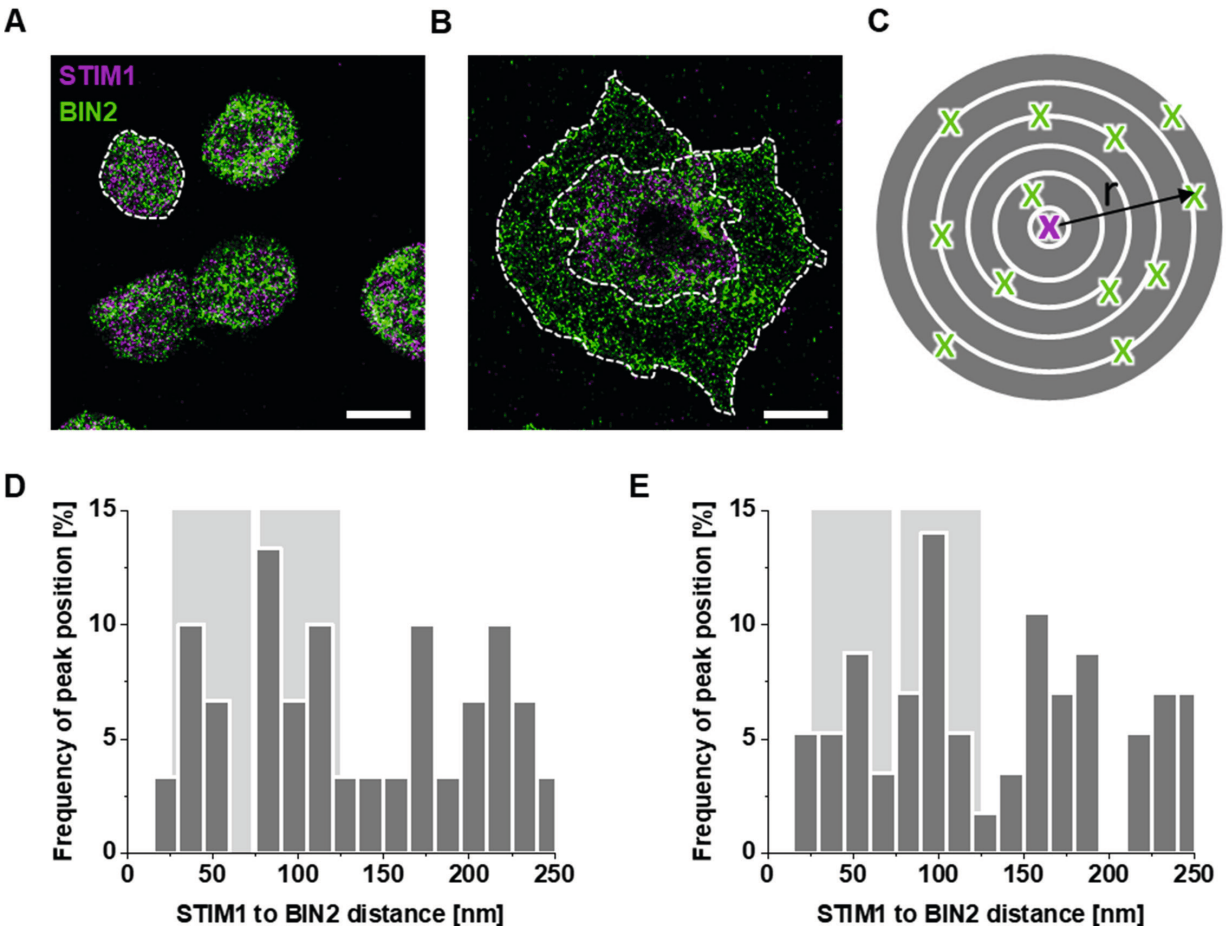
Platelets are the smallest cells of the hematopoietic system and produced by giant precursor cells in the bone marrow, the megakaryocytes (MKs). At sites of vascular injury, platelets adhere and become activated, resulting in the formation of a hemostatic plug. In diseased vessels this can result in pathological thrombus formation, causing ischemia and infarction. Furthermore, the interaction of platelets with immune cells plays a major role in the maintanence of vascular integrity during inflammation, under ischemic conditions and in the context of malignancies.

RESEARCH HIGHLIGHTS

Store-operated calcium entry (SOCE) is the major route of Ca^{2+} influx in activated platelets, but the underlying molecular machinery is still ill-defined. We have now identified the BAR-domain protein *bridging integrator 2* (BIN2) as an essential component of the SOCE complex in platelets, which interacts with the intracellular Ca^{2+} sensor molecule STIM1 and thereby enables efficient platelet activation in response agonist stimulation (J Clin Invest 2020).

Increasing evidence suggests that platelets play a predominant role in cancer metastasis, but the underlying mechanisms remain elusive. We have now shown that the platelet receptor GPVI interacts with the tumor cell-expressed receptor galectin-3 to promote the metastasis of colon and breast cancer cells, indicating that GPVI might be a promising target for antimetastatic therapies. (Blood 2020).

Maintenance of tumor vasculature integrity is indispensable for tumor growth and platelets have been identified to play a role in this process. We have now demonstrated that targeting platelet GPVI rapidly induced tumor hemorrhage and facilitated the accumulation of coadministered chemotherapeutic agents, such as Doxil and paclitaxel, thereby resulting in a profound antitumor effect. These results could lead the way to developing of antitumor strategies based on interfering with platelet function (Blood 2019).



Super-resolution microscopy data of resting (A) and activated platelets (B) shows the distribution of BIN2 (green) and STIM1 (magenta). Particularly, our neighbor density analysis (C) revealed an accumulation of BIN2 in the close vicinity to STIM1 at characteristic distance regions of 50 and 100 nm (for both resting (D) and activated (E) human platelets). These findings point to co-localization hotspots of STIM1 and BIN2 that have not been described before.

FUTURE PLANS

With the new focus of the Rudolf Virchow Center on Bioimaging, we will be able to develop and employ advanced imaging methods such as super-resolution and expansion microscopy for molecular studies on signal transduction and cytoskeletal dynamics in platelets and megakaryocytes. This research area will be further strengthened by the new professorship for *Vascular Imaging* in the RVZ, which will focus on intravital imaging of thrombo-inflammatory processes *in vivo*.

In July 2018, the new Collaborative Research Center/ Transregio (CRC/TR 240 "Platelets" Würzburg-Tübingen) started its work under the leadership of our institute. We have now started to plan the research program of the CRC/TR 240 for the next funding period, which will integrate further projects in Würzburg and other research sites.

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Volz J, Kusch C, Beck S, Popp M, Vögtle T, Meub M, Scheller I, Heil HS, Preu J, Schuhmann MK, Hemmen K, Premsler T, Sickmann A, Heinze KG, Stegner D, Stoll G, Braun A, Sauer M, Nieswandt B. BIN2 orchestrates platelet calcium signaling in thrombosis and thrombo-inflammation. J Clin Invest., Nov. 2020, Volume: 130, Issue: 11, Pages: 6064-6079, doi: 10.1172/JCI136457.

Mammadova-Bach E, Gil-Pulido J, Sarukhanyan E, Burkard P, Shityakov S, Schonhart C, Stegner D, Remer K, Nurden P, Nurden AT, Dandekar T, Nehez L, Dank M, Braun A, Mezzano D, Abrams SI, Nieswandt B. Platelet glycoprotein VI promotes metastasis through interaction with cancer cell-derived galectin-3. BLOOD, Apr. 2020, Volume: 135, Issue: 14, Pages: 1146-116. doi: 10.1182/blood.2019002649.

GROUP LEADER
at the Rudolf Virchow Center

Prof. Markus Sauer

GOAL

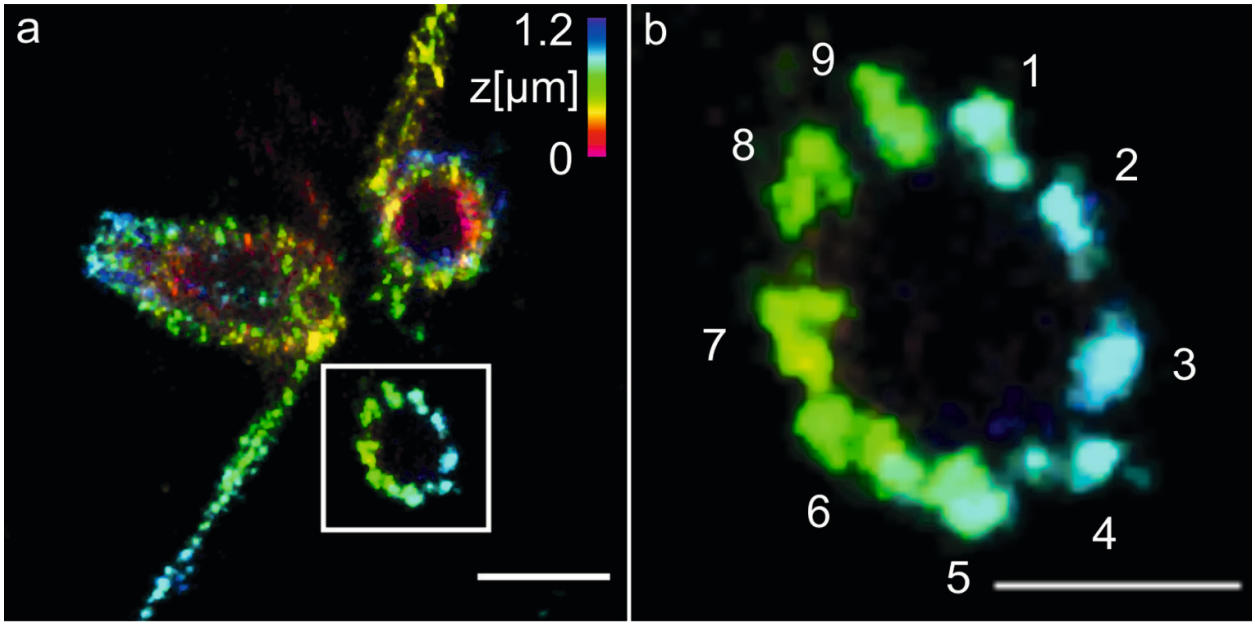
We develop refined single-molecule fluorescence spectroscopy and imaging methods with high spatial and temporal resolution. In particular, we focus on super-resolution fluorescence imaging by *direct* stochastic optical reconstruction microscopy (*d*STORM) as well as Expansion Microscopy (ExM), and their applications in biomedicine.

RESEARCH BACKGROUND

In order to understand how a cell functions and which mechanisms occur in the case of a dysfunction or disease, it is essential to understand how biomolecules are organized into complexes and the dynamics of this organization. In the last decade, super-resolution microscopy has evolved into a very powerful method for sub-diffraction resolution fluorescence imaging of cells and structural investigations of cellular organelles. Super-resolution microscopy methods can now provide a spatial resolution that is well below the diffraction limit of light microscopy, enabling invaluable insights into the spatial organization of proteins in biological samples.

RESEARCH HIGHLIGHTS

Current super-resolution measurements become error-prone below 25 nm. An alternative approach to bypass the diffraction limit and enable “super-resolution imaging” on standard fluorescence microscopes, is the physical expansion of the cellular structure of interest, called Expansion Microscopy, (ExM). By linking a protein of interest into a dense, cross-linked network of a swellable polyelectrolyte hydrogel, biological specimens can be physically expanded, allowing ~70 nm lateral resolution by confocal laser scanning microscopy. We use ExM in combination with super-resolution microscopy to visualize intracellular pathogens and resolve the double-membrane of gram-negative bacteria in infected cells. We can then characterize the morphology of mitochondrial cristae, and unravel details of the molecular organization of multiprotein complexes and organelles including the synaptonemal complex (SC) and centrioles. Very recently, we succeeded in combining ExM with *d*STORM and demonstrated that post-labeling ExM resolves the current limitations of super-resolution microscopy. Post-labeling ExM-*d*STORM preserves ultrastructural details, improves the labeling efficiency and reduces the positional error arising from linking fluorophores into the gel, thus paving the way for super-resolution imaging of immunolabeled endogenous proteins with true molecular resolution.



Images: (a) 3D Ex-*d*STORM image of a 3.2-fold expanded centriole. (b) Expanded view of the white rectangle in (a) shows the 9-fold symmetry of the procentriole. Scale bar, 500 nm. (c) 3D Ex-*d*STORM image of 3.1-fold expanded tubulin filaments of a cell. Scale bar, 1 µm. (d) Expanded view of the white rectangle in (c) shows one tubulin filament. (e) xz side view cross section reveals the hollow structure of microtubulues. Scale bar, 500 nm (d,e).

FUTURE PLANS

We will use super-resolution microscopy and ExM to quantify tumor-associated antigens on primary cells and investigate the effectiveness of CAR T cells to improve personalized molecular immunotherapy. Furthermore, we will use our experience in single-molecule spectroscopy and genetic code expansion with unnatural amino acids and site-specific click-labeling to overcome current limitations in super-resolution microscopy, to provide reliable ultra-resolution imaging, with true molecular resolution at 1-5 nm with visible light.

SELECTED PUBLICATIONS

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Zwettler FU, Reinhard S, Gambarotto D, Bell TDM, Hamel V, Guichard P, Sauer M. Molecular resolution imaging by post-labeling expansion single-molecule localization microscopy (Ex-SMLM). Nat. Commun. 11, 3388 (2020)
doi: 10.1038/s41467-020-17086-8.

GROUP LEADER
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, drives 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 deciphering the molecular basis of life. Our research efforts are concentrated into two areas: (1) The modification of proteins with ubiquitin or ubiquitin-like modifiers with a focus on the activating enzymes, selected ubiquitin ligases and the AAA ATPase p97. (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 today artemisinin-based combination therapies constitute state-of-the-art antimalarial drug regime. In mammalian systems, artemisinins have also been implicated in the modulation of various cellular processes. Following up on the recent discovery that artemisinins interact with the inhibitory neurotransmitter receptor anchoring protein gephyrin, our team structurally and functionally characterized the interactions between these drugs and gephyrin, which revealed how they modulate inhibitory neurotransmission by destabilizing the gephyrin-glycine/$GABA_A$ receptor scaffold. Subsequently, we investigated the interaction between artemisinins and another identified molecular target, the central metabolic enzyme pyridoxal kinase (PDXK).

PDXK catalyzes the ATP-dependent conversion of B6 vitamers into pyridoxal phosphate, the active form of vitamin B6, which, in turn, acts as an essential cofactor in various essential enzymatic transformations, including the biosynthesis of the inhibitory neurotransmitter GABA by glutamic acid decarboxylase (GAD). Enzyme kinetic studies demonstrated that artesunate and artemisinin inhibit PDXK. A crystal structure of the ternary PDXK-ATPγS-artesunate complex revealed that the drug bound in proximity to the ATP cofactor, at a

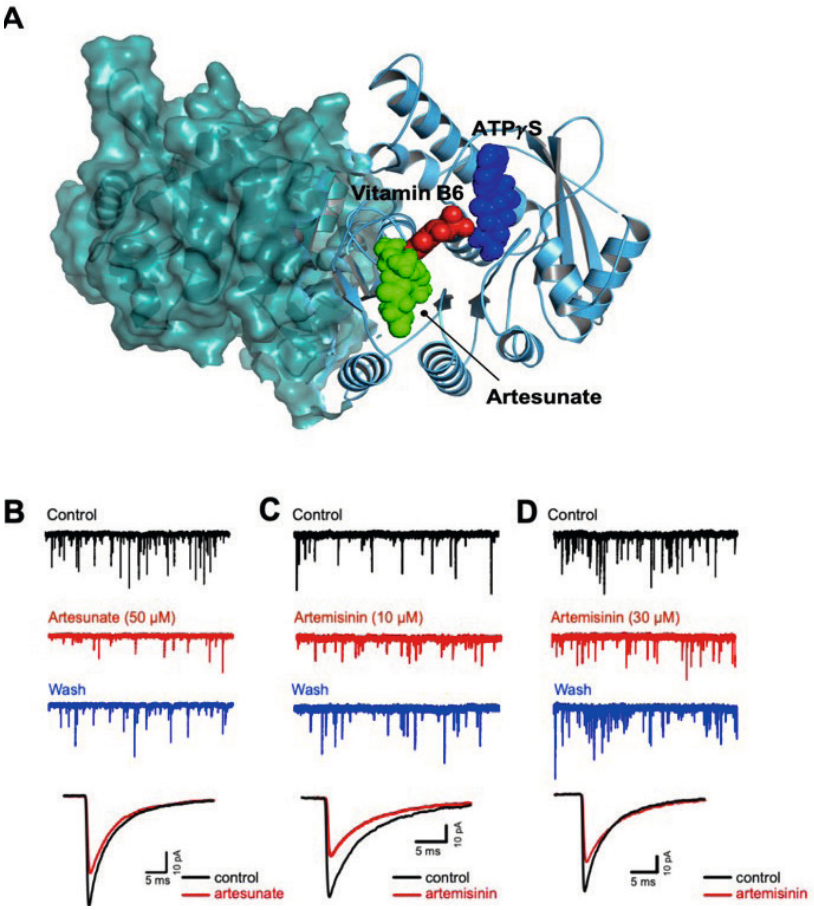


Figure: (A) Crystal structure of the ternary PDXK-ATPγS-artesunate complex (one monomer in surface and the other in ribbon respresentation) reveals how artesunate (green) interferes with vitamin B6 (red) binding. (B-D) Artemisinin-induced differences in electrophysiological recordings.

site normally occupied by the B6 vitamers, prior to their transformation into vitamin B6. These findings suggest that inhibition of PDXK by artemisinins decrease cellular vitamin B6 levels, thereby also inhibiting GAD. Quantification of GABA levels in primary hippocampal neurons in the presence of artemisinin indeed revealed a significant reduction in GABA levels. Finally, the impact of artemisinins on inhibitory neurotransmission was quantified by whole-cell voltage-clamp recordings in hippocampal slices. These studies confirmed the postsynaptic action of the drugs, since the amplitudes of miniature inhibitory postsynaptic recordings were significantly reduced. At slightly higher drug concentrations the firing frequencies were also found to be reduced, in line with the presynaptic action of these compounds via the PDXK-GAD axis. Thus, these data provide a comprehensive model for the regulation of inhibitory neurotransmission by artemisinins at both presynaptic and postsynaptic sites.

Since 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 with the aim of developing novel treatment concepts.

SELECTED PUBLICATIONS

Kasaragod VB, Pacios-Michelena A, Schaefer N, Zheng F, Bader N, Alzheimer C, Villmann C, Schindelin H. (2020) Pyridoxal Kinase Inhibition by Artemisinins Downregulates Inhibitory Neurotransmission.Proc Natl Acad Sci U S A. 2020 Dec 29;117(52):33235-33245.
doi: 10.1073/pnas.2008695117.

Kasaragod V B, Hausrat TJ, Schaefer N, Kuhn M, Christensen NR, Tessmer I, Maric HM, Madsen KL, Sotriffer C, Villmann C, Kneussel M, & Schindelin H. (2019). Elucidating the Molecular Basis for Inhibitory Neurotransmission Regulation by Artemisinins. Neuron, 101(4), 673–689. doi: 10.1016/j.neuron.2019.01.001.

GROUP LEADER
at the Rudolf Virchow Center

Dr. Andreas Schlosser

GOAL

We are analyzing immunopeptidomes by mass spectrometry in order to identify new targets for cancer immunotherapy, for vaccination against viruses and fungi, and for immunotherapeutic intervention against autoimmune diseases.

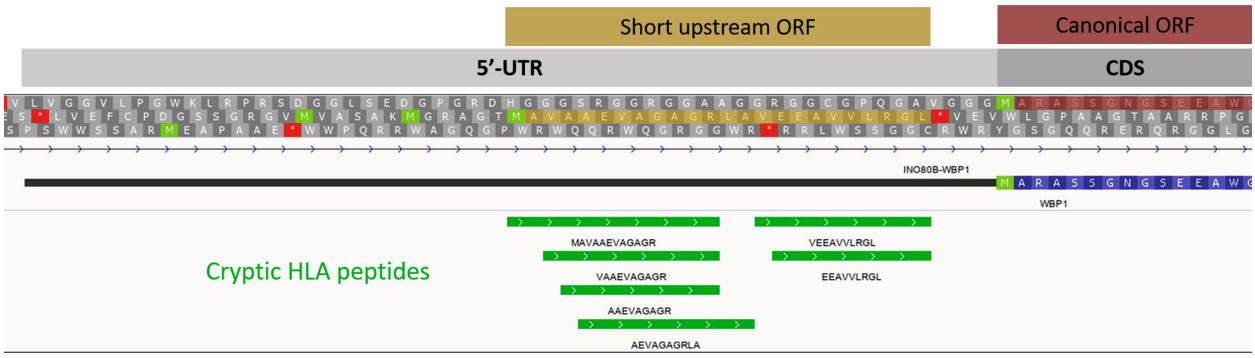
RESEARCH BACKGROUND

Human leukocyte antigen class I (HLA-I) peptides are the key players in the cellular immune response. These peptides are presented on the surface of all human cells and constitute the so-called immunopeptidome. The immunopeptidome is continuously scanned by cytotoxic T cells, enabling the immune system to recognize nonself HLA peptides (e.g. from viral proteins) or neoantigens (e.g. peptides with tumor-specific mutations), and then to eradicate pathogen-infected cells as well as tumor cells. HLA peptides can be isolated directly from the relevant cells or tissue (e.g. tumor tissue) and identified by mass spectrometry.

RESEARCH HIGHLIGHTS

Whereas the majority of HLA-I peptides originate from protein-coding regions of the human genome, there is accumulating evidence for the existence of HLA-I peptides with unusual origin (the “dark matter” of immunopeptidomes). These so-called cryptic peptides are derived either from allegedly non-coding regions of the human genome, such as the 5’- and 3’-untranslated regions (UTRs) of mRNAs, non-coding RNAs (ncRNAs) or introns, or from translation of short open reading frames (sORFs) in a non-canonical reading frame.

In close collaboration with Florian Erhard (Institute for Virology and Immunobiology, University of Würzburg), we have developed a new *de novo* sequencing-based data analysis workflow (PeptidePRISM) that made the comprehensive identification of cryptic peptides possible for the first time. With our new approach, we have been able to identify thousands of cryptic HLA peptides that completely escaped identification before. For some HLA allomorphs, such as A*03:01, up to 15% of all presented HLA peptides turned out to be cryptic. We have been able to demonstrate that cryptic peptides represent a significant part of tumor immunopeptidomes, and that some of them appear to be tumor-specific.



Example of the mass spectrometric identification of cryptic HLA-I peptides in the 5'-UTR of an mRNA.

FUTURE PLANS

By comparing a large set of immunopeptidomes from different types of tumors (e.g. melanoma, colorectal cancer and leukemia) with the immunopeptidomes of healthy cells we have already identified a number of cryptic HLA-I peptides that appear to be not only tumor-specific, but also recurrently found on tumors from different patients. This makes these cryptic peptides highly attractive as potential new targets for cancer immunotherapy.

We will further extend our efforts in identifying new targets for cancer immunotherapy by expanding our immunopeptidome analyses (e.g. to additional types of cancer) and by applying complementary methods, such as RNA-seq and Ribo-seq. We will apply various immunological assays for the best candidate peptides to confirm their immunogenicity. Our long-term goal is to evaluate the potential of the best immunogenic cryptic peptides in cancer immunotherapy in clinical trials.

SELECTED PUBLICATIONS

Erhard F, Dölken L, Schilling B, Schlosser A. Identification of the cryptic HLA-I immunopeptidome. Cancer Immunol Res. 2020
doi: 10.1158/2326-6066.CIR-19-0886.

Adhikari B, Bozilovic J, Diebold M, Schwarz JD, Hofstetter J, Schröder M, Wanior M, Narain A, Vogt M, Dudvarski Stankovic N, Baluapuri A, Schönemann L, Eing L, Bhandare P, Kuster B, Schlosser A, Heinzlmeir S, Sotriffer C, Knapp S, Wolf E. PROTAC-Mediated Degradation Reveals a Non-Catalytic Function of AURORA-A Kinase. Nat. Chem. Biol. 2020. doi.org/10.1038/s41589-020-00652-y.

GROUP LEADER
at the Rudolf Virchow Center

Dr. Grzegorz Sumara

GOAL

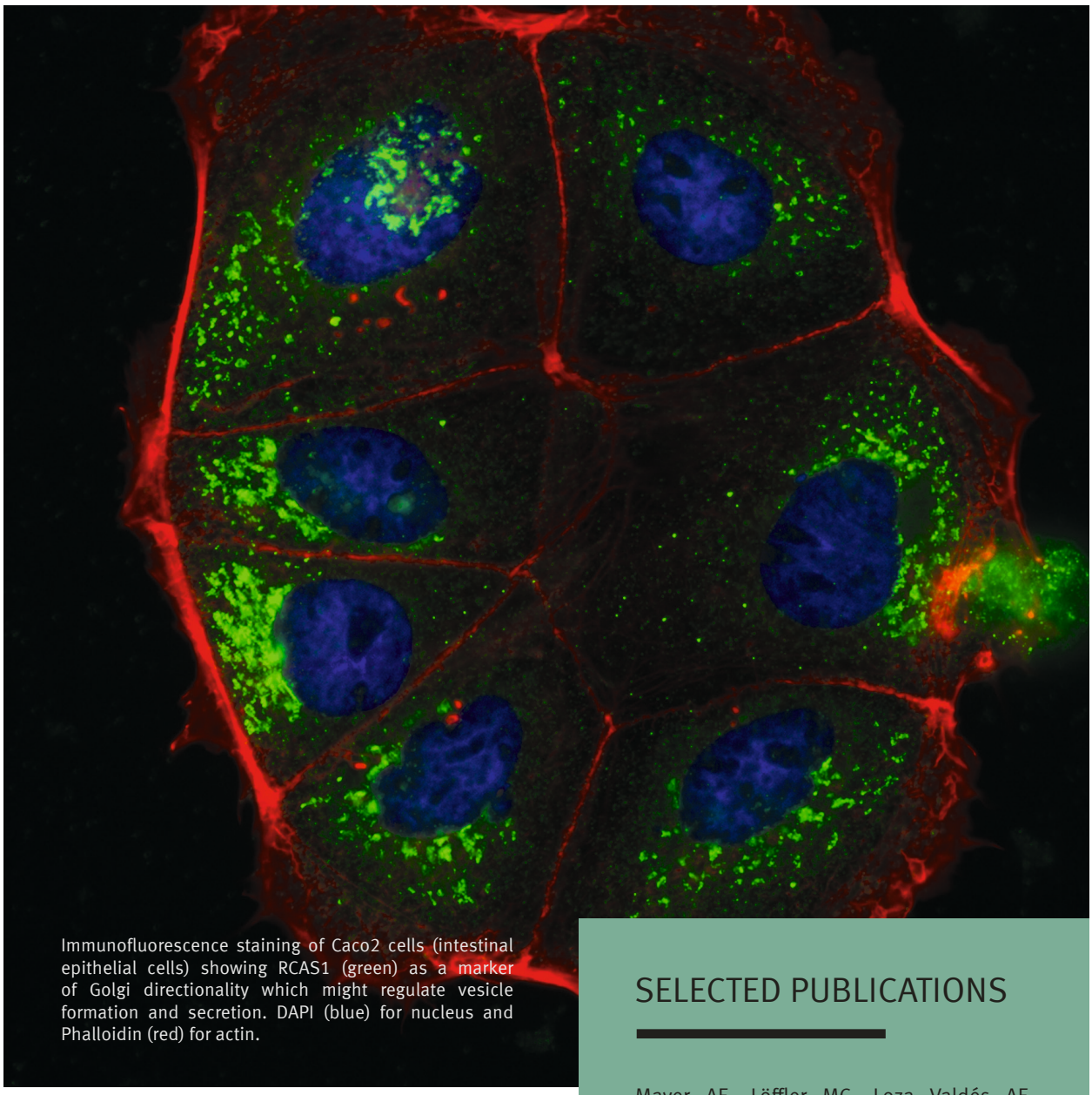
Our research group aims to unravel signaling cascades aberrantly activated during the development of metabolic diseases such as obesity or type 2 diabetes (T2D) and to understand their impact on the progression of these disorders.

RESEARCH BACKGROUND

Over 1.9 billion people worldwide are obese or overweight. Obesity itself is rather an esthetic and gravitational problem. However, obesity promotes the deposition of lipids in many organs, which changes the metabolism of the organism by affecting so-called signaling cascades. This results in perturbations in the rate of basic metabolic processes such as lipolysis and lipogenesis in adipose tissue and the liver, or absorption of nutrients in the intestine, which leads to the further progression of the metabolic diseases.

RESEARCH HIGHLIGHTS

Perturbations in signaling cascades regulating metabolic processes in adipose tissue, the intestine, and the liver result in metabolic imbalance and metabolic diseases. Excessive absorption of lipids and other nutrients in the intestines promotes adiposity. In adipocytes, elevated lipogenesis and lipolysis in combination with reduced energy dissipation are the hallmarks of obesity and T2D. Increased lipogenesis also contributes to the development of fatty liver disease. In our research group, we aim at understanding the complex signaling network regulating the above-mentioned metabolic processes. For this purpose, we combine cell biology, biochemical, and omics approaches with mouse genetics. Using high throughput siRNA-based screening we identified a number of novel kinases regulating lipolysis. This includes Extracellular-regulated kinase 3 (Erk3), which is released from ubiquitin-proteasome mediated degradation upon ß-adrenergic stimulation and is strictly required for ß-agonists-induced lipolysis (El-Merahbi R et al., Genes&Development, 2020). Using a targeted mouse genetics approach we identified that members of diacylglycerol activated protein kinase D are central regulators of enterocyte, and hepatocyt metabolism, and are potential targets for the treatment of obesity and T2D (Mayer AE et al., Science Signaling 2019 and Trujillo Viera J et al., manuscript under revision).



Immunofluorescence staining of Caco2 cells (intestinal epithelial cells) showing RCAS1 (green) as a marker of Golgi directionality which might regulate vesicle formation and secretion. DAPI (blue) for nucleus and Phalloidin (red) for actin.

FUTURE PLANS

In the future, we plan to investigate the identified pathways in the context of metabolic diseases. In parallel, we will use screening approaches to identify novel, noncanonical signaling modules (components of the ubiquitin system) regulating abundance, localization, and phosphorylation of kinases and their targets implicated in the regulation of metabolism. By identifying and characterizing essential signaling networks in enterocytes and adipocytes this project will contribute to more targeted pharmacological strategies for the treatment of metabolic diseases such as obesity and T2D.

SELECTED PUBLICATIONS

Mayer AE, Löffler MC, Loza Valdés AE, Schmitz W, El-Merahbi R, Viera JT, Erk M, Zhang T, Braun U, Heikenwalder M, Leitges M, Schulze A, Sumara G. The kinase PKD3 provides negative feedback on cholesterol and triglyceride synthesis by suppressing insulin signaling. Sci Signaling, 2019.

El-Merahbi R, Viera JT, Valdes AL, Kolczynska K, Reuter S, Löffler MC, Erk M, Ade CP, Karwen T, Mayer AE, Eilers M, Sumara G. The adrenergic-induced ERK3 pathway drives lipolysis and suppresses energy dissipation. Genes&Development, 2020.

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 techniques.

RESEARCH BACKGROUND

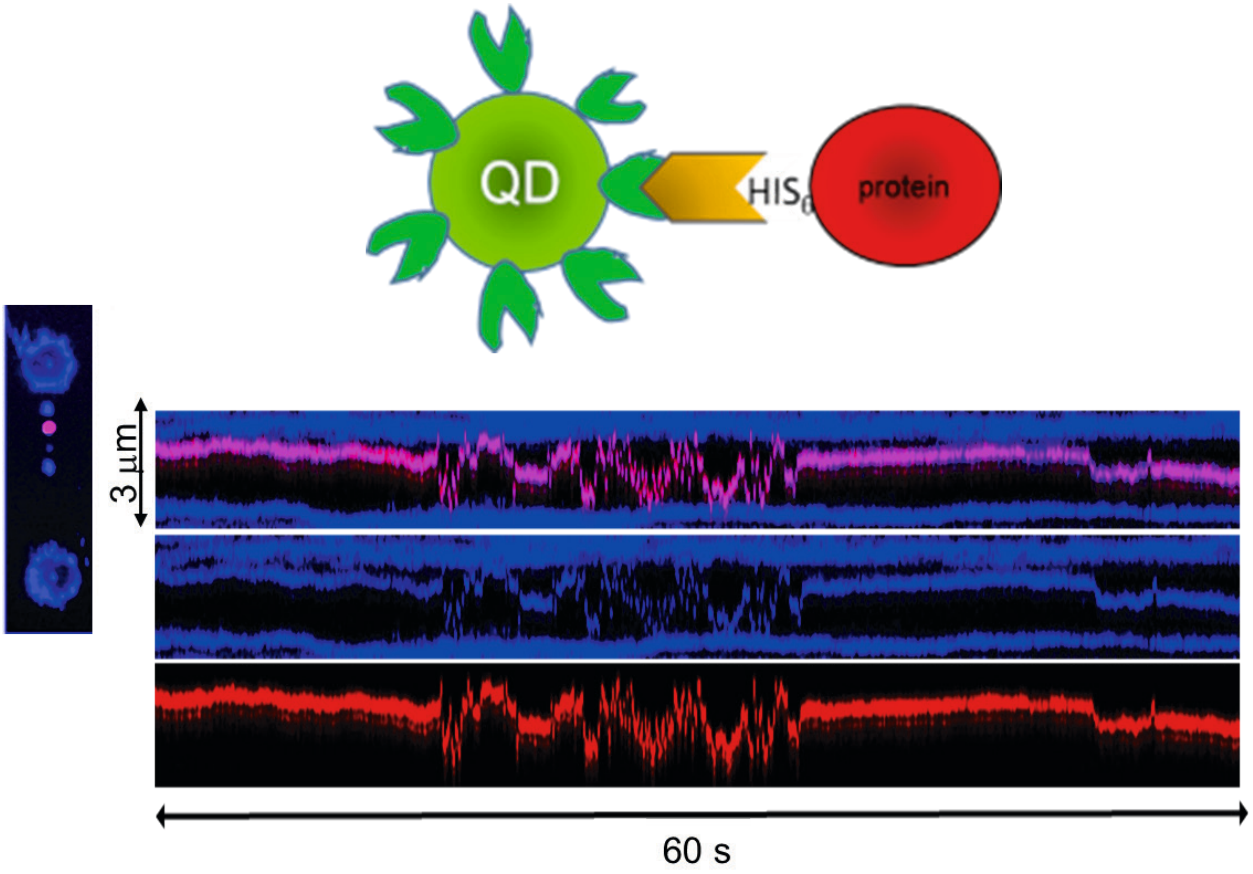
Our work aims at understanding general and specific features of DNA damage recognition strategies in different DNA repair systems, as well as the interplay between these different systems. We also investigate protein interactions involved in DNA replication in collaborations with Dr. Helmut Pospiech, Leibniz Institute on Aging, Jena, and Prof. H.P. Nasheuer's laboratory at the University of Galway, Ireland. In our studies, we use single molecule imaging by fluorescence and atomic force microscopy (AFM), combined with other biophysical and biochemical approaches.

RESEARCH HIGHLIGHTS

In vivo, many proteins function within different pathways, and different pathways are interlinked in a complex manner. We have recently been able to resolve one such link between different DNA repair pathways, by directly showing recruitment of UvrA, the initiating enzyme of prokaryotic nucleotide excision repair (NER) by the alkyltransferase-like protein, ATL. Our data further showed ATL transporting UvrA along DNA in search of target lesions.

In collaboration with Prof. Katrin Heinze's laboratory, we have established an automated, unbiased, high throughput approach to conformational analyses of protein-DNA complexes as well as structural properties of DNA lesions. We applied this novel tool to reveal initial lesion-sensing strategies by base excision repair glycosylases.

SV40 large T antigen forms hexameric assemblies on DNA. Two hexamers have been shown to load in a head-to-head fashion, to create the replication bubble, and function as the replicative helicase in the simplified viral system. Interestingly, our studies revealed a role for monomeric T antigen in lagging strand synthesis. In our model, RPA and monomeric T antigen both support hexameric T antigen helicase activity by filling up the evolving ssDNA in its wake. In addition, we also demonstrate loading of the priming polymerase by monomeric T antigen.



Overlay of ATL (labeled with blue fluorescent quantum dots) and UvrA (labeled with red fluorescent quantum dots) kymographs demonstrates co-translocation of UvrA and ATL on undamaged DNA.

FUTURE PLANS

We are interested in resolving the structural basics of the recruitment of UvrA by ATL, as well as the functional consequences on alkyl-lesion repair. Our studies on pre-selection criteria in glycosylase lesion search have revealed a so far unknown, transient conformation of the glycosylase AAG that repairs alkylated adenine in DNA, which we will investigate in more detail in future studies. Furthermore, the glycosylase hOGG1 has been reported to be involved in transcription regulation. We have recently started studying protein interactions by hOGG1 and their implications on transcription initiation.

SELECTED PUBLICATIONS

Rill N, Mukhortava A, Lorenz S, Tessmer I. Alkyltransferase-like protein clusters scan DNA rapidly over long distances and recruit NER to alkyl-DNA lesions. Proceedings of the National Academy of Sciences of the USA, April 2020.
doi: 10.1073/pnas.1916860117.

Bangalore D, Heil H, Mehringer C, Hirsch L, Hemmen K, Heinze K, Tessmer I. Automated AFM analysis of DNA bending reveals initial lesion sensing strategies of DNA glycosylases. Scientific Reports, September 2020.
doi: 10.1038/s41598-020-72102-7.

GROUP LEADER
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.

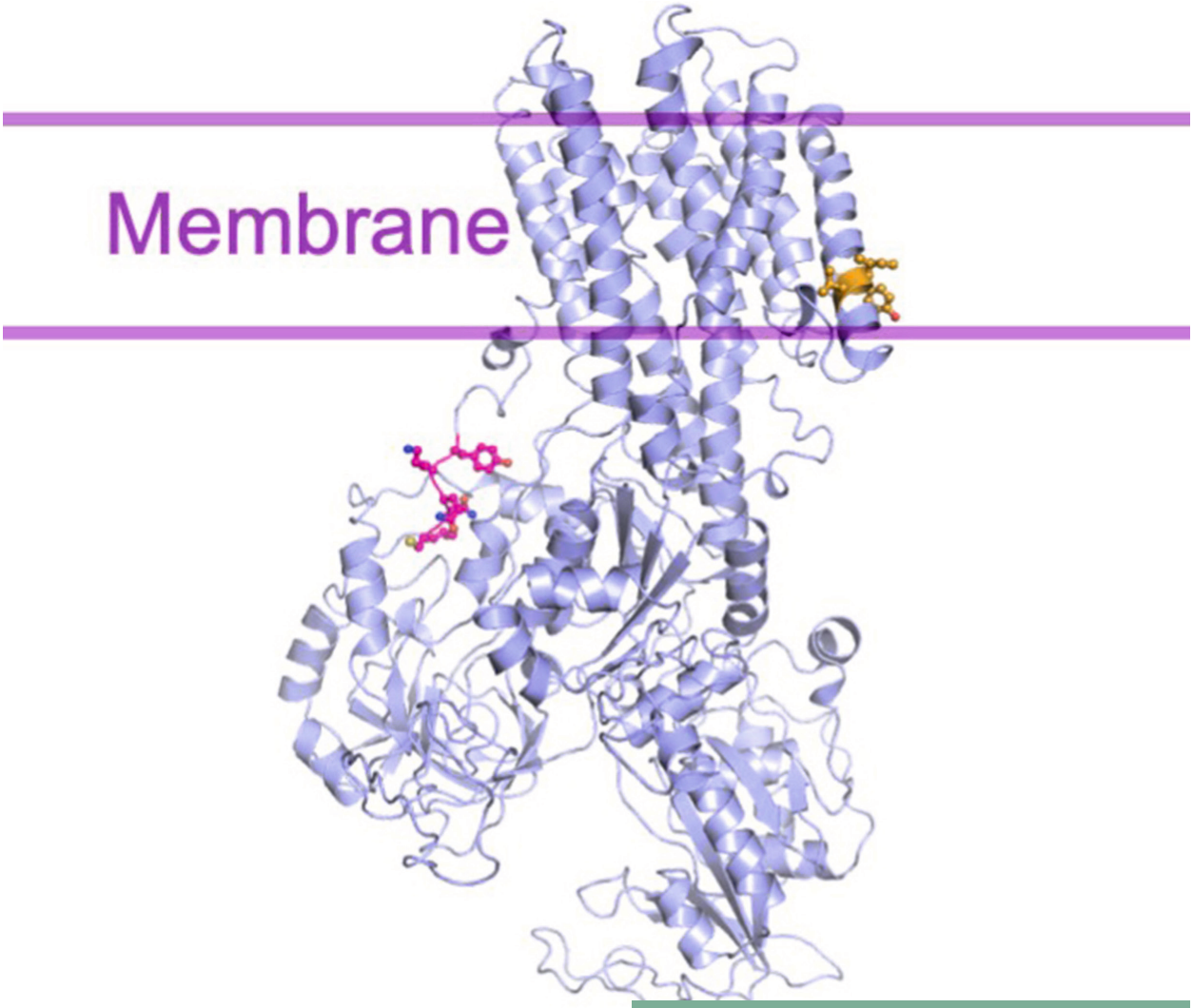
RESEARCH BACKGROUND

Extracellular vesicles are released by cells, from bacterial to human. They remodel cell membranes after injury and send signals between cells. Extracellular vesicles released in body fluids also serve as non-invasive biomarkers. Despite the many roles of extracellular vesicles, the mechanisms behind their formation, function, and clearance are unclear. I have established a model for plasma membrane budding to release extracellular vesicles centered around the phospholipid flippase TAT-5. Our lab also discovered that 1 µm extracellular vesicles are cleared by LC3-associated phagocytosis.

RESEARCH HIGHLIGHTS

To track extracellular vesicles *in vivo*, our lab developed degron-based reporters to label extracellular vesicles (Nat Comm 2019), as 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 these reporters, we were able to quantify extracellular vesicle accumulation *in vivo* (Front Cell Dev Biol 2020). We further demonstrated that degron protection assays revealed superresolution insights into membrane topology during cell division, as well as helped define the localization and orientation of proteins (Nat Comm 2019). Degron approaches therefore add an important method to the cell biologist's toolkit.

In addition, our lab discovered the opposing effects of the lipids phosphatidylserine (PS) and phosphatidylethanolamine (PE) on the phagocytosis of cell corpses and other cellular debris (Front Cell Dev Biol 2020). While PS exposure on the surfaces of cells led to an increase in phagocytosis, exposing PE blocked phagocytosis, which correlated with the extent of extracellular vesicle release. Since these lipids are often externalized together, this work reveals the conflicting signals these poorly understood lipids can send.



The lipid flippase TAT-5 internalizes phosphatidylethanolamine and inhibits extracellular vesicle release.

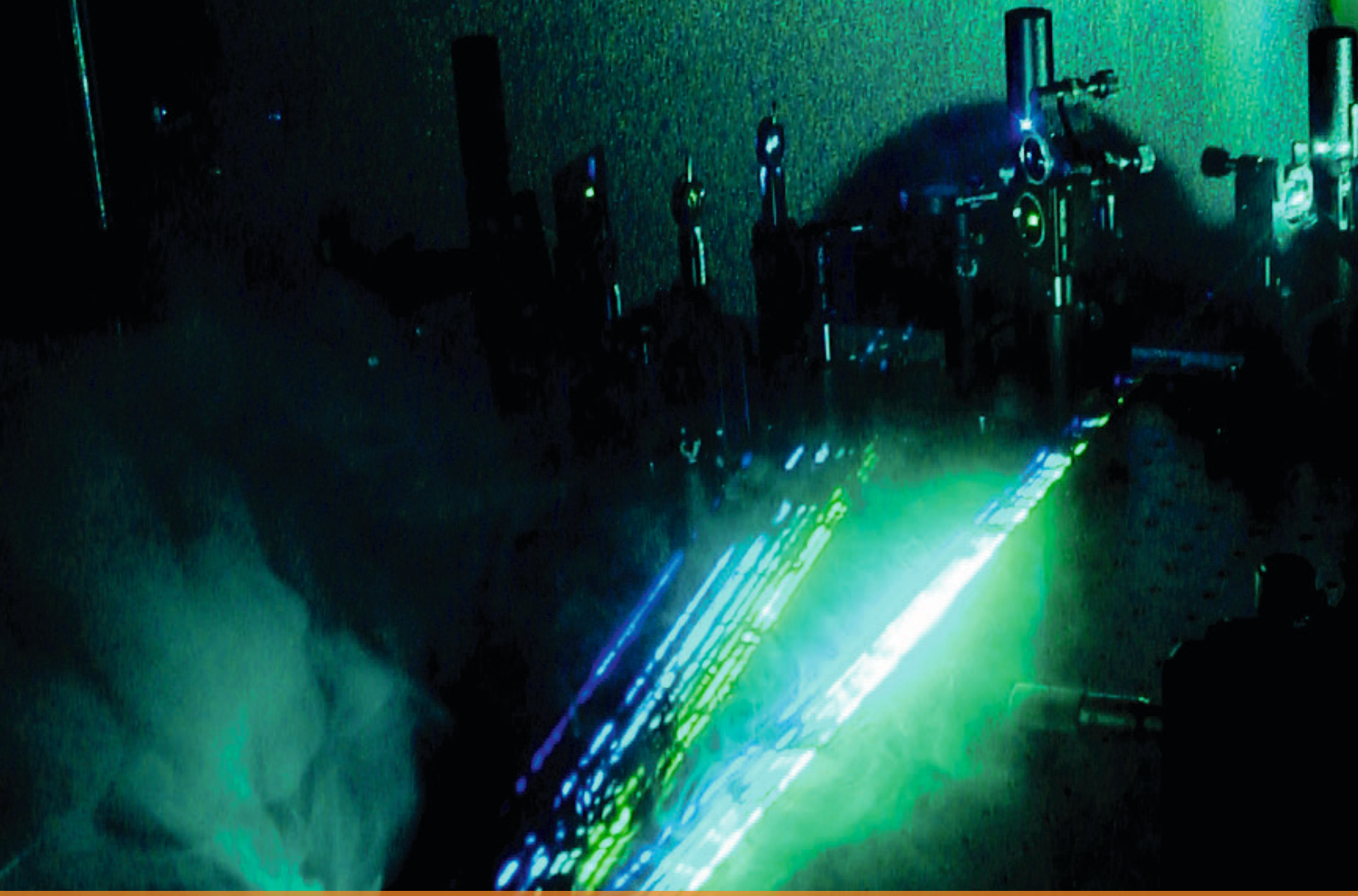
FUTURE PLANS

After seven productive years at the RVZ, our lab moved in 2020 to the University of Denver in the United States of America. We are continuing our studies on extracellular vesicle biology, phagocytic clearance, and programmed necrosis, while enjoying views of the Rocky Mountains. We will continue to use our innovative degron approach to gain novel insights into fundamental aspects of membrane dynamics, which are tightly regulated during development and normal physiology, and dysregulated in many diseases.

SELECTED PUBLICATIONS

Beer KB, Fazeli G, Judasova K, Irmisch L, Causemann J, Mansfeld J, Wehman AM. Degron-tagged reporters probe membrane topology and enable the specific labelling of membrane-wrapped structures. Nat Commun, August 2019, doi: 10.1038/s41467-019-11442-z.

Fazeli G, Beer KB, Geisenhof M, Tröger S, König J, Müller-Reichert T, Wehman AM. Loss of the Major Phosphatidylserine or Phosphatidylethanolamine Flippases Differentially Affect Phagocytosis. Front Cell Dev Biol, July 2020. doi: 10.3389/fcell.2020.00648.



INFRASTRUCTURE

SUPPORT

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

LARGE SCALE PROTEIN EXPRESSION

The recombinant protein expression facility run by Lars Schönemann 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.

22
EXTERNAL USERS

87
EXTERNAL RUNS

3920
HOURS USED

IMAGING

The Core Unit Fuorescence Imaging run by Katrin Heinze offers advanced light microscopy approaches ranging from superresolution to whole organ imaging. Besides *d*STORM, 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 FLIM, FRET and FCS.

38
EXTERNAL USERS

1551
EXTERNAL RUNS

5349
HOURS USED

MASS SPECTROMETRY

The technology platform mass spectrometry and proteomics, headed by Andreas Schlosser, offers a wide range of methods to all institutes at 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.

40
EXTERNAL USERS

4100
EXTERNAL RUNS

8200
HOURS USED

ANNUAL EVENT

RVZ RETREAT

One of the most important joint activities of all research groups at the Rudolf Virchow Center is the annual RVZ retreat. The retreat is an ideal opportunity for new group leaders and their PhD 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 as well as new collaborations.

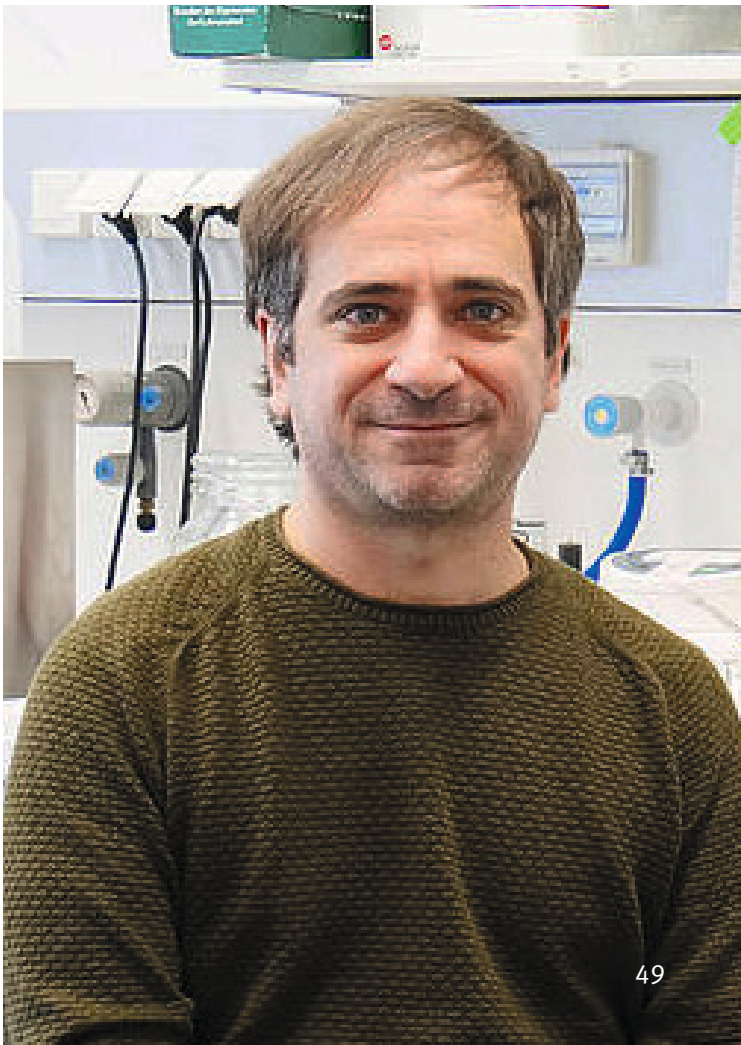
PUBLIC OUTREACH

Dr. Andrea Thorn, a structural biologist, is leading an international coronavirus research network. The results of her work are important for developing vaccines and drugs. Although scientists already know a lot about the virus they still lack detailed knowledge in many areas.

Andrea Thorn and her team aim to provide these missing details. Together they form the “Coronavirus Structural Task Force“ – an international network of experts in the field of structural biology. Their goal is to validate our existing knowledge of the molecular structures of the coronavirus and to fill knowledge gaps – or as she puts it: “To get as much as possible out of the data“.

The recipe for a publication in Nature? A good idea, perseverance, the courage to put all your eggs in one basket, a committed team and an environment that offers the necessary technical, thematic and personnel support. In the case of Dr. Sebastian Geibel, this mix of ingredients was the basis for the biochemist being able to publish a highly regarded paper in the renowned journal.

The structural biology of mycobacteria – the pathogens that cause tuberculosis – is Geibel‘s main research focus. In the above paper published in Nature, he describes for the first time the structure of a nanomachine that the bacterium uses to evade attack by the human immune system and ensures its survival in the organism it infects. His findings on the so-called type VII secretion system provide the basis for new active agents to combat a disease whose pathogens are increasingly resistant to the usual drugs.



PUBLIC SCIENCE CENTER
at the Rudolf Virchow Center

SCIENCE FOR SOCIETY

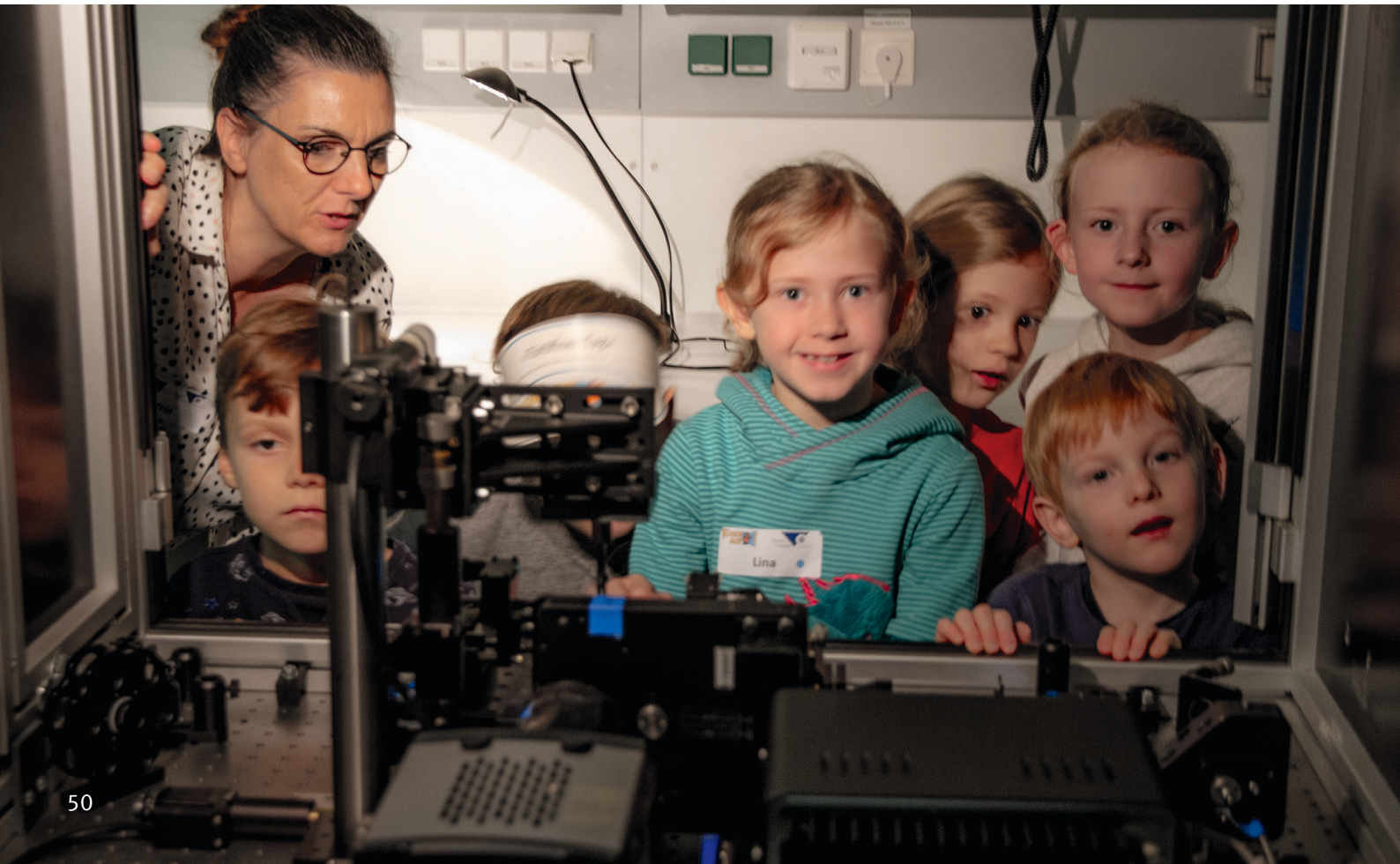
The Public Science Center (PSC) is an independent division at the Rudolf Virchow Center. It fosters the dialog between science and society by sharing the research work at the Rudolf Virchow Center with the public.

A variety of public engagement activities is offered for children and adults throughout the year.

At “Rudis Forschercamp” children aged between 8 and 12 have the opportunity to get to know a real laboratory and explore the natural sciences using exciting hands-on experiments. Over several days the children explore biology, chemistry, physics and medicine. To date more than 1000 children have spent exciting afternoons in Rudis Forschercamp.

The Virchowlab is designed for high school pupils to become familiar with the (daily) work of a scientist. After an introduction, they experience practical research work in our school lab with their class mates and their teacher. Current topics such as infectious diseases and genetic engineering raise the young people‘s interest in science and give them insights into career prospects in science.

Our RVZ scientists are supported and advised by the PSC regarding interacting with the press and online media, and the latest research results are regularly



published in press releases on our website and in various social media channels.

The Center is also involved in external scientific communication, for example related to visits of guest speakers and events, as well as in internal communication and scientific recruitment.

HIGHLIGHTS

On October 3rd 2019, the PSC encouraged conversations about biomedical sciences by opening the doors to the public as part of the Open Day "Sendung mit der Maus WDR Türöffner-Tag". School children had the chance to watch and perform experiments in our labs. Their parents took the opportunity to visit the labs and ask our scientists various questions about their research.

In spring 2020, Rudis Forschercamp opened its doors for the first time to the "Förderschulen", for example for the Maria-Stern-Schule Würzburg and Sonderpädagogisches Förderzentrum Würzburg. This gave the children the chance to visit a lab and perform simple experiments under intensive supervision, and to experience the world of science from the inside.

In November 2020, our PSC school lab participated for the first time at the digital MINT Day, where various participants from science and education meet each other online and present their educational offerings.

The PSC is also involved in "Netzwerk Wissen²", a local association of several educational institutions and the City of Würzburg. In 2020, a new cooperation agreement was signed by all partners to further consolidate the collaboration and increase the association's visibility.

In 2020, Würzburg celebrated the discovery of X-rays by Wilhelm Conrad Röntgen. The RVZ, together with many other local research institutions, presented the modern applications of X-rays in an exhibition for the general public.

In addition, the PSC accompanied and supported several camera crews from different television stations visiting the RVZ and reporting on our research.

In 2019 and 2020, the PSC published 19 press releases providing information about research results and events as well as developments at the RVZ.

BSc / MSc programs in Biomedical Sciences

BACKGROUND

The Faculty of Medicine and the Faculty of Biology at the University of Würzburg offer a joint program in biomedicine, where students are trained at the interface between sciences and clinical research. The program was launched in accordance with the interdisciplinary philosophy of the "old" and "new" RVZ, which particularly includes promoting the training of future generations of scientists. Thus, most of the RVZ groups provide teaching modules and key training to our curious students.

The core curriculum consists of research-oriented training with intensive laboratory courses in small groups and early immersion in current research topics. Additional intensive internships support students to get a taste of the latest research, and to find an exciting project for their bachelor's or master's thesis with their research group of choice.

While the bachelor program is tightly structured and strictly specified, the master's program gives the students plenty of room to set their own priorities and offers a unique, comprehensive course on model organisms throughout the first semester. Our Biomedicine program encourages students to go for practical courses abroad. Most students accept the challenge and spend several weeks or even several months abroad and learn to embrace scientific and cultural diversity — an essential ingredient for a young researcher's career.

Dean of Studies Professor Katrin Heinze (middle) in her laboratory with students.

HIGHLIGHTS

The students elect representatives who closely interact with local and national student bodies. Over the years this has grown into a very interactive, enthusiastic and creative Students Council.

Supported by the Dean of Studies (Prof. Manfred Gessler until 2019, Prof. Katrin Heinze taking over in 2019) they organized several local student activities, e.g. the "3rd Würzburger BIOMEDICA" on November 23, 2019, a symposium for students and alumni with approximately 120 participants. Alumni from Germany and abroad came together for this event and gave scientific or career talks. We are looking forward to the next event in 2021, which is planned as a hybrid or online symposium due to the pandemic.

Internships abroad are one important highlight for our Master students. The UK (England, Scotland), Sweden, France, Portugal, Spain, USA and Australia were the favored destinations in 2019 and 2020. Equally popular have been internships within Germany, particularly in pharmaceutical industry or applied research settings; here companies such as Roche and Fresenius, and research institutions from the Leibniz, Helmholtz, or Fraunhofer associations, such as DKFZ and FZ Jülich were preferentially selected.

Every year, the Biomedicine program provides 35 places in the BSc program as well as 16 places in the MSc program. Demand is continuously increasing and the selection process is highly competitive. Typically, less than 10% of the applicants are invited to enroll in the program. After a successful Master's program, most of our graduates opt for higher scientific qualifications through a PhD degree, about 40% of them in Würzburg. It is a pleasure to see these young scientists thrive and to further support them on their diverse, and often ambitious, career paths.

Flanking programs exist in Biochemistry (BSc/MSc) and Translational Medicine (additional studies and an MSc program within the Elite Network of Bavaria). These studies focus on either the molecular and functional understanding of basic processes of life, or the transition between basic research and clinical research. Here, again, several RVZ research groups participate in training these students at the interface of "bench" and "bedside" with lectures, practical courses and lab rotations.

Graduate School of Life Sciences

The GSLS building between Campus Hubland North and South

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. Since 2019, the State of Bavaria and the University of Würzburg are strongly committed to supporting the GSLS to assure its sustainability for the next seven years.

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 PhD study program. Currently, more than 700 PhD researchers from 53 countries and more than 300 principal investigators contribute to the interdisciplinary and international spirit of the GSLS. A core element of structured PhD training at the GSLS is the three-person thesis committee that identifies individual elements of training ("prescription") depending on the PhD 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! 2020" as online edition.

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 PhD degree in the natural sciences (Ph.D., Dr. rer. nat.).

Among the research institutions contributing to the GSLS doctoral program is the Rudolf Virchow Center with its 12 research groups. Historically, the Virchow Graduate Program was the nucleus of the GSLS and served as a role model for the entire graduate school training concept. Central elements of the PhD training at the Rudolf Virchow Center, besides the regular research group seminars, are the RVZ colloquia and the PhD students' afternoon at the annual Rudolf Virchow Center retreat where all new PhD students introduce themselves and their projects.

HIGHLIGHTS

After being several years in the RVZ/IMIB building on the medical campus, the GSLS moved into a new building on the Campus Hubland North. 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 Initiative (2012).

One of the most prominent GSLS activities is the annual PhD Students' Symposium entirely organized by the GSLS PhD 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 2020, the organizing committee met the challenge of the COVID-19 pandemic and organized the 15th edition, EUREKA!2020, as an online symposium with 150 participants and 100 poster contributions.

APPENDICES
Annual Report 2019 & 2020

RVZ GUEST SPEAKERS

17.01.2019	Dr. Jens Peter von Kries Leibniz-Forschungsinstitut für Molekulare Pharmakologie	”Exploring biological systems by usage of drugs, interfering RNA and CRISPR-CAS in HTS“
24.01.2019	Prof. Dr. Ralf Baumeister Albert-Ludwigs-Universität Freiburg	”Signaling from a distance: non-cellautomous induction of stem-cell tumors in C. elegans“
31.01.2019	Dr. Günter Roth Albert-Ludwigs-Universität Freiburg	”Microarray Copying - a novel approach for novel (and old) microarrays“
13.02.2019	Prof. Stanley Riddell Fred Hutchinson Cancer Research Center (Washington)	”Recent innovations in engineered cellular therapies“
05.03.2019	Prof. Janet Iwasa University of Utah	”Animating biology“
15.05.2019	Prof. Marsha Rosner University of Chicago	”Rewiring signaling pathways in cancer cells“
16.05.2019	Dr. Charlotte Uetrecht Heinrich-Pette-Institut	”Flying viruses - from biophysical to structural characterization“
23.05.2019	Prof. Dr. Ute A. Hellmich Johannes Gutenberg-University Mainz	”TRP ion channel termini – a (somewhat) unexplored playground for structural biologists“
24.06.2019	Prof. Dr. Julian Stingele Ludwig-Maximilians-Universität München	”DNA-protein crosslink repair: proteases as DNA repair enyzmes“
27.06.2019	Prof. Dr. Tobias Madl University of Gratz	”Deciphering the intricate role of FOXO proteins in health and disease“
08.07.2019	Prof. Katrin Rittinger The Francis Crick Institute London	”Structural and mechanistic characterisation of multi-domain E3 ligases that regulate immune signalling“
11.07.2019	Dr. Martina Schweiger Institut für Molekulare Biowissenschaften Universität Graz	”Adipocyte lipolysis in control of the metabolic balance“
18.07.2019	Dr. Marti Duocastella Instituto Italiano di Tecnologia	”Inertia-free focus control for fast volumetric bio-imaging“
09.09.2019	Dr. Achim Werner NIH/NIDCR, USA	”Dissecting neurodevelopmental diseases one ubiquitin linkage at a time“
17.10.2019	Dr. Christian Specht Ecole Normale Supérieure (ENS, Paris)	”Ultra-structure and regulation of mixed inhibitory synapses using dual-colour super-resolution imaging“
22.11.2019	Prof. Luke Chao Harvard University	”Molecular mechanism for mitochondrial inner-membrane fusion by Opa1“
05.12.2019	Prof. Meytal Landau Technion Israel Institute of Technology	”Functional protein fibrils in infectious and aggregation diseases“
13.10.2020	Dr. Lothar Schermelleh Oxford University	”Advanced 3D super-resolution imaging of chromatin organisation“
19.11.2020	Prof. Hugo Sanabria Clemson University South Carolina	”Dynamic organization in the supertertiary structure of PSD-95 scaffold protein“
15.12.2020	Prof. Konstantinos Stellos Newcastle University	”RNA modifications in immunovascular communication in ischemic heart disease“

SELECTED MAJOR SCIENTIFIC EVENTS IN THE BUILDING WITH RVZ SUPPORT (2019 & 2020)

- Mildred-Scheel Symposium (Feb 2019)
- Forum dissertation projects (Jul 2019)
- GSLS Symposium EUREKA (Oct 2019)
- Biomedica (Nov 2019)
- Physicomedia (Dec 2019)
- Forum dissertation projects (Jan 2020)

MAJOR COLLABORATIVE RESEARCH 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

2019

Enzym PKD1 aktiviert die Fettspeicherung (14/1/2019)
New findings about the molecular effectiveness of the anti-malaria drug Artemisinin (29/1/2019)
Substantial differences between the tumor-promoting enzymes USP25 und USP28 identified (27/3/2019)
Megakaryocytes act as “bouncers“ restraining cell migration in the bone marrow (16/7/2019)
New models and better data for macromolecular structure determination (23/7/2019)
Identifcation of a ferroptosis suppressor protein allows for new anticancer treatment approach (23/10/2019)
Architecture of a bacterial power plant decrypted (13/11/2019)

2020

Besondere Auszeichnung für Würzburger Thromboseforscher (11/3/2020)
Universität Würzburg stärkt biomedizinische Mikroskopie (27/3/2020)
Switch for DNA repair tool discovered (3/4/2020)
Tracking down cryptic peptides (23/6/2020)
Touchable coronaviruses (31/7/2020)
Specific control molecule in platelets identified (6/8/2020)
Puzzle solved after 16 years (15/10/2020)
It’s all about the right balance (21/10/2020)
Bacteria under stress (5/11/2020)
A damage foreseen is a danger avoided (11/11/2020)
Speed control on the DNA (17/11/2020)
Extending our understanding of how antimalarial artemisinin drugs affect inhibitory neurotransmission (15/12/2020)

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Rudolf-Virchow-Zentrum
Center for Integrative and Translational Bioimaging
der Julius-Maximilians-Universität Würzburg
Josef-Schneider-Str. 2, Haus D15
97080 Würzburg
Tel.: +49 931 31 80330
Fax: +49 931 31 83255
E-Mail: rvz@virchow.uni-wuerzburg.de
www.uni-wuerzburg.de/rvz

Editors:
Dr. Judith Flurer
Dr. Ole Riemann

Project Management:
Dr. Judith Flurer

Contributions:
Responsible for the content are Caroline Kisker, Bernhard Nieswandt, Markus Sauer and the group leaders of the Rudolf Virchow Center.

Layout:
Dr. Judith Flurer
Dr. Sandy R. Westermann (SCIGRAPHIX)

Lectorate:
Dr. Avril Arthur-Goettig (BioXpess)

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Daniel Peter (p. 4, 13, 34); Christoph Weiss (p. 4, 12); Hans Jürgen Landes (p. 2, 5); Schmelz-Fotodesign (p. 4, 14, 24, 28, 32, 36, 38, 40, 42, 44); Gunnar Bartsch (p. 20); Dr. Stephan Schröder-Köhne (p. 53); Jonas Weinrich (p. 53); Wolfgang Dürr (p. 68); RVZ: Dr. Ole Riemann (p. 48); Dr. Jochen Kuper (p. 26); Dr. Daniela Diefenbacher (p. 18, 30, 49, 50, 51); Dr. Judith Flurer (p. 15, 16, 22, 49, 51, 52).

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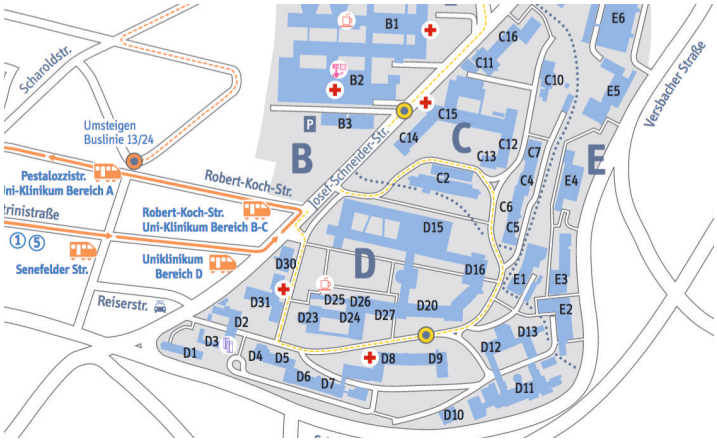

CONTACT INFORMATION

Rudolf-Virchow-Zentrum
Center for Integrative and Translational Bioimaging
der Universität Würzburg
Josef-Schneider-Str. 2
Haus D15
97080 Würzburg
Tel.: +49 931 31 80330
Fax: +49 931 31 83255

rvz@virchow.uni-wuerzburg.de

www.uni-wuerzburg.de/rvz