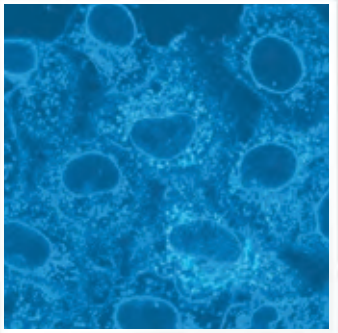
LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

GENE CENTER MUNICH

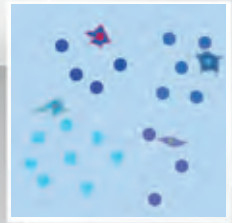
Report 2015-2020

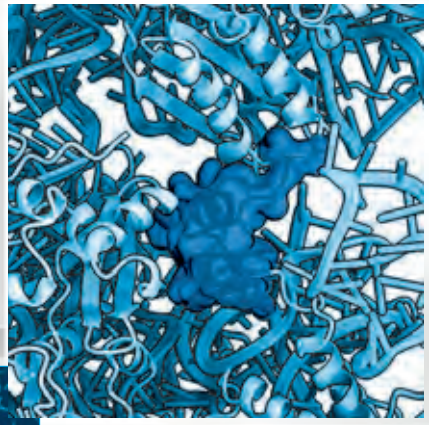
Some of the latest research highlights at the Gene Center



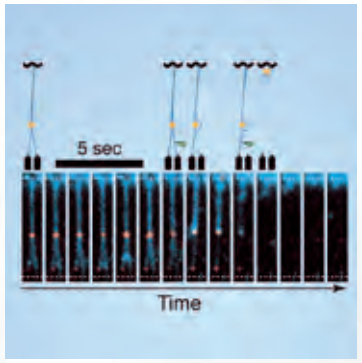
HeLa cells showing perturbed mitochondria after being stressed. Nature 2020, 579(7799):433–437.

Sphetcher: new method for sketching large single-cell datasets. iScience. 2020, 23(6):101126.



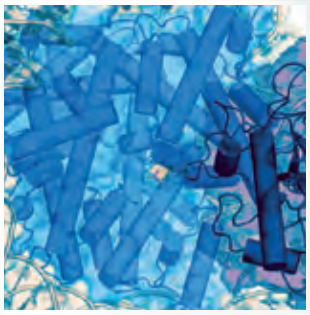


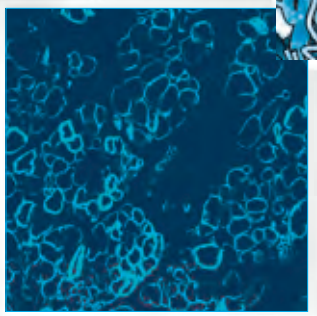
SARS-Cov-2 Nsp1 blocking the ribosome. Science 2020, 369(6508):1249-1255.



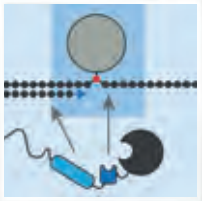
A conserved ATP- and Scc2/4-dependent activity for cohesin in tethering DNA molecules. Sci Adv. 2019, 5(11):eaay6804.

cGAS bound to the histone proteins of a nucleosome. Nature 2020. doi: 10.1038/s41586-020-2748-0.

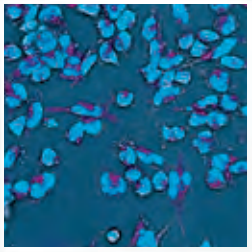




Restoration of dystrophin expression by CRISPR/Cas in a porcine DMD model. Nat Med. 2020, 26(2):207-214.



DNA structure-specific cleavage of DNA-protein crosslinks by the SPRTN protease. Mol Cell. 2020, 80:1-12.



TLR8 Is a sensor of RNase T2 degradation products. Cell. 2019,179 (6):1264-1275.e13.

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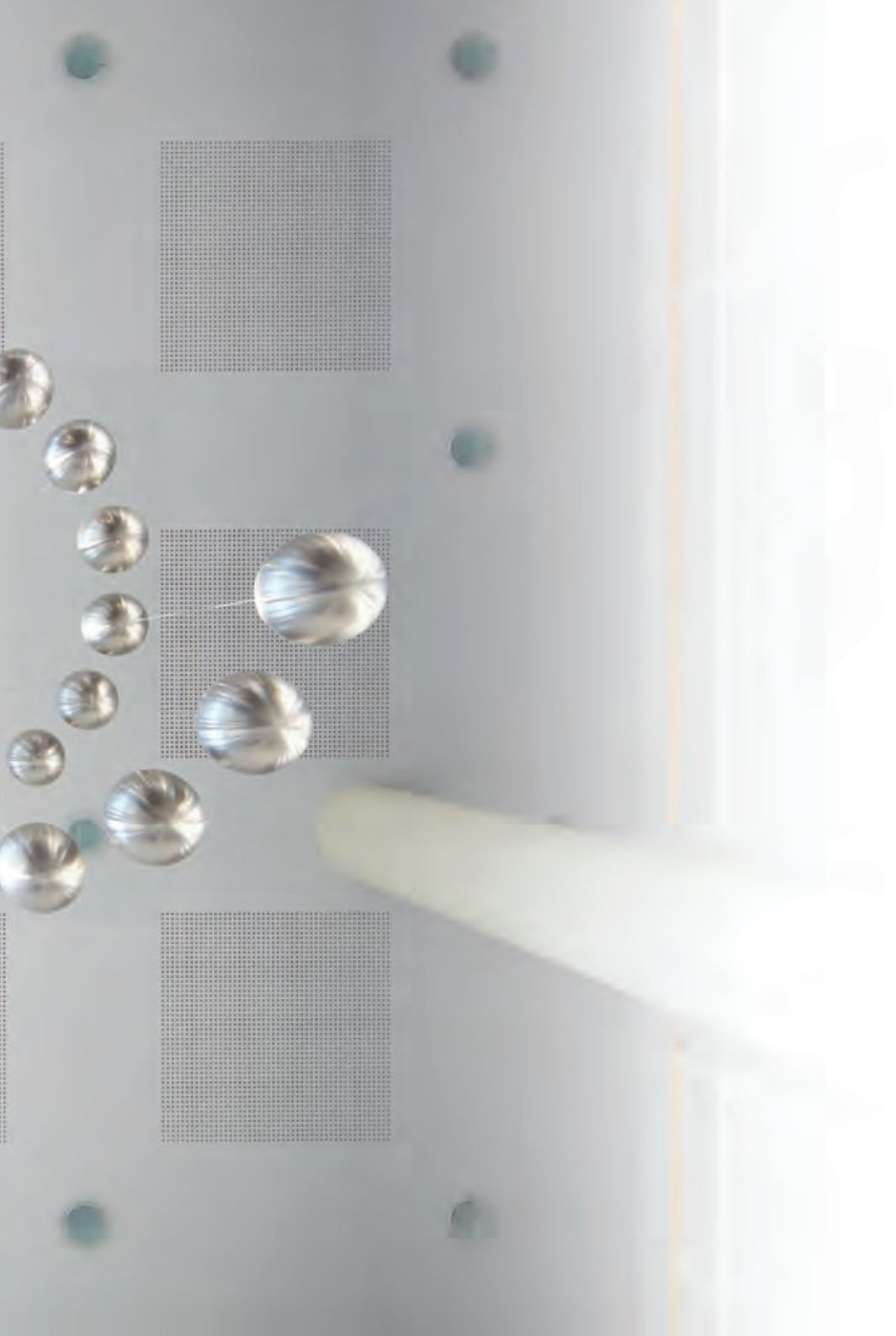

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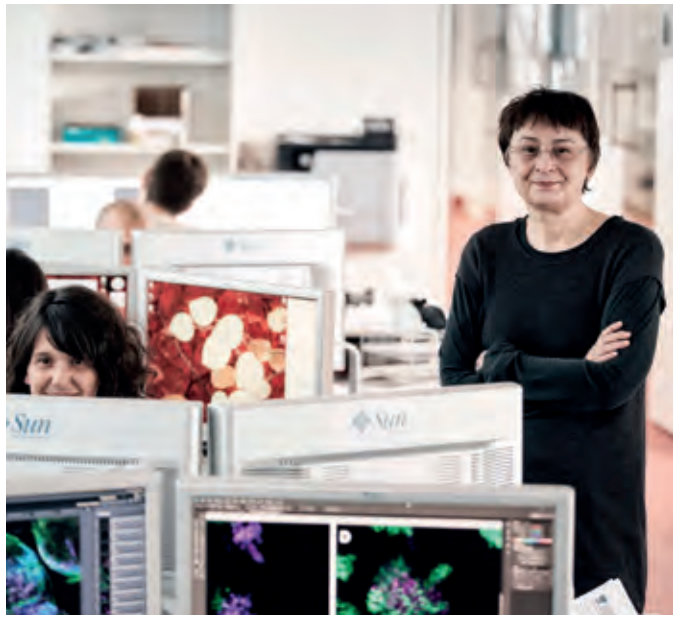
Director's Report

The Gene Center is a central scientific institution of the Ludwig-Maximilians-Universität München. Our mission is to find answers to fundamental scientific questions in basic and translational molecular life sciences, with a focus on genome biology, immunology and biomedicine. 2015-2020 has been a highly dynamic, rich and productive period, but not without its challenges and difficult moments. From my perspective, the main challenges were the main successes as well: outstanding people left and outstanding people joined. Over the past years, we recruited or started to host eleven new junior and senior faculty, which contribute to exciting new scientific topics and questions, enabled us to implement new research directions and especially fostered the link between basic and translational research. Numerous breakthrough scientific results, prestigious research awards, and cutting-edge interdisciplinary research made this period not only very prosperous, they demonstrate the Gene Center's role as a leading life-science institution and set the stage for productive and competitive research in the coming years.

New Faculty

The leaving of Patrick Cramer in 2014 (Director 2004-2014, now at the Max-Planck-Institute for Biophysical Chemistry in Göttingen), who shaped the institute for a decade, was an incisive moment. With the recruitment of Veit Hornung in 2015 (Chair of Immunobiochemistry), the Gene Center established a new research area in biomedical sciences, bridging both basic and medical scientific questions around how immunity and inflammation is triggered in health and disease. In 2018, Veit Hornung received the Gottfried-Wilhelm Leibniz award for his work on the innate immune system. Biomedical research is further strengthened by Oliver Keppler (Chair of Virology) and Barbara Adler (Biology of Cytomegaloviruses) from the Medical Faculty, who's research is aimed at understanding the interplay between viruses and host immunity. Our new colleagues Marion Subklewe (Translational Cancer Immunology), Michael von Bergwelt (Director, Medical Clinic III), and Sebastian Theurich (Cancer and Immunometabolism) are both researchers and active clinicians at the University Hospital and established research laboratories around cancer immunology and metabolism.

We are particularly happy to have been able to recruit five outstanding young scientists over the past years as independent group leaders or tenure-track W2 professors. Julian Stingele (Maintenance of Genome Stability) uses cell biology and biochemistry to study how cells repair DNA damage in the form of protein-DNA crosslinks. Stefan Canzar (Algorithmic Genomics) heads a computational biology group developing algorithms to analyze and reconstruct information from sequencing data. Johannes Stigler (Biophysics of Structural Dynamics in Chromosomes) uses single-molecule optical methods to study the mechanism of chromosome proteins. Lucas Jae (Functional Genomics) uses genome editing and functional genomics to unravel the genetic basis of cellular processes underlying human disease. Henriette Uhlenhaut (Molecular Endocrinology, now W3 professor at TUM) joined the Gene Center as Helmholtz Alliance professor, heading a laboratory studying molecular endocrinology and the metabolic control of gene regulation. A W2tt professorship in systems immunology is currently underway with the goal of strengthening computational methods at the Gene Center.
Julien Gagneur, Mario Halic, Fabiana Perocchi, Henriette Uhlenhaut, Petra Wendler and Daniel Wilson left the Gene Center. We thank them for their excellent science and contributions to the Gene Center over the past years.
With Ulrike Gaul, an inspiring colleague and Alexander von Humboldt Professor of Organismic Biochemistry, a sharp mind and warm and generous friend, passed away on June 14, 2020. By having a leading role in establishing systems biology research at the LMU, culminating in the establishment of the BioSysM research building and the Graduate School of Quantitative Biosciences Munich, Ulrike Gaul made tremendous and long-lasting contributions to both research and training at the Gene Center and the LMU. We will miss her.



Start of BioSysM

2016 marked a highlight and starting point for a new era of the Gene Center with the inauguration of the "BioSysM" research building. BioSysM was conceived by Patrick Cramer and Ulrike Gaul to establish research on molecular biosystems such as how different proteins, regulatory cellular networks and genes cooperate to generate cell function. While our research in molecular biosystems since then changed towards immunological and biomedical questions, thus taking a more medically and disease-oriented direction, the important scientific questions and fundamental ingredients remain: successful research in this future direction needs to tightly integrate experimental and computational tools in order to make use of the vast amount of data we are now able to obtain and to answer how complex biological systems work. These technological directions and our research foci will enable us to contribute to human health by addressing the molecular principles of the immune system and its role in diseases, for instance during infections, in immunotherapies and inflammatory and autoimmune diseases.

ERC Advanced Grant 2020
Roland Beckmann
Structural Biology
of Human Ribosome
Biogenesis

ERC Advanced Grant 2019
Karl-Peter Hopfner
Mechanism of ATP Dependent
Chromatin Modelling and
Editing by INO80 Remodellers

ERC Starting Grant 2015
Franz Herzog
Molecular Structure and
Cell Cycle Regulated Assembly
of the Kinetochore

ERC Starting Grant 2018
Lucas Jae
Suppression of
Organelle Defects in
Human Disease

ERC Consolidator Grant 2015
Veit Hornung
GENEtic DiSsection
of Innate Immune Sensing
and Signalling

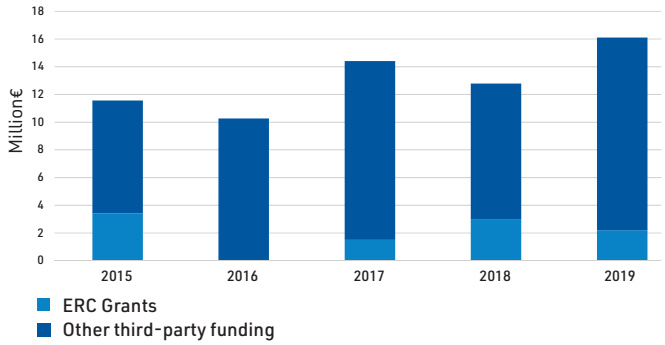
ERC Starting Grant 2018
Julian Stingele
DNA-protein Crosslinks:
Endogenous Origins and
Cellular Responses

ERC Starting Grant 2017
Johannes Stigler
Chromosomal Domain Formation,
Compartmentalization
and Architecture

Publications, Funding and Awards

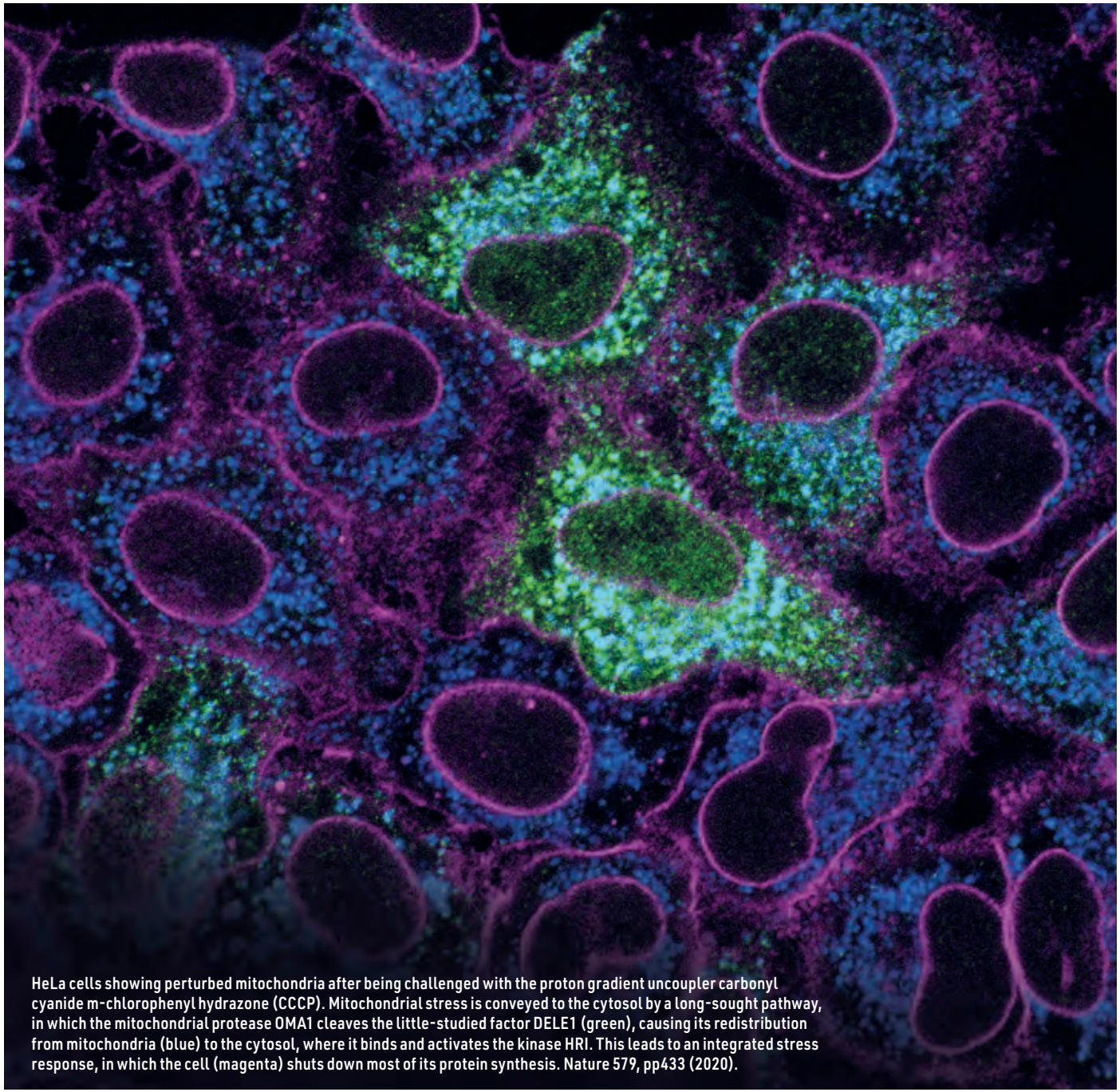
Overall, groups at the Gene Center published ~750 scientific papers during the reporting period. Among those were more than 30 publications in one of the three leading journals Cell, Nature and Science. Many of the publications have names from more than one research group at the Gene Center on them, showing a high amount of collaborative research. The Gene Center hosts, or co-hosts national collaborative research or training centers with TRR127 „Xenotransplantation", GRK1721 „Hybrid Methods in Genome Biology", TRR237 „Nucleic Acid Immunity", and QBM „Quantitative Biosciences Munich". Furthermore, PIs of the Gene Center participate in many other collaborative research centers. In total, Gene Center groups secured ~65 Mio Euro in extramural funding in the past five years, among them substantial funding by the European Research Council.
With two Gottfried Wilhelm Leibniz-Prizes, the Liliane Bettencourt Prize, two Heinz Maier Leibnitz-Prizes, the Alfried Krupp-Prize, the Bayer Early Excellence in Science Award, seven ERC grants, one Emmy-Noether Grant, a Helmholtz-Alliance professorship, and others, we can look back to a spectacularly rewarding period in the history of the institute. It is particurlarly important to note that the newly recruited young investigators received many of the prestigious awards as well as four ERC starting grants, which shows that the Gene Center is very attractive in the international highly competitive market for the best young talents. Two of our ERC funded young independent group leaders successfully obtained a tenure-track W2 professorship at the LMU. We thank the LMU leadership for this program, which strongly added to the attractiveness of the institution to top young academics.

Third-party funding

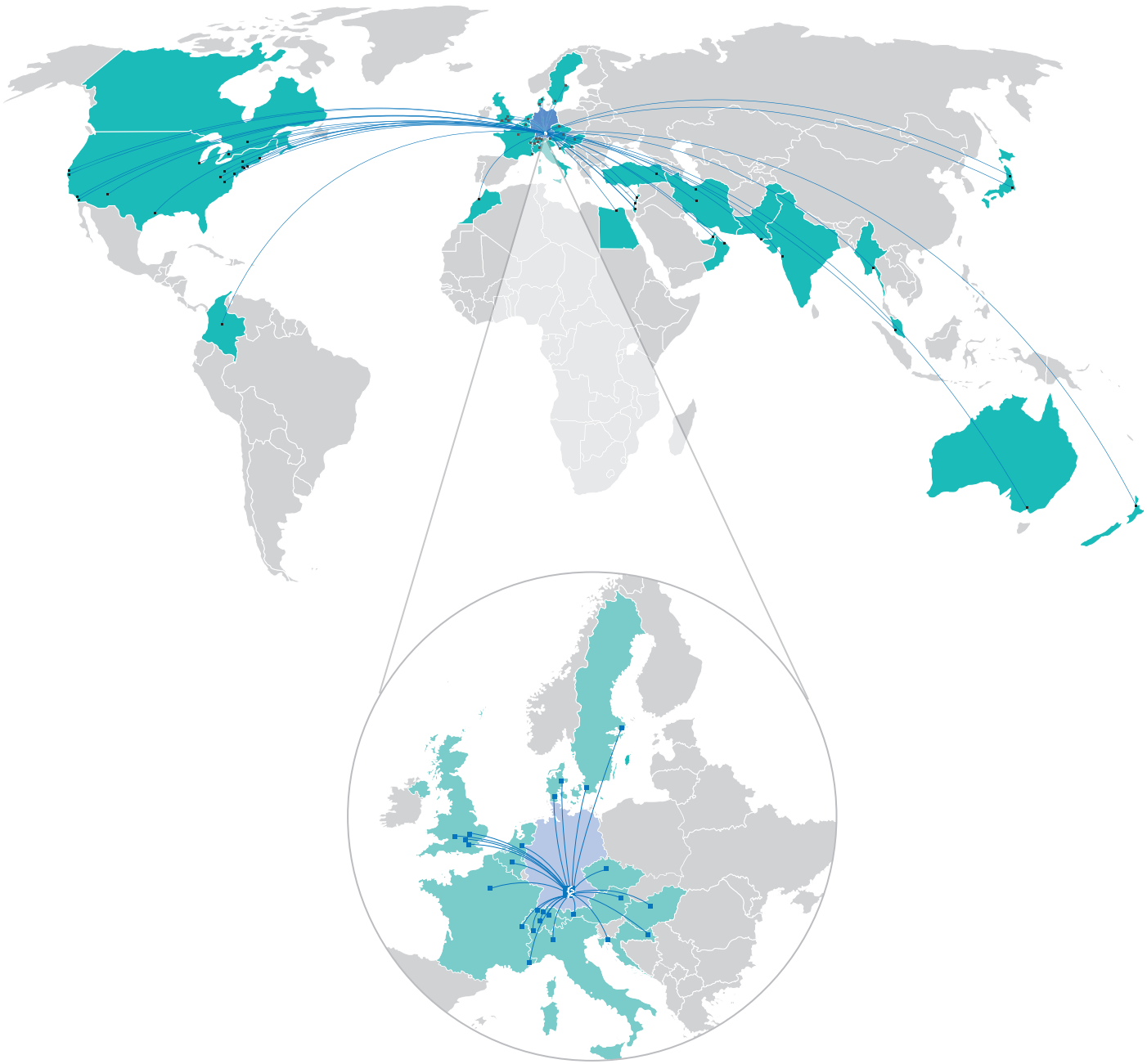


Research Highlights

I briefly report on some breakthroughs in the reporting period although it is difficult to single out research highlights among the many important results Gene Center groups have achieved in the past years. A multidisciplinary collaboration including the team of Eckhard Wolf demonstrated the efficacy of new immuno-regulatory strategies in enabling life-supporting cardiac xenotransplantation, a major achievement in biomedical research (Nature 564, pp430 (2018)). Lucas Jae's lab discovered a new pathway that signals the cell stress in the energy converting factories of our cells, the mitochondria, helping devise strategies against mitochondrial dysfunction in human disease (Nature 579, pp433 (2020)). Julian Stingele's lab revealed the mechanism how DNA-protein crosslinks are repaired through proteolytic cleavage (Molecular Cell 64, pp668 (2020)). Klaus Förstemann's lab in collaboration with LAFUGA teams discovered a new mechanism how small RNA molecules are shuttled from the nucleus to the cytosol in RNA interference (Nucleic Acids Research 48, pp3906 (2020)). Veit Hornung's lab discovered that a critical sensor of the innate immune system detects extracellular ribonucleic acids through sensing special degradation products, thereby alarming the immune system to the presence of infections by viruses (Cell 179, pp1264 (2019)). Oliver Keppler's, Marion Subklewe's and collaborators' laboratories at the Gene Center and other institutions discovered and developed new therapeutic strategies against acute myeloid leukemia using small molecule (Nature Medicine 23, pp2050 (2017)) and antibody-based approaches (Blood 132, pp484 (2018)). The Klein lab along with colleagues at the Gene Center and other institutions found that mutations in enzymes that alter the cell's chromatin structure are a molecular basis for misregulation of blood cells (granulocytes) in human disease syndromes including acute myeloid leukemia (Nature Genetics 49, pp742 (2017)). Karl-Peter Hopfner's lab determined the cryo-electron microscopy structure of a multisubunit chromatin remodeler and revealed the mechanism behind the reconfiguration of chromatin (Nature 556, pp386 (2018)). Roland Beckman's lab used cryoelectron microscopy to determine how ribosomes, the cell's machinery for producing proteins, are assembled in a complex pathway (Nature 558, pp249 (2018)). Our research spans basic molecular biology to translational biomedicine and therapeutic applications.



HeLa cells showing perturbed mitochondria after being challenged with the proton gradient uncoupler carbonyl cyanide m-chlorophenyl hydrazone (CCCP). Mitochondrial stress is conveyed to the cytosol by a long-sought pathway, in which the mitochondrial protease OMA1 cleaves the little-studied factor DELE1 (green), causing its redistribution from mitochondria (blue) to the cytosol, where it binds and activates the kinase HRI. This leads to an integrated stress response, in which the cell (magenta) shuts down most of its protein synthesis. Nature 579, pp433 (2020).



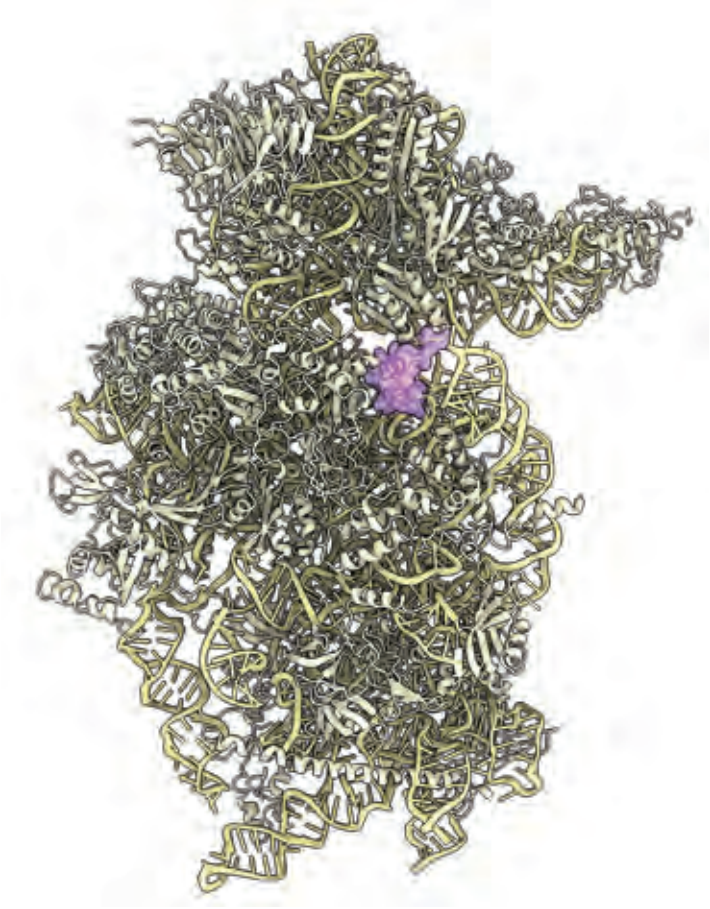
Networks and Collaborations

A strong feature of Gene Center groups are national and international networks and collaborations. The Gene Center plays an active role in fostering statewide collaborative research and to this end is very happy to host the coordination office of Bavarian research networks (coordinated by Ulrike Kaltenhauser). The network "BioSysNet" addressed fundamental questions in biosystems research and concluded in 2017, laying also the foundation for research at BioSysM. With Bayresq.net, in 2019 a new network focusing on battling multiresistant pathogens started. The topic could not be more timely given the pandemic threats we face at the time of the writing of this report. Ulrike Kaltenhauser received the Bavarian order of merit for her work in 2019 and we cordially congratulate her for this well-diserved recognition!
Gene Center researchers have numerous collaborations and interactions with top scientific institutions worldwide and we regularly host leading scientists in our seminar series or as visiting scientists. In Munich, the Gene Center plays an active and central role in campus development and scientific interactions between different faculties and institutions.
We have many collaborations and interactions with the Max-Planck-Institute of Biochemistry (where KP Hopfner and V Hornung are members or fellows), surrounding faculties of the LMU, the Biomedical Center and the Helmholtz Zentrum München (through a shared professorship). Close ties are formed to the Max-von-Pettenkofer Institute, the Klinikum of the LMU, and the von Haunersche Kinderklink through hosting of research groups.

Training

Scientific training at the Gene Center is of utmost importance and happens at all academic levels. Here, the Gene Center is a place for vivid scientific exchange and discussions among and between scientists at all career stages. Undergraduate training is done in several programs together with colleagues at the Departments of Chemistry and Biology. Our joint master program in Biochemistry, taught in English, as well as PhD level research and training programs have about 30-40% international students. Training at the graduate and post-graduate level is done in a research-oriented manner, with intramural seminar series performed by doctoral and postdoctoral researchers. Scientific exchange and discussions between early career and advanced

researchers is fostered in an annual retreat. An important element of further academic training is early academic independence of its young group leaders and tenure-track professors. In my experience, this together with flat hierarchies is one of the most important elements to attract talented researchers in an international setting. It also helps young academics to take on responsibilities at early career stages and grow into leadership positions. We are very proud that our young PIs are so successful in obtaining prestigious grants and awards.



Devastating effect: how virus protein Nsp1 (pink) binds to the ribosome. Science 2020.

SARS-CoV-2 Research

Early on, Gene Center groups in collaboration with others were highly active in the SARS-CoV-2 caused pandemic with research efforts towards developments of sensitive and accurate high-throughput tests, development of vaccines and antibodies, basic structural research aimed at understanding the mechanism of host-translation control by the virus, analysis of virus genomes and infection chains by next generation sequencing and others. Especially at those times, the institute and its researchers took on responsibility towards the public threat and our efforts provide data, resources and reagents. Gene Center groups were furthermore very active in outreach both to the public and the government. However, I would like to stress that what I found most important are the effortless collaborations that formed between different institutions and laboratories. We worked actively together with the Max-Planck-Institute for Biochemistry (protein core facility), Human Biology (antibody unit), the Max-von-Pettenkofer Institute, the University Hospital and Medical Faculty and groups at the Technical University Munich. I would like to direct the reader to the contribution by our founding director Ernst-Ludwig Winnacker on the roles and responsibilities of research institutions for the greater public benefit.

In April 2020 the Bavarian Science Minister Bernd Sibler visited the Gene Center and obtained information about ongoing SARS-Cov-2 research.

Outlook

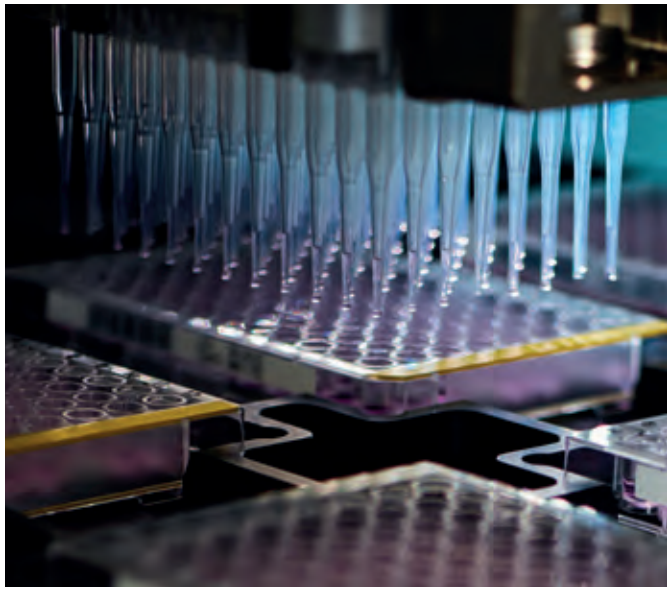
I am very happy to report on five extremely successful and productive years and look forward to the coming period.
In this transition time, we established new research directions and made significant progress in all our research areas with many spectacular results. I believe our strengths are the highly collaborative and multidisciplinary research as well as shared facilities, flat hierarchies and early scientific independence. These ingredients lead to a potpourri of intense scientific exchange and cutting-edge multidisciplinary research, the fruits of which can be seen by high-level collaborative publications. They make me confident that our institutional model is attractive for leading investigators at all levels, which is of course the most important feature for have enduring institutional success and performing cutting-edge research. In my opinion, instrumental for future success are the full tenure-track model up to the W3 level, a continuous commitment to have state of the art research facilities and the integration of computational and experimental research.
The position of the Gene Center as one of the leading institutions in the life and biomedical sciences is a result of the dedication and hard work of all of its scientific members, from undergraduate students, doctoral and postdoctoral researchers, staff scientists and facility managers, to the principal investigators. However, a strong, supportive and highly committed administrative and technical support team, including administration, secretaries, financial services, IT, workshop services, outreach and lab services, are as important as the scientists. I thank all members and personnel at the Gene Center for their excellent contributions!
In the next period, we'll tackle the integrative analysis of complex cellular processes, from structural biology to the experimental and computational analysis of molecular biosystems, and their translation into clinical applications. Hereby, we'll focus on two related questions: how is the genomic information maintained and processed and how is self from non-self and aberrant distinguished. Answers to these questions are the basis to understand and to target auto-immune and pathogen-caused diseases as well as cancer.

Science and Society

by Ernst-Ludwig Winnacker

Professor Emeritus, August 2020

Like sunbeams concentrating in the focal point of a magnifying lens the Corona crisis bundles strengths and weaknesses within our society including the various aspects of the relationship between Science and Society. Even though our life as individuals and as a human society is more than ever dependent on scientific issues many people are totally unable to cope with the intricacies of the technology with which they are surrounded. Thus, the support and the acceptance of scientific progress is almost totally dependent on trust and confidence in what science has to offer. The question thus arises whether this trust is justified. This is not for the scientific community to answer but it can develop strategies which demonstrate that the scientific community can and does react responsibly.

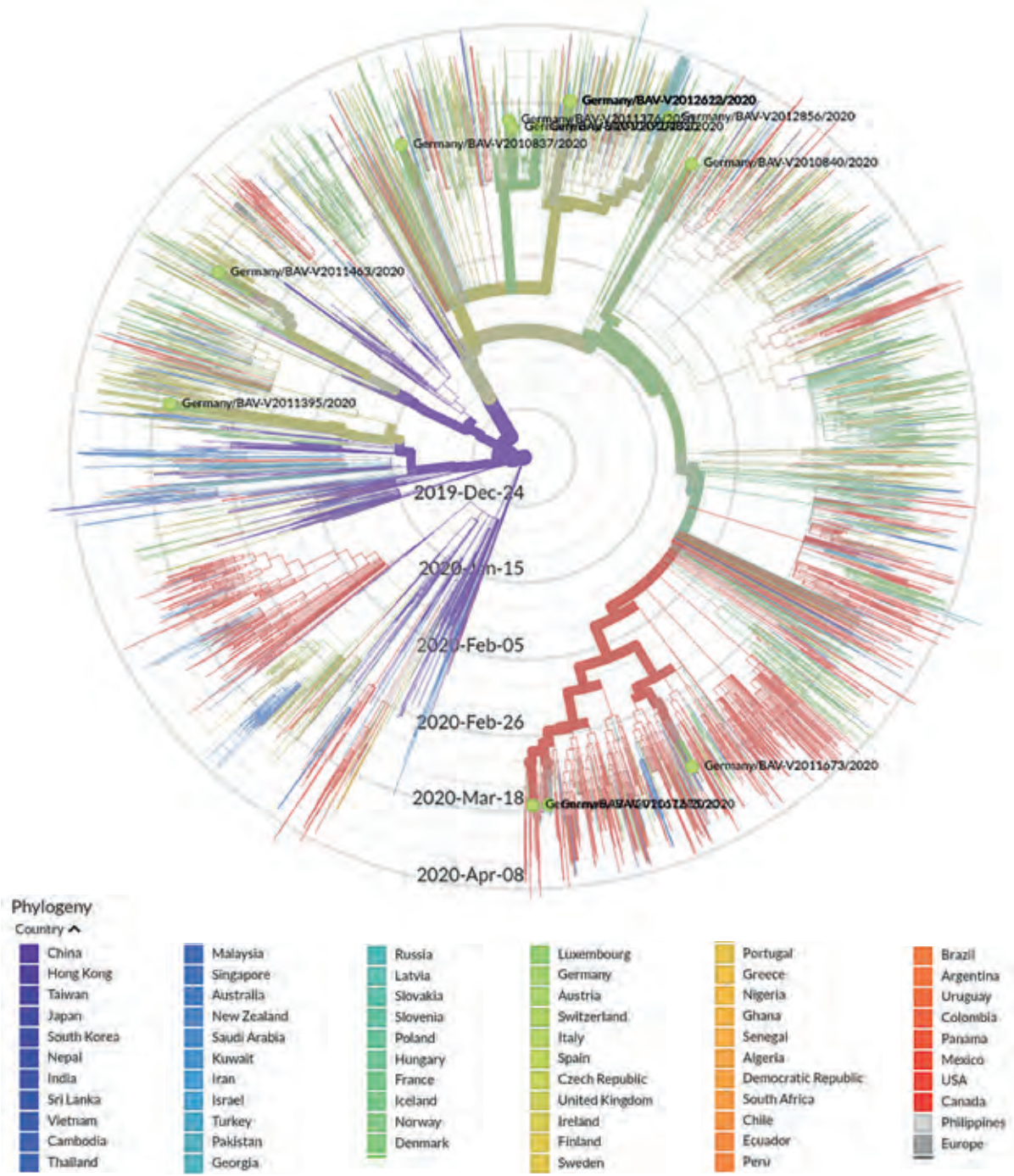


Giving advice to politicians is such a challenge. This can be like walking a tight rope for a couple of reasons. For once, it has to be given unbiased, i.e. it should not be expressed either in order to please one or the other political party or simply be politically correct and finally it has to honor the scientific process. Science is a method to search for the truth. Most of the time it works somewhat like the annual dancing procession of Echternach, one step forward and two steps backwards. Handling of this inbuilt uncertainty is particularly relevant in times of a novel crisis, like the current corona pandemic. The fact that a SARS-CoV-2 outbreak became pandemic was unexpected. Initially the rules and parameters describing its proliferation were totally unknown since pandemics are rare and since every virus behaves differently. Patient numbers were quite small such that the laws of statistics and epidemiology could not be properly applied. And yet, politician expected clear answers and predictions. Thanks to the knowledge and experience of some of our colleagues, as well as the insight of our political class, Bavaria and Germany as a whole did quite well as compared to many other countries where scientists were not heard or even vilified and even fired once they presented facts which were not in line with values and norms of their political leaderships. It requires stamina and fearlessness as well as a strong believe in the strength of the scientific process to confront situations of this kind.

One good example of this kind is the Gene Center Munich, a comparatively small research institution of the LMU and yet enormously effective when faced with a situation as shocking as a viral pandemic. Once it became obvious in January 2020 that the world is beginning to face a SARS-CoV-2 induced pandemic, scientist at the Gene Center started to refocus their scientific endeavors towards the Covid-19 problem trying to see where their expertise could help and expedite our knowledge of this pandemic. By now (summer 2020) there are already quite a number of successful examples of their efforts. The Beckmann group, for example, has shown how a viral, non-structural protein, NSP1, inhibits protein synthesis in the host cell. Using high-resolution electron microscopy, they could show how this protein binds to the cellular machinery responsible for the synthesis of proteins thereby overcoming the various defense mechanisms within human cells against SARS-CoV-2 attacks. The resolution of the interaction of the participating protein is of such an extent that drugs are now being designed and developed which interfere with these interactions. Other groups, i.e. those of Profs Keppler, Hopfner and

Hornung, have optimized existing tests for SARS-CoV-2 antibodies in order to follow the exact course of a Covid-19 infection in more detail than possible until now. In order to gain experience with the evolution of SARS-CoV-2 the group of Dr. Blum has developed sequencing methods to see how the viral genome changes over time thereby obtaining clues as to the possible course of the pandemic. The group of Prof. Subklewe has designed novel therapeutic approaches for the treatment of patients suffering from SARS-CoV-2 infections using an antibody originally prepared to treat rheumatoid arthritis. The group of Prof. Conzelmann explores innovative approaches for vaccine development. These and other examples are not "fake news" but they demonstrate how basic research can rapidly adapt to immediate problems thereby delivering important support to society. This has happened elsewhere and in other fields. But the Gene Center Munich is a good example because it is important to demonstrate to the taxpayers that their money is not only spent for "merely" curiosity-driven research but that this type of research has intrinsic societal value which permits it to be applied immediately to topical problems.

We may appear to be losing the battle against digital misinformation. However, in order to win it we need examples of the type which I presented here.



Barbara Adler

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1992	PhD, Albert-Ludwigs-University, Freiburg
1992 - 1995	Postdoc, Institute of Veterinary Virology, Bern, Switzerland
1995 – 1997	Postdoc, Dana Farber Cancer Institute and Harvard Medical School, Boston, USA
1997-2005	Research Assistant, Helmholtz Center Munich and Max von Pettenkofer-Institute, LMU
Since 2005	Group leader, Max von Pettenkofer-Institute & Gene Center LMU

Biology of Cytomegaloviruses

Goals and Impacts for Society

Human cytomegalovirus (HCMV) infections are a major cause of morbidity and mortality in immunocompromised humans like transplant patients or the unborn or prematurely born child. Currently available anti-HCMV treatments are very costly, associated with severe side effects, and the development of drug resistance. A licensed vaccine to protect from HCMV infection does not exist. Our research focus is CMV gH/gL glycoprotein complexes. We study the role of these complexes in virus infections, their potential as vaccine antigens, and when using CMV as a vaccine vector, their role in shaping the vaccine-induced immune response.

Research Highlights

Viral envelope glycoproteins are mainly considered as keys to enter host cells. Accordingly, the gH/gL complexes of cytomegaloviruses serve as entry mediators by binding to cellular receptors on host cells. This makes them interesting for vaccine research. As cytomegaloviruses always express two different gH/gL complexes, it is crucial to understand their roles in virus infection. HCMV expresses a trimeric gH/gL/gO and a pentameric gH/gL/UL(128,130,131A) complex. These complexes recognize different receptors.

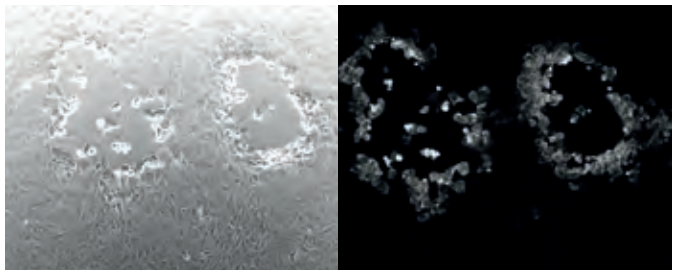
For many years and despite intense efforts, the cellular receptors for HCMV could not be identified. In 2017, simultaneously with two other groups, we could identify the first HCMV entry receptor, PDGFR-α, which is recognized by the gH/gL/gO complex. PDGFR-α is abundantly expressed and thus explains the very broad cell tropism of HCMV. Using numerous virus mutants to dissect the role of the gH/gL complexes in HCMV infection, we could show that virus particles derived from different cell types carry different outfits of gH/gL complexes and that these different outfits direct the virus to different destinations in the host. This way, HCMV uses its target cells to navigate through the infected host.

The infection of mice with murine cytomegalovirus (MCMV) is an established animal model to study HCMV infections in vivo. We identified the MCMV gH/gL complexes which allowed us to study the role of CMV gH/gL complexes also in vivo. We could show that in primary infection, the trimeric gH/gL/gO complex is crucial for infection of first target cells which makes this complex a promising vaccine target. The MCMV homologue of the pentameric gH/gL/pUL(128, 130,131A) complex of HCMV promotes infection of immune cells like monocytes and dendritic cells and spread to virus-shedding organs like salivary glands which ensure horizontal spread of CMV.

Interestingly, the pentameric complex also shapes the antiviral immune response, both because it promotes infection of monocytes and dendritic cells and because it contains an active chemokine (UL128) which attracts and activates immune cells.

Future Directions

Based on our insights in the roles of gH/gL complexes gained during the last years, we will study the potential of the gH/gL/gO complex as an immunogen for vaccination against HCMV. As cytomegaloviruses are also promising vectors for vaccination against other pathogens or tumors, we are currently extending our knowledge how the pentameric gH/gL complex and the complex-associated chemokine can modulate the immune response of CMV vaccine vectors and whether this modulation can be used to create tailored vectors for different pathogens.



Green fluorescent protein-expressing HCMV spreading in a fibroblast culture, phase contrast and fluorescence microscopy

Selected Publications

(1) Yunis J, Farrell HE, Bruce K, Lawler C, Wyer O, Davis-Poynter N, Brizić I, Jonjić S, **Adler B**, Stevenson PG (2019). **Murine cytomegalovirus glycoprotein O promotes epithelial cell infection in vivo**. J Virol. 93(3): e01378.

(2) Wu Y, Prager A, Boos S, Resch M, Brizic I, Mach M, Wildner S, Scrivano L, **Adler B** (2017). **Human cytomegalovirus glycoprotein complex gH/gL/gO uses PDGFR-α as a key for entry.** PLoS Pathog. 13(4):e1006281.

(3) Hagen C, Dent KC, Zeev-Ben-Mordehai T, Grange M, Bosse JB, Whittle C, Klupp BG, Siebert CA, Vasishtan D, Bäuerlein FJ, Cheleski J, Werner S, Guttmann P, Rehbein S, Henzler K, Demmerle J, **Adler B**, Koszinowski U, Schermelleh L, Schneider G, Enquist LW, Plitzko JM, Mettenleiter TC, Grünewald K (2015). **Structural Basis of Vesicle Formation at the Inner Nuclear Membrane.** Cell. 163(7):1692-701.

(4) Lemmermann NA, Krmpotic A, Podlech J, Brizic I, Prager A, Adler H, Karbach A, Wu Y, Jonjic S, Reddehase MJ, **Adler B** (2015). **Non-redundant and redundant roles of cytomegalovirus gH/gL complexes in host organ entry and intra-tissue spread.** PLoS Pathog. 11(2):e1004640.

Roland Beckmann

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1995	PhD (Dr. rer. nat.), Free University Berlin
1995-2000	Postdoc, Rockefeller University, New York, USA
2001-2006	Group leader Volkswagenstiftung, Charité, Humboldt University, Berlin
Since 2006	Professor and Chair, Gene Center and Department of Biochemistry, LMU

Structural Ribosome Biochemistry

Goals and Impacts for Society

The ribosome is the main component of the translational machinery and plays a central role in protein and mRNA homeostasis. Research of my group focuses on essential cellular processes in which the ribosome participates, e.g ribosome biogenesis, mRNA turnover, translation regulation and protein translocation. Mainly using cryo-electron microscopy, we aim at obtaining structures of ribosomal complexes involved in these processes in order to elucidate the underlaying molecular mechanisms.

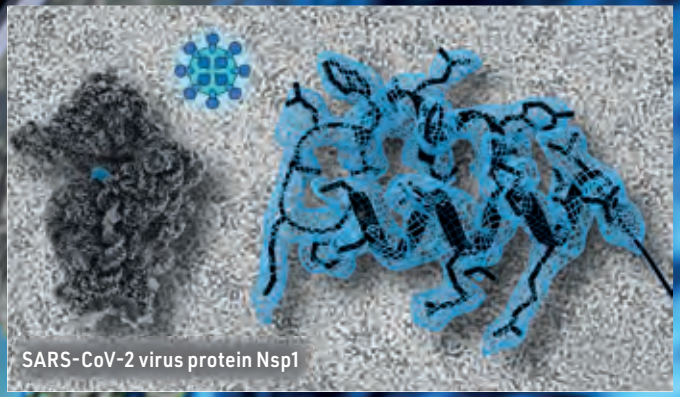
Research Highlights

In eukaryotes, the life cycle of a ribosome begins in the nucleolus, where it is assembled from a large rRNA precursor. Maturation of ribosomal subunits involves the coordinated action of a plethora of assembly factors which aid in folding, modification and processing the precursor before near-mature particles are exported to the cytoplasm. In the past years, we obtained molecular insights into various aspects of ribosome maturation. After affinity purification from mainly fungal species, we determined cryo-EM structures of early 90S or pre-40S and pre-60S particles at various stages of assembly. As highlights, we determined the overall architecture of the giant 90S small subunit processome. Several 90S-structures revealed that 18S rRNA is folded first in its 3'-located domains and thus in reverse order to transcription. Furthermore, structures were obtained showing a number of subsequent states of human cytoplasmic 40S biogenesis, leading to a detailed understanding how the active site of the 40S is formed.
Mature 40S and 60S can then engage in translation of mRNAs into proteins, during which translation efficiency by a so far unknown mechanism affects the life-time of mRNA. In particular, mRNAs with so-called "non-optimal" codons have a short lifespan and are target to translation-mediated decay. We could show that a component of the Ccr4-Not complex, Not5, plays a crucial role in recognizing ribosomes engaged with non-optimal mRNA. Not5 recognizes concomitantly empty A- and E-sites and communicates this status to the mRNA decay machinery, thereby linking translation efficiency of mRNA to its half-life.

In contrast, when engaging erroneous mRNA, the ribosome can completely stall. This leads to collision of the following ribosomes which is a trigger to initiate mRNA degradation. Following collision, small subunit proteins are ubiquitinated, the mRNA is cleaved and the stalled ribosomes is recycled. Our lab provided first structural insights into how such collided ribosomes are arranged and discovered a unique structural interface at the contact site of these ribosomes. At this interface, the ubiquitinated ribosomal proteins are in close spatial vicinity, providing an explanation on how collided ribosomes can serve as specific binding hub for quality control factors executing and coordinating subsequent events.
Very recently, we also contributed to understanding how Nsp1, a major virulence factor of SARS-CoV-2, binds to ribosomes, explaining how this factor leads to shutdown of mRNA translation and blockage of innate immune responses.

Future Directions

In the next years the group will extend its focus on human ribosome biogenesis. Compared to yeast, this process is even more complex in humans, especially with respect to pre-rRNA processing and the number of biogenesis factors involved. Here our work will focus on the challenging preparation of nuclear intermediates, which will be structurally characterized by cryo-EM. Moreover, the group will continue to investigate events following ribosome collision, with a special focus on the known machineries for ribosomal protein ubiquitination and disassembly of poly-ribosome structures. Finally, efforts will be taken to further understand, how SARS-CoVs hijack the host translation machinery to translate viral mRNAs.



SARS-CoV-2 virus protein Nsp1

Selected Publications

(1) Cheng J, Lau B, La Venuta G, Ameismeier M, Berninghausen O, Hurt E, **Beckmann R** (2020). **90S pre-ribosome transformation into the primordial 40S subunit.** Science. 369(6510):1470-1476.

(2) Thoms M, Buschauer R, Ameismeier M, Koepke L, Denk T, Hirschenberger M, Kratzat H, Hayn M, Mackens-Kiani T, Cheng J, Straub JH, Stürzel CM, Fröhlich T, Berninghausen O, Becker T, Kirchhoff F, Sparrer KMJ, **Beckmann R** (2020). **Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2.** Science. 369(6508):1249-1255.

(3) Buschauer R, Matsuo Y, Sugiyama T, Chen YH, Alhusaini N, Sweet T, Ikeuchi K, Cheng J, Matsuki Y, Nobuta R, Gilmozzi A, Berninghausen O, Tesina P, Becker T, Coller J, Inada T, **Beckmann R** (2020). **The Ccr4-Not complex monitors the translating ribosome for codon optimality.** Science. 368(6488).

(4) Su T, Izawa T, Thoms M, Yamashita Y, Cheng J, Berninghausen O, Hartl FU, Inada T, Neupert W, **Beckmann R** (2019). **Structure and function of Vms1 and Arb1 in RQC and mitochondrial proteome homeostasis.** Nature. 570(7762):538-542.

Selected Awards and Honors

2018 Honorary Doctorate (PhD h.c.) from University of Stockholm, Sweden

2020 ERC Advanced Grant

Stefan Canzar

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2008	PhD Max-Planck-Institute for Informatics, Saarbrücken, and LORIA, Nancy, France
2009-2012	Postdoc at CWI Amsterdam, The Netherlands
2012-2014	Postdoc at Johns Hopkins University, Baltimore, USA
2014-2016	Research Assistant Professor, TTIC, Chicago, USA
since 2016	Group Leader, Gene Center, LMU

Computational Genomics

Goals and Impacts for Society

The research focus of my group is the development of computational methods for the accurate reconstruction and comparative analysis of the transcriptome from high-throughput sequencing measurements. We design and engineer algorithms that are tailored to different sequencing technologies and that can provide estimates of the transcriptome at various resolutions, necessary and sufficient to address a wide range of biological and medical question.

Research Highlights

We have developed methods CIDANE for the assembly of full-length transcript from short-read RNA-seq, SpliceHunter (4) for the inference and annotation of transcripts from long reads produced by PacBio SMRT sequencing, and BASIC for the assembly of full-length heavy and light chains of B cell receptor sequences from single-cell RNA-seq (scRNA-seq).
The open-source software tools we develop address important biological and medical questions that arise in close collaborations with biologists and clinicians. Our accurate reconstruction and comparison of the transcriptome and its dynamic changes during development has contributed to the discovery of the embryonic origin of adult neural progenitors (3) and has revealed the epitranscriptomic temporal control of mouse brain development. We have helped to interpret non-coding variants associated in mice with traits relevant to human disease by linking them to the regulation of gene expression. And in fission yeast meiosis we have revealed a staggering splicing complexity at the resolution of full-length isoforms (4).
Single cell RNA-sequencing (scRNA-seq) can illuminate the dynamic changes in gene expression underlying biological processes such as differentiation and development. We have developed Trajan (2), a novel method to compare complex trajectories from two conditions. In an alignment of single-cell trajectories describing human muscle differentiation and myogenic reprogramming, Trajan identifies the correspondence between core paths without prior information, from which we are able to reproduce recently reported barriers to reprogramming.

Another fundamental task in scRNA-seq analysis is the identification of transcriptionally distinct groups of cells. We have proposed method Specter whose core algorithmic innovation allows it to cluster a dataset comprising 2 million cells in under half an hour. The ensemble learning approach implemented in Specter is able to utilize multimodal omics measurements such as RNA and surface protein expression to resolve subtle transcriptomic differences between subpopulations of, e.g., memory T cells.
In practice, scRNA-seq analysis methods are often run on a smaller subset of the data whose enormous size exceeds the capabilities of existing analysis methods. We have developed method Sphetcher (1) that efficiently picks representative cells that accurately capture the geometry of the transcriptional space occupied by the original data. The resulting sketch of single cells highlights rare cell types, facilitates visualization and sharing of large datasets and accelerates downstream analyses such as trajectory inference.

Future Directions

We will develop computational methods that can help transform multiple measurements of molecular information in individual cells to a better understanding of cellular identity and function in health and disease.
To exploit the full potential of single-cell genomics technologies, we devise and engineer algorithms that can narrow the gap between the scalability of current analytical methods and the sheer volume of the data being produced. At the same time, the computational methods that we develop will link multiple modalities measured by emerging technologies, including genome, transcriptome, epigenome, and proteome, in a biologically meaningful manner, taking into account the spatial context in tissues.
Implemented in open-source software, our methods will help to piece together the many parts of the bigger puzzle of gene regulatory networks within cells and interactions between cells.

Selected Publications

(1) Van Do H, Elbassioni K, **Canzar S** (2020). Sphetcher: **Spherical thresholding improves sketching of single-cell transcriptomic heterogeneity.** iScience. doi: 10.1016/j.isci.2020.101126.

(2) Van Do H, Blažević M, Monteagudo P, Borozan L, Elbassioni K, Laue S, Rojas Ringeling F, Matijević D, **Canzar S** (2019). **Dynamic pseudo-time warping of complex single-cell trajectories.** RECOMB. LNBI 11467:294-296.

(3) Berg DA, Su Y, Jimenez-Cyrus D, Patel A, Huang N, Morizet D, Lee S, Shah R, Ringeling FR, Jain R, Epstein JA, Wu QF, **Canzar S**, Ming GL , Song H, Bond AM (2019). **A Common Embryonic Origin of Stem Cells Drives Developmental and Adult Neurogenesis.** Cell. 177(3):654-668.

(4) Kuang Z, Boeke JD, **Canzar S** (2017). **The dynamic landscape of fission yeast meiosis alternative-splice isoforms.** Genome Res. 27(1):145-156.

Karl-Klaus Conzelmann

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1988	Dr. rer. nat., University of Tübingen
1989-1994	Scientist – Federal Research Center for Virus Diseases of Animals (BFAV) Tübingen
1995-1998	Head (comm.) Department of Clinical Virology, BFAV Tübingen
1999 – pres	Professor, LMU Munich
2012-2015	Interim Chair of Virology, Max von Pettenkofer-Institute, LMU Munich

RNA Virus Biology

Goals and Impacts for Society

Co-evolution with their hosts has made viruses skillful specialists in cell biology and biochemistry. We are studying negative strand RNA viruses (*Mononegavirales*) to learn how they exploit cellular machineries for virus propagation and how they trick host defenses. Identification of their achilles heels is needed to devise rational antiviral strategies and drugs, and their talents are being exploited to develop biomedical tools for gene therapy, oncolytic virotherapy, and vaccination.

Research Highlights

A key technology in the lab is the genetic engineering of these RNA viruses (reverse genetics) which was developed in our laboratory. A major topic in the laboratory is the immune- and neurobiology of rabies virus. This virus is unique in that it spreads in the host brain exclusively via synaptic connections and goes largely unrecognized by the host innate immune system. Rabies virus cannot only prevent production of immune stimulating RNA PAMPs activating PKR and other pattern recognition receptors (PRR), but also block PRR signaling which is studied in a Transregio SFB237 (Nucleic acid immunity) project. The unique transsynaptic spread of the virus is being exploited in the Munich SFB870 (Neuronal Networks). "Monosynaptic" rabies virus tracers and indicator viruses which can spread from an initially infected neuron only to directly connected neurons, but not further, are used widely by neurobiologists to study connectivity of neuronal circuits.
The related VSV is a high level gene expression machine, and we are working on VSV platforms for oncolytic virotherapy and vaccine development, including vaccines against COVID-19. One critical aspect of such vectors is biological safety, which we address by development of vectors whose replication can be stopped by small drugs.

Future Directions

With the advent of COVID-19 the need of rapid and effective vaccine platforms for pandemic agents, like VSV became unmistakable. As safety of such vectors is crucial, we are implementing spreading-deficient vaccine and oncolytic vectors, as well as replication competent vectors which are engineered such that they can be stopped by approved medical drugs. Further development of rabies vectors to assay the activity and function of neurons and circuits will help in uncovering the complexity and function of brain wiring. In combination with viral vectors for repair of damaged neuronal circuits, the studies ultimately aim at curing major neurodegenerative diseases.

Selected Publications

(1) Göbel J, Engelhardt E, Pelzer P, Sakthivelu V, Jahn HM, Jevtic M, Folz-Donahue K, Kukat C, Schauss A, Frese CK, Giavalisco P, Ghanem A, **Conzelmann KK**, Motori E, Bergami M (2020). **Mitochondria-Endoplasmic Reticulum Contacts in Reactive Astrocytes Promote Vascular Remodeling**. Cell Metab. 31(4):791-808.e8.

(2) Schubert R, Trenholm S, Balint K, Kosche G, Cowan CS, Mohr MA, Munz M, Martinez-Martin D, Fläschner G, Newton R, Krol J, Scherf BG, Yonehara K, Wertz A, Ponti A, Ghanem A, Hillier D, **Conzelmann KK**, Müller DJ, Roska B (2018). **Virus stamping for targeted single-cell infection in vitro and in vivo.** Nat Biotechnol. 36(1):81-88.

(3) Douglass AM, Kucukdereli H, Ponserre M, Markovic M, Gründemann J, Strobel C, Alcala Morales PL, **Conzelmann KK**, Lüthi A, Klein R (2017). **Central amygdala circuits modulate food consumption through a positive-valence mechanism.** Nat Neurosci. 20(10):1384-1394.

(4) Falkner S, Grade S, Dimou L, **Conzelmann KK**, Bonhoeffer T, Götz M, Hübener M (2016). **Transplanted embryonic neurons integrate into adult neocortical circuits.** Nature. 539(7628):248-253.

Selected Awards and Honors

Editorial board of Journal of Virology

Klaus Förstemann

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1998 - 2002	PhD Swiss Institute of Cancer Research, Lausanne, Switzerland
2002 - 2003	Postdoc Swiss Institute of Cancer Research, Lausanne, Switzerland
2003 - 2006	Postdoc University of Massachusetts Medical School, Worcester, USA
since 2006	Professor, LMU München, Germany

Biology of Non-Coding RNAs

Goals and Impacts for Society

Non-coding RNAs are major players in the regulation of gene expression and defense against external as well as internal pathogens. We study the biogenesis and function of short interfering RNAs (siRNAs) and microRNAs (miRNAs) to gain a fundamental understanding of *when*, *why* and *how* a small RNA response is triggered to neutralize an invader or to compensate a change in the environment. We focus on the role of small RNAs in somatic surveillance of transposable elements, a parasitic form of DNA that can be found in the genomes of all organisms. This response is mechanistically and evolutionarily related to the anti-viral action of siRNAs, which we can study in part through experimental mimics of infection. Insects rely heavily on the resilience that siRNAs and miRNAs can provide and the corresponding biochemical pathways are highly active, facilitating experimental access. We therefore use the fruit fly *Drosophila melanogaster* as a model system.

Our work is fundamental research that provides a deeper understanding of biological principles. As such, it has no impact on society whatsoever. But then - why bother? Many insects and other arthropods such as spiders and ticks are disease vectors. For example, the malaria mosquito *Anopheles* is the most dangerous animal for humans in Africa. Currently, many of the transmitted diseases are limited to tropical and sub-tropical regions by the habitat boundaries of their animal vectors. With the advancing climate change, some vector species will establish resident populations in the temperate zones of Europe. A profound understanding of arthropod biology will then become an important medical need.

Research Highlights

We discovered that a DNA double-strand break can trigger a small RNA response in *Drosophila*. According to the enzymes involved in their biogenesis and the repressive activity they convey, the DNA break fortuitously triggers the response that we constitutively observe for transposable elements. While small RNAs play no local role in DNA repair, the phenomenon is an extraordinary tool for mechanistic studies of genome surveillance and the establishment of a persistent equilibrium between pathogen virulence and host defense. Combined with the CRISPR-cas "toolshed", we have temporal control and the necessary genomic precision to elucidate cis-acting elements that mark a transcript as foreign and trigger an siRNA response. For example, small RNA generation is substantially stimulated by stalled spliceosomes on the transcript that is affected by a DNA break. This is consistent with the notion that while invading nucleic acids employ host RNA biogenesis pathways to hide from quality control systems, they use them inefficiently and this may be their Achilles heel.

Double-stranded RNA (dsRNA) is an essential intermediate during siRNA biogenesis and we have a long-standing interest in how this molecular species is generated, transported and processed by the biogenesis machinery. In particular, the dynamic interaction of proteins with dsRNA can be studied with a combination of biochemical, biophysical and genetic tools. We also discovered a protein that fosters the export of dsRNA with nuclear origin to the cytoplasm for further processing and incorporation into active RNA-protein complexes. Modern tools such as genome editing and next-generation RNA sequencing have considerably expanded our ability to manipulate and analyze the small and non-coding RNA universe *in vitro* as well as *in vivo*.

Future Directions

We are building the mechanistic link between stalled splicing and antisense transcription triggered by a DNA break. This is the key event that triggers dsRNA formation and thus siRNA biogenesis. Furthermore, the role of liquid-liquid phase separation must be considered for all aspects of RNA biology. Our take on this is to study whether dsRNA, which forms a rigid structure lacking the flexibility of "normal" RNA, can nucleate phase separation.

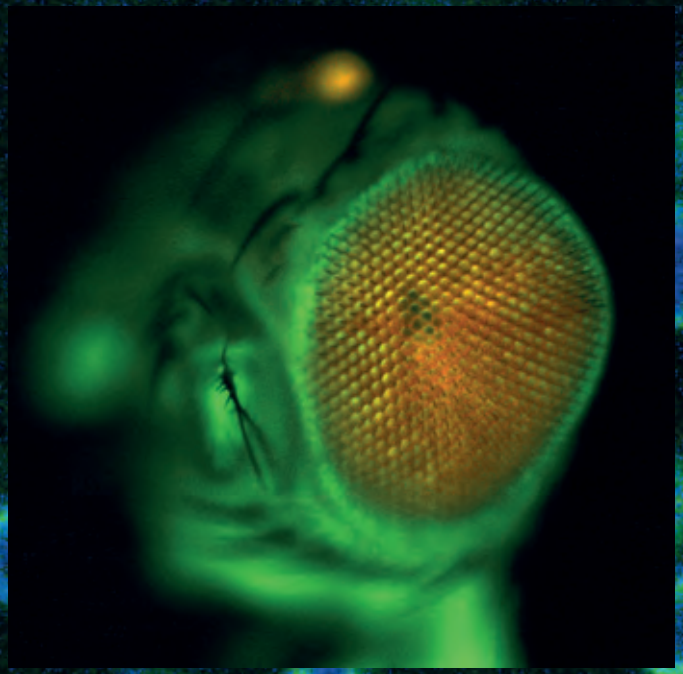
Selected Publications

(1) Nitschko V, Kunzelmann S, Fröhlich T, Arnold GJ, **Förstemann K** (2020). **Trafficking of siRNA precursors by the dsRBD protein Blanks in Drosophila.** Nucleic Acids Res. 48(7):3906-3921.

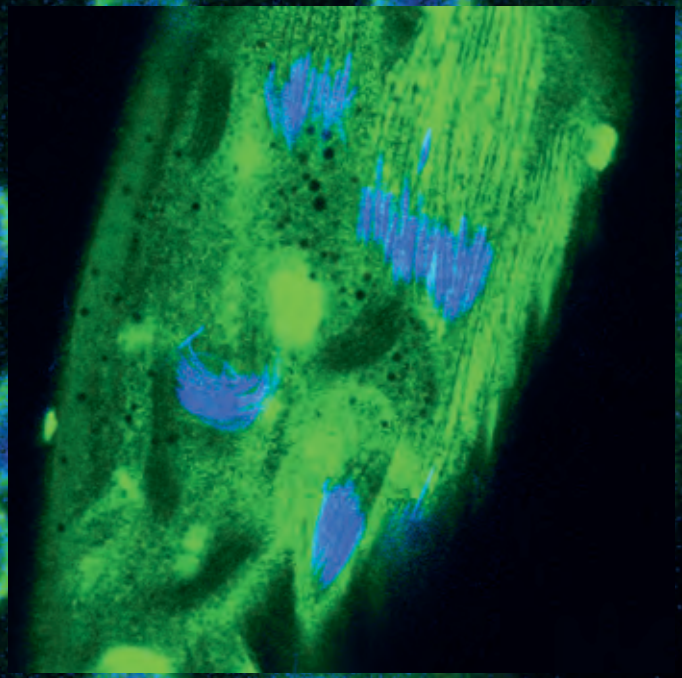
(2) Tants JN, Fesser S, Kern T, Stehle R, Geerlof A, Wunderlich C, Juen M, Hartlmüller C, Böttcher R, Kunzelmann S, Lange O, Kreutz C, **Förstemann K**, Sattler M (2017). **Molecular basis for asymmetry sensing of siRNAs by the Drosophila Loqs-PD/Dcr-2 complex in RNA interference.** Nucleic Acids Res. 45(21):12536-12550.

(3) Merk K, Breinig M, Böttcher R, Krebs S, Blum H, Boutros M, **Förstemann K** (2017). **Splicing stimulates siRNA formation at Drosophila DNA double-strand breaks.** PLoS Genet. 13(6):e1006861.

(4) Michalik KM, Böttcher R, Förstemann K (2012). **A small RNA response at DNA ends in Drosophila.** Nucleic Acids Res. 40(19):9596-603.



Due to its highly versatile genetics, its deeply annotated genome sequence and the excellent biochemical accessibility, the fruit fly *Drosophila melanogaster* is an excellent model organism to study the biology on non-coding RNAs.



Non-coding RNA can play a major role in cytoplasmic, epigenetic inheritance; Oocytes and spermatids (pictured) represent opposite extremes of cytoplasmic contribution to the offspring. Accordingly, RNA-binding proteins (green) become progressively "extruded" from the sperm heads with the condensed DNA (blue).

Coding and non-coding RNA is synthesized in the nucleus (blue) and in many cases it must be exported to the cytoplasm. The protein blanks binds to structured RNA in the nucleus and interfaces with the export machinery; in certain cells the localization at the nuclear periphery is striking.

Ulrike Gaul

1988	PhD University of Tübingen
1989-1993	Postdoc, University of California, Berkeley, USA
1993-2000	Assistant Professor, Rockefeller University, New York, USA
2000-2009	Tenure-Track Professor, Rockefeller University, New York, USA
2009-2020	Alexander von Humboldt-Professor and Chair, Gene Center and Department of Biochemistry, LMU Munich
2020	Deceased on June 14, 2020

Systems Biology of Gene Regulation

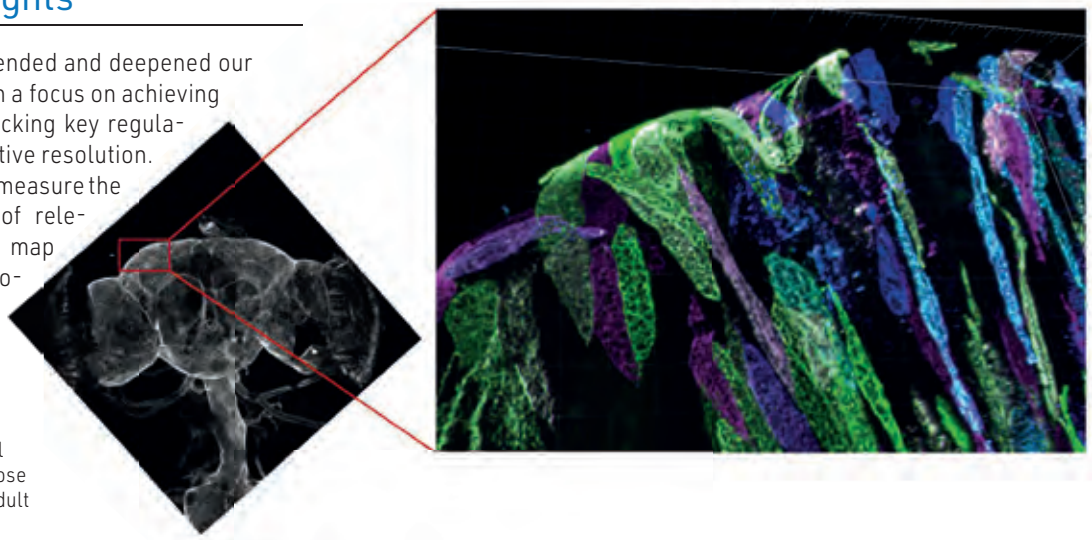
Goals and Impacts for Society

The establishment of complex spatio-temporal patterns of gene expression lies at the heart of animal development. Our lab had a long-standing interest in deciphering the underlying 'regulatory code', from the interaction between regulatory factors and DNA or RNA to their interplay in complex networks. Combining experimental and computational approaches, we developed appropriate methods and concepts to analyze these processes at a systems level. The second line of research in the lab focused on the function of glial cells in nervous system development and homeostasis which has an important implication for human medicine. Glia constitute the majority of cells in the CNS of all higher animals, but their contribution has long been neglected. We discovered numerous novel glial genes, including a GPCR pathway involved in blood-brain barrier formation. We also became interested in a new problem - the interaction between glia and neurons in nervous system homeostasis in the mature animal, a question that has much bearing on the causation and development of neuro-degenerative diseases.

Research Highlights

During the past years we extended and deepened our research in several ways, with a focus on achieving higher throughput and on tracking key regulatory events at higher quantitative resolution. We established techniques to measure the binding affinity landscapes of relevant transcription factors, to map factor binding to DNA genome-wide, and to measure enhancer/promoter activity in high throughput. We completed a systems-level analysis of the key transition from non-periodic to periodic expression patterns within the segmentation network and began to investigate the regulatory role of nucleosomes, finding more complex occupancy patterns and correlations with genic features than previously thought. In addition, we launched a major effort to dissect the *Drosophila* core promotor, using both genomic and large-scale synthetic biology approaches. The long-term goal of these studies was an integrated quantitative model of gene regulation that realistically captures the underlying molecular mechanisms. In another approach we did a large screen, were we characterized all glial subtypes in the adult *Drosophila* brain. This work, together with other genetic tools we developed, will enable researchers to systematically assess the role of glia in brain homeostasis and neurodegeneration.

Aside from our own research, we strengthened the environment for systems biological research in Munich. We set up and improved key instrumentation facilities (bioimaging, robotics) and contributed to important initiatives such as the new research building BioSysM and took the lead in establishing the Graduate School of Quantitative Biosciences Munich.



3D-reconstruction from confocal fluorescence sections of perineural glia cells (on the right), which enclose the entire brain of the *Drosophila* adult fruit fly (on the left).

Selected Publications

(1) Schnepf M, Ludwig C, Bandilla P, Ceolin S, Unnerstall U, Jung C, **Gaul U** (2020). **Sensitive Automated Measurement of Histone-DNA Affinities in Nucleosomes.** iScience. 23(2):100824.

(2) Bozek M, Cortini R, Storti AE, Unnerstall U, **Gaul U**, Gompel N (2019). **ATAC-seq reveals regional differences in enhancer accessibility during the establishment of spatial coordinates in the Drosophila blastoderm.** Genome Res. 29(5):771-783.

(3) Jung C, Bandilla P, von Reutern M, Schnepf M, Rieder S, Unnerstall U, **Gaul U** (2018). **True equilibrium measurement of transcription factor-DNA binding affinities using automated polarization microscopy.** Nat Commun. 9(1):1605.

(4) Kremer MC, Jung C, Batelli S, Rubin GM, **Gaul U** (2017). **The glia of the adult Drosophila nervous system.** Glia. 65(4):606-638.

Franz Herzog

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2003-2006	PhD from the Research Institute of Molecular Pathology and University of Vienna, Austria
2007	Postdoc at the Research Institute of Molecular Pathology, Vienna
2008-2012	Postdoc at the Swiss Federal Institute of Technology, Zurich, Switzerland
since 2012	Group Leader, Gene Center, LMU

Biological Mass Spectrometry

Goals and Impacts for Society

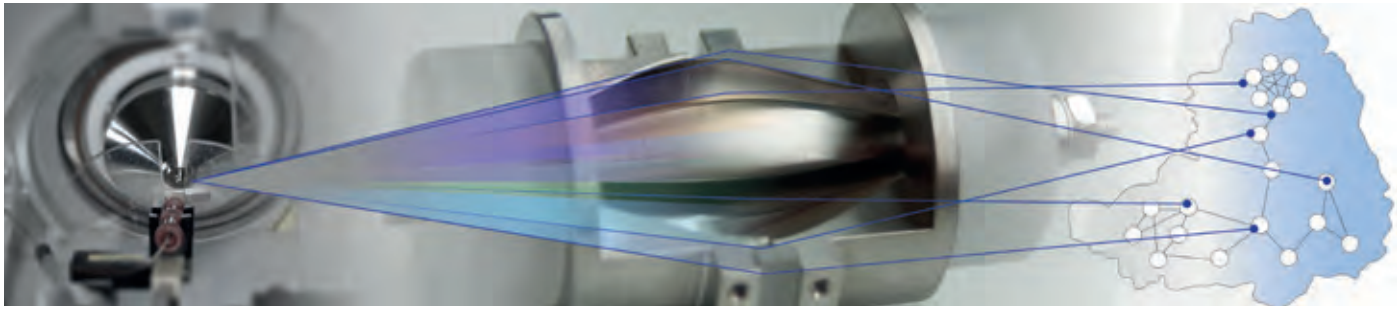
The equal distribution of the genetic material to the progeny during cell division is a fundamental process in all proliferating organisms. Once a cell has decided to enter a new cell cycle, the DNA is duplicated and compacted into chromosomes. A complex machinery distributes the chromosomes to the emerging cells. Our goal is to study the assembly of the kinetochore and its role in regulating the accurate segregation of chromosomes. The kinetochore is a key cellular structure of more than 100 proteins that connects chromosomes to the spindle apparatus and integrates safeguard mechanisms, which coordinate the separation of chromosomes with the dramatic structural rearrangements of the cell during division in order to ensure the fidelity of genetic inheritance.

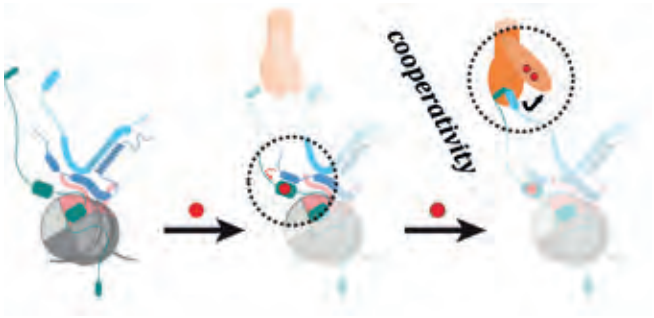
Defects in this process can lead to aneuploidy, which is associated with tumorigenesis, congenital trisomies, and aging. Understanding the build-up of the kinetochore and how this structure serves as sensor and hub for feedback control is vital for identifying the molecular basis of diseases and the development of therapeutic strategies. Our approach is based on the mass spectrometric identification of chemical crosslinks that detects protein binding interfaces. We apply bioinformatics approaches, biochemistry and cell biology to demonstrate the importance of distinct protein interactions for chromosome segregation.

Research Highlights

Chromosomes have to be aligned and bi-oriented at the cell equator in order to be equally distributed during cell division. The kinase Aurora B, a subunit of the chromosomal passenger complex, is the key effector of a regulatory mechanism that corrects improperly aligned chromosomes. By performing crosslink-guided in vitro reconstitution of the budding yeast kinetochore we revealed that the chromosomal passenger complex is recruited to the inner kinetochore and that this interaction is critical for the fidelity of chromosome segregation. If the binding of Aurora B to the inner kinetochore was perturbed, we could restore the accuracy of chromosome segregation by artificially tethering the Aurora B kinase to the inner kinetochore. This study contributed to the molecular understanding of the fundamental process of how cells establish correct chromosome biorientation at the spindle apparatus in order to faithfully disseminate the genetic information.

Crosslinking and mass spectrometry (XLMS) is widely used to acquire spatial restraints for integrative structural biology and interaction proteomics of complex systems like organelles. Crosslinks determine distances on protein structures and indicate the domains that establish the protein interactions. In a recent work, we have developed a novel crosslinking approach that uses the quantification of crosslinks to estimate protein





binding affinities. Studying the assembly of the budding yeast kinetochore, we could show that phosphorylation induces a high-affinity link to the centromeric nucleosome which is required for transmitting the forces of depolymerizing spindle microtubules to the chromosomes. Using our quantitative crosslinking approach we estimated a 300-fold increase in affinity that cooperatively stabilized the kinetochore at the centromeric nucleosome. This work demonstrated that quantitative crosslinking and mass spectrometry of protein assemblies provides mechanistic insights beyond a structural description, which will significantly contribute to the modelling of biological systems.

Future Directions

In nearly all eukaryotes, centromere identity is epigenetically specified by the physical properties of CENP-A containing nucleosomes. DNA replication reduces CENP-A levels by about half as the pool of CENP-A is distributed to the daughter centromeres. Our future efforts will focus on revealing the protein complexes and their interactions that mediate CENP-A distribution, which will provide functional insights into how centromere identity is maintained through generations.

Selected Awards and Honors

2015 Human Frontier Science Program Grant

2015 ERC Starting Grant

Selected Publications

(1) Fischbock-Halwachs J, Singh S, Potocnjak M, Hagemann G, Solis-Mezarino V, Woike S, Ghodgaonkar-Steger M, Weissmann F, Gallego LD, Rojas J, Andreani J, Kohler A, **Herzog F** (2019). **The COMA complex interacts with Cse4 and positions Sli15/Ipl1 at the budding yeast inner kinetochore**. Elife 8.

(2) Solis-Mezarino V, and **Herzog F** (2017). **compleXView: a server for the interpretation of protein abundance and connectivity information to identify protein complexes.** Nucleic Acids Res. 45, W276-W284.

(3) Weir JR, Faesen AC, Klare K, Petrovic A, Basilico F, Fischbock J, Pentakota S, Keller J, Pesenti ME, Pan D, Vogt D, Wohlgemuth S, **Herzog F**, Musacchio A (2016). **Insights from biochemical reconstitution into the architecture of human kinetochores.** Nature 537, 249-253.

(4) Grimm M, Zimniak T, Kahraman A, **Herzog F** (2015). **xVis: a web server for the schematic visualization and interpretation of crosslink-derived spatial restraints.** Nucleic Acids Res. 43, W362-369.

Karl-Peter Hopfner

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1997	PhD Max-Planck-Institute for Biochemistry and Technical University Munich
1998-2001	Postdoc at The Scripps Research Institute, USA
2001-2007	Tenure-Track Professor, Gene Center, LMU
since 2007	Professor and Chair, Gene Center and Department of Biochemistry, LMU
since 2015	Director of the Gene Center

Structural Genome Biology

Goals and Impacts for Society

The maintenance of the genetic information is a fundamental process in all of life. Genome instability due to DNA damage or pathogenic nucleic acids are major causes for cancer and immune related diseases. Using structural biology and protein science, we aim at revealing how cells shape, defend and repair their genomic information, and aim at developing multifunctional therapeutic proteins that help remove diseased cells. We combine basic science with translational research to understand the molecular basis of human disease and contribute to innovative approaches for cancer immunotherapy.

Research Highlights

Many human diseases originate from DNA damage and all cells must maintain the integrity of the genome to remain healthy and respond to threats caused by damaged or pathogenic nucleic acids. Cells possess powerful protein machineries that sense and signal the presence of damaged chromosomes, or foreign nucleic acids, and trigger host responses such as DNA repair or the antiviral interferon response.
Determining the molecular basis of cellular responses to nucleic acid stress is key to understand cancer and immune diseases. A key question we currently address in our research is how potent cellular response reactions are caused by small amounts of danger-associated or damaged DNA but not by the large amount of intact chromosomal DNA. We use cryo-electron microscopy combined with biochemistry and molecular biology to determine the structures and mechanisms of central macromolecular complexes involved in genome maintenance and could achieve several breakthroughs in the past years.
We for the first time could determine structures of DNA double-strand break repair and signaling factors Mre11-Rad50, bound to DNA and show how this complex specifically recognizes and processes DNA strand breaks. In human cells, Mre11-Rad50 helps activate the central DNA damage response kinase ATM that orchestrates the repair of DNA double-strand breaks and we could determine a near atomic resolution structure of the entire 700 KDa kinase dimer. The structure revealed details of the kinase active site and aids developing ATM inhibitors that are currently in clinical development against cancer.
We could also determine the first high-resolution cryo-EM structures of a multisubunit chromatin remodeller. This remodeller, INO80, plays an important role in genome maintenance but also several other genome-associated processes, and emerges as a central factor that shapes chromatin. Our pioneering structures are considered a breakthrough in the field and revealed how these megadalton molecular machines bind to nucleosmes and use ATP to alter nucleosome position and configuration.
We also made fundamental progress in the analysis how cells detect pathogenic DNA. Here, we could show, using structural and molecular biology approaches, that the mammalian sensor for cystosolic DNA cGAS distinguishes nucleic acids on their basis how efficiently they can trigger cGAS oligmerization, a process that helps sense "long" pathogen-associated cytosolic.
We also developed in the past years a novel format for multispecific antibodies, with the goal of combining specific tumor targeting with tumor-redirected immune checkpoint blockade and activation of anti-tumor immune cells. We could show efficacies of this approach in the context of tumor redirected blocking of the CD47-Sirpa and PD1-PDL1 axes of immune checkpoints and markers of self.

Future Directions

In the coming years, we will use cryo-EM work on genome biology factors with the major goal to understand at the atomic level DNA double-strand break repair and signaling in eukaryotic cells and how it is achieved in chromatin. Hereby, it will be also important to derive structures of the INO80 remodeller in different functional states and reveal how it can position, slide and edit nucleosomes. Finally, we aim at finishing the pre-clinical development of our multifunctional antibody constructs that combine tumor targeting with immune checkpoint blockade.

Selected Publications

(1) Michalski S, de Oliveira Mann CC, Stafford C, Witte G, Bartho J, Lammens K, Hornung V, **Hopfner KP** (2020). **Structural basis for sequestration and autoinhibition of cGAS by chromatin.** Nature. doi: 10.1038/s41586-020-2748-0.

(2) Käshammer L, Saathoff JH, Lammens K, Gut F, Bartho J, Alt A, Kessler B, **Hopfner KP** (2019). **Mechanism of DNA End Sensing and Processing by the Mre11-Rad50 Complex.** Mol Cell. 76(3):382-394.

(3) Eustermann S, Schall K, Kostrewa D, Lakomek K, Strauss M, Moldt M, **Hopfner KP** (2018). **Structural basis for ATP-dependent chromatin remodelling by the INO80 complex**. Nature. 556(7701):386-390.

(4) Andreeva L, Hiller B, Kostrewa D, Lässig C, de Oliveira Mann CC, Jan Drexler D, Maiser A, Gaidt M, Leonhardt H, Hornung V, **Hopfner KP** (2017). **cGAS senses long and HMGB/TFAM-bound U-turn DNA by forming protein-DNA ladders.** Nature. 549(7672):394-398.

Selected Awards and Honors

2015 M4 Award for Personalized Medicine

2017 Gottfried Wilhelm Leibniz-Prize

2019 ERC Advanced Grant

Veit Hornung

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2004	Doctorate (Dr. med.), University of Munich, LMU
2003-2006	Research fellow / Postdoctoral research fellow in the Division of Clinical Pharmacology at the University, Hospital Munich, LMU
2006-2008	Postdoc at the University of Massachusetts Medical School in Worcester, USA
2008-2013	Professor of Clinical Biochemistry (W2), Institute for Clinical Chemistry and Clinical Pharmacology, University Hospital, University of Bonn
2014-2015	Director, Institute of Molecular Medicine, University Hospital, University of Bonn
since 2015	Professor and Chair, Gene Center and Department of Biochemistry, LMU

Innate Immunity

Goals and Impacts for Society

Our immune system plays a pivotal role in protecting and maintaining the homeostasis of our organism, both against exogenous and endogenous threats. Central to this critical task is the innate branch of the immune system that employs a diverse set of sensing mechanisms to directly recognize infectious agents or to indirectly respond to harmful or dangerous perturbations. Employing cellular biology, molecular biology and biochemical tools, we strive to understand how our innate immune systems discriminates self from non-self or harmless from harmful, respectively. A particular focus of our work is to decipher the exact molecular mechanisms of the sensing interface of this intricate system: What receptors are being employed, what molecular structures are detected by these receptors and how do they initiate signaling cascades to set off an immune response?

Research Highlights

Inflammasomes constitute a family of cytosolic sensors that can directly detect microbial molecules, but also indirectly sense damage by detecting the perturbation of cellular homeostasis. Within the recent years a lot of progress has been made in the characterization of inflammasome components and their pivotal role in host defense. In addition, it has become evident that many non-communicable diseases are triggered or perpetuated by inflammasomes and as such inflammasomes have also become a prime focus for the development of novel anti-inflammatory therapies. Inflammasomes are large multimeric pro-caspase-1 activating platforms that are essential for the processing and thus activation of the proinflammatory cytokines IL-1β and IL-18. Another important substrate of caspase-1 is GSDMD, which upon cleavage executes a unique type of cell death, known as pyroptosis. Employing genome engineering tools, we have focused our efforts to understand the role of this important sensing machinery in the human system. Here, we made two important discoveries in the past years that also have implications for potential therapeutic applications. On the one hand, we uncovered a new inflammasome signaling paradigm in human monocytes, a cell type that constitutes a major source of pro-inflammatory cytokines. We named this pathway "the alternative inflammasome", since its signaling cascade and outcomes diverge from previous studies conducted in mice [1]. Secondly, we identified how the detection of cytosolic DNA is linked to inflammasome activation in human myeloid cells. Cytosolic delivery of DNA results in the activation of the cGAS-STING signaling axis that drives the activation of antiviral immune defenses. Our studies revealed an additional functionality of this cascade, namely a cell death pathway that is triggered downstream of STING [2]. Engagement of this cell death resulted in the secondary activation of the inflammasome pathway, which connects cytosolic DNA recognition to the activation of a pro-inflammatory response in these cells.

Another important focus of our research are the mechanisms of nucleic acid recognition. Several receptors in different compartments of the cell function to detection non-self nucleic acids. A prominent group of receptors are DNA and RNA sensing toll-like receptors (TLRs) that are within the endolysosomal compartment. In most cases, these receptors detect degradation products of DNA or RNA rather than long stretches of intact nucleic acid molecules. An important receptor in myeloid cells that orchestrates the recognition of pathogens is TLR8. TLR8 detects RNA degradation products via two distinct binding pockets. Probing for the contribution of different nucleases, we were able to identify RNase T2 as an essential enzyme that functions to degrade RNA into small fragments that can be detected by TLR8 [3]. These results provide unprecedent insight into how nucleic acid metabolism is connected to innate immune responses.

Future Directions

In future studies, we will further explore the mechanisms of inflammasome signaling. A particular focus will be put on the mechanism of NLRP3 activation, which plays a central role in many sterile inflammatory diseases. Moreover, we will try to understand how nucleic acid metabolism is connected to the detection of non-self nucleic acids. Beyond focusing on basic research, we also aim to develop strategies to manipulate these sensing interfaces for therapeutic applications.

Selected Publications

(1) Gaidt MM, Ebert TS, Chauhan D, Schmidt T, Schmid-Burgk JL, Rapino F, Robertson AA, Cooper MA, Graf T, **Hornung V** (2016). **Human Monocytes Engage an Alternative Inflammasome Pathway.** Immunity. 44(4):833-46.

[2] Gaidt MM, Ebert TS, Chauhan D, Ramshorn K, Pinci F, Zuber S, O'Duill F, Schmid-Burgk JL, Hoss F, Buhmann R, Wittmann G, Latz E, Subklewe M, **Hornung V** (2017). **The DNA Inflammasome in Human Myeloid Cells Is Initiated by a STINGCell Death Program Upstream of NLRP3.** Cell. 171(5):1110-1124.e18.

[3] Greulich W, Wagner M, Gaidt MM, Stafford C, Cheng Y, Linder A, Carell T, **Hornung V** (2019). **TLR8 Is a Sensor of RNase T2 Degradation Products.** Cell. 179(6):1264-1275.e13.

[4] van den Boorn JG, Jakobs C, Hagen C, Renn M, Luiten RM, Melief CJ, Tüting T, Garbi N, Hartmann G, **Hornung V** (2016). **Inflammasome-Dependent Induction of Adaptive NK Cell Memory.** Immunity. 44(6):1406-21.

Selected Awards and Honors

2015 ERC Consolidator Grant
2015 Elected EMBO Member
2016 Elected Leopoldina Member
2018 Liliane Bettencourt Prize for Life Sciences
2018 Gottfried Wilhelm Leibniz Prize (DFG)
2020 William B. Coley Award

Lucas Jae

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2015	PhD, The Netherlands Cancer Institute, Amsterdam and Utrecht University
2016	Postdoc at The Netherlands Cancer Institute, Amsterdam
2017	Independent Group Leader, Gene Center, LMU
since 2019	Tenure-Track Professor, Gene Center and Department of Biochemistry, LMU

Functional Genomics

Goals and Impacts for Society

Functioning of the eukaryotic cell relies on the concerted activity of biological machines like mitochondria, defects in which can cause incurable human disease, including metabolic disorders and neurodegeneration. Using a combination of state-of-the-art genome-engineering and genome-wide phenotypic screening at the single cell level, we seek to map the genetic dependencies of these organelles under physiological conditions and in the context of human disease. This sheds light on unknown signaling processes and genetic exploits that may inform future strategies of tackling hitherto 'undruggable' conditions.

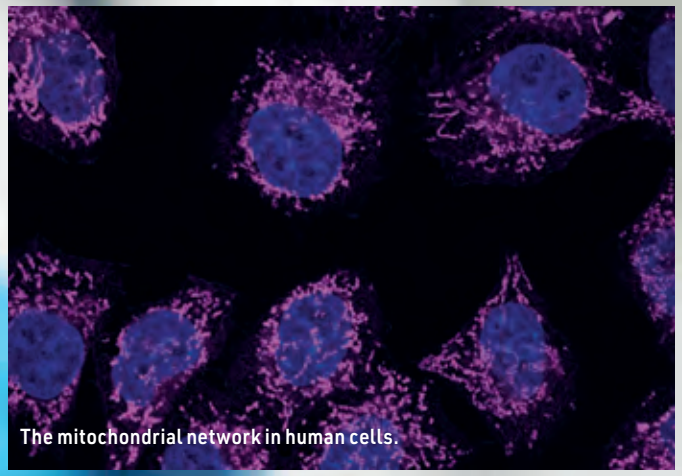
Research Highlights

While cells are more than the sum of their parts, inherited or exogenously triggered dysfunction of organelles and macromolecular complexes undercuts important biological activities and can thus lead to severe human disease. This is particularly exemplified by mitochondria, for which more than 250 disease genes have identified to date but in most cases, cures are sorely lacking. This is principally caused by the difficulty to restore loss-of-function phenotypes by classical means.
To overcome this limitation, it is critical to unbiasedly identify the genetic make-up of these organelles under normal conditions and understand how it is re-shaped in the context of mitochondrial malfunction. In particular, charting the landscape of genetic interactions can be used to identify cellular resilience mechanisms and reveal suppressor phenotypes that may hold therapeutic promise.
During my postdoctoral training with Thijn Brummelkamp at The Netherlands Cancer Institute, we developed an unbiased approach to mapping genetic interactions in the human cell that solely relies on genomic mutations in haploid cells (4). This showed, for the first time, that the abundance of genetic interplay observed in simpler yeast cells, encouragingly, is mirrored in the human system.
While systematically mapping genetic interactions through cellular growth rates has led to landmark discoveries in cellular biology, fitness represents a readout of low specificity and is not

readily applicable to many important aspects of organelle functioning, such as signaling events. To overcome this limitation, we subsequently developed a unique method of single cell phenotypic screening by flow cytometry that can be used to resolve protein fates at unprecedented resolution. This revealed new regulators in diverse cellular signaling cascades, including a proteolytic off-switch in G-protein signaling feeding into AKT activation, a pathway frequently deregulated in human cancers (3).
Using a similar strategy, we were able to implicate the little-studied proteins CMTM4 and CMTM6 as novel regulators of PD-L1 stability at the surface of the cell (2). Cancer cells exploit PD-L1 to avoid being attacked by the immune system, rationalizing the immense academic and pharmaceutical efforts put into modulating this pathway in cancer therapy.
Currently, we are focusing on the role of mitochondria in the context of cellular stress. Using CRISPR-Cas, we recently engineered cells with a reporter for the integrated stress response – the principal mechanism of mammalian cells to deal with protein homeostatic insults. A suite of genome-wide screens in these engineered cells allowed us to identify the mitochondrial protease OMA1, together with the little-studied protein DELE1 and the heme-regulated kinase HRI as the elusive pathway that relays mitochondrial insults to the cell (1).

Future Directions

Going forward, we are most interested in combining phenotypic profiling of cellular stress response mechanisms with genetic interaction mapping. This will provide critical insights into cellular buffering mechanisms and epistatic arrangements, which we hope to exploit to devise innovative strategies for rooting out malignant cells and restoring lost organelle functionality.



The mitochondrial network in human cells.

Selected Publications

(1) Fessler E, Eckl EM, Schmitt S, Mancilla IA, Meyer-Bender MF, Hanf M, Philippou-Massier J, Krebs S, Zischka H, J**ae LT** (2020). **A pathway coordinated by DELE1 relays mitochondrial stress to the cytosol**. Nature. 579(7799):433-437.

(2) Mezzadra R, Sun C, **Jae LT**, Gomez-Eerland R, de Vries E, Wu W, Logtenberg MEW, Slagter M, Rozeman EA, Hofland I, Broeks A, Horlings HM, Wessels LFA, Blank CU, Xiao Y, Heck AJR, Borst J, Brummelkamp TR, Schumacher TNM (2017). **Identification of CMTM6 and CMTM4 as PD-L1 protein regulators.** Nature. 549(7670):106-110.

(3) Brockmann M, Blomen VA, Nieuwenhuis J, Stickel E, Raaben M, Bleijerveld OB, Altelaar AFM, **Jae LT**, Brummelkamp TR (2017). **Genetic wiring maps of single-cell protein states reveal an off-switch for GPCR signalling.** Nature. 546(7657):307-311.

(4) Blomen VA, Májek P, **Jae LT**, Bigenzahn JW, Nieuwenhuis J, Staring J, Sacco R, van Diemen FR, Olk N, Stukalov A, Marceau C, Janssen H, Carette JE, Bennett KL, Colinge J, Superti-Furga G†, Brummelkamp TR (2015). **Gene essentiality and synthetic lethality in haploid human cells.** Science. 350(6264):1092-6.

Selected Awards and Honors

2016 Antoni van Leeuwenhoek Award

2018 Heinz Maier-Leibnitz Prize

2018 ERC Starting Grant

Oliver T. Keppler

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1995	Medical Degree, University of Heidelberg
1997-2002	Postdoctoral Fellow, Department of Applied Tumor Virology at the German Cancer Research Center Heidelberg and Gladstone Institute of Virology and Immunology, University of California, San Francisco
2005	Habilitation in Experimental Virology, University of Heidelberg
2012-2015	Director of the Institute of Medical Virology, Chair of Virology, Johann-Wolfgang-Goethe University Frankfurt am Main
since 2015	Professor and Chair, Max von Pettenkofer Institute, LMU Munich

HIV-Host Interactions and Chemo-Sensitization

Goals and Impacts for Society

HIV/AIDS has become one of the most devastating pandemics in recorded history. AIDS is the fourth-biggest global killer and the leading cause of death in Africa. HIV/AIDS persists as a major cause of morbidity in Western societies, since currently available pharmacotherapies can only partly control, but not cure this immunodestructive viral infection. Furthermore, these drugs frequently cause severe side effects and HIV drug resistance development is rapidly emerging. Globally, the lack of effective treatment regimens causes immense human suffering and high cost for society. My laboratory seeks to better understand the pathological interplay of HIV with the host's immune system and its target cells with the goal of providing new approaches for prophylaxis and therapy.

Research Highlights

1. Intrinsic immunity and resting CD4 T-cells

2. HIV pathogenesis *ex vivo*

3. Novel cellular interactors of HIV

4. SAMHD1's role in oncology

5. Contributions to SARS-CoV-2 research (http://www.mvp.uni-muenchen.de/coronavirus-covid-19/forschung/)

Future Directions

Our overriding goal is to decipher HIV biology and in particular HIV reservoir formation to educate new strategies to purge the viral reservoir in HIV-infected individuals. Moreover, we want to advance diagnostics tool and evidence-based PCR- and antibody-centered testing strategies in the battle to control the SARS-CoV-2 pandemic and contribute with our collaborators to the development of effective antiviral therapy.

Selected Publications

(1) Oellerich T, Schneider C, Thomas D, Knecht KM, Buzovetsky O, Kaderali L, Schliemann C, Bohnenberger H, Angenendt L, Hartmann W, Wardelmann E, Rothenburger T, Mohr S, Scheich S, Comoglio F, Wilke A, Ströbel P, Serve H, Michaelis M, Ferreirós N, Geisslinger G, Xiong Y, **Keppler OT**, Cinatl J Jr (2019). **Selective inactivation of hypomethylating agents by SAMHD1 provides a rationale for therapeutic stratification in AML**. Nat Commun. 10(1):3475.

(2) Schneider C, Oellerich T, Baldauf HM, Schwarz SM, Thomas D, Flick R, Bohnenberger H, Kaderali L, Stegmann L, Cremer A, Martin M, Lohmeyer J, Michaelis M, Hornung V, Schliemann C, Berdel WE, Hartmann W, Wardelmann E, Comoglio F, Hansmann ML, Yakunin AF, Geisslinger G, Ströbel P, Ferreirós N, Serve H, **Keppler OT**, Cinatl J Jr (2017). **SAMHD1 is a biomarker for cytarabine response and a therapeutic target in acute myeloid leukemia**. Nat Med. 23(2):250-255.

(3) Baldauf HM, Stegmann L, Schwarz SM, Ambiel I, Trotard M, Martin M, Burggraf M, Lenzi GM, Lejk H, Pan X, Fregoso OI, Lim ES, Abraham L, Nguyen LA, Rutsch F, König R, Kim B, Emerman M, Fackler OT, **Keppler OT** (2017). **Vpx overcomes a SAMHD1-independent block to HIV reverse transcription that is specific to resting CD4 T cells.** PNAS USA. 114(10):2729-2734.

(4) Baldauf HM, Pan X, Erikson E, Schmidt S, Daddacha W, Burggraf M, Schenkova K, Ambiel I, Wabnitz G, Gramberg T, Panitz S, Flory E, Landau NR, Sertel S, Rutsch F, Lasitschka F, Kim B, König R, Fackler OT, **Keppler OT** (2012). **The deoxynucleoside triphosphate triphosphohydrolase SAMHD1 restricts HIV-1 infection in resting CD4+ T cells.** Nat Med. 18(11):1682-7.

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1995-2000	Clinical Fellow and Instructor, Boston Children's Hospital and Dana Farber Cancer Institute, Harvard Medical School
2000-2008	Tenure-Track Professor, Department of Pediatric Hematology/Oncology, Hannover Medical School
2008-2011	Professor and Chair, Department of Pediatric Hematology/Oncology, Hannover Medical School
since 2011	Director, Department of Pediatrics, LMU Munich

Translational Molecular Pediatrics-Rare Diseases of the Immune System

Goals and Impacts for Society

Children with rare and monogenic diseases, currently in most instances therapeutic orphans, may be pioneers of a new era of personalized medicine. Studying the genetic etiology and pathomechanisms of monogenic diseases bears great potential for the discovery of general principles orchestrating the differentiation and function of cells, tissues, and organs. Our laboratory has established a global alliance of physicians and scientists joining forces to shed light on rare diseases of the immune system and to develop targeted therapies.

Research Highlights

Inborn errors of the immune system may manifest as immunodeficiency, autoimmunity, autoinflammation, or cancer.
Our studies in rare children with congenital neutropenia associated with bone marrow failure and acute myeloid leukemia revealed novel mutations in SMARCD2, a nucleosome positioning factor implicated in stem cell differentiation [4]. We use state-of-the-art genome wide sequencing technologies paired with in vitro and in vivo modeling systems (e.g. in transgenic mice or zebrafish) to validate genetic findings in children and to perform functional studies.
We have also assembled the world's largest cohort of children with very early onset inflammatory bowel diseases to decipher genes and pathways controlling intestinal immune homeostasis. We discovered the first patients with loss-of-function mutations in TGFB1 [2], the principle member of the transforming growth factor family of proteins with pleiotropic functions in human immunity. In this project, we used high-dimensional FACS and CyTOF-based immune phenotyping to determine rare immune subpopulations in intestinal tissues.

Severe combined immunodeficiency associates a spectrum of diseases affecting differentiation and function of T and B cells. We discovered the first children with mutations in FCHO1 [1], a critical factor for the initiation of clathrin-coated pits. Surprisingly, the defect affects primary T-cell differentiation, as shown by a series of CRISPR-Cas9-mediated editing and cell biological experiments.

Future Directions

In the future, we plan to resume preclinical and clinical studies in hematopoietic stem cell gene therapy using novel gene editing tools in monogenic hematopoietic disorders. We also expand our genome sequencing studies and embark upon novel multi-omics-based phenotyping analyses in children with rare diseases of the blood and immune system. We will focus on the development of innovative cell and gene-based therapies, along with potential repurposing studies of known pharmacological agents.

Selected Publications

[1] Schober T, Magg T, Laschinger M, Rohlfs M, Linhares ND, Puchalka J, Weisser T, Fehlner K, Mautner J, Walz C, Hussein K, Jaeger G, Kammer B, Schmid I, Bahia M, Pena SD, Behrends U, Belohradsky BH, **Klein C**, Hauck F. (2017). **A human immunodeficiency syndrome caused by mutations in CARMIL2**. Nat Commun. 23(8):14209.

[2] Witzel M, Petersheim D, **Klein C**, Fan Y, Bahrami E, Racek T, Rohlfs M, Puchałka J, Mertes C, Gagneur J, Ziegenhain C, Enard W, Stray-Pedersen A, Arkwright PD, Abboud MR, Pazhakh V, Lieschke GJ, Krawitz PM, Dahlhoff M, Schneider MR, Wolf E, Horny HP, Schmidt H, et al. (2017). **Chromatin-remodeling factor SMARCD2 regulates transcriptional networks controlling differentiation of neutrophil granulocytes.** Nat Genet. 49(5):742-752.

[3] Kotlarz D, Marquardt B, Barøy T, Lee WS, Konnikova L, Hollizeck S, Magg T, Lehle AS, Walz C, Borggraefe I, Hauck F, Bufler P, Conca R, Wall SM, Schumacher EM, Misceo D, Frengen E, Bentsen BS, Uhlig HH, Hopfner KP, Muise AM, Snapper SB, Strømme P, **Klein C** (2018). **Human TGF-β1 deficiency causes severe inflammatory bowel disease and encephalopathy.** Nat Genet. 50(3):344-348.

(4) Łyszkiewicz M, Ziętara N, Frey L, Pannicke U, Stern M, Liu Y, Fan Y, Puchałka J, Hollizeck S, Somekh I, Rohlfs M, Yilmaz T, Ünal E, Karakukcu M, Patiroğlu T, Kellerer C, Karasu E, Sykora KW, Lev A, Simon A, Somech R, Roesler J, Hoenig M, Keppler OT, Schwarz K, **Klein C** (2020). **Human FCHO1 deficiency reveals role for clathrin-mediated endocytosis in development and function of T cells.** Nat Commun. 11(1):1031.

Johannes Stigler

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2012	PhD at Technical University Munich
2013–2016	Postdoc at Columbia University, New York
2017	Postdoc at Technical University Munich
since 2017	Emmy Noether Group leader, Gene Center, LMU
since 2018	Tenure-Track Professor, Gene Center and Department of Biochemistry, LMU

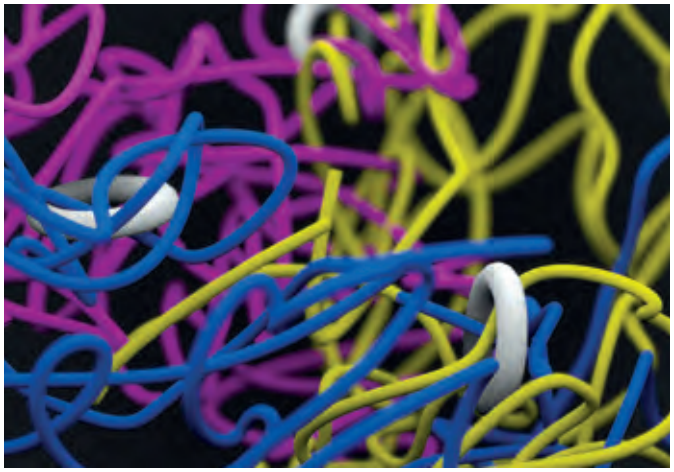
Biophysics of Structural Dynamics in Chromosomes

Goals and Impacts for Society

Chromosomes provide the fundamental scaffold for the maintenance, regulation and propagation of genetic information. Eukaryotic chromosomes are highly structured and the three-dimensional folding of chromosomes is directly linked to gene regulation. Our lab employs biophysical single molecule techniques to determine the processes that lead to the three-dimensional folding of chromosomes.

Research Highlights

Interphase chromosomes in higher eukaryotes are hierarchically structured on different levels, ranging from DNA wrapped around histones, to chromatin fibers, up to large chromosomal domains encompassing hundreds of kilobases. Hi-C experiments have shown that these topologically associating domains (TADs), which consist of regions of increased interactions of certain genomic regions, are a structural feature of all higher eukaryotes. TADs are generally isolated by domain boundaries from adjacent regions.



Computer model of tangled chromatin fibers.

Current models indicate that TADs are formed by the action of chromosomal architectural proteins, chiefly members of the SMC (structural maintenance of chromosomes) family, such as cohesin or condensin. With the help of genomic insulators, such as CTCF, SMC proteins act as intra-molecular crosslinkers and tether distant genomic sites together. The thus-established three-dimensional architecture of chromosomes is directly linked to gene regulation.

Our lab has set out to decipher the protein-protein and protein-DNA interactions of chromosomal architectural proteins that lead to the formation of three-dimensionally folded chromosomes.

We could visualize the binding of single fluorescently tagged cohesin complexes to DNA on multiplexed DNA curtain microfluidic chips and determine biochemical interaction parameters of their interactions with DNA and other proteins. In earlier work, we could show that cohesin is able to bind DNA topologically. We further determined the functional size of cohesin's topological lumen in its DNA-bound configuration from diffusive properties on DNA and its interactions with DNA-bound obstacles. These models have since been corroborated by CryoEM structures.

In more recent work, we proceeded to investigate the DNA tethering and compaction properties of cohesin. Our results indicate that cohesin is able to create tethers between DNA molecules in cis and trans with heterogenous mechanical strength. Our current interest lies in studying the mechanical properties of SMC complexes and their tethering interactions in greater detail.

Future Directions

In the future, we aim to apply our toolbox of coupled force and fluorescence single molecule methods to a wider range of questions in the context of genome biology. To this end, we plan to study the action of chromosomal architectural proteins in the presence of nucleosomes and to investigate the role of remodelers. We will further work on the development of pipelines and methods to extract thermodynamically exact parameters from our measurements.

Selected Publications

(1) Gutierrez-Escribano P, Newton M, Llauro A, Huber J, Tanasie L, Davy J, Aly I, Aramayo R, Montoya A, Kramer H, **Stigler J**, Rueda D, Aragon L (2019). **A conserved ATP- and Scc2/4-dependent activity for cohesin in tethering DNA molecules.** Science Advances. 5:eaay6804.

(2) **Stigler J**, Çamdere GÖ, Koshland DE, Greene E (2016): **Single-Molecule Imaging Reveals a Collapsed Conformational State for DNA-Bound Cohesin.** Cell Reports. 15:988–998.

(3) Ramm B, **Stigler J**, Hinczewski M, Thirumalai D, Herrmann H, Woehlke G, Rief M (2014). **Sequence-resolved free energy profiles of stress-bearing vimentin intermediate filaments.** PNAS. 111:11359–11364.

(4) **Stigler J**, Ziegler F, Gieseke A, Gebhardt JCM, Rief M (2011). **The complex folding network of single calmodulin molecules**. Science. 334: 512–516.

Selected Awards and Honors

2017 ERC Starting Grant

Julian Stingele

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2015	PhD, Max-Planck-Institute of Biochemistry and LMU Munich
2014-2017	Postdoctoral research fellow at The Francis Crick Institute, UK
since 2017	Tenure-Track Professor, Gene Center and Department of Biochemistry, LMU

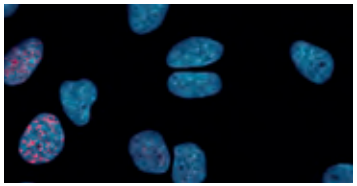
Maintenance of Genome Stability

Goals and Impacts for Society

The integrity of our genetic information is constantly challenged by structural and chemical alterations. Such DNA lesions require constant repair by cellular DNA repair pathways in order to maintain genome stability. Germline mutations of crucial DNA repair genes cause a range of human syndromes characterized by cancer predisposition, premature aging, immunodeficiency and neurodegeneration. DNA repair genes are also frequently mutated in tumor cells, which renders them highly vulnerable to DNA-damaging chemotherapeutic agents. Moreover, the loss of certain DNA repair pathways makes tumor cells sensitive to pharmacological inhibition of other repair enzymes, which can be exploited for personalized anti-cancer therapies. Thus, a detailed understanding of the cellular pathways repairing DNA lesions will not only reveal the principles of essential biological processes but also guide the development of new therapeutic strategies.

Research Highlights

Covalent DNA-protein crosslinks (DPCs) are particularly toxic DNA lesions, because they block chromatin processes such as transcription and replication. DPCs are induced by various endogenous and exogenous agents (e.g. reactive aldehydes) and are also caused by covalent trapping of enzymes such as topoisomerases. It was assumed that these lesions were merely targeted by canonical DNA repair pathways. This has changed with my discovery of a protease-based DPC-specific repair mechanism, which is conserved from yeast to humans.
During my PhD studies in the laboratory of Prof. Stefan Jentsch at the Max Planck Institute of Biochemistry (Martinsried, Germany), I revealed that yeast cells possess a specialized metalloprotease – Wss1 – which degrades DPCs. Using *in vitro* experiments, I discovered that Wss1 processes its substrates in a unique DNA-dependent manner. Its unprecedented activity enables the enzyme to process virtually any substrate protein as long as it is presented on DNA. The data obtained during my PhD revealed that Wss1 acts directly on the protein component of DPCs thereby enabling replication of DPC-containing templates and thus ensuring genome stability.



Human cell nuclei stained for DNA (blue) and the repair enzyme SPRTN (red).

Then, I moved as an EMBO long-term fellow to the group of Prof. Simon Boulton at the Francis Crick Institute (London, UK), where I not only revealed the homologous pathway in higher eukaryotes, but also obtained detailed insights into its regulation. Importantly, germ line mutations of SPRTN are causative for Ruijs-Aalfs syndrome, which is characterized by premature aging and early-onset hepatocellular carcinomas. The underlying molecular cause of this syndrome was however unclear. I established that the disease-causing mutations either abolish SPRTN's proteolytic activity towards DPCs or compromise its ability to be efficiently recruited to chromatin. Accordingly, my results strongly suggest that faulty DPC repair is the molecular defect underlying Ruijs-Aalfs syndrome.

Future Directions

Our data indicate that DPCs are key drivers of genome instability and that there is an entire unexplored pathway regulating protease-based DPC repair. The overarching objective of the work in my laboratory is thus to reveal the sources of endogenous DPCs and to understand the cellular responses to these threats not only in mechanistic detail but also on a global scale. We will identify the currently unknown components of the cellular pathway regulating protease-based DPC repair in mammalian cells using genome-wide screening approaches in combination with functional assays. Moreover, we are developing novel broadly applicable methods to overcome current technical limitations to study DPCs and their repair in a global system-wide manner. This will allow us to ask "What proteins are crosslinked where in the genome?" in any given experimental scenario. Finally, we aim to unravel the origins of endogenous DPC formation, which will have wide-ranging implications for our understanding of cancer development and aging.

Selected Publications

(1) Reinking HK, Kang HS, Goetz MJ, Li H-Y, Kieser A, Zhao S, Acampora AC, Weickert P, Fessler F, Jae LT, Sattler M, **Stingele J**. **DNA Structure-Specific Cleavage of DNA-Protein Crosslinks by the SPRTN Protease.** Mol Cell (in press).

(2) **Stingele J**, Bellelli R, and Boulton SJ (2017). **Mechanisms of DNA-protein crosslink repair.** Nat Rev Mol Cell Biol. 18(9):563-573.

(3) **Stingele J**, Bellelli R, Alte F, Hewitt G, Sarek G, Maslen SL, Tsutakawa SE, Borg A, Kjaer S, Tainer JA, Skehel JM, Groll M, Boulton SJ (2016). **Mechanism and regulation of DNA-protein crosslink repair by the DNA-dependent metalloprotease SPRTN**. Mol Cell. 64(4):688-703.

(4) **Stingele J**, Schwarz MS, Bloemeke N, Wolf PG , Jentsch S (2014). **A DNA-dependent protease involved in DNA-protein crosslink repair**. Cell. 158:327-38.

Selected Awards and Honors

2015 EMBO Long-Term Fellowship

2018 Alfried Krupp-Förderpreis für junge Hochschullehrer

2018 ERC Starting Grant

2019 Bayer Early Excellence in Science Award

Marion Subklewe

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1995	Medical Dissertation, University of Cologne, Department of Internal Medicine, Hematology / Oncology
2005	Board Certificate Internal Medicine
2007	Board Certificate Hematology & Oncology
2007	Habilitation in Internal Medicine, Charité, Berlin
since 2009	Head of Flow Cytometry, Laboratory of Leukemia Diagnostics, University Hospital, LMU Munich
since 2014	Professor, University Hospital, LMU Munich
since 2017	Head of the Laboratory for Translational Cancer Immunology, University Hospital, LMU Munich

Translational Research

for Immunotherapy of Hematological Malignancies

Goals and Impacts for Society

Hematologic malignancies include a large number of genetically diverse tumors that affect the blood, bone marrow, lymph, and lymphatic system. In the last decades, antibody-based immunotherapies have revolutionized the treatment strategies of such malignancies. We seek to understand the evolution of the disease and the dynamic interaction with the immune system. Our aim is to understand, develop and improve T cell-based immunotherapy for hematologic neoplasms. Analysis of clinical aspect of the patient with a thorough assessment of static and dynamic parameters in combination with translational and basic research create the basis for improving such strategies.

Research Highlights

Assessment of Minimal Residual Disease (MRD) allows for the detection of residual malignant cells. We were able to show that MRD detection in Acute Myeloid Leukemia (AML) by flow cytometry has a negative prognostic impact in patients who are in complete remission by conventional criteria (1). We were able to show for the first time that MRD Flow assessment at a very early time point is highly predictive of relapse. MRD Flow assessment will serve as a platform to gain a deeper understanding of the biology of hematologic malignancies and offers the unique possibility to purify rare, biologically highly relevant subpopulations (funding: SFB1243).

Dendritic Cells (DCs) are important regulators of immunity. We evaluated DCs matured by different cytokine cocktails for expression of stimulatory and inhibitory molecules and correspondent activation of T helper 1 (Th1) and natural killer (NK) cells. We showed that TLR-DCs, due to their costimulatory profile and their high IL-12p70 secretion, are superior with respect to Th1 polarization and activation of NK cells. Based on these data a phase I/II clinical trial using RNA-transfected TLR 7/8 matured DCs was completed for AML patients with high risk of relapse (2). We demonstrated that vaccination with next-generation LAA-expressing DCs in AML is feasible, safe, and induces anti-leukemic immune responses *in vivo*. Our *in vitro* data support the hypothesis that the vaccine effects on T-cell activation could be further enhanced by blockade of PD-1 and LAG-3 (3). A follow up trial utilizing dual checkpoint inhibition in combination with hypomethylating agents is under way and will start recruiting patients Q3, 2020.

Antibody-based immunotherapy represents a promising strategy to target and eliminate chemo-resistant leukemic cells. We evaluated a novel class of bispecific T cell engaging antibodies (BiTE®) which direct T cells to the tumor cells. The CD33/CD3-BiTE® AMG 330 recognizes CD33 on AML cells and recruits $CD3^+$ T cells independent of their specificity. Using a long-term culture system for primary AML cells, we were able to show that AMG 330 recruited and expanded residual memory T cells. AMG 330 mediated cytotoxicity resulted in complete lysis of AML cells in the majority of cases. Based on our findings, we developed a clinical study protocol in close collaboration with AMGEN and initiated a multi-center phase I study. We aim to better understand the mode of action of BiTE®/BiTE-like constructs as well as the mode of resistance. We showed that tumor cells escaped the immunological attack by upregulation of inhibitory immune-checkpoint ligands (4). In collaboration with the group of KP Hopfner we generated novel, bifunctional constructs ("CiTEs") that block an inhibitory molecule superficially on an AML cells and thereby reversing adaptive immune escape.

Future Directions

In the coming years, we will work on a deeper understanding of the co-evolution of T cell function and its modulation through the malignant cell, e.g. leukemia or lymphoma cells. Understanding the immunobiology during the course of the disease and its modulation through immunotherapeutic strategies will enable further developments. In the future, analysis of MRD will guide personalized immunotherapeutic approaches to eliminate chemorefraktory malignant cells. Individualized off-the-shelf bispecific antibody constructs, also in conjunction with adoptive transfer of genetically modified T cells will be studied in the setting of an MRD setting. Suitable preclinical development will be the basis for initiating first-in-human clinical trials.

Selected Publications

(1) Köhnke T, Bücklein V, Rechkemmer S, Schneider S, Rothenberg-Thurley M, Metzeler KH, Sauerland MC, Hiddemann W, Spiekermann K, **Subklewe M**. (2019). **Response assessment in acute myeloid leukemia by flow cytometry supersedes cytomorphology at time of aplasia, amends cases without molecular residual disease marker and serves as an independent prognostic marker at time of aplasia and post-induction. Haematologica.** haematol.2018.215236.

(2) Lichtenegger FS, Schnorfeil FM, Rothe M, Deiser K, Altmann T, Bücklein VL, Köhnke T, Augsberger C, Konstandin NP, Spiekermann K, Moosmann A, Boehm S, Boxberg M, Heemskerk MH, Goerlich D, Wittmann G, Wagner B, Hiddemann W, Schendel DJ, Kvalheim G, Bigalke I, **Subklewe M**. (2020). **Toll-like receptor 7/8-matured RNA-transduced dendritic cells as post-remission therapy in acute myeloid leukaemia: results of a phase I trial.** Clin Transl Immunol. 9: e1117.

(3) Lichtenegger FS, Rothe M, Schnorfeil FM, Deiser K, Krupka C, Augsberger C, Schlüter M, Neitz J, **Subklewe M**. (2018). **Targeting LAG-3 and PD-1 to Enhance T Cell Activation by Antigen-Presenting Cells.** Front Immunol. 9:385.

(4) Herrmann M, Krupka C, Deiser K, Brauchle B, Marcinek A, Ogrinc Wagner A, Rataj F, Mocikat R, Metzeler KH, Spiekermann K, Kobold S, Fenn NC, Hopfner KP, **Subklewe M**. (2018). **Bifunctional PD-1 x αCD3 x αCD33 fusion protein reverses adaptive immune escape in acute myeloid leukemia.** Blood. 132(23): 2484-2494.

Selected Awards and Honors

2015 M4-Award: Startup support for the development of a novel multispecific antibody derivatives

2016 Else Kröner Fresenius Kolleg for Clinician Scientists "Cancer Immunotherapy"

2018 ASH Abstract Achievement award (also 2013, 2015, 2016)

2019 Else Kröner Fresenius Kolleg for Clinician Scientists, 2nd funding period

Sebastian Theurich

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2006	Dissertation (M.D.), Max-Delbrück-Center for Molecular Medicine and Charité, Humboldt-University Berlin
2012	Board Certification for Internal Medicine, Hematology and Oncology
2013-16	Postdoctoral Research Fellow, Max-Planck-Institute for Metabolism Research, Cologne
2015	Habilitation (venia legendi, internal medicine), Medical Faculty, University of Cologne
2018	Attending Physician, Dpt. of Medicine III, LMU University Hospital
2020	Professor, Dpt. of Medicine III, LMU University Hospital

Cancer- and Immunometabolism

Goals and Impacts for Society

Complex metabolic networks generate and transform energy and building blocks for cellular fitness, function and growth. Whereas the basic biochemical principles of metabolism have been uncovered in the last century, in-depth understanding of cell specific mechanisms and their impact on the regulation of immune response and cancer biology has emerged only recently. Metabolic and immunologic alterations have now been acknowledged as "emerging hallmarks of cancer", and it is accepted that certain types of cancer are associated with metabolic disturbances such as obesity – a increasing health burden worldwide. Our research group aims to understand the reciprocal interactions of cytotoxic immune cells and cancer on a metabolic level, and how metabolic host factors impact on these processes. Using basic lab methodologies and translational approaches we ultimately intend to develop novel immunometabolic strategies for the diagnosis and treatment of cancer as well as to understand and modulate the individual contributing host factors.

Research Highlights

Obesity is associated with systemic chronic low-grade inflammation (so-called metaflammation) which represents a significant pathophysiologic state for the development of diabetes and cancer. However, the exact relationships between metaflammation and neoplasia formation and progression are still incompletely understood but might be of particular interest in the context of cancer immunotherapy.
We and others could recently identify Natural Killer (NK) cells, which are key immune cells to fight against neoplastic and infected cells, as central mediators of metaflammation and insulin dependent glucose metabolism (1). More specifically, we identified a distinct and interleukin-6 /Stat3 dependent, obesity-associated NK cell subpopulation that could represent a novel cellular target to treat obesity and diabetes (2). We are now aiming to characterize the role of this NK cell subset in the context of selected obesity-associated cancers.

Another focus of the group is to identify metabolic host factors that influence cancer treatment responses, as well as to understand and therapeutically modulate the tumor microenvironment by local approaches. Employing computational analyses of clinical routine data we could identify significant gender-specific metabolic effects on outcomes after chemo-immunotherapy (3). Moreover, we could demonstrate that local modulation of the tumor microenvironment, e.g. by radiotherapy, in addition to systemic cancer immunotherapy by the CTLA4 checkpoint inhibitor ipilimumab induced strong anti-tumor immune responses in melanoma patients, which resulted in doubled overall survival rates (4).

Future Directions

Based on our previous work, we will analyze the specific role of NK cell subsets in obesity associated cancers as well as to investigate strategies to modulate specific energy metabolism pathways in cytotoxic immune cells for improved anti-cancer activities. To this end, we will employ cutting edge single cell resolution technologies as well as metabolomics with our cooperation partners. On a clinical level, we aim to implement personalized metabolic interventions for cancer patients into routine practice. Therefore, our group together with our collaborators at the University Hospital Cologne just initiated a multicenter investigator-initiated prospective clinical trial supported by the "Gemeinsamer Bundesausschuss" to investigate a combined nutrition and exercise program during cancer treatment ("INTEGRATION Programm"). https://innovationsfonds.g-ba.de/

Selected Awards and Honors

	Associate Editor, Cochrane Haematology
2018	Basic Research Award, Glaxo-Smith-Kline Foundation
2019	Researcher of the German Cancer Consortium (DKTK)

Selected Publications

(1) FM, Jelenčić V, Valentić S, Šestan M, Wensveen TT, **Theurich S**, Glasner A, Mendrila D, Štimac D, Wunderlich FT, Brüning JC, Mandelboim O, Polić B (2015). **NK cells link obesity-induced adipose stress to inflammation and insulin resistance.** Nat immunol. 16(4): 376–385.

(2) **Theurich S**, Tsaousidou E, Hanssen R, Lempradl AM, Mauer J, Timper K, Schilbach K, Folz-Donahue K, Heilinger C, Sexl V, Pospisilik JA, Wunderlich FT, Brüning JC (2017). **IL-6/Stat3-Dependent Induction of a Distinct, Obesity-Associated NK Cell Subpopulation Deteriorates Energy and Glucose Homeostasis.** Cell Metab. 26(1): 171-184.e6.

(3) Fürstenau M, Hopfinger G, Robrecht S, Fink AM, Al-Sawaf O, Langerbeins P, Cramer P, Tresckow JV, Maurer C, Kutsch N, Hoechstetter M, Dreyling M, Lange E, Kneba M, Stilgenbauer S, Döhner H, Hensel M, Kiehl MG, Jaeger U, Wendtner CM, Goede V, Fischer K, von Bergwelt-Baildon M, Eichhorst B, Hallek M, **Theurich S** (2020). **Influence of obesity and gender on treatment outcomes in patients with chronic lymphocytic leukemia (CLL) undergoing rituximab-based chemoimmunotherapy**. Leukemia 34(4): 1177–1181.

(4) **Theurich S**, Rothschild SI, Hoffmann M, Fabri M, Sommer A, Garcia-Marquez M, Thelen M, Schill C, Merki R, Schmid T, Koeberle D, Zippelius A, Baues C, Mauch C, Tigges C, Kreuter A, Borggrefe J, von Bergwelt-Baildon M, Schlaak M (2016). **Local Tumor Treatment in Combination with Systemic Ipilimumab Immunotherapy Prolongs Overall Survival in Patients with Advanced Malignant Melanoma.** Cancer Immunol Res. 4(9):744-54.

Eckhard Wolf

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1990	Dr. med. vet., LMU Munich
1991-1993	Postdoc, LMU Munich
1994	Group leader, University of Veterinary Sciences Vienna
since 1995	Professor and Chair, Gene Center and Department of Veterinary Sciences, LMU Munich
since 2005	Director of the Laboratory for Functional Genome Analysis (LAFUGA), Gene Center, LMU Munich

Translational Disease Models

Goals and Impacts for Society

Research into disease mechanisms is an important basis for the development of novel, targeted therapies. Suitable animal models, which allow predictions on the efficacy and safety of novel therapies, are inevitable in this process. Rodent models are most widely used, but are often limited in the resemblance of human disease mechanisms and phenotypes. Due to the establishment of efficient and precise techniques for genetic modification, it is possible to generate tailored pig models, which mimic human disease mechanisms and phenotypes on a molecular and functional level. Moreover, genetically multi-modified pigs are promising donors for organ xenotransplantation.

Research Highlights

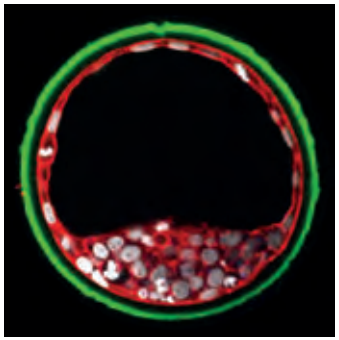
Within the German Center for Diabetes Research (DZD; https://www.dzd-ev.de/), we generated genetically diabetic or prediabetic pig models, performed treatment studies, and analyzed diabetic complications and organ cross-talk using multi-omics designs (1). Another focus is the generation of pig models for monogenic diseases, including cystic fibrosis, Laron syndrome and Duchenne muscular dystrophy (DMD). DMD is the most common hereditary muscular disease among children, often forcing victims into the wheelchair before the age of twelve and reducing life expectancies. Our tailored pig model for DMD was instrumental for the development of a CRISPR/Cas based therapy that may provide relief for those suffering from DMD (2).

The number of donated human organs and tissues for transplantation falls far short of the need. Alternatives such as xenotransplantation (the use of animal organs and tissues) are therefore urgently needed. Due to anatomical and physiological similarities with humans the pig is the preferred donor species. Within the DFG-funded Transregional Collaborative Research Center 127 "Biology of xenogeneic cell, tissue and organ transplantation – from bench to bedside" (Spokesperson: E. Wolf) we are tailoring donor pigs to overcome rejection mechanisms and physiological incompatibilities of pig-to-primate xenografts. Hearts from genetically multi-modified pigs lacking αGal carbohydrate epitopes and expressing human CD46 and human thrombomodulin functioned for up to 195 days after orthotopic transplantation (heart replacement) in baboons (3), which is regarded as a milestone on the way to clinical cardiac xenotransplantation.

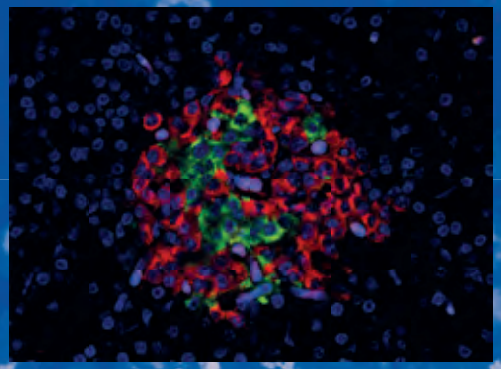
Finally, biology of reproduction in livestock species is an interesting research topic since many aspects resemble human reproductive biology more closely than rodent models do. During preimplantation development, the first cell lineages differentiate while a proportion of cells retains pluripotency. In mouse embryos, loss of the transcription factor OCT4 causes failure of primitive endoderm development (shown by the lack of cells expressing GATA6), while cells expressing the pluripotency marker gene NANOG are not affected. In contrast, bovine OCT4 deficient embryos retain cells that express GATA6 but lose NANOG entirely (4). A recent study on the function of OCT4 in early human development revealed the same mechanism as in bovine, suggesting bovine embryos as an interesting model for studying human development.

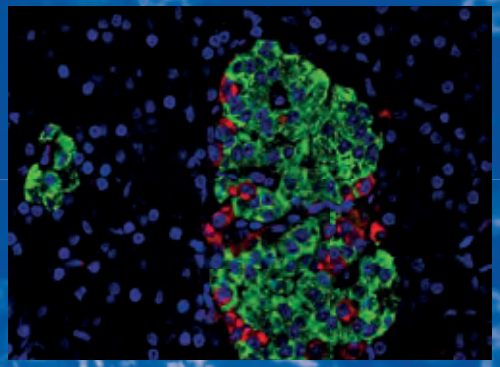
Future Directions

Since our Center for Innovative Medical Models (CiMM; www.lmu.de/cimm) is now fully established, we have excellent conditions for generating, characterizing and implementing genetically tailored disease models. In addition to diabetes and other endocrine disorders, models for cardiovascular diseases are currently under development. These will be assets for the research program of the Interfaculty center for endoCrine and cardiOvascular disease Network modelling and clinical transfer (ICON) that will be established together with the Medical Faculty as a new research building at the Campus Großhadern. ICON will also be instrumental to bring xenotransplantation of porcine hearts and pancreatic islets to clinical application.



Bovine blastocyst.





Pancreatic islets from a genetically diabetic pig (left) and a wild-type control (right).

Selected Publications

(1) Backman M, Flenkenthaler F, Blutke A, Dahlhoff M, Ländström E, Renner S, Philippou-Massier J, Krebs S, Rathkolb B, Prehn C, Grzybek M, Coskun Ü, Rothe M, Adamski J, de Angelis MH, Wanke R, Fröhlich T, Arnold GJ, Blum H, **Wolf E** (2019). **Multi-omics insights into functional alterations of the liver in insulin-deficient diabetes mellitus**. Mol Metab. 26(8):30-44.

(2) Moretti A, Fonteyne L, Giesert F, Hoppmann P, Meier AB, Bozoglu T, Baehr A, Schneider CM, Sinnecker D, Klett K, Fröhlich T, Rahman FA, Haufe T, Sun S, Jurisch V, Kessler B, Hinkel R, Dirschinger R, Martens E, Jilek C, Graf A, Krebs S, Santamaria G, Kurome M, Zakhartchenko V, Campbell B, Voelse K, Wolf A, Ziegler T, Reichert S, Lee S, Flenkenthaler F, Dorn T, Jeremias I, Blum H, Dendorfer A, Schnieke A, Krause S, Walter MC, Klymiuk N, Laugwitz KL, **Wolf E**, Wurst W, Kupatt C (2020). **Somatic gene editing ameliorates skeletal and cardiac muscle failure in pig and human models of Duchenne muscular dystrophy.** Nat Med. 26(2):207-214.

(3) Längin M, Mayr T, Reichart B, Michel S, Buchholz S, Guethoff S, Dashkevich A, Baehr A, Egerer S, Bauer A, Mihalj M, Panelli A, Issl L, Ying J, Fresch AK, Buttgereit I, Mokelke M, Radan J, Werner F, Lutzmann I, Steen S, Sjöberg T, Paskevicius A, Qiuming L, Sfriso R, Rieben R, Dahlhoff M, Kessler B, Kemter E, Kurome M, Zakhartchenko V, Klett K, Hinkel R, Kupatt C, Falkenau A, Reu S, Ellgass R, Herzog R, Binder U, Wich G, Skerra A, Ayares D, Kind A, Schönmann U, Kaup FJ, Hagl C, **Wolf E**, Klymiuk N, Brenner P, Abicht JM (2018). **Consistent success in life-supporting porcine cardiac xenotransplantation.** Nature. 564(7736):430-433.

(4) Simmet K, Zakhartchenko V, Philippou-Massier J, Blum H, Klymiuk N, **Wolf E** (2018). **OCT4/POU5F1 is required for NANOG expression in bovine blastocysts.** PNAS 115(11):2770-2775.

Selected Awards and Honors

2014 Corresponding Member, Austrian Academy of Sciences

2018 Walter Frei Prize, University of Zurich

Genetically multi-modified donor pigs for organ xenotransplantation.

Julien Gagneur

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2004	PhD in Applied Mathematics, École Centrale Paris, France
2002 - 2005	Computational scientist, Cellzome AG, Heidelberg, Germany
2005 - 2012	Staff scientist, EMBL, Heidelberg, Germany
2012 - 2015	Group leader, Gene Center, LMU, Munich, Germany
2016 - 2020	Assistant professor, TUM, Munich, Germany
since 2020	Professor, TUM, Munich, Germany

Computational Biology

Goals

Our goal is an improved understanding of the genetic basis of gene regulation and its implication in diseases. To this end, we employ statistical modeling of ‚omic data and work in close collaboration with experimentalists.

Research Highlights

At TUM:
We set up Kipoi, a repository of machine-learning models to give clinical researchers access to the latest algorithms that interpret genetic variations and omics data (Avsec et al Nat biotech 2019).
www.tum.de/nc/en/about-tum/news/press-releases/details/35471/
We developed a new strategy for pinpointing cause of rare genetic disorders by looking at RNA and not only DNA. Kremer et al. Nat communs 2017
www.tum.de/nc/en/about-tum/news/press-releases/details/33970/

At Gene Center:
We developed with Patrick Cramer TT-seq, a new protocol to map short-lived RNAs and study their metabolism. Schwalb et al, Science, 2016.
www.tum.de/nc/en/about-tum/news/press-releases/details/33140/

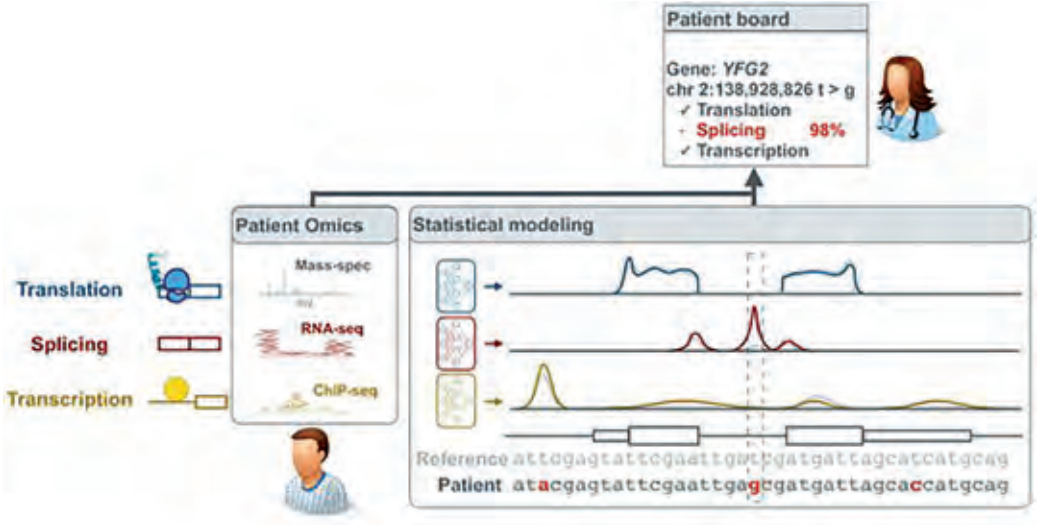
Selected Publications

(1) Schwalb B, Michel M, Zacher B, Frühauf K, Demel C, Tresch A, **Gagneur J**, Cramer P (2016). **TT-seq maps the human transient transcriptome.** Science. 352(6290):1225-1228.

(2) Eser P, Wachutka L, Maier K, Demel C, Boroni M, Iyer S, Cramer P, **Gagneur J** (2016). **Determinants of RNA metabolism in the Schizosaccharomyces pombe genome.** Mol Syst Biol. 12:857

(3) Bader, D, Wilkening, S, Lin, G, Tekkedil, MM, Dietrich K, Steinmetz, LM, **Gagneur J** (2015). **Negative feedback buffers effects of regulatory variants**. Mol Syst Biol. 11:785

(4) Glas J, Dumcke S, Zacher B, Poron D, **Gagneur J**, Tresch A (2015). **Simultaneous characterization of sense and antisense genomic processes by the double-stranded hidden Markov model.** Nucleic Acids Res. 44(5):e44.



Research overview. We study how gene regulation, the control of gene activity, is encoded in the genome, build computational models that predict the implications of genetic modifications on gene regulation, and integrate genetic and molecular data of patients to support diagnostics of genetic disorders. (Gagneur, Systembiologie.de, 2017).

Regulation of Genome Expression

Goals

Regulation of genome expression is required for many cellular processes including cell proliferation, differentiation, development and viability. Heterochromatin, a silent fraction of chromatin, maintains genome stability and defects in heterochromatin formation lead to aberrant centromere and telomere function, aneuploidy and cancer. We are focusing on molecular mechanism of recognition of repetitive and transposable genetic elements and epigenetic silencing by heterochromatin formation. We combine genetics and genomics with biochemistry and cryo-EM to study how various proteins recognize and modify chromatin structure.

Research Highlights

Our work has contributed to the understanding of fundamental process of how genomes recognize repetitive and transposable elements and target them into heterochromatin (Halic and Moazed, Cell, 2010; Marasovic, Mol Cell, 2013). To achieve this, the host cells generate small RNAs that scan the transcriptome to distinguish self from non-self (Marasovic et al, Mol Cell, 2013). We have also shown that degradation of Argonaute-bound small RNAs is essential in providing fidelity in RNAi mediated silencing (Pisacane and Halic, Nature Communications, 2017) and that chromatin bound lncRNAs heterochromatin (Broenner et al, Genome Research, 2017).
Our recent cryo-EM structures reveal how nucleosomes open and unwrap DNA and how the histone octamer adapts to DNA unwrapping (Bilokapic et al, NSMB, 2018). We have also shown that the histone octamer core rearranges and deforms the nuclesome to translocate DNA. Nucleosome plasticity observed in our structures is likely exploited byvarious chromatin machineries (Bilokapic et al, 2018, NSMB; Bilokapic et al, Nature Communications, 2018). Our latest work shows that charged transient interactions form and shape the histone H1-transport complex and that Nuclear Pore Complex contributes to its disassembly (Ivic et al, Molecular Cell, 2019).

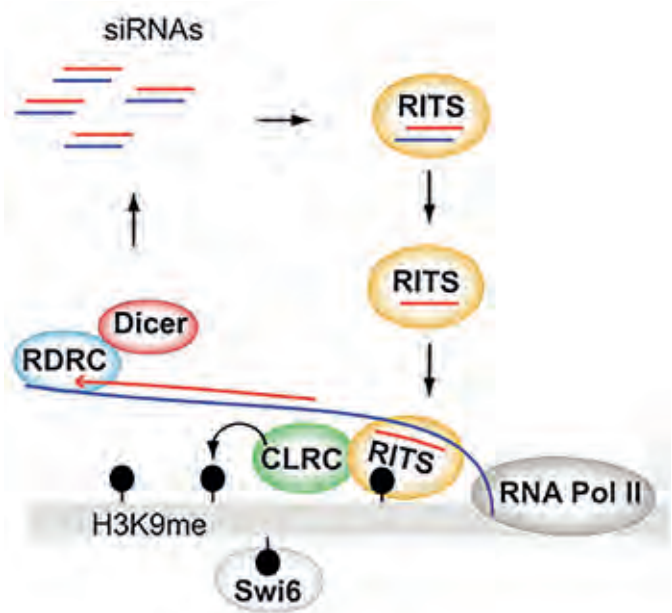
Selected Publications

(1) Ivic M, Potocnjak M, Solis-Mezarino V, Herzog F, Bilokapic S, **Halic M** (2019). **Fuzzy interactions form and shape the histone transport complex.** Mol Cell. 73(6):1191-1203.e6.

(2) Bilokapic S, Strauss M, **Halic M** (2018). **Histone octamer rearranges to adapt to DNA unwrapping.** Nat Struct Mol Biol. 25(1):101-108.

(3) Bilokapic S, Strauss M, **Halic M** (2018). **Structural rearrangements of the histone octamer translocate DNA.** Nat Comm. 9(1):1330.

4) Brönner C, Salvi L, Zocco M, Ugolini I, **Halic M** (2017). **Accumulation of RNA on chromatin disrupts heterochromatic silencing.** Genome Res. 27(7):1174-1183.



Model of small RNA mediated heterochromatin formation in fission yeast

Mario Halic

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2005	PhD from Humboldt University in Berlin, Germany
2005 - 2007	Postdoc at Humboldt University in Berlin and Gene Center in Munich, Germany
2007 - 2011	Postdoc at Harvard University in Boston, USA
2011 - 2018	Tenure-Track Professor, Gene Center and Department of Biochemistry, LMU
since 2018	Associate Member, St. Jude Children's Research Hospital, Memphis, USA

Fabiana Perocchi

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E-mail	fabiana.perocchi@helmholtz-muenchen.de

2007	PhD from European Molecular Biology Laboratory in Heidelberg and Heidelberg University
2008-2011	Postdoc at Harvard Medical School and Massachusetts General Hospital, USA
2011-2012	Postdoc at the Centre for Genomic Regulation in Barcelona, Spain
2012-2017	Junior Group Leader of the Bavarian Research Network for Molecular Biosystems, Gene Center, LMU
2013-2017	Emmy Noether Junior Research Group Leader at the Institute of Human Genetics, Helmholtz Zentrum München
since 2017	Head of Functional Genomics of Mitochondria Unit, Institute for Diabetes and Obesity, HMGU

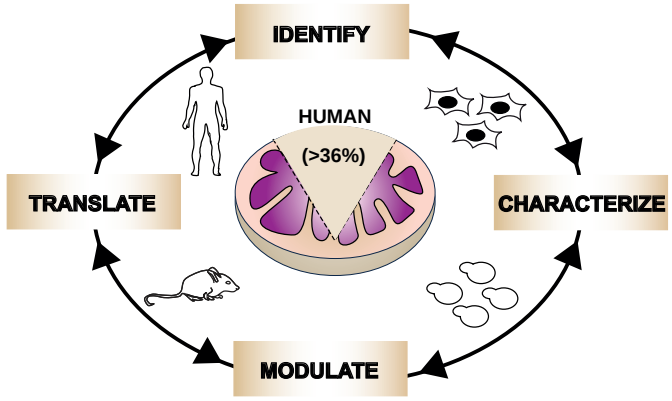
Functional Genomics of Mitochondria

Goals

To identify, characterize and target the molecular components of signaling networks in human mitochondria.

Research Highlights

Our research group is interested in understanding the molecular basis of mitochondrial function in human physiology and pathophysiology. Mitochondria are double membrane organelles found in virtually all eukaryotic cells and are central to energy production, ion homeostasis, intermediary metabolism, and cell death. Inherited defects in mitochondria cause the most common inborn errors of metabolism, but a growing body of evidence links them to virtually all age-associated diseases, ranging from diabetes and cancer to neurodegeneration. Human mitochondria contain a tiny genome encoding 13 well-studied proteins, while all the remaining estimated 1,500 mitochondrial proteins are encoded from nuclear genes, translated in the cytosol, targeted and imported into the organelle. As a consequence of the dual genetic origin of mitochondrial proteins, mitochondrial biogenesis and function require a robust coordination between cellular and mitochondrial machineries. Bi-directional signaling exists between mitochondria and other cellular components that regulate the dynamic and complex remodeling of mitochondrial shape, motility, metabolism, and proteome in response to environmental stimuli and energetic requirements during growth and development. However, in many instances, the molecular links between intracellular signals and mitochondrial responses remain unknown. What are the mitochondrial proteins that sense, modulate, and propagate intracellular signals? How is the mitochondrial signaling "toolkit" regulated? How do mitochondria integrate into signal transduction cascades? What happens when mitochondrial signaling networks are compromised and how can we prevent deleterious effects?



Systems biology approach to study mitochondria

Selected Publications

(1) Wettmarshausen J, Goh V, Huang KT, Arduino DM, Tripathi U, Leimpek A, Cheng Y, Pittis AA, Gabaldón T, Mokranjac D, Hajnóczky G, **Perocchi F** (2018). **MICU1 Confers Protection from MCU-Dependent Manganese Toxicity.** Cell Rep. 25(6):1425-1435.e7.

(2) Cheng Y, Jiang L, Keipert S, Zhang S, Hauser A, Graf E, Strom T, Tschöp M, Jastroch M, **Perocchi F.** (2018) **Prediction of Adipose Browning Capacity by Systematic Integration of Transcriptional Profiles.** Cell Rep. 23(10):3112-3125.

(3) Arduino DM, Wettmarshausen J, Vais H, Navas-Navarro P, Cheng Y, Leimpek A, Ma Z, Delrio-Lorenzo A, Giordano A, Garcia-Perez C, Médard G, Kuster B, García-Sancho J, Mokranjac D, Foskett JK, Alonso MT, **Perocchi F** (2017). **Systematic Identification of MCU Modulators by Orthogonal Interspecies Chemical Screening.** Mol Cell. 67(4):711-723.e7.

(4) Cheng Y, **Perocchi F.** (2015) **ProtPhylo: identification of protein-phenotype and protein-protein functional associations via phylogenetic profiling.** Nucleic Acids Res. 43(W1):W160-8.

Selected Awards and Honors

2015	The Bert L and N Kuggie Vallee Foundation Young Investigator Award
2018	Helmholtz Young Investigator in Diabetes (HeIDi) Award

Molecular Endocrinology

Goals

To understand the molecular mechanisms underlying the regulation of metabolic homeostasis by nuclear receptors and their associated transcription factors. Nuclear hormone receptors comprise a large family of ligand-gated transcription factors that act as important regulators of numerous physiological processes such as reproduction, metabolism, homeostasis, inflammation and development. We apply cutting edge genomic and genetic techniques in preclinical models to map gene networks relevant for immunometabolic diseases.

Research Highlights

We found that the circadian clock plays a large role in controlling not only glucose, but also lipid and amino acid metabolism in peripheral tissues such as liver and muscle. We could also show that the Glucocorticoid Receptor plays an important role in sustaining daily rhythms of gene expression, and that these patterns change after high fat diet feeding. We also identified a novel factor contributing to the development of adverse effects of glucocorticoid therapy, such as hyperlipidemia, hyperglycemia and hepatic steatosis.

Selected Publications

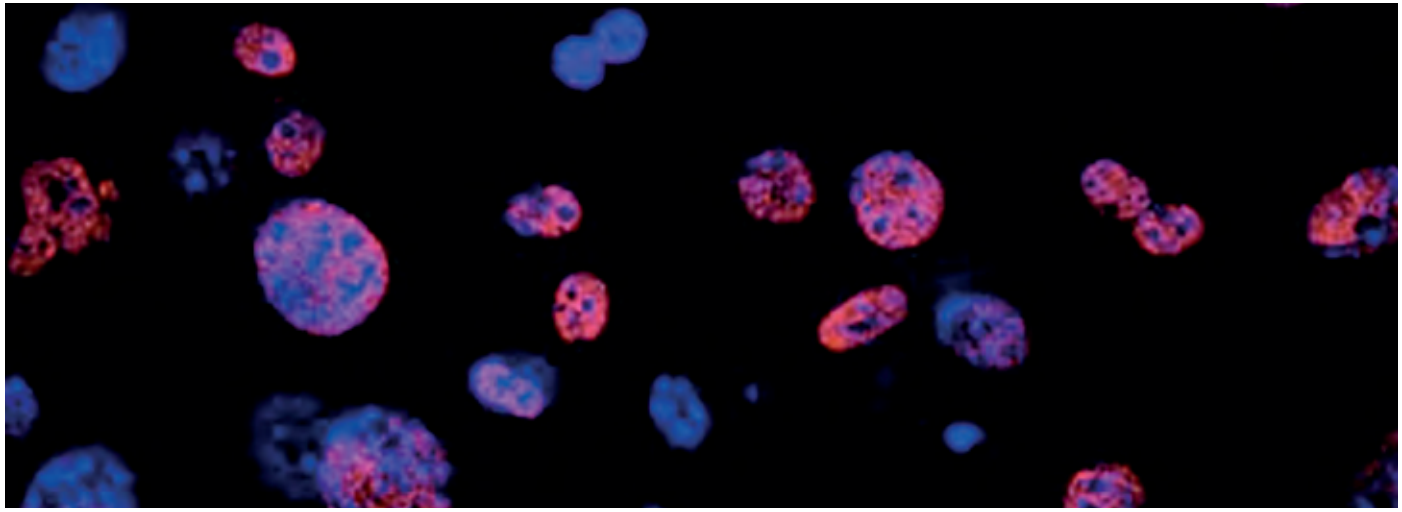
(1) Hemmer MC, Wierer M, Schachtrup K, Downes M, Hübner N, Evans RM, **Uhlenhaut NH** (2019). **E47 modulates hepatic glucocorticoid action**. Nat Commun. 10(1):306.

(2) Dyar KA, Hubert MJ, Mir AA, Ciciliot S, Lutter D, Greulich F, Quagliarini F, Kleinert M, Fischer K, Eichmann TO, Wright LE, Peña Paz MI, Casarin A, Pertegato V, Romanello V, Albiero M, Mazzucco S, Rizzuto R, Salviati L, Biolo G, Blaauw B, Schiaffino S, **Uhlenhaut NH** (2018). **Transcriptional programming of lipid and amino acid metabolism by the skeletal muscle circadian clock.** PLoS Biol. 16(8):e2005886.

Selected Awards and Honors

2015 Friedmund Neumann Prize of the Schering Stiftung

2019 Heinz Maier-Leibnitz Prize of the German Research Foundation DFG



Nina Henriette Uhlenhaut

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2007 PhD, EMBL & University of Heidelberg, Germany

2007 - 2008 Postdoc at EMBL Heidelberg, Germany

2008 - 2010 Postdoc at The Salk Institute for Biological Studies, La Jolla, USA

2010 - 2013 Postdoc at MDC for Molecular Medicine, Berlin, Germany

2013 – 2018 Emmy Noether Group Leader at Helmholtz Diabetes Center, Munich

2018 – 2019 Tenure-Track Professor, LMU & Head of Division Molecular Endocrinology, Helmholtz Diabetes Center, Munich, Germany

since 2019 Professor and Chair, TUM School of Life Sciences Weihenstephan & Institute Director at Helmholtz Zentrum München

Petra Wendler

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2004	PhD at Humboldt University Berlin, Germany
2004-2009	Postdoc at Birkbeck College London, UK
2009-2016	Emmy-Noether Group Leader, Gene Center, LMU
since 2016	Professor and Chair, University of Potsdam, Germany

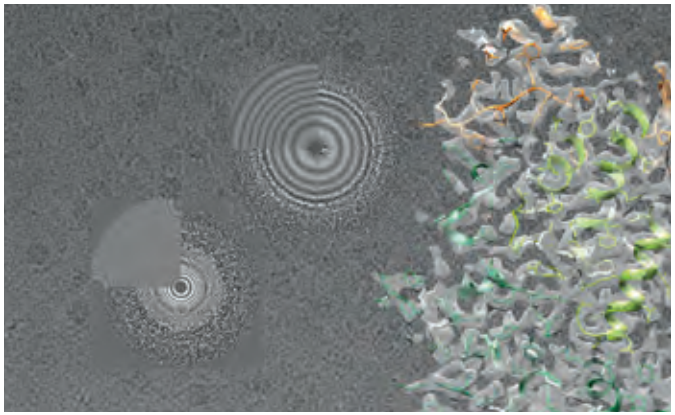
Protein Remodeling and AAA+ Assemblies

Goals

Our aim is to solve the conformational dynamics of molecular machines at the highest possible resolution using single particle cryo-EM. Our main research interest are molecular machines that hydrolyze ATP or fixate CO_2.

Members of the large protein superfamily of AAA+ proteins (ATPases associated with various cellular activities) are at the core of many essential multi protein assemblies involved in re-organisation and recycling processes of membranes, proteins or DNA in the cell. They convert chemical energy into mechanical work, and our lab aims to obtain a structural view on the complex conformational dynamics of these molecular machines in action.

Efficient enzymatic fixation of carbon dioxide would allow for industrial carbon sequestration from the atmosphere. We aim to structurally characterize two different molecular machines involved in this process. Rubisco, the enzyme responsible for carbon fixation in photosynthetic organisms, is slow, lacks specificity and is error prone. The AAA+ complex rubisco activase is responsible for rescuing inactivated rubisco. We investigate how rubisco activases interact with rubisco. Metal-containing formate dehydrogenases catalyze the reversible oxidation of formate to carbon dioxide, which is coupled to NAD^+ reduction. We study the structure and electron transport pathway of this enzyme to enable its use in biotechnological applications.



3.4 Å cryo-EM structure of *Rhodobacter sphaeroides* rubisco. (Bhat et al, 2017)

Research Highlights

We have solved the structure of *Rhodobacter sphaeroides* Rubisco at 3.4 Å resolution and showed that rubisco activase repairs the defective enzyme with remarkable precision, avoiding global structure perturbation. We also analyzed the role of rubisco accumulation factor1 (Raf1), which acts as an assembly chaperone in rubisco biogenesis stabilizing dimers of the large rubisco subunit RbcL. The peroxisomal proteins Pex1 and Pex6 form a hexameric AAA+ complex that fuels protein transport across peroxisomal membranes. Our biochemical and structural study of the yeast Pex1/6 complex shows inter-domain allosteric communication between the proteins .

Selected Publications

(1) Bhat JY, Miličić G, Thieulin-Pardo G, Bracher A, Maxwell A, Ciniawsky S, Mueller-Cajar O, Engen JR, Hartl FU, **Wendler P**, Hayer-Hartl M. (2017). **Molecular Surgery: Enzyme Repair by the AAA+ Chaperone Rubisco Activase.** Mol Cell 67(5), 744-756..

(2) Hauser T, Bhat JY, Miličić G, **Wendler P**, Hartl FU, Bracher A, Hayer-Hartl M (2015). **Structure and mechanism of the Rubisco assembly chaperone Raf1.** Nat Struc Mol Biol. 22(9):720-8.

(3) Ciniawsky S, Grimm I, Saffian D, Girzalsky W, Erdmann R, **Wendler P** (2015). **Molecular snapshots of the Pex1/6 AAA+ complex in action.** Nat Commun. 6:7331.

(4) Kock M, Nunes MN, Hemann M, Kube S, Dohmen RJ, Herzog F, Ramos PC, **Wendler P** (2015). **Proteasome assembly from 15S precursors involves major conformational changes and recycling of the Pba1-Pba2 chaperone.** Nat Commun. 6:6123.

Selected Awards and Honors

2014	Care-For-Rare Science Award (http://www.care-for-rare.org/)
2017	Member of the DFG Cluster of Excellence UniCat
2018	Member of the DFG Cluster of Excellence UniSysCat

Protein Synthesis and Ribosome Structure

Goals

In every living organism, translation of the genetic code into functional proteins is performed on the ribosome. Indeed, the fundamental importance of translation is reflected by the fact that the ribosome is a major target in the cell for natural antibiotics. The Wilson lab takes a combined structure-function approach to address how specific ligands, such as antibiotics as well as protein factors, modulate gene expression via interaction with the translational apparatus.

Research Highlights

Research highlights include cryo-electron microscopy structures of stalled ribosomes, namely, an ErmBL ribosome stalled by the antibiotic erythromycin and a ribosome stalled because of the presence of polyproline sequences in the polypeptide chain. In the latter study, we also determined structures in the presence of the elongation factor EF-P, which binds to the polyproline-stalled ribosomes and rescues them. Ribosomes stalled because of truncated mRNAs (non-stop ribosomes) can be rescued by a variety of different systems in bacteria. Another highlight was the structure of a non-stop ribosome being rescued by the alternative rescue factor A (ArfA) in conjunction with release factor RF2. We also determined cryo-EM structures of hibernating ribosomes from *Bacillus subtilis* and *Escherichia coli*. The structures illustrated that the hibernation promoting factor (HPF) causes the 70S ribosomes to dimerize into hibernating 100S particles by dimerization of the C-terminal domain of HPF. Finally, we also determined structures of many diverse inhibitors in complex with the ribosome, including antibiotics such as the orthosomycins evernimicin and avilamycin as well as a variety of antimicrobial peptides, such as Apidaecin 137. Investigation into how antibiotics inhibit the ribosome also provide insights in the fundamental process of translation, for example, by employing Apidaecin 137 to inhibit translation, we gained insights into the process of translation termination. Apidaecin trapped both the translation termination factors RF1 and RF3 in multiple states revealing how RF3 drives intersubunit rotation to promote dissociation of RF1 from the ribosome.

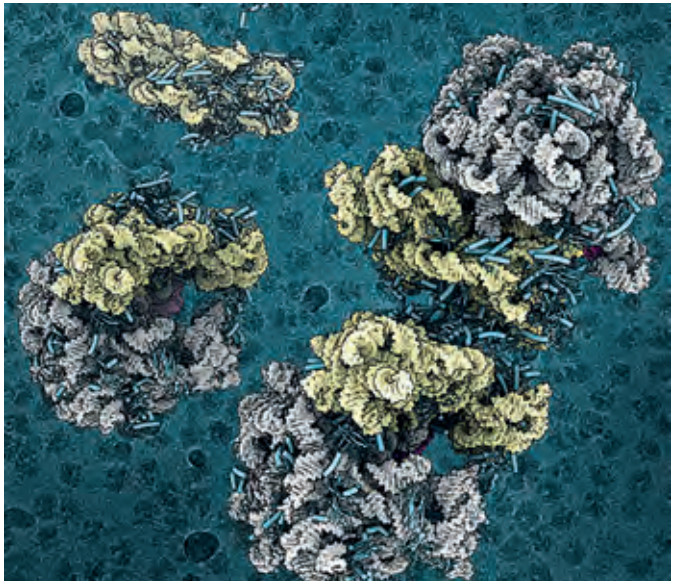
Selected Publications

(1) Beckert B, Turk M, Czech A, Berninghausen O, Beckmann R, Ignatova Z, Plitzko JM, **Wilson DN** (2018). **Structure of a hibernating 100S ribosome reveals an inactive conformation of the ribosomal protein S1**. Nat Microbiol. 3(10):1115-1121.

(2) Huter P, Arenz S, Bock LV, Graf M, Frister JO, Heuer A, Peil L, Starosta AL, Wohlgemuth I, Peske F, Novácek J, Berninghausen O, Grubmüller H, Tenson T, Beckmann R, Rodnina MV, Vaiana AC, **Wilson DN** (2017). **Structural Basis for Polyproline-Mediated Ribosome Stalling and Rescue by the Translation Elongation Factor EF-P.** Mol Cell 68:515-527.

(3) Huter P, Müller C, Beckert B, Arenz S, Berninghausen O, Beckmann R, **Wilson DN** (2017). **Structural basis for ArfA-RF2-mediated translation termination on mRNAs lacking stop codons.** Nature 541:546-549.

(4) Graf M, Huter P, Maracci C, Peterek M, Rodnina MV, **Wilson DN** (2018). **Visualization of translation termination intermediates trapped by the Apidaecin 137 peptide during RF3-mediated recycling of RF1**. Nat Commun. 2018 Aug 3;9(1):3053.



Structure of *E. coli* hibernating ribosome (modified from Ref. 1)

Daniel Wilson

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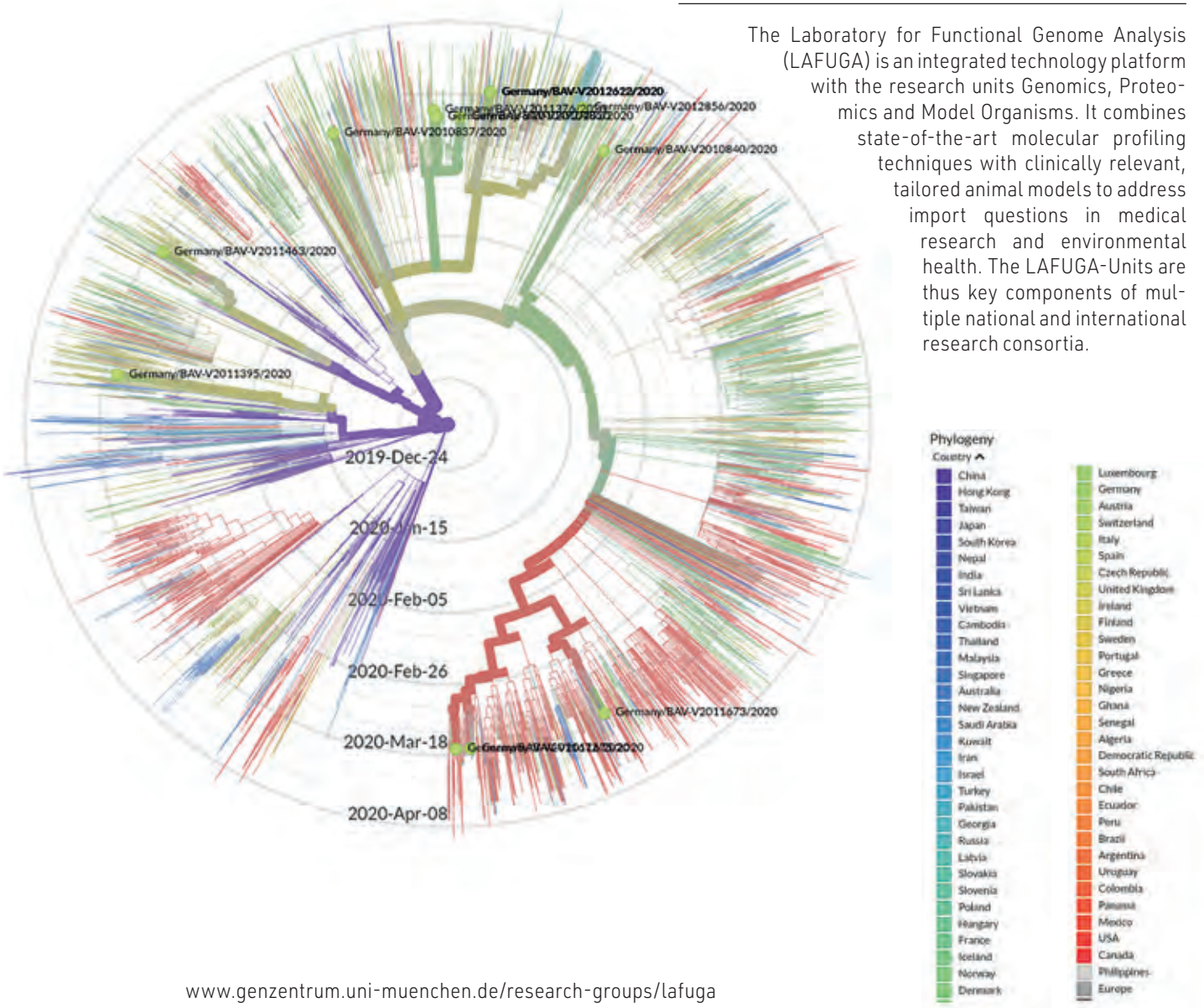
1999	PhD from University of Otago, Dunedin, New Zealand
2000-2002	Alexander von Humboldt fellow, Max-Planck-Institute for Molecular Genetics, Berlin, Germany
2002-2006	Postdoc, Max-Planck-Institute for Molecular Genetics, Berlin, Germany
2007-2016	Group Leader, Gene Center, LMU
since 2016	Professor and Chair, University of Hamburg, Germany

LAFUGA

Goals and Impacts for Society

The Laboratory for Functional Genome Analysis (LAFUGA) is an integrated technology platform with the research units Genomics, Proteomics and Model Organisms. It combines state-of-the-art molecular profiling techniques with clinically relevant, tailored animal models to address import questions in medical research and environmental health. The LAFUGA-Units are thus key components of multiple national and international research consortia.



www.genzentrum.uni-muenchen.de/research-groups/lafuga

Research Highlights

LAFUGA-Genomics

Helmut Blum
Email: blum@genzentrum.lmu.de

The rapidly evolving field of high-throughput sequencing (NGS) provides powerful approaches for the detailed analyses of transcriptomes and genomes. It generates hundreds of millions of short DNA sequences in a single run and thus may capture complex eukaryotic transcriptomes and genomes with unsurpassed sensitivity. In addition to the Illumina technology, LAFUGA-Genomics also performs long-read sequencing with nanopores and thus creates new areas of application for NGS. It enables previously unforeseen reading lengths with RNA and DNA and detects modified bases in native nucleic acids. We use this technology platform to study key questions in reproductive biology, early mammalian embryogenesis, hematopoietic malignancies and molecular epidemiology. Furthermore, several genomics projects analyze transgenic pigs as models for metabolic diseases.
LAFUGA-Genomics carried out projects in the fields of mammalian reproduction, early embryonic development and evolution of hematopoietic malignancies as part of international and national research consortia (EU-project "Fecund", DFG SFB 1243 "Cancer Evolution"). As part of cross-omics analyses, transcriptomic studies on transgenic pigs as model organism for insulin deficient diabetes were performed providing unsurpassed insights into molecular basis of functional alterations of the liver. Single cell sequencing was applied to study transcriptomes of blastomeres during major genome activation of early bovine embryos. Furthermore, a platform for sequencing and analysis of SARS-CoV2 genomes was established and more than 200 genomes have been sequenced and uploaded to the Global Initiative on Sharing All Influenza Data (GISAID).

LAFUGA-Proteomics

Georg J. Arnold

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LAFUGA-Proteomics

Thomas Fröhlich

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Advances in modern mass spectrometry-based proteomics in sensitivity, specificity and throughput have allowed proteomics to become an established part of translational biomedical research. For proteomic analysis, we use latest mass spectrometry instruments (e.g. Q Exactive HFX, TripleTOF 5600+) facilitating the accurate quantification of thousands of proteins out of complex protein mixtures like cell lysates. For targeted approaches, the SRM technology (Selected Reaction Monitoring) is applied, to precisely quantify low-abundant proteins in the attomole range.
Within international and national research consortia (e.g. EU-project "Fecund", DFG FOR 1041 "Germ cell potential"), LAFUGA-proteomics carried out projects in the fields of mammalian reproduction and early embryonic development. Further research activity comprises proteomic characterization of large animal disease models for molecular biomedical research, which are created in LAFUGA-Model Organisms. Within the EU-project "DohART-NET", we analyze effects of maternal diabetes on the proteomes of various tissues from neonatal offspring of transgenic pig models for (pre)-diabetes. Proteomic studies on a pig model for Duchenne muscular dystrophy recently discovered clinically relevant molecular pathways, reflecting the different pathology and kinetic of DMD progression in skeletal and heart muscle. Funded by SFB 1357 (coordinated by Prof. Laforsch, University Bayreuth), we address effects of microplastics on several model organisms and cell systems.

LAFUGA-Model Organisms

Eckhard Wolf

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This unit is specialized in the generation and analysis of rodent and large animal models for biomedical research. In addition to mouse models, our group has a unique expertise in the development, characterization and implementation of genetically tailored pigs as models for diabetes research and for rare monogenic diseases, and as donors of cells, tissues and organs for xenotransplantation. The Center for Innovative Medical Models (CiMM; www.lmu.de/cimm/) is now fully established to accommodate these models and perform preclinical studies. We are thus the core facility for large animal models in a number of national and international research consortia, including the German Center for Diabetes Research (DZD), the DFG SFB/TR 127 "Biology of xenogeneic cell, tissue and organ transplantation – from bench to bedside", and for the EU project iNanoBIT "Integration of Nano- and Biotechnology for Beta-Cell and Islet Transplantation". For highlights of our research, please see the report of the Wolf group.

Future Perspectives

LAFUGA aims to continue its general strategy but improve the depth and spatial resolution of its molecular analyses and refine its large animal models to allow tissue-specific and/or developmental stage-specific analyses of disease mechanisms. With the establishment of CiMM, treatment trials of clinically relevant large animal models will – in concert with the LAFUGA-Genomics and -Proteomics Units – enable the discovery of molecular biomarkers for safety and efficacy of novel therapies.

Selected Publications

(1) **Functional changes of the liver in the absence of growth hormone (GH) action - Proteomic and metabolomic insights from a GH receptor deficient pig model.** Riedel EO, Hinrichs A, Kemter E, Dahlhoff M, Backman M, Rathkolb B, Prehn C, Adamski J, Renner S, Blutke A, de Angelis MH, Bidlingmaier M, Schopohl J, **Arnold GJ, Fröhlich T, Wolf E**. Mol Metab. 2020 Mar 18:100978. doi: 10.1016/j.molmet.2020.100978.

(2) **Somatic gene editing ameliorates skeletal and cardiac muscle failure in pig and human models of Duchenne muscular dystrophy.** Moretti A, Fonteyne L, Giesert F, Hoppmann P, Meier AB, Bozoglu T, Baehr A, Schneider CM, Sinnecker D, Klett K, **Fröhlich T**, Rahman FA, Haufe T, Sun S, Jurisch V, Kessler B, Hinkel R, Dirschinger R, Martens E, Jilek C, Graf A, Krebs S, Santamaria G, Kurome M, Zakhartchenko V, Campbell B, Voelse K, **Wolf A**, Ziegler T, Reichert S, Lee S, Flenkenthaler F, Dorn T, Jeremias I, **Blum H**, Dendorfer A, Schnieke A, Krause S, Walter MC, Klymiuk N, Laugwitz KL, **Wolf E**, Wurst W, Kupatt C. Nat Med. 2020 Feb;26(2):207-214.

(3) **Detection of collagens by multispectral optoacoustic tomography as an imaging biomarker for Duchenne muscular dystrophy.** Regensburger AP, Fonteyne LM, Jüngert J, Wagner AL, Gerhalter T, Nagel AM, Heiss R, Flenkenthaler F, Qurashi M, Neurath MF, Klymiuk N, Kemter E, **Fröhlich T**, Uder M, Woelfle J, Rascher W, Trollmann R, **Wolf E**, Waldner MJ, Knieling F. Nat Med. 2019 25(12):1905-1915.

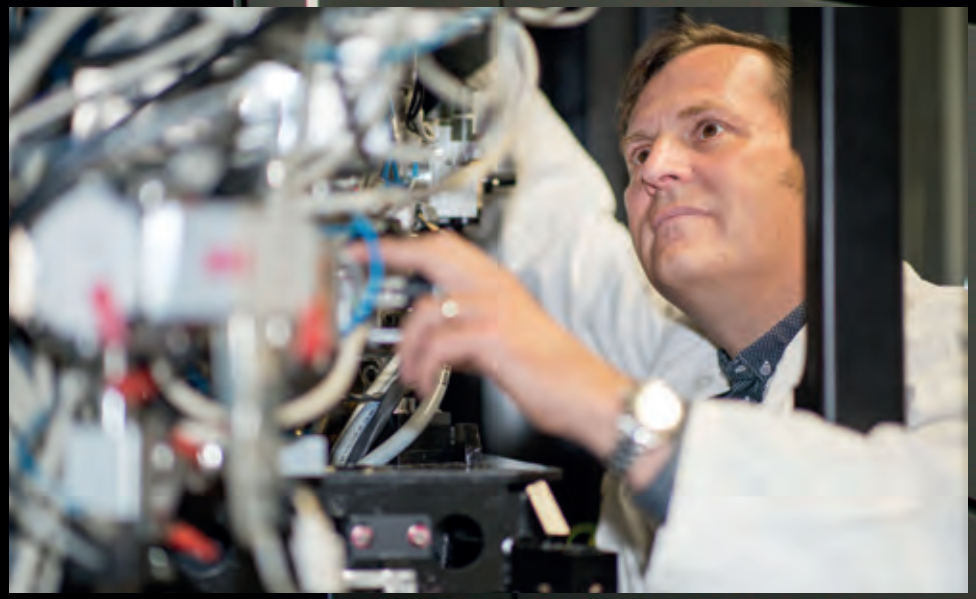
(4) **Multi-omics insights into functional alterations of the liver in insulin-deficient diabetes mellitus.** Backman M, Flenkenthaler F, Blutke A, Dahlhoff M, Ländström E, Renner S, Philippou-Massier J, Krebs S, Rathkolb B, Prehn C, Grzybek M, Coskun Ü, Rothe M, Adamski J, de Angelis MH, Wanke R, **Fröhlich T, Arnold GJ, Blum H, Wolf E**. Mol Metab. 2019 Jun 4. pii: S2212-8778(19)30186-3.

(5) **Single-cell RNA sequencing reveals developmental heterogeneity of blastomeres during major genome activation in bovine embryos.** Lavagi I, Krebs S, Simmet K, Beck A, Zakhartchenko V, **Wolf E, Blum H**. Sci Rep. 2018 Mar 6;8(1):4071.

Other Research Facilities

A hallmark and key element of the Gene Center's research infrastructure are several shared research facilities. These facilities help the Gene Center's research groups carry out world-class research using a broad range of state of the art technologies and approaches.

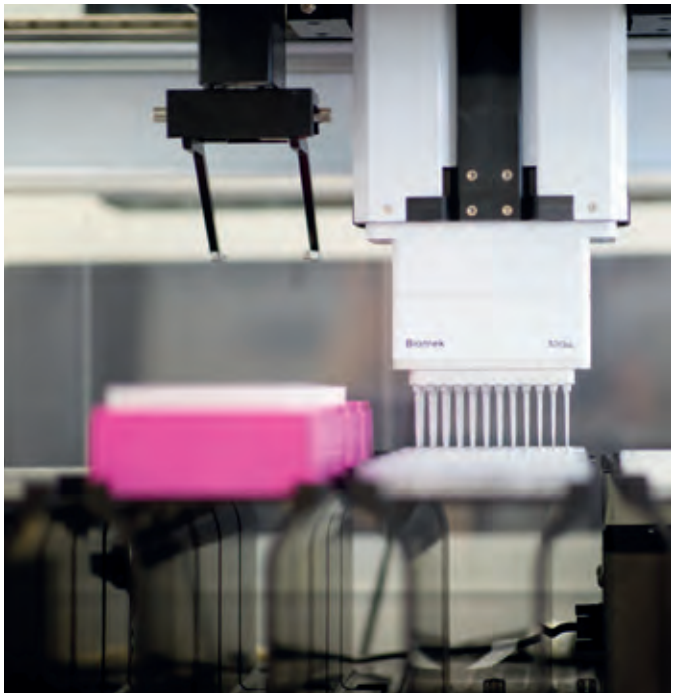
The **cryo-electron microscopy facility** permits large-scale data collection for single particle reconstruction to obtain structures of biomolecules at near atomic resolution. The facility was established 2006 and 2018 extended with a second high-end microscope. For high-resolution cryo-EM we can use two high-end 300 KeV Titan Krios electron microscopes, one equipped with a Falcon 2 direct electron detector the other with a Falcon 3 direct electron detector, phase plate and K2 direct electron detector with energy filter. A 120 kV Tecnai Spirit and 100 kV Morgagni transmission electron microscope (EM) can be used for initial cryo EM sample screening and negative stain data collection respectively.

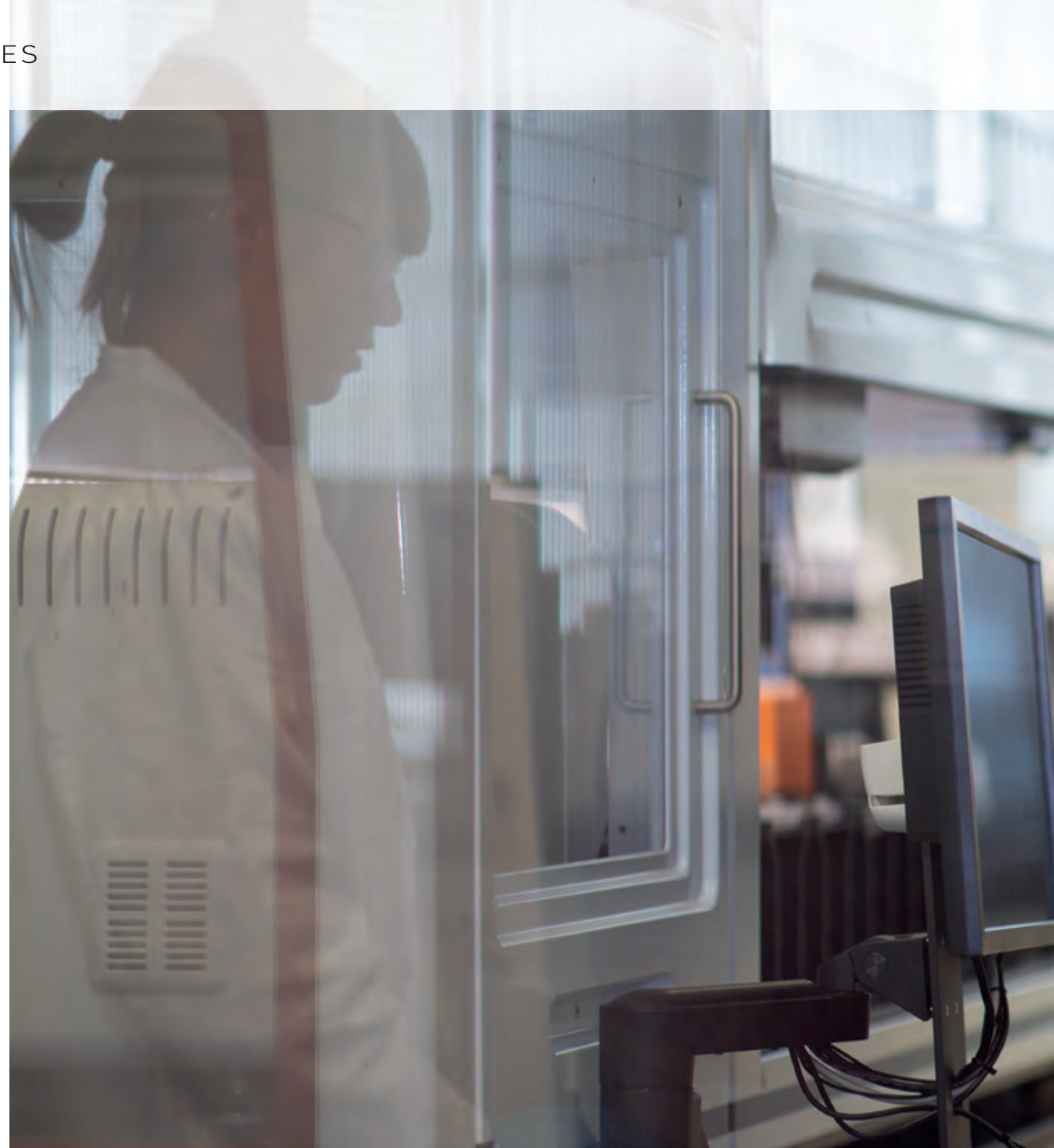


A **crystallization facility** allows for semi-automated macromolecular crystallization using different approaches. State-of-the art liquid handling systems enable fast and easy preparation of crystallization screens and setups. The lab provides vibration-free incubators for crystallization trials and also has the necessary lab space and equipment for crystal manipulation and storage in liquid nitrogen.

The **biophysics facility** offers instrumentation to characterize sample properties and protein-ligand interactions. The lab is equipped with a surface plasmon resonance device, microscale-thermophoresis, dynamic light scattering, size-exclusion chromatography coupled static light scattering, realtime-PCR-based DSF, nanoDSF, platereader, isothermal titration calorimetry, spectral photometers & fluorimeter, and different chromatography systems. For 3D-printing of molecular structures, rapid prototyping of labware and parts we use a 3D FDM printer.

Robotic high-throughput facility: A robotic high-throughput facility has been established and provides state-of-the-art instrumentation and expertise to advance industrial-type research in academia. The facility is equipped with three high-end robotic streets. These are flexible liquid handling workstations, into which additional instruments are integrated for sample management, handling and various types of assays. In addition, the facility houses detection and analysis systems, which permit assay read-out and quality control. Through this integrated design, high-throughput projects can be carried from assay development, to assay transfer, automation, validation and, finally, screening. Long the province of industry, the facility makes it possible to carry out a wide range of high throughput, genome-scale projects in an academic setting.



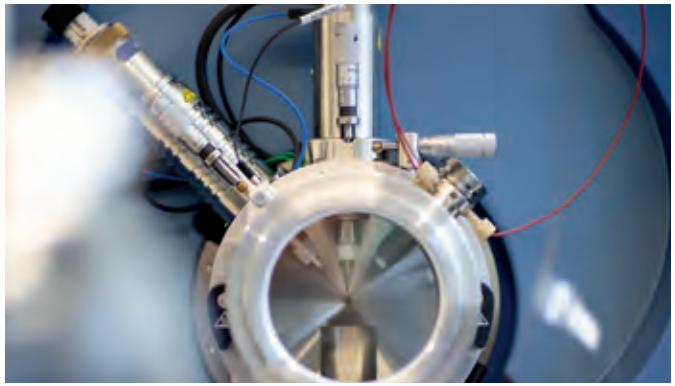


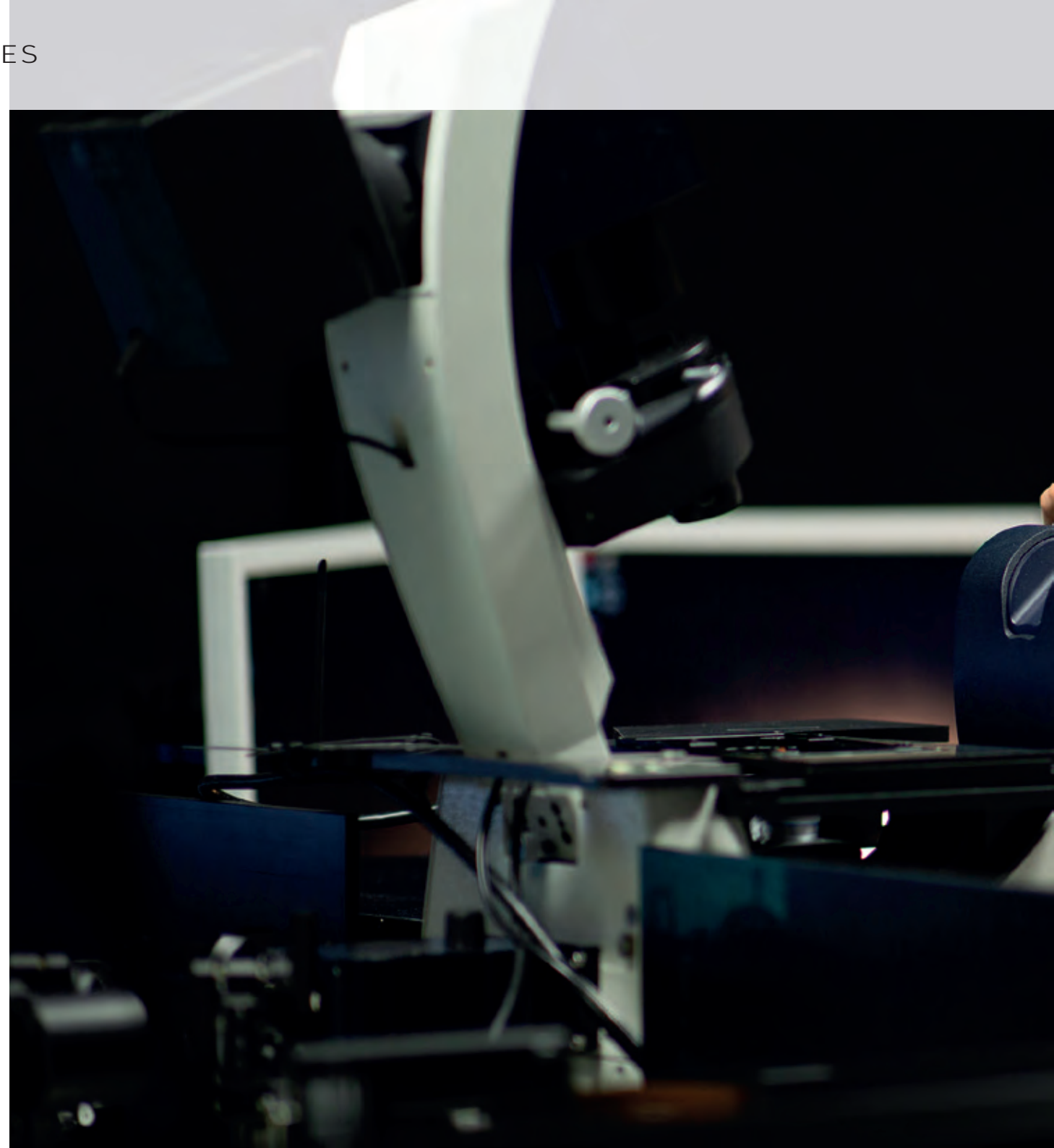
Our **high-throughput sequencing platform** includes technologies for short read sequencing (Illumina, HiSeq 1500) and long read sequencing (Oxford Nanopore, PromethION, MinION). For short read sequencing, a variety of protocols are established, like e.g. exome sequencing, mRNAseq, nonrRNAseq or targeted re-sequencing. Long read sequencing enables sequencing of genomes, epigenomes, full-length cDNA or native DNA and RNA. Data analysis is performed on a Galaxy platform hosted on a cooperative data processing infrastructure.

Flow Cytometry: A state-of-the-art flow cytometry facility that is equipped with one high end analytical (BD LSRFortessa) and two preparative flow cytometers (BD FACSAria Fusion and BD FACSMelody) has been established in the BioSysM building. The facility provides a wide range of flow cytometry-based services such as project planning, panel design and optimization, instrument operation and sorting and data analysis. Analytical and preparative flow cytometry can be conducted under BSL1 and BSL2 conditions.

Located in the BioSysM building (2nd floor), the **Bio-Imaging Facility** offers powerful tools for advanced light-microscopy and image processing. We provide microscope training, assistance to design imaging assays, and for automated image analysis. Our instruments comprise a state-of-the art LEICA SP8 confocal microscope equipped with a white light laser (WLL), hybrid detectors with single-photon counting capability, a stagetop incubator for live cell imaging, and an integrated image deconvolution software pipeline. In addition, two other confocal microscopes (ZEISS LSM710 and LSM510) and an epifluorescence microscope (inverted Leica DM6000) are available, as well as a custom-built single objective light-sheet microscope (soSPIM) for fast and highly-sensitive imaging of living organisms.

We have also extended our **mass spectrometry facilities**. The LAFUGA proteomics platform provides instrumentation for protein identification using nano-chromatography and latest high-resolution FT mass spectrometers including a Q Exactive-HFX. Targeted proteomics to quantify protein sets down to the attomolar range is performed by nano-LC-QTRAP mass spectrometry and selected reaction monitoring approaches. An Orbitrap Elite mass spectrometer is dedicated to the identification of cross-linked peptides which determine distance restraints for the structural analysis of macromolecular complexes.





Our **fermentation facility** contains one small (15 l) and one large (200 l) fermenter for the cultivation of yeast cells. All fermentation parameters including temperature, pressure, stirring rate and oxygen level can be controlled externally, resulting in highly reproducible cultivation conditions.

The **scientific computing infrastructure** is constantly being extended as the need for data processing and storage increases rapidly. The computing resources available range from high-end 3D workstations and dedicated servers to multiple computing clusters (GPU and CPU).

Administration and Infrastructure

The Gene Center's administration and infrastructure is run by a team whose philosophy is to assist all of our scientists – from principal investigators to students – in the most efficient and supportive way. We enable our scientists to focus on their research by reducing the time they spend on administrational matters to an unavoidable minimum. Thus, we contribute to the creation of a stimulating atmosphere for scientists, which is one of the keys to the Gene Center's success.

Since summer 2014, administration and infrastructure at the Gene Center have been headed by **Dr. Carola Vogt**, who has worked as a program officer at the DFG and Baden Württemberg-Stiftung. Since her parental leave in August 2018, she has been represented by **Dr. Sabine Bergelt**. Support is provided by **Aleksandra Grilc** who has been working as an assistant at the Department of Chemistry and thus, is very experienced with administrative matters at the university.

In 2013 **Dr. Markus Hohle** became the physics lecturer and later on coordinator of the Graduate School of Quantitative Biosciences Munich (QBM). He was supported by **Dr. Julia Schlehe** as administrative coordinator and by **Mara Kieke** as assistant.

Dr. Beate Hafner, who replaced **Dr. Petra Runge-Wollmann** in 2020, is mainly coordinating the GRK 1721 but she is also responsible for public outreach activities such as maintaining the Gene Center's website or the compilation of this report.

At the core of our administration team there are our secretaries **Stephanie Wolf**, **Aleksandra Grilc**, **Annika Ginkel** and **Xiaoshan Hu**, and **Sylvia Hornig**. They are responsible for human resources in cooperation with LMU's central staff office, traveling and events, apart from many other things. They are supported part-time by **Petra Fulde**.

Accounting and financial controlling of our regular budget and our extensive third-party funding is provided efficiently by **Andrea Schwane-Pieloth** and **Thomas Stein**.

With an ever increasing impact of the computational infrastructure and its maintenance, particularly in structural biology, computational biology, and systems biology at the Gene Center and BioSysM, we are lucky to rely on the expertise and assistance of **Leslie Heinz** and **Wilmer Montenegro**. They are of course supported by computational experts from different labs, foremost **Dr. Gregor Witte** as head of the IT team.

Dr. Heidi Feldmann, **Dr. Birgitta Beatrix**, **Dr. Johanna Turck**, and **Dr. Louiza Papatheodorou** have been doing and are doing a fantastic job for the Gene Center's education of students. Amongst their versatile tasks are assisting students, taking care of exams and organizing practical courses.

Michael Englschall, supported by **Gabriela Bittner**, is in charge of the Gene Center's general supply with chemicals, gases, consumables and basic lab equipment. Together with **Michael Till** and **Dieter Zech** from the Gene Center's precision mechanics and electronic workshops they do a great job in running the labs smoothly, and in helping new groups getting their labs started within a short time.

Olga Fettscher supports the labs with the preparation of media. **Natasa Boskovski**, **Kanchana Koblitz**, **Homa Popal**, and **Dorchanai Schams** run the sculleries and take care of labware dishwashing, altogether providing efficient support for the research groups.

Dr. Georg Arnold, **Dr. Helmut Blum**, **Dr. Thomas Fröhlich**, **Dr. Dietmar Martin**, and **Michael Englschall** provide the Gene Center groups with great expertise in biological, workplace, fire and radiation safety. LMU's former company doctor, **Dr. Winfried Kapfhammer**, regularly offered in-house medical check-ups and advice before he retired in 2018.

Undergraduate Teaching

Education of students is a key part and central mission of our work at the Gene Center and Department of Biochemistry. Gene Center scientists are actively involved in conducting undergraduate courses, ranging from basic training in biochemistry to more advanced methods courses. Young students enrolling each year in a Bachelor program Chemistry and Biochemistry receive a sound basic education in both fields and can decide during the first years in which field they want to specialize and continue their studies in advanced Master courses.

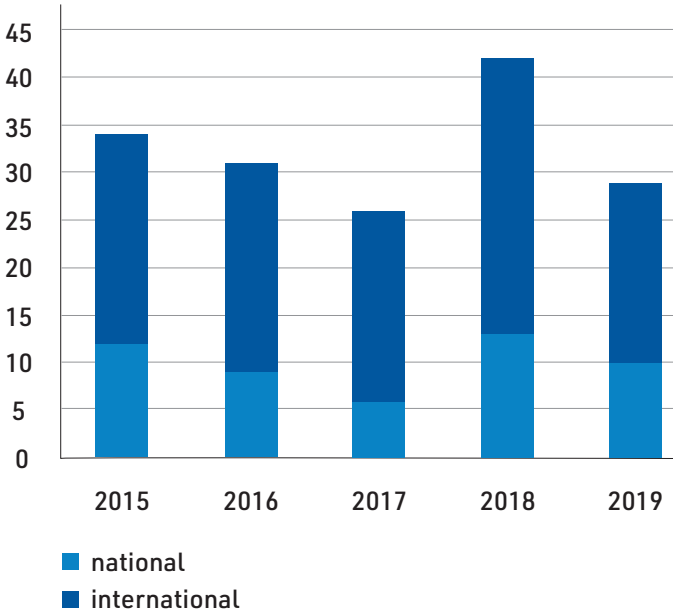
Over the last five years 205 students have been selected for the Master program in Biochemistry. This program optimally prepares young scientists for a future career in academia and industry. All courses are taught in English, which improves students' language skills, enables international Professors to contribute to teaching and makes the program very attractive for foreign students. In fact, about 30% of our master students are from abroad. In 2016 new study rules were implemented and the choice of eighteen subjects in various combinations leaves students with a high flexibility and many options to pursue their interests. The Gene Center is situated on the Campus Grosshadern/Martinsried and embedded in a community of institutes in the life and medical sciences ranging from different Faculties of the LMU, the Helmholtz- and Max-von-Pettenkofer Institutes and two Max-Planck Institutes. The close proximity of education and research provides a state of the art environment and guarantees students to be taught at a high standard. Well-equipped labs allow for hands-on teaching of modern methods in practical courses. In addition, students are encouraged to obtain research experience in laboratories both on campus and abroad by doing internships or carrying out their master thesis projects nationally or internationally.

The high standard of education and training owes much to the commitment of our engaged teaching team which consists of the teaching coordinator **Dr. Johanna Turck** supported by **Dr. Louiza Papatheodorou** and **Dr. Birgitta Beatrix**. They organize the structure of the program, support students with personal advice and ensure flexibility of changing teaching needs. The corona pandemic posed them to the enormous challenge of converting all teaching (lectures, practical courses and exams) for the summer term 2020 to online teaching within a few weeks, which they mastered with excellence.

Graduate Training

The training of young scientists continues with our support of PhD students at the Gene Center. PhD students are the heartblood of the research at our institute. In 2015-2019, 162 PhD students graduated in Biochemistry at the LMU, 51% of whom were female and 31% came from abroad. Graduate students participate in the Gene Center graduate program, which involves an annual retreat and a weekly research seminar series in which renowned international speakers as well as Gene Center PhD students and postdoctoral researchers present their work. The training is complemented by courses offered by the GraduateCenterLMU to improve writing and oral presentation skills. Many PhD students also participate in specialized graduate schools and programs. These include, amongst others, the International Max-Planck Research School for Molecular Life Sciences 'From Biological Structures to Neural Circuits' (IMPRS-LS) at the neighboring Max Planck Institute of Biochemistry. Since 2012, two graduate schools funded by the German Research Council DFG are located at the Gene Center. In 2016 the 'Graduiertenkolleg' on the 'Integrated Analysis of Macromolecular Complexes and Hybrid Methods in Genome Biology', coordinated by Karl-Peter Hopfner successfully applied for the second funding period. The Graduate School of

PhD theses in Biochemistry



Quantitative Biosciences Munich (QBM) which was founded by **Ulrike Gaul** is now coordinated by **Erwin Frey**. **Dr. Markus Hohle** works as administrative coordinator and lecturer (mathematics and physics) of QBM together with the life science lecturer **Dr. Dietmar Martin**. Investigators from LMU and the Technical University Munich, the Max Planck Institute for Biochemistry and the Helmholtz Center Munich participate in both graduate programs. Gene Center PhD students also participate in eight different Collaborative Research Centers (Sonderforschungsbereiche).

Networking Tradition in the Gene Center

For twenty years now, the Gene Center has been home to the managing office of a whole range of collaborative research programs that span all over Bavaria. Many of these network programs have already been successfully completed, such as the Bavarian Genome Research Network (BayGene) and the Bavarian Research Network for Molecular Biosystems (BioSysNet).

Collaborative research contributes directly to scientific success. The high level of interdisciplinary expertise and regular exchange of information helps to deal with complex issues quickly and successfully.

Current Networks

At the moment, the managing office coordinates two research networks which are funded by the Bavarian State Ministry for Science and the Arts: the Bavarian Climate Research Network (bayklif) and the research program „New strategies against multi-resistant pathogens using digital networking" (bayresq.net).

The research network bayklif focuses on climate impact research and climate protection and strengthens climate research in Bavaria through interdisciplinary cooperation. While its research content lies outside of the Gene Center, it deserves to be mentioned since its networking character represents the core of all programs coordinated through the managing office.

bayresq.net

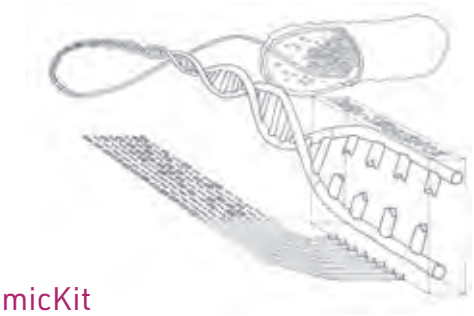
The aim of bayresq.net is to promote basic scientific research from six selected and innovative projects against multi-resistant germs from various research groups at Bavarian universities. Under the direction of **Prof. Dr. Horst Domdey** and **Dr. Ulrike Kaltenhauser**, the research program supports a variety of interdisciplinary scientific areas, such as biology, bioinformatics, chemistry, biophysics, medicine and mathematics. An additional important focus lies on the development of a shared open data management and communication platform under the direction of **Andreas Hauser**.

Networking between the institutes will significantly support targeted basic research in the future in order to find new mechanisms for the development of novel therapies. The advantages of digital networking are prototyped for future programs; bayresq.net is a core element of the long-term strategy BAYERN DIGITAL.

According to a study by the Charité Berlin, the number of annual deaths due to multi-resistant pathogens could exceed ten million people by 2050. The Free State of Bavaria faces this highly relevant challenge in terms of health policy through the foundation of the Bavarian research network bayresq.net and provides over 10 million euros in funding to do justice to the pioneering future research in this field.

The projects funded within the framework of the research network will strengthen Bavaria in both the life sciences and data management. New insights produced by basic research into fundamental processes will lay the foundation for future therapies against multi-resistant pathogens.

bayresq.net: funded projects



DynamicKit

Artificial intelligence to fight multidrug-resistant tuberculosis

IRIS

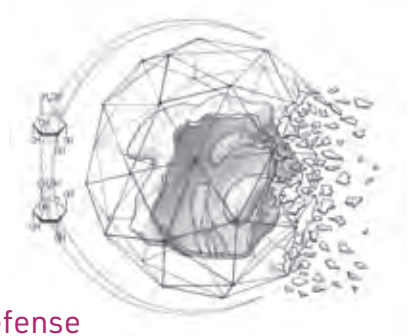
Control instances of the immune system against multi-resistant germs

Helicopredict

Genome-based resistance prediction for Helicobacter pylori

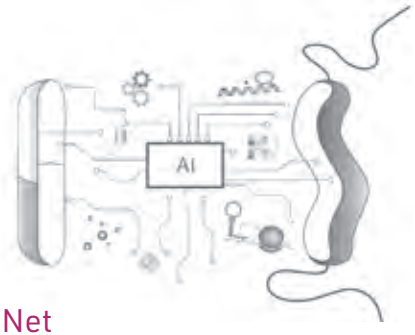
Rbiotics

New RNA-based antibiotics



Metabodefense

Can metabolism protect us against pathogens?



StressRegNet

Effect of stress on the pathogenicity of bacteria

bayresq.net research sites in Bavaria

The Gene Center at the LMU had always had a prime focus on interdisciplinary cutting-edge research and is the perfect environment for the headquarters of all of these outstanding research network programs. These surroundings, in which ambitious scientists carry out interdisciplinary research at the highest level, represent exactly the right place for pioneering programs such as bayresq.net and all the other research networks coordinated by the managing office.

Barbara Adler

2015

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Roland Beckmann

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Trafficking of siRNA precursors by the dsRBD protein Blanks in *Drosophila*

Published: 06 February 2020 Article history

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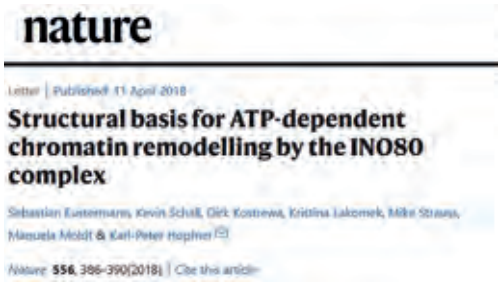
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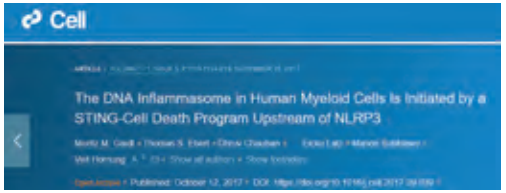

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WO2017076880A1 Samhd1 modulation for treating resistance to cancer therapy

(Inventors: **Oliver Till Keppler**, Jindrich Cinatl, Constanze Schneider, Hanna-Mari Baldauf, Sarah-Marie Schwarz, Hubert Serve, Thomas Oellerich, Gerd Geisslinger, **Veit Hornung**) issued 2017-05-11

Lucas Jae

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nature

Article | Published: 04 March 2020

A pathway coordinated by DELE1 relays mitochondrial stress to the cytosol

Evelyn Fessler, Eva-Maria Eckl, Sabine Schmitt, Igor Alves Mancilla, Matthias F. Meyer-Bender, Monika Hanf, Julia Philippou-Massier, Stefan Krebs, Hans Zischka & Lucas T. Jae

Nature 579, 433–437(2020) | Cite this article

Oliver T. Keppler

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(Inventors: **Oliver Till Keppler**, Jindrich Cinatl, Constanze Schneider, Hanna-Mari Baldauf, Sarah-Marie Schwarz, Hubert Serve, Thomas Oellerich, Gerd Geisslinger, Veit Hornung) issued 2017-05-11

WO2017076880A1 Samhd1 modulation for treating resistance to cancer therapy

(Inventors: **Oliver Till Keppler**, Jindrich Cinatl, Constanze Schneider, Hanna-Mari Baldauf, Sarah-Marie Schwarz, Hubert Serve, Thomas Oellerich, Gerd Geisslinger, **Veit Hornung**) issued 2017-05-11

Christoph Klein

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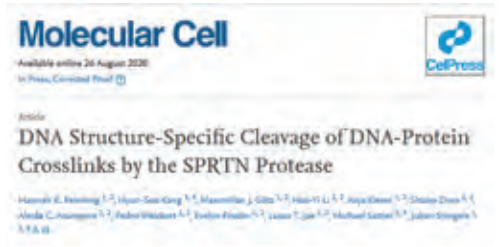

Marion Subklewe

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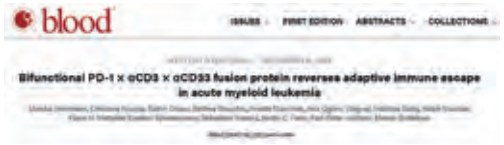

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Consistent success in life-supporting porcine cardiac xenotransplantation

Matthias Längin, Tanja Mayr, [...] Eckhard Wolf, Nikolai Klymiuk, Paolo Brenner & Jan-Michael Abicht

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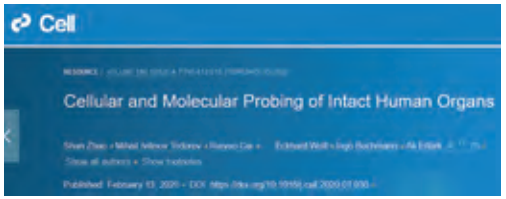

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(Inventors: **Eckhard Wolf**, Nikolai Klymiuk, Lelia Wolf-van Buerck, Jochen Seißler) issued 2019-05-14

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(Inventors: Bruno Reichart, Jan-Michael Abicht, Tanja Mayr, Matthias Längin, Paolo Brenner, **Eckhard Wolf**, Nikolai Klymiuk) filed 2019-03-29

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Speaker	Institution	Title	Date
2015			
Johan Elf	University of Uppsala, Sweden	Probing intracellular kinetics at the level of single molecules	12.01.15
Liedewij Laan	TU Delft, The Netherlands	How yeast fixes a broken polarization machine: towards a mechanistic understanding of evolutionary change	19.01.15
Thorsten Friedrich	Universität Freiburg	On the mechanism of respiratory complex I	02.02.15
Lotte Sogaard-Andersen	MPI für terrestrische Mikrobiologie, Marburg	Regulation of cell division in bacteria	09.02.15
Stefan Raunser	Max-Planck-Institut für molekulare Physiologie, Dortmund	How to kill a mocking bug - Structural Insights into Tc toxin complex action	16.03.15
Kathrin Lang	Technische Universität München	Applications of an expanded genetic code - novel methods for labelling proteins	23.03.15
Ralf Erdmann	Ruhr-Universität Bochum	Peroxisomes	13.04.15
Andres Leschziner	Harvard University, Boston, USA	Mechanism and regulation of cytoplasmic dynein	20.04.15
Michael Groll	Technische Universität München	Exploiting Nature's Rich Source of Proteasome Inhibitors as Starting Points in Drug Development.	27.04.15
Jasmin Fisher	Microsoft Res. Cambridge, USA	Computing Cancer	04.05.15
Ed Hurt	BZH, University of Heidelberg	Nuclear pore complex and ribosome assembly	18.05.15
Karsten Borgwardt	ETH Zürich, Switzerland	Data Mining for Personalized Medicine	08.06.15
Caroline Kisker	Rudolf-Virchow-Zentrum, Universität Würzburg	The double edged sword of DNA repair	15.06.15
Oliver Stegle	EMBL Outstation Hinxton, Cambridge, UK	Modeling transcriptional heterogeneity between people and single cells	29.06.15
Anton Enright	EMBL Hinxton, Cambridge, UK	Computational discovery and analysis of long non-coding RNAs in the Murine germline and Drosophila mesoderm	06.07.15
Toshifumi Inada	Tohoku University, Sendai, Japan	Novel Roles Of Ribosome Ubiquitination In Quality Control Systems	20.07.15
Werner Kühlbrandt	Max-Planck-Institut für Biophysik, Frankfurt am Main	Cryo-EM of membrane protein complexes	14.09.15
Ewan Birney	EMBL-EBI, Cambridge, UK	Big data in biology: impact in basic and translational research	21.09.15
Danesh Moazed	Harvard Medical School, Boston, USA		28.09.15
Boris Shraiman	KITP Santa Barbara, USA	Mechanics and Growth Control in Animal Development	12.10.15
Andrea Sinz	Martin Luther University, Halle	The Advancement of Chemical Cross-linking / Mass Spectrometry for Studying Protein-Protein Interactions	09.11.15
Nina Henriette Uhlenhaut	Helmholtz Zentrum München	Nuclear receptor cistromes: how hormones touch the genome	16.11.15
Petr Cejka	University of Zürich, Switzerland	Homologous recombination pathway	30.11.15
Susan Gasser	Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland	Does spatial organization of genome matter?	14.12.15

Speaker	Institution	Title	Date
2016			
Andrej Sali	University of California, San Francisco, USA	Integrative modeling of biomolecular assemblies and pathways	11.01.16
Richard Neher	MPI Tübingen	Quantifying and predicting evolution of viruses and bacteria	25.01.16
Bas van Steensel	Netherlands Cancer Institute	Genomics of chromosome architecture and gene regulation	01.02.16
Ralf Jungmann	MPI for biochemistry, Munich	Super-Resolution Microscopy with DNA Molecules	15.02.16
Roland Kontermann	University of Stuttgart	Bispecific and bifunctional antibody fusion proteins for cancer therapy	29.02.16
Vincent Noireaux	University of Minnesota, USA	Cell-free TX-TL: from gene circuit to self-assembly in a test tube	14.03.16
Gunter Meister	Universität Regensburg		30.05.16
Bernd Bukau	ZMBH, Heidelberg	Mechanisms of chaperone assisted protein folding	06.06.16
Sunney Xie	Harvard University, Cambridge, USA	Life at the Single Molecule Level: From Single Molecule Enzymology to Single Cell Genomics	20.06.16
Christian Klein	Roche Glycart, Schlieren, Switzerland	Engineered therapeutic antibodies for cancer (immuno-) therapy	20.06.16
Carlo Camilloni	Technische Universität München	Characterising the dynamics of complex systems with simulations and experimental data	18.07.16
Sarah Teichman	Wellcome Trust Sanger Institute, UK	Understanding cellular heterogeneity	19.09.16
Paula da Fonseca	MRC Cambridge, USA	Cryo-EM in the fight against malaria: the high resolution structure of the Plasmodium 20S proteasome in drug discovery	24.10.16
Mick Watson	The Roslin Institute, University of Edinburgh, UK	Can bioinformatics help feed the world?	31.10.16
Yukihide Tomari	University of Tokyo, Japan	Biochemical and biophysical analyses of RNA silencing pathways	07.11.16
Domenico Libri	Institut Jacques Monod, Paris, France	Pervasive transcription in yeast: generation, control and function	28.11.16
2017			
Christine Voge	NY University, USA	The ups and downs of protein expression regulation	16.01.17
Helen Saibil	Birkbeck University of London, UK	Protein aggregation and disaggregation in situ and in vitro	23.01.17
Bart Deplancke	EPFL, Lausanne, Switzerland	Understanding and predicting complex phenotypes using genetic and molecular data	13.02.17
Irmgard Sinning	Heidelberg University	Insights into co-translational protein targeting and folding	20.02.17
Ethan Garner	Harvard University, USA	Watching rods form out of spheres, how bacteria form and grow in defined widths	13.03.17
Jeff Coller	The Center for RNA Molecular Biology, Case Western Reserve University, USA	Codon optimality is a major determinant of mRNA stability in Eukaryotes	24.04.17
Grant Jensen	California Institute of Technology, USA	Discovering and dissecting cellular machines with electron cryotomography	08.05.17

Speaker	Institution	Title	Date
Raúl Méndez	IRB, Barcelona, Spain	The CPEB family of RNA-binding proteins: Post-transcriptional (re)programing gene expression in homeostasis and disease	15.05.17
Christine Mayr	Memorial Sloan Kettering Cancer Center, Cornell University, USA	Regulation of protein functions by 3'UTR-mediated protein-protein interactions	23.05.17
Tamir Gonen	Howard Huges Medical Institute, USA	Membrane proteins at the interface of life	12.06.17
Jean-Luc Imler	University of Strasbourg, France	Antiviral innate immunity	19.06.17
Eva Nogales	UC Berkeley, USA	The human transcription initiation machinery: structure, interactions and dynamics	05.07.17
Yosef Yarden	Weizmann Institute, Israel	EGFR and HER_2: mechanisms and targeting in hard to treat cancers	10.07.17
Jan Huisken	Morgridge Institute for Research, Wisconsin, USA	Multi-scale imaging with personalized light sheet technique	24.07.17
Kim Newton	Genentech, San Francisco, USA	Supression of cell death an inflammation by Ripk1 and Caspase-8	09.10.17
Christine Jacobs-Wagner	Yale University, USA	How to achieve cellullar replication without fail: Lessons from bacterial cells	11.10.17
Nicolas Manel	Institut Curie, Paris, France	Innate immunity	16.10.17
Terry Hwa	University of California San Diego, USA	Quantitative study of gene expression: from transcriptome to proteome	23.10.17
Andrea Musacchio	Max Planck Institute of Molecular Physiology, Dortmund	Reconstituting (parts of) cell division	27.11.17
Frank Pugh	Pennsylvania State University, USA	How to achieve cellullar replication without fail: Lessons from bacterial cells	04.12.17
2018			
Ruedi Aebersold	ETH Zürich, Switzerland	The proteome in context	15.01.18
Rickard Sandberg	Ludwig Institute for Cancer Research & Karolinska Institutet, Stockholm	Deciphering gene regulation using single-cell transcriptomics	19.02.18
Herbert Nar	Boehringer Ingelheim Pharma, Biberach	Exploiting allosteric inhibition of GTP Cyclohydrolase I for treating pain disorders	05.03.18
Bridget Carragher	NY Structural Biology Center, USA	Challenges and opportunities for cryoEM automation	12.03.18
Matthias Selbach	MDC, Berlin	Proteome dynamics	16.04.18
Geeta Narlikar	UCSF, USA	ATP-dependent and independent mechanisms of regulating chromatin	18.05.18
Hao Wu	Harvard Medical School, USA	Inflammasomes and GSDMDs- Structure, Function and therapeutic Intervention	11.06.18
Nigel Goldenfeld	University of Illinois, USA	Evolutionary transitions at the dawn of life: the emergence of the genetic code and biological homochirality	02.07.18
Peter Baumann	Stowers Institute for Medical Research/Universität Mainz	Architecture and dynamics of chromosome ends and the inheritance of genetic information	09.07.18
Robert Endres	Imperial College London, UK	Information processing by the "probrain": how bacteria sense and respond to chemicals	23.07.18

Speaker	Institution	Title	Date
Andrew Jackson	University of Edinburgh, UK	teaser junior group	08.10.18
Martin Jinek	Universität Zürich, Switzerland	CRISPR-Cas genome editors: structures, mechanisms and applications	15.10.18
Mike Stubbington	10X Genomics, Cambridge, UK	Antigen receptor repertoires at single-cell resolution	22.10.18
Dagmar Iber	ETH Zürich, Switzerland	From Networks to Function-Computational Models of Organogenesis	19.11.18
Olivier Martin	GQE-Le Moulon, Gif-sur-Yvette, France	Quantitative modeling of dynamical intra-cellular networks	26.11.18
Judith Zaugg	EMBL, Heidelberg	Regulatory Genomics: From Basic Biology to Disease Mechanisms	03.12.18
Ernst-Ludwig Winnacker	Gene Center, LMU München	Crispr-Babies: International Summit on Human Genome Editin-Report of an Eye Witness	05.12.18
2019			
Lothar Hennighausen	National Institute of Diabetes and Digestive and Kidney Diseases NIH, Bethesda	Understanding gene regulation through genome-wide biochemical studies and advanced genome editing	25.02.19
Christoph Kurat	Biomedical Center, Munich	DNA Replication through a Chromatin Environment	03.06.19
Jonathan Schmid-Burgk	Broad Institute, Cambridge, UK	Scalable analysis of proteome dynamics using barcoded gene tagging	06.06.19
Jörg Vogel	Institute for Molecular Infection Biology, Würzburg	RNA-based infection biology: from microbiota manipulation to single-cell RNA-seq	24.06.19
Gunnar Rätsch	ETH Zürich, Switzerland	Transcriptome Alterations in Cancer: Challenges and Opportunities	01.07.19
Teresa Teixeira	Laboratoire de Biologie Moleculaire et Cellulaire des Eucaryotes, Paris, France	Telomeres and the control of cell proliferation	08.07.19
Ala Trusina	Niels Bohr Institute, University of Copenhagen, Denmark	Distilling simplicity behind morphological complexity of organs and organism	15.07.19
Pakorn Kanchanawong	National University of Singapore	Nanoscale Architecture of Cell Adhesion Complexes	16.09.19
Haissi Cui	Scripps Research Institute, San Diego, USA	Nuclear functions of an aminoacyl-tRNA Synthetase upon metabolite fluctuation	19.09.19
Clare Watermann	National Institutes of Health (NIH), Bethesda, USA	Integrating Actin and Adhesion Dynamics in Cell Migration and Innate Immunity	23.09.19
Kurt Schmoller	Helmholtz Zentrum München	Coordination of protein and organelle homeostasis with cell size	21.10.19
Peter Cowan	St. Vincent's Hospital Melbourne, USA	Xenotransplantation: finally close to the clinic?	28.10.19
Shelley L. Berger	Perelman School of Medicine, University of Pennsylvania, USA	Epigenetic pathways as targets in human disease	18.11.19
Stefan Raunser	Max Planck Institute of Molecular Physiology, Dortmund	The power of cryo-EM to elucidate biological mechanisms	02.12.19
Micha Drukker	Helmholtz Zentrum München	Human Pluripotent Stem Cell Lineage-Choice Research	16.12.19
2020			
Matthias Altmeyer	University of Zurich, Switzerland	Charting cellular responses to genotoxic stress: A tale of PARP inhibitors and their mechanism(s) of action	13.01.20
Philip Kranzusch	Harvard Medical School, USA	cGAS-like enzymes in human immunity and host-microbe signaling	03.02.20

Date	Title	Investigator	Media
15.02.15	Neuer Juniorverbund: Wenn die Kraftwerke der Zellen streiken	Julien Gagneur	LMU press release
13.03.15	Neue Immuntherapie - Wie funktioniert Impfen gegen Krebs?	Marion Subklewe	Podcast Bayern 2 - IQ - Wissenschaft und Forschung
02.07.15	Paradigmenwechsel im Kampf gegen den Krebs, Autorin: Dr. Nicole Schaenzler	Marion Subklewe	Auszug aus der SZ-Anzeigensonderveröffentlichung „Forum Spitzenmedizin“
11.08.15	Vallee Foundation: Fabiana Perocchi erhält renommierten Preis	Fabiana Perocchi	LMU press release
19.10.15	Transplantationsmedizin: Dein ist mein Schweineherz	Eckhard Wolf	Frankfurter Allgemeine Zeitung (online/print)
01.12.15	Biomedizinische Forschung: LMU-Wissenschaftler erhalten m⁴ Award	Karl-Peter Hopfner, Marion Subklewe	LMU press release
07.12.15	Antibiotika: Blockade an ungewohnter Stelle	Daniel Wilson	LMU press release
2016	Bericht über das BioSysM	Ulrike Gaul	Bayerisches Fernsehen
30.03.16	Immunology: An alternative route to inflammation	Veit Hornung	LMU press release
08.04.16	Können Tierorgane Menschenleben retten?	Eckhard Wolf	Stuttgarter Zeitung (online/print)
06.07.16	Immune system: Natural killer cells have a memory	Veit Hornung	LMU press release
15.07.16	Antibiotics: An unusual spot for a roadblock	Daniel Wilson	LMU press release
20.08.16	Tierische Organspender	Eckhard Wolf	Südwest Presse (online)
08.12.16	Leibniz-Preis der DFG: LMU-Biochemiker Karl-Peter Hopfner ausgezeichnet	Karl-Peter Hopfner	LMU press release
2017	Frauen in der Wissenschaft - Treffen mit Angela Merkel	Ulrike Gaul	
26.01.17	RNA Metabolism: Burn after Reading	Roland Beckmann	LMU press release
16.03.17	Karl-Peter Hopfner - Leibniz Prize 2017	Karl-Peter Hopfner	DFG Mediathek
14.04.17	Uni München klont Schweine für die Wissenschaft	Eckhard Wolf	tz (online/print)
10.08.17	Schweine für den Operationssaal	Eckhard Wolf	WDR
28.08.17	Transplantation „Schweineorgane passen gut zum Menschen“	Eckhard Wolf	Frankfurter Rundschau (online/print)
13.09.17	Innate Immunity: To operate, insert dimers	Karl-Peter Hopfner	LMU press release
13.09.17	Research Awards: Johannes Stigler receives ERC Starting Grant	Johannes Stigler	LMU press release
13.10.17	Immunology: An alternative route to inflammation	Veit Hornung	LMU press release

Date	Title	Investigator	Media
14.12.17	Leibniz Prize: LMU's Veit Hornung among awardees	Veit Hornung	LMU press release
05.01.18	Ribosome Biogenesis: Finding form by folding	Roland Beckmann	LMU press release
06.03.18	Mammalian Development: Blastocyst architecture	Eckhard Wolf	LMU press release
20.03.18	Veit Hornung - Leibniz Prize 2018	Veit Hornung	DFG Mediathek
26.03.18	Intracellular transport in 3D: Structural view on the molecular architecture of the co-translational machinery for N-glycosylation	Roland Beckmann	LMU press release
27.03.18	Heinz Maier-Leibnitz-Prize: Lucas Jae is one of the 2018 Heinz Maier-Leibnitz prize winners	Lucas Jae	LMU press release
01.04.18	Organspender aus dem Stall - zu Besuch bei Schweinen	Eckhard Wolf	Deutschlandfunk
11.04.18	Structural Biology: The art of unpacking	Karl-Peter Hopfner	LMU press release
11.06.18	Ribosome Maturation: Until the last cut	Roland Beckmann	LMU press release
19.06.18	Julian Stingele erhält Alfried Krupp- Förderpreis für junge Hochschullehrer 2018	Julian Stingele	Alfried Krupp von Bohlen und Halbach-foundation press release
04.09.18	Chromatin Structure: Slip-sliding away ...	Karl-Peter Hopfner	LMU press release
06.12.18	Ein Herz von Tieren	Eckhard Wolf	Tagesspiegel (online/print)
06.12.18	Xenotransplantation: Schweineherzen schlagen sechs Monate in Pavianen	Eckhard Wolf	Www.Aerzteblatt.De (online/print)
06.12.18	Paviane leben über sechs Monate mit Schweineherz	Eckhard Wolf	Welt (online/print)
14.12.18	Bettencourt Prize: Renommierte Auszeichnung für Veit Hornung	Veit Hornung	LMU press release
20.12.18	Structural Biology: A molecular hammock for cotranslational modification	Roland Beckmann	LMU press release
01.02.19	Metabolic Research: Causes of cortisone-induced side effects identified	Nina Henriette Uhlenhaut	LMU press release
28.03.19	EU Research Awards: Three LMU researchers among the winners	Karl-Peter Hopfner	LMU press release
2019	SFB 127: Genetisch modifizierte Schweine als Organspender für die Xenotransplantation	Eckhard Wolf	Biotechnologie in Bayern (print)
26.04.19	Interview "Children's Rights in Hospital"	Christoph Klein	ZDF logo
29.04.19	Interview "1st Children's Health Summit in Germany"	Christoph Klein	ZDF heute journal
Mai 19	Bruno Reichart, Eckhard Wolf: Herz vom Schwein	Eckhard Wolf	Technology Review (print)

Date	Title	Investigator	Media
05.05.19	Interview "Situation of Children's Hospitals in Germany"	Christoph Klein	B5 aktuell
05.05.19	SZ-Forum Gesundheit - Xenotransplantation	Eckhard Wolf	Süddeutsche Zeitung (online/print)
12.06.19	Xenotransplantation – ein Herz für uns	Eckhard Wolf	Zeit (online/print)
26.06.19	Cell Biology: Cut the CAT tails off and save mitochondria	Roland Beckmann	LMU press release
11.07.19	New winners of Bayer Early Excellence in Science Award: EUR 30,000 for international research scientists	Julian Stingele	Bayer Science & Education Foundation press release
01.08.19	Halb Schwein, halb Mensch – darum geht es gar nicht	Eckhard Wolf	ZEIT (online)
07.08.19	Schweine als Organspender: Tierzucht für den Operationssaal	Eckhard Wolf	Deutschlandfunk
02.09.19	DNA Repair: Opening the hatch to heal the break	Karl-Peter Hopfner	LMU press release
11.10.19	Herzensangelegenheit	Eckhard Wolf	Wirtschaftswoche
01.11.19	Bruno Reichart, Eckhard Wolf: Meet the pigs that could solve the human organ transplant crisis	Eckhard Wolf	MIT Technology Review (print/online)
18.11.19	Gentechnik: Schweine als „Ersatzteillager" für Menschen	Eckhard Wolf	BR 24, Podcast
18.11.19	Ein Herz von Tieren: In Deutschland könnten Patienten bald Schweineherzen transplantiert werden	Eckhard Wolf	Tagesspiegel
19.11.19	Report Munich: Eckhard Wolf, Bruno Reichart, Tiere als Ersatzteillager	Eckhard Wolf	ARD
28.11.19	Immunology: Activation by breakdown	Veit Hornung	LMU press release
29.11.19	Organhandel und Alternativen zu menschlichen Organen	Eckhard Wolf	Schweizer Fernsehen
05.01.20	Bruno Reichart, Eckhard Wolf: Dürfen wir Tiere zu unserem Ersatzteillager machen?	Eckhard Wolf	BR 5, Podcast
11.01.20	Ersatzteillager Tier: das Dilemma der Xenotransplantation	Eckhard Wolf	BR 24, Podcast
28.01.20	New gene correction therapy: Gene scissors against incurable muscular disease	Eckhard Wolf	LMU press release
31.01.20	Structural Biology: Special delivery	Roland Beckmann	LMU press release
25.02.20	Virus ist längst unter uns	Oliver T. Keppler	Münchner Merkur
25.02.20	Eine weltweite Ausbreitung ist nicht zu stoppen	Oliver T. Keppler	Münchner Merkur
27.02.20	Rare diseases. Challenges for pediatric medicine, Publisher special	Christoph Klein	Frankfurter Allgemeine Zeitung

Date	Title	Investigator	Media
27.02.20	Rare diseases: Key insights from small samples	Christoph Klein	LMU press release
04.03.20	Cell Biology: Maintaining mitochondrial resilience	Lucas Jae	LMU press release
15.03.20	Epidemische Ausbreitung und die Maßnahmen	Oliver T. Keppler	Bayerisches Fernsehen
25.03.20	Wie gefährlich ist Corona?	Oliver T. Keppler	BR Extra
26.03.20	Wie besiegen wir Corona?	Oliver T. Keppler	BR Extra
31.03.20	European Research Council: Four ERC Advanced Grants at LMU	Roland Beckmann	LMU press release
17.04.20	Cell Biology: Your number's up!	Roland Beckmann	LMU press release
27.04.20	Wie lange dauert die Corona Krise?	Oliver T. Keppler	BR Extra
03.05.20	Wie wird die „Neue Normalität" im Konzert"?	Oliver T. Keppler	BR Klassik
04.05.20	Neue Normalität: Bald auch im Konzertsaal?	Oliver T. Keppler	BR Podcast
11.05.20	Antikörper sind kein Schutzwall	Oliver T. Keppler	Interview Süddeutsche Zeitung
17.05.20	Die Tests sind derzeit nicht wirklich aussagekräftig	Oliver T. Keppler	Welt am Sonntag
18.05.20	Warum Corona-Schnelltests nicht funktionieren	Oliver T. Keppler	Welt.de
28.05.20	Die Corona Lage: Auslandsreisen	Oliver T. Keppler	BR Extra
29.05.20	Verreisen: Was Sie wegen Corona beachten müssen	Oliver T. Keppler	Bayerisches Fernsehen
03.06.20	Lockerungen zu Lasten der Risikogruppen?	Oliver T. Keppler	Bayerisches Fernsehen, Münchner Runde
11.06.20	Ein Beitrag zur Impfstoffentwicklung	Oliver T. Keppler	ARD Tagesschau
17.07.20	COVID-19: Viral shutdown of protein synthesis	Roland Beckmann	LMU press release
21.07.20	Die schwierige Rückkehr ins Stadion	Oliver T. Keppler	Spiegel
01.08.20	Corona-Virus und Immunsystem	Roland Beckmann	Bayerisches Fernsehen

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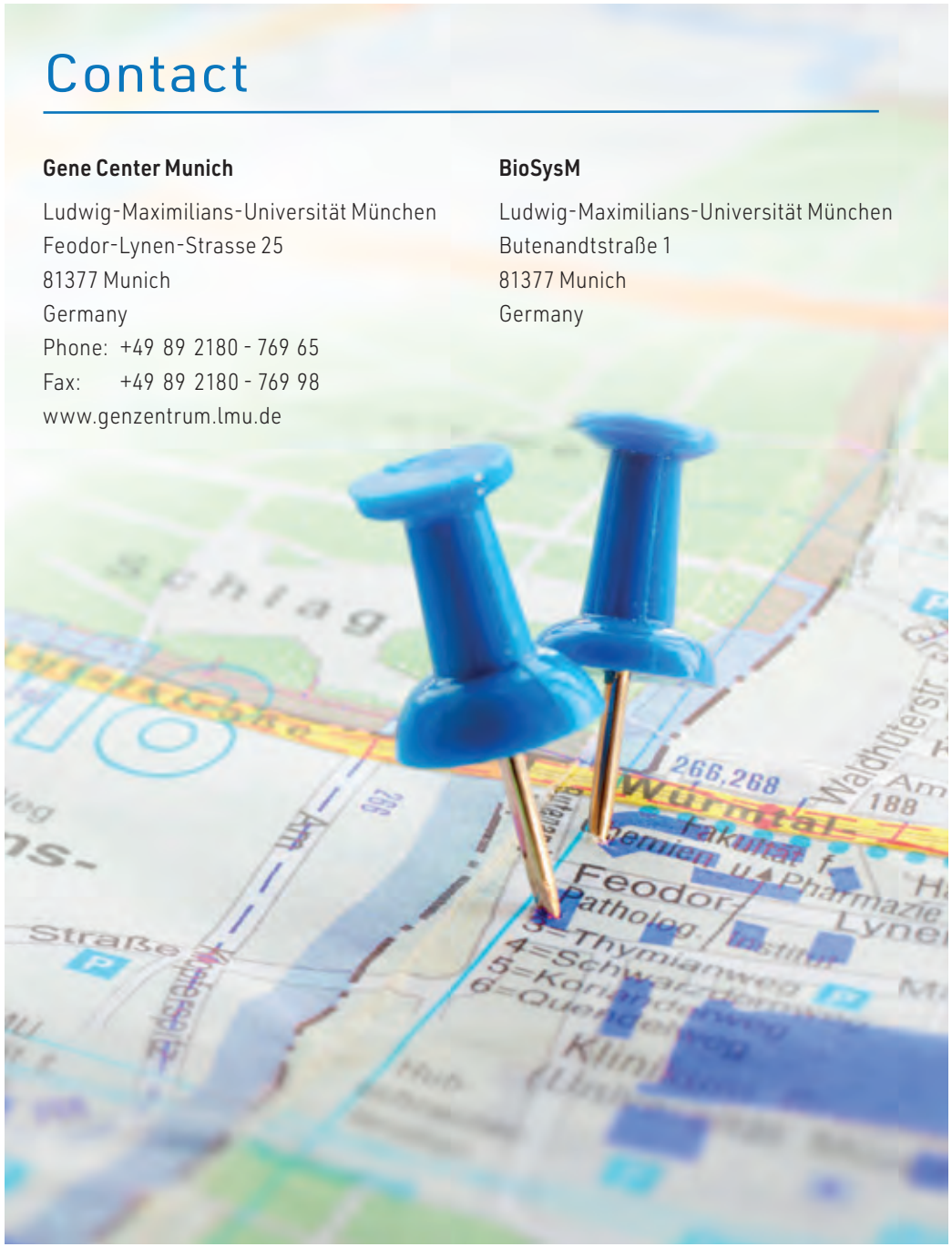

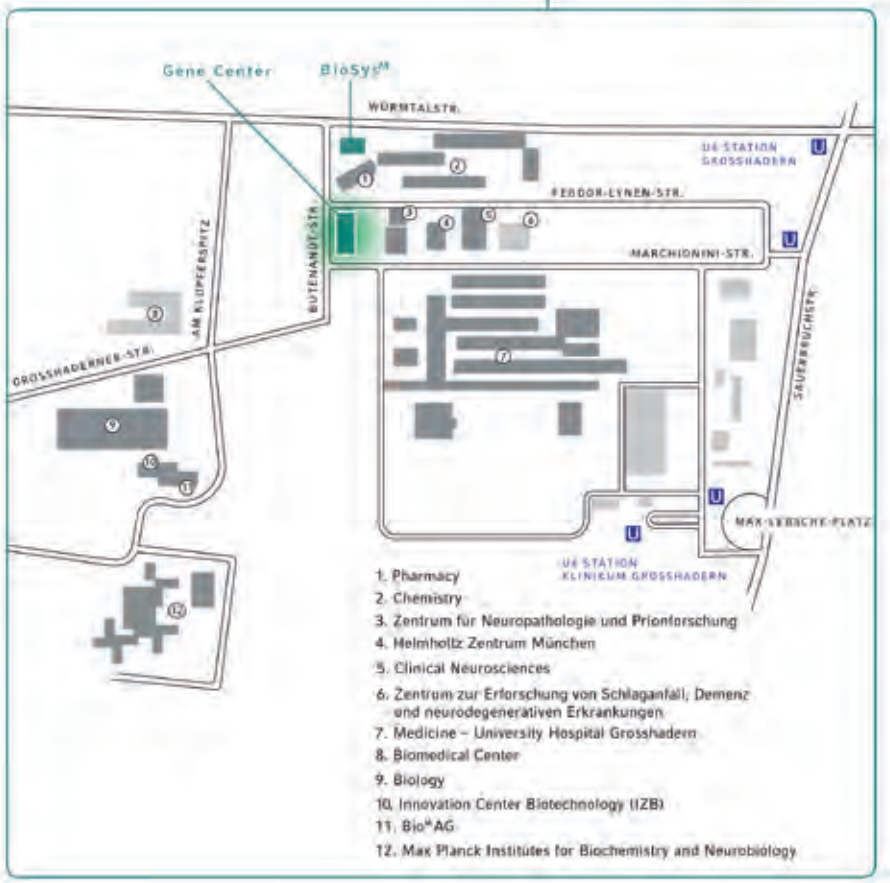

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