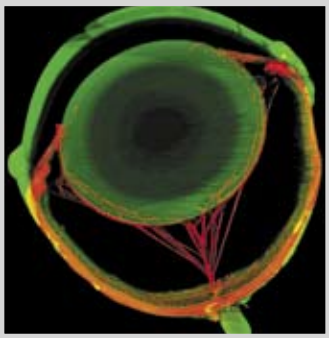
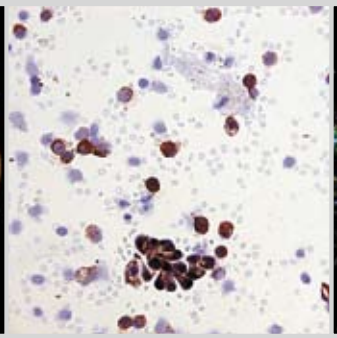
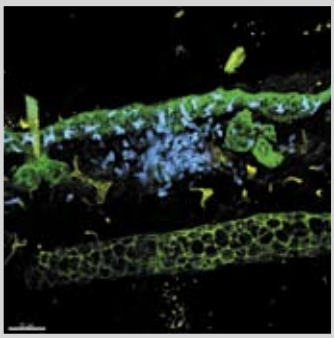
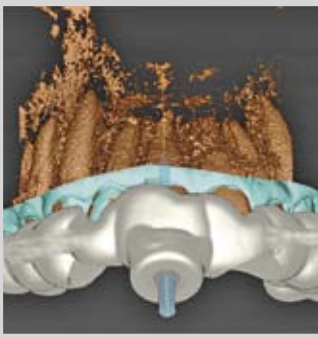
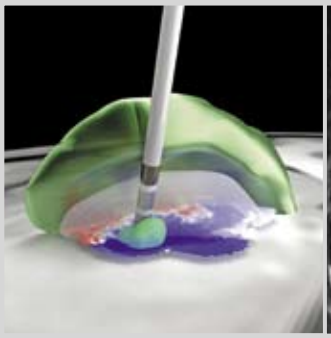
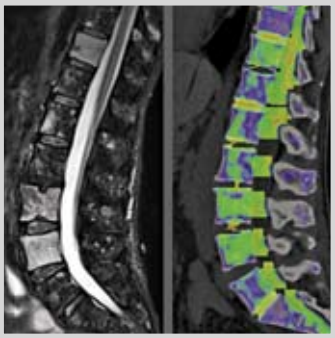
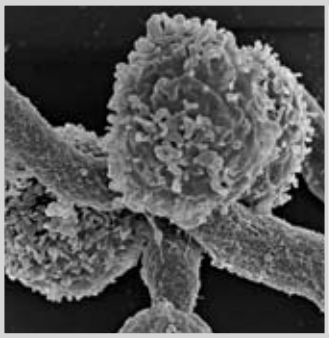
Faculty of Medicine
University of Würzburg

RESEARCH REPORT 2019

Julius-Maximilians-
UNIVERSITÄT WÜRZBURG


Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Content

Foreword

Dear readers,

Successfully bridging the gap between research and education as well as the profession as a physician and doctor in academic healthcare is a challenge to university-based medicine. Establishing the necessary framework is one of the great concerns of the Faculty of Medicine, not only to inspire the best minds sustainably into viewing Würzburg as a centre of science. It is thus my great pleasure to introduce a number of new colleagues who were appointed by our Faculty during the last two years:
Professor Dr. Stefan Frantz took over as Director of the Department of Internal Medicine I, Professor Dr. Hubert Kübler as Director of the Department of Urology and Paediatric Urology, and Professor Dr. Christoph Maack as Director of the Department of Translational Research at the Comprehensive Heart Failure Center Würzburg (CHFC). Moreover, a number of new chairs were established at the Faculty of Medicine. Professor Dr. Philip Tovote occupied the newly established Chair of Systems Neurobiology at the Institute of Clinical Neurobiology within the framework of a Heisenberg professorship. Professor Dr. Cynthia Sharma was appointed Chair of Molecular Infection Biology II in the Institute of Molecular Infection Biology, while the appointment of Professor Dr. Oliver Kurzai heralded the establishment of the first and currently sole Chair of Medical Microbiology and Mycology in Germany. In conjunction with the foundation of the Max-Planck Research Group for Systems Immunology, we were able to appoint Professor Dr. Wolfgang Kastenmüller and Professor Dr. Georg Gasteiger as the newly established Chairs of Systems Immunology I and II. The Faculty of Medicine also underwent structural expansion through the founding of the Institute of General Practice in January 2018 under the leadership of Professor Dr. Ildikó Gágyor and Professor Dr. Anne Simmenroth, who share the tasks of teaching and research. Furthermore, a total of 11 W2 and 4 W1 professorships were newly appointed in both the clinical and preclinical-theoretical fields of medicine in 2017 and 2018. Their work is portrayed in depth in this edition of the research report.
Motivating students into participating actively in science as early as possible and preparing them for a scientific career or scientifically related activity through suitable measures is a primary focus of the Faculty of Medicine. To live up to this aspiration is also the aim of the new "elite degree programmes" on offer, "Translational Medicine" and "Translational Neuroscience", which are on offer to medical students as additional courses of study. These degree programmes, financed by the Elite Network in Bavaria, are characterized by a particularly demanding range of courses taught, excellent by international standards, on the basis of novel interdisciplinary concepts and highly intensive supervision.
The Faculty of Medicine has also reacted in a timely manner to the problems of recruiting the next generation of scientists in clinical research by creating the infrastructure and positions to enable clinicians in specialty training the time to carry out research in addition to the time-consuming treatment and care of patients. In order to continue meeting this aim, we have developed lasting infrastructure and concepts of qualification with the foundation of the Integrative Clinician Scientist College (ICSC), which provides the next generation of scientifically active doctors the freedom to research and qualifies them specifically on their path towards becoming clinician scientists. The ICSC is located within the Interdisciplinary Center for Clinical Research (IZKF) and acts as an umbrella providing standards with respect to organizational framework and quality, alongside a wide range of continuing/further education opportunities. One of the clinician-scientist programmes available is a programme funded by the DFG since 2018 titled "Understanding InterOrgan Networks in Cardiac and Vascular Diseases (UNION-CVD)", which deals with the translational research into organ interactions in cardiac and vascular disease as well as cardiac and vascular symptoms of non-cardiovascular conditions/diseases. In a highly competitive application procedure with the aim of combatting the shortage of young scientists in cancer research, the Faculty of Medicine has succeeded in its bid to establish one of only five nationwide Mildred-Scheel-Junior-Research Centers. A total of ten million Euros over the next five years were awarded to provide the ideal working environment and work-life balance to young talents from the fields of medicine and the natural sciences. Up to eight research groups will soon be able to embark on their research work on the medical campus. A distinctive feature of the programme is the concept of supporting interdisciplinary tandems of clinician scientists and medical scientists, which was seen by the reviewers' panel as exceptionally trendsetting.
Another central concern of the Faculty of Medicine is to expand particularly promising fields of research gradually and consolidate their infrastructure. With completion of the move into the new research building for the German Comprehensive Heart Failure Center in January 2017, scientists and clinicians from various disciplines may now focus their attention on basic and clinical research as well as patient care, united under one roof. This step has underlined once again the internationally visible and nationally leading role of heart failure research in Würzburg, last but not least strengthened through the previous-

Professor Dr. Jörg Vogel (left), founding director of the Helmholtz Institute for RNA-based Infection Research, together with the Bavarian State Minister for Economy and Media, Energy and Technology Ilse Aigner (centre) and Professor Dr. Dirk Heinz (right), Scientific Director of the Helmholtz Centre for Infection Research, pictured at the official contract-signing ceremony in the Prince's Hall of the Residence in Würzburg on 24 May 2017. (Photo: Rudi Merkl)

ly mentioned appointment of Professor Dr. Christoph Maack.
The successful establishment of two new extramural institutions is viewed as an outstanding milestone for Würzburg as a centre of science. In May 2017, the Julius-Maximilians-University Würzburg and the Helmholtz Association celebrated the inauguration of the Institute for RNA-Based Infection Research (HIRI), seated within the Helmholtz Centre for Infection Research (HZI). Since its foundation, the development of the HIRI has advanced a long way and six further workgroup leaders from Germany, the USA, France, Ireland, and Turkey have been recruited in Würzburg alongside the founding director Professor Dr. Jörg Vogel. To strengthen the links between the current research foci of the participating institutions, the sum of 1.9 million Euros has already been distributed among scientists at the HIRI, the University of Würzburg, and the HZI for use in joint research initiatives. Last but not least, work on establishing the Max-Planck Research Group for Systems Immunology is pressing ahead. In addition to the appointment of Professor Dr. Georg Gasteiger and Professor Dr. Wolfgang Kastenmüller, two further junior research groups have taken up research work in Würzburg.
Numerous successful applications bear witness to the strength of biomedical research in Würzburg, including a series of newly funded transregional collaborative research centers, in which the university-based medical center in Würzburg, as an attractive partner together with other locations, is committed to current topics in medicine for the wellbeing of the population.
At this point I would like to express my gratitude to the Executive Board of the University, all the research funding organizations, politicians, ministerial employees, and friends of the Faculty of Medicine. It is only with your help, promotion, and support that the excellent potential that exists in Würzburg can fully unfold.

Würzburg, May 2019
Professor Dr. Matthias Frosch
Dean

Honours awarded by the Faculty of Medicine

Conferral of an honorary doctorate to **Professor Dr. Dr. h.c. mult. Otmar Wiestler** during the doctorate award ceremony in the "Neubaukirche" on 13 May 2017. Professor Dr. Dr. h. c. mult. O. Wiestler initially accepted the chair of neuropathology at the University of Bonn in 1992, where he built up the Institute of Neuropathology into a leading centre of research into brain tumours, human epilepsy, and neural stem cells. He moved to Heidelberg in 2004, where he took over the position as Director of the Board and Scientific Director of the German Cancer Research Centre as successor to Professor Dr. Dr. h. c. mult. Harald zur Hausen. In 2015, Professor Dr. Dr. h. c. mult. O. Wiestler was appointed as president of the Helmholtz Community of German Research Centres. With Professor Dr. Dr. h. c. mult. O. Wiestler, the Faculty of Medicine honoured an outstanding scientist and far-sighted scientific politician setting new standards. With the foundation of the Helmholtz Institute for RNA-Based Infection Research, the University of Würzburg is now also structurally integrated into the Helmholtz Association.

Professor Dr. Dr. h. c. mult. Otmar Wiestler (3rd from left) framed by the well-wishers: Professor Dr. Jörg Vogel (left), Professor Dr. Matthias Frosch (2nd from left), Professor Dr. Georg Ertl (3rd from right), Professor Dr. Hermann Einsele (2nd from right) und Professor Dr. Ralf Bargou (right). (Photo: Angie Wolf)

The History of the Faculty of Medicine in Würzburg

The Faculty of Medicine in Würzburg ranks among the four oldest medical faculties in Germany. It was preceded only by Heidelberg, Cologne and Erfurt, and thus has today a history of more than 600 years behind it. Together with theology and law, medicine had its place among the three higher faculties in 1402 already, at the original foundation of Würzburg University. It is not clear, however, to what degree formal medical teaching was inaugurated at the time. Certainly, any regular teaching activities must have come to an end within a few decades, due to the rapid decline of the University as a whole. Long before 1402 already, Würzburg was held in high esteem as a center of medical learning, however. Already in the late 13th century, the Abbot of the monastery of Aldersbach in Lower Bavaria undertook a journey of more than 300 kilometers to consult the learned physicians in Würzburg about his failing health. About the same time, probably around 1280, one of the most influential vernacular medical handbooks of the Middle Ages was written, the "Arzneibuch" of Ortolf von Baierland who called himself explicitly a "physician from Würzburg". Compiled "from all the Latin medical books I have ever read", Ortolf's "Arzneibuch" offered of a *summa* of medieval medical learning. From the mid-14th century, a topographical illustration of the brain by the Würzburg canon Berthold von Blumentrost has come down to us, which attributed the major rational faculties – imagination, cogitation and memory – to the various cerebral ventricles. This made perfect sense within the ruling Galenic paradigm, which associated the rational faculites with the very subtle and mobile animal spirits that were assumed to move in the ventricles rather than within the cerebral substance itself.

Restart: University and Julius-Spital

In the 16th century, various learned physicians of renown were active in Würzburg, Burckhard von Horneck, for instance, and the physician-poet Johannes Posthius. Only with the second foundation of the University in 1582, however, formal academic medical teaching was put into place. Again, medicine ranked among the University's three higher faculties from the start, though it took several years until the Faculty of Medicine truly came to life. In 1587, the Faculty's statutes were approved. By 1593, finally, the professors had been appointed and began teaching. Würzburg had come to offer exceptionally good conditions for a sound medical education. Adriaan van Roomen, also known as Adrianus Romanus, had been appointed to the first and most prestigious professorship, the chair for medical theory. Within a couple of years, van Roomen, who was also a mathematician of international acclaim, succeeded in establishing a flourishing culture of medical dissertations and disputations and promoted a number of medical students to doctors. At the same time, conditions for clinical, practical training had markedly improved, thanks to the newly founded Julius-Spital. In contrast to many other contemporary hospitals, which cared almost exclusively for the aged and infirm, the Julius-Spital was, from its very beginning, explicitly designated also as a hospital "in aegrorum curationem", i.e. for the medical treatment of the curable sick. The Julius-Spital thus offered medical students a welcome opportunity to observe various kinds of diseases and to witness the effects of different curative approaches. Such bedside teaching was very popular among contemporary medical students and was a major reason, why numerous medical students crossed the Alps to study in Montpellier or at one of the Northern Italian universities, where they were commonly allowed to accompany the professors on their visits to patients in the hospitals and in private homes.

After van Roomen's retirement and death and due to the recurring outbreaks of plague and the Thirty Years War the Faculty of Medicine in Würzburg lost much of its international renown, however. Only very few medical students continued to find their way to Würzburg and even fewer were promoted to doctors of medicine. From the late 17th century, the government tried to counteract this trend and initiated important reforms. The number of medical chairs was raised to five in 1709; originally there were only two or three. Following the example of leading protestant universities such as those in Leiden and Halle a botanical garden was set up – botanical gardens were then considered important teaching tools which helped medical students become familiar with the various plants used as medicinal drugs. An anatomical theater was built in the garden pavilion of the Julius-Spital and the famous Parisian surgeon Louis Sievert was brought in to improve anatomical teaching. The professor of anatomy was instructed to dissect a corpse at least every four weeks in the winter time, in the presence of the other professors. Academic disputations and dissertations were encouraged. Yet these efforts bore little fruit, at first. The Faculty lacked professors whose fame could attract medical students from further away, and the teaching methods remained rather old-fashioned. In 1739, the professors still had to be explicitly forbidden to dictate their lectures word by word. In 1758, Karl Philipp von Greiffenklau began his request for a survey of the Faculty's state bluntly by asking: "Wherein lies the cause of the immense decline of the Medical Faculty?"

On the way towards modernity: The Siebold-Dynasty

It was due primarily to the incessant activities of one man, Carl Caspar Siebold, that this rather desolate situation changed within a couple of decades and the Würzburg Medical Faculty became one the foremost institutions of its kind in Germany. Siebold, since 1769 professor of anatomy, surgery and obstetrics, began a systematic drive to improve medical education, introducing new modern teaching methods. Since 1766, medical students had been offered regular clinical instruction again, in the Julius-Spital. Towards the end of the 18th century, large-scale reconstruction work created space for about 200 curable patients and thus markedly improved the conditions for bedside teaching. Siebold was also a driving force behind the rebuilding of the *Theatrum anatomicum* and behind the establishment, in 1805, of a modern operation theatre in the Julius-Spital. Siebold's sons were to follow their father's footsteps and like him contributed to the modernization of in-patient care and medical instruction. Johann Barthel von Siebold who worked primarily as an anatomist and surgeon lectured on pathological anatomy. Adam Elias von Siebold continued his father's efforts to improve obstetrical training for medical students and midwives. In 1805, he opened the first obstetrical hospital in Würzburg in a building which formerly housed epileptics.

The rapid ascent of the Medical Faculty under Siebold and his sons was ultimately crucial for the survival of the University as a whole. When Würzburg came under Bavarian rule in 1803, it was the university in Bamberg rather than the one in Würzburg that was closed. In the process, the Würzburg Medical Faculty even saw its fame further promoted by leading professors from the former Bamberg institution. One of Germany's foremost anatomists, physiologists and embryologists, Ignaz Döllinger, joined its ranks. Like Döllinger, Wilhelm von Hoven, a former school mate of Friedrich Schiller, came from Bamberg to Würzburg. Later he became a major medical figure in Nuremberg, and was, by all appearances, the driving force behind the first double-blind trial in history, which was organized in Nuremberg in 1835 in an attempt to disprove the efficacy of homeopathic drugs. The strongest attraction on German medical students was exerted, for a couple of years, by the philosopher Wilhelm Schelling who sought to put medicine on new, philosophi-

cal foundations. At the height of his fame in Würzburg, 270 medical students immatriculated in one year. Soon, growing disillusionment set in, however, and his audience shrank rapidly.

Schönlein - Virchow - Röntgen

Over the following decades, Würzburg increasingly developed into a center of empirical-observational and, finally, laboratory-based, experimental approaches. Clinical instruction was further improved by a massive expansion of policlinical care. Thousands of out-patients provided medical students with unique possibilities to visit and observe patients in their homes and to take responsibility for their care, guided by a more experienced physician. Johann Lukas Schönlein, the founder of the so-called "natural history school" in medicine, introduced scores of students to his approach. He called for a detailed and unprejudiced observation of signs and symptoms as the basis of a new, empirically founded nosology. Based on his method, Schönlein described various diseases for the first time and some like the Schoenlein-Henoch purpura carry his name to this day. Nikolaus Anton Friedreich gave an account of facial nerve paralysis. Johann Georg Pickel and Johann Joseph von Scherer helped lay the groundwork for a modern science of pharmaceutics and medical chemistry respectively. Around the middle of the 19th century, Franz von Rinecker was the Faculty's dominant figure. He made important contributions to pediatrics, psychiatry and dermatology alike and thanks to his efforts Würzburg can boast one the first pediatric hospitals at any university in the world. Under Rinecker's leadership, Rudolf Virchow and Albert Kölliker were appointed professors, who helped turn anatomy and pathology into modern laboratory sciences and, in the case of Virchow's cellular pathology, provided contemporary medicine as a whole with a new theoretical basis. Outstanding contributions also came from researchers outside of the Medical Faculty, from the biologists Julius Sachs and Theodor Boveri, for example, and from the physicist Wilhelm Conrad Röntgen who discovered the x-rays.
By 1900, the Julius-Spital – in 1800 still to a large degree a last resort for poor, single patients and invalids – and the various university hospitals had become the most important providers of in-patient care in Würzburg. In the 1920s, the close and fruitful, though sometimes conflict-ridden ties between the Juliusspital and the Medical Faculty were somewhat loosened when the new Luitpold-Hospital was built in Grombühl.

Fig. 1: The University Hospital in Grombühl (aerial view, 1950s).

The National Socialist era

The National Socialist period left deep marks on the Würzburg Medical Faculty. The Institut für Vererbungswissenschaft und Rasseforschung (Institute of Hereditary Science and Racial Research) conducted large scale genetic surveys of the population in the area around Würzburg. Werner Heyde, who was appointed professor of psychiatry in Würzburg in 1939, played a leading role in the so-called „Aktion T4", the organized mass murder of 10,000s of psychiatric patients and handicapped men, women and children between 1939 und 1941. Based on the „Gesetz zur Verhütung erbkranken Nachwuchses" (1933) sterilizations and abortions were performed against the women's will in the Maternity Hospital under Carl Gauß. The Anatomical Institute obtained numerous corpses of people who had been executed for political reasons as well as, through Heyde, about 80 corpses of men and women who by all appearances had been murdered – possibly in the gas chambers – with carbon monoxide. Most of the other hospitals and institutes were also in some way or other implicated in National Socialist medicine and almost all professors lost their chairs after 1945.

After 1945

The massive air raid in the spring of 1945 damaged or destroyed large parts of the University and the hospitals. Already a couple of days after the raid, the first operations were performed again, however, and out-patient care as well as work on the wards resumed. Only ten years after the end of the war, the Faculty counted three of the big names in contemporary Western medicine among its members, the surgeon Werner Wachsmuth, the internist Ernst Wollheim and the otorhinolaryngologist Horst Wullstein. Wullstein not only acquired international fame with his new method of tympanoplasty and his special operation microscope. As the driving force behind the foundation of a "head clinic" he also paved the road towards the establishment of interdisciplinary centers which increasingly came to shape the Faculty and which acted as crucial catalysts for cutting-edge biomedical research. In 1992, a new center for biomedical research was opened on the Hubland, which today brings together members of ten different institutions, from the faculties of medicine, chemistry and pharmacy as well as biology., In 2002, the "Virchow Zentrum" was established as a national research center for experimental biomedicine, endowed with a number of research professorships and research groups headed by junior researchers, which also plays a major role in the "Graduate School of Life Sciences". Würzburg has come to house a center for research on infectious diseases and a center for interdisciplinary clinical research. In addition, since 1971, a fair number of so-called "Sonderforschungsbereiche" (large, often interdisciplinary research networks) have been active, financed by large grants from the Deutsche Forschungsgemeinschaft. The trend towards interdisciplinary research and medical care gained further momentum over the last years, with the creation of the Center for Operative Medicine, the Center for Internal Medicine and the Center for Experimental and Molecular Medicine. 2017 also saw the inauguration of the research building for the Comprehensive Heart Failure Centre in Würzburg, setting yet another high point in the structural development of the Faculty of Medicine.

Professor Dr. med. Dr. phil. Michael Stolberg
Institute for the History of Medicine

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Institutes and Departments

Preclinical Institutes and Chairs

Theoretical-clinical Institutes

Center for Operative Medicine (ZOM)

Center for Internal Medicine (ZIM)

Center for Radiology (ZRAD)

Gynecology, Pediatrics, and Dermatology

Head Clinic

Center for Mental Health (ZEP)

Scientific Institutions

Center for Dental, Oral and Maxillofacial Health (ZMKG)

Institute of Anatomy and Cell Biology, Chair of Anatomy I

CONTACT DETAILS

Professor Dr. med. Süleyman Ergün
(acting Head)

Koellikerstr. 6
97070 Würzburg
Phone: 0931/31-82707
Fax: 0931/31-82712
E-mail: sueleyman.erguen@uni-wuerzburg.de
www.anatomie.uni-wuerzburg.de

Professor Dr. med. Dr. rer. nat.
Barbara M. Braunger
(since 11/2017)
Phone: 0931/31-84387

Mission and Structure

At the Department I of the Institute for Anatomy and Cell Biology, the research work focuses on the topics of neuronal and neurovascular processes and the role of microglial cells in these processes as well as on the tumor microenvironment, angiogenesis and tumor extracellular matrix. The research group Retina (head: Prof. B. M. Braunger) has the overall goal to identify mechanisms and cell populations contributing to the development of retinal diseases. To achieve this, the research group focuses on mechanisms leading to neuroprotection or –degeneration, mechanisms promoting vascular maintenance, microglia cells in the context of vascular pathologies and neurodegeneration and the role of CEACAM1 within the retina. The research group Tumor microenvironment and angiogenesis (head: Dr. E. Henke, Prof. S. Ergün) is focusing on elucidating the influence of the tumor extracellular matrix (tumor matrisome) on growth, vascularization, therapeutic resistance and, consequently, the course of disease.

Research at Department I is performed by 3 post-doctoral researchers, 3 Ph.D. students and 2 technical assistants.

Research Foci

Mechanisms leading to neuroprotection or –degeneration
(B. Braunger, N. Wagner, S. Schmitt, C. Bielmeier, K. Elsner)

Hereditary retinal degenerations or age-related macular degeneration (AMD) are common causes of blindness in western countries. Eventually, apoptosis of photoreceptors leads to an impaired vision with no existing causative treatment. However, first clinical trials show that the application of the neuroprotective factor ciliary neurotrophic factor (CNTF) slows the progression of retinal degenerations concomitant with a stabilization of the remaining visual acuity. Still, the regulatory network of neuroprotective growth factors in the retina is not fully understood yet. The retina research group aims to identify neuroprotective signaling pathways in the retina. We focus on the neuroprotective properties of the transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF) and endothelin- receptor type B (EDNRB) signaling pathways. In this context, our overall aim is to understand and unravel the impact of the signaling pathways on the different cellular populations in the retina involved in neuroprotection or –degeneration. We use transgenic mice and conditional knockout animal models and use different, complementary damage models, for example the light damage model or genetic models of photoreceptor degeneration. Furthermore, we use cell culture systems, in which we delete genes of interest (e.g. EDNRB) to unravel the molecular cellular mechanisms leading to neurodegeneration or –protection. Midterm, our results could promote the development of new neuroprotective therapies.

Mechanisms promoting vascular maintenance
(B. Braunger, A. Schlecht (Alumni))

In this project, the retina group focuses on the development and maintenance of retinal/choroidal vessels. Currently, our research concentrates on the development of choroidal neovascularization (CNV), a pathology that can frequently be observed in patients suffering from the wet form of age-related macular degeneration (AMD). Here, CNV breaks through the Bruch's membrane, an extracellular matrix component, invading the subretinal space in an uncontrolled manner. Recently, we could demonstrate that the deletion of TGF-β signaling specifically within endothelial cells is sufficient to promote the development of CNV (Schlecht et al., 2017). Prof. Braunger presented these data at the Biennial Symposium on AMD at the Harvard University in Boston, USA (October 2018). Now we aim to clarify the specific role of endothelial TGF-β signaling in maintaining anatomical barriers in the eye. Furthermore, we will identify secreted molecular factors that could lead to the degradation of extracellular matrix. Our long-term vision for this project is that the stabilization of vascular beds, concomitant with the maintenance for anatomical barriers might inhibit the progression of retinal/choroidal vasculopathies at a very early time point.

Microglia cells in the context of vascular pathologies and neurodegeneration
(B. Braunger)

In the near future, the research group will also work on the impact of local inflammatory cells, e.g. microglia cells, in the development of CNV. To this end, we will use our genetic animal models and the model of la-

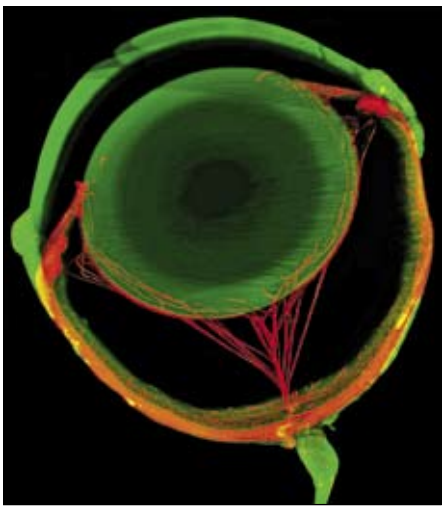


Fig. 1: Light-sheet fluorescence microscopy of a transparent eye of a six-week-old lectin-injected mouse with a deletion of Tgfbr2 in the entire eye. We observe an irregular arrangement of the retinal plexus with anastomoses between retinal and choroidal vessels and a persistence of the hyaloid artery, a vessel, that is present only during development of the eye.

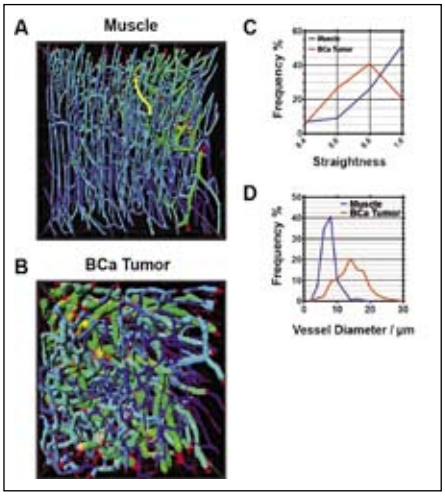


Fig. 2: Quantitative modeling of transformations of the tumor vasculature. 3D-Representation of the vasculature in muscle (A) and breast carcinoma tissue (B). After image analysis the diameter of the vessels in encoded by different colors. The analysis results in the calculation of various parameters, including the straightness (C) and the diameter of the capillaries (D). Vessels in tumors diverge strongly from normal tissue: they are contorted (aberration from the value 1.0 of straight vessels) and their average diameter is not only significantly larger, but the broad curve also indicates a strong variance.

ser-induced CNV. We aim to clarify the specific role of endothelial TGF-β signaling on the initial development of CNV and if microglia cells have an additive effect. In the larger context of our research, we consider microglia cells as a very promising subpopulation of cells that might promote the beginning of diseases like AMD.

The role of CEACAM1 in the retina
(B. Braunger, J. Müller, N. Wagner, F. Kleefeldt, S. Ergün)

The Carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM1) is a signaling cell adhesion receptor that is involved in several biological processes including blood vessel morphogenesis and the regulation of endothelial barrier function. Our data show, that CEACAM1 knockout animals do not exhibit obvious alterations in retinal morphology. However, we detected significantly elevated TGF-β1 mRNA levels in the retina and the appearance of microglia/macrophages in the subretinal space in older mice. One reason for this could be an impaired outer blood retinal barrier, a scenario that we will start to investigate. Furthermore, we aim to analyze, if CEACAM1 knockout animals demonstrate an increased immune reaction concomitant with an increased angiogenic response following laser induced CNV.

Modulation of the tumor matrisome to increase efficacy of cancer therapy
(E. Henke, R. Nandigama, S. Ergün)

The tumor stroma consists of a multitude of cell types and the extracellular matrix (ECM). This tumor microenvironment strongly influences tumor behavior, its growth, its malignancy and its response to therapy. Compared to normal organs, the tumor stroma is significantly altered. For example, tumors produce increased amounts of matrix proteins as well as enzymes the cause cross-linking and stiffening of the ECM. The increased rigidity of the tumor ECM results in reduced permeability for oxygen and nutrients but also for therapeutic agents. Thus, the poorly permeable ECM acts as a physical barrier protecting the tumor cells from drug exposure. We explore the possibility to improve response to cancer therapy by developing applicable pharmacological interventions to modulate the tumor ECM. An approach that also could result in a minimization of side effects of current therapeutics.
Another focus of our research is the interaction of the various components of the tumor microenvironment, and the interplay between the pathologically altered tumor ECM and cells of the immune system in particular. A targeted destabilization of the tumor ECM enhances infiltration of immune cells and thereby improves control of the tumor by the patient's own immune defense.

Quantitative modeling of transformations of the tumor vasculature
(E. Henke, R. Nandigama, S. Ergün)

Blood vessels in tumors are often defective and dysfunctional. This results in a constant undersupply and consequently in increased malignancy and resistance to therapy. A range of therapeutic approaches has been suggested to improve this situation. However, to successfully develop these novel methods a quantitative endpoint describing the degree of dysfunctionality of the vasculature is needed.
In collaboration with the Rudolf-Virchow-Zentrum we develop quantitative models of the vasculature in a range of breast tumors. For comparison these models are supplemented with data of the vasculature in normal organs. For this approach we use state-of-the-art microscopy techniques (laser fluorescence light sheet microscopy) and 3D-image analysis (Fig. 2). We aim at a full parameterization of the various vessel systems and a subsequent ranking of these parameters with respect to their value in quantifying vessel system quality.
Using transgenic mouse models and vascular-targeted therapeutics we study the effect of the tumor blood vessels and their quality on therapeutic efficacy. The pharmacological data is than correlated with the data of the virtual vessel system models.

Teaching

Courses in microscopic and macroscopic anatomy, neuroanatomy and cell biology are held for medical, and dentistry students. Additionally, the theses of medical and dentistry doctoral students, PhD students (biology), Bachelor and Master students of neurosciences and biomedicine are supervised.

SELECTED PUBLICATIONS

Kugler M, Schlecht A, Fuchshofer R, Schmitt SI, Kleiter I, Aigner L, Tamm ER, Braunger BM. (2017) SMAD7 deficiency stimulates Müller progenitor cell proliferation during the development of the mammalian retina. Histochem Cell Biol. 148:21-32.

Nandigama R, Upcin B, Aktas BH, Ergün S, Henke E. (2018) Restriction of drug transport by the tumor environment. Histochem Cell Biol 150:631-648.

Rohrig F, Vorlova S, Hoffmann H, Wartenberg M, Escorcia FE, Keller S, Tenspolde M, Weigand I, Gatzner S, Manova K, Penack O, Scheinberg DA, Rosenwald A, Ergün S, Granot Z, Henke E. (2017) VEGF-ablation therapy reduces drug delivery and therapeutic response in ECM-dense tumors. Oncogene 36:p1-12.

Rossow L, Veitl S, Vorlová S, Wax JK, Kuhn AE, Maltzahn V, Upcin B, Karl F, Hoffmann H, Gätzner S, Kallius M, Nandigama R, Scheld D, Irmak S, Herterich S, Zernecke A, Ergün S, Henke E. (2018) LOX-catalyzed collagen stabilization is a proximal cause for intrinsic resistance to chemotherapy. Oncogene 37:4921-4940.

Schlecht A, Leimbeck SV, Jägle H, Feuchtinger A, Tamm ER, Braunger BM. (2017) Deletion of endothelial TGF-β signaling causes choroidal neovascularization Am J Pathol 187:2570-2589.

Institute of Anatomy and Cell Biology, Chair of Anatomy II

CONTACT DETAILS

Professor Dr. med. Süleyman Ergün (Head)

Koellikerstr. 6
97070 Würzburg
Phone: 0931/31-82707
Fax: 0931/31-82712
E-mail: sueleyman.erguen@uni-wuerzburg.de
www.anatomie.uni-wuerzburg.de

Professor Dr. Srikanth Karnati (since 8/2018)
Phone: 0931/31-81522

Mission and Structure

In Department II of the Institute of Anatomy and Cell Biology research activities are performed in the following areas: the cardiovascular research group (AG) (head: Prof. S. Ergün) is looking into a) the role of the cell adhesion molecule CEACAM1 in regulation of the endothelial barrier and atherosclerosis, and b) the role of the vascular wall-resident stem cells in myocardial infarction. The AG Tumor angiogenesis (head: Prof. S. Ergün and Dr. E. Henke) studies a) the role of CEACAM1 in tumor vascularization and metastatic spreading, b) the role of vascular wall-resident stem cells in these processes in *in vivo-tumor* models and c) the influence of the extracellular matrix on tumor angiogenesis. Work in the AG Stem cells and regenerative medicine (head: Prof. S. Ergün, Dr. P. Wörsdörfer) is focused on the generation of iPS (induced pluripotent stem) cells and vascularized organoids (brain, tumor and cardiac organoids) as well as on the mechanisms of differentiation and regenerative potential of stem cells from the "vasculogenic zone" in the adventitia of adult blood vessels. The AG Neuromorphology (head: Prof. E. Asan) studies the influence of the monoaminergic and peptidergic systems on processing of emotional stimuli in the amygdala. The AG Peroxisomes in cardiovascular biology (head: Prof. S. Karnati) studies the molecular mechanisms of how peroxisomes participate in cellular redox communication networks in cardiovascular diseases. The core-unit AG Imaging (S. Ergün, S. Karnati, E. Asan, N. Wagner) provides a platform for imaging using confocal and conventional electron microscopy as well as serial block face REM-CLEM technology.

Research at Department II is carried out by 10 post-doctoral scientists, 6 doctoral students and 5 technical assistants.

Research Foci

Stem Cells and Regenerative Medicine
(S. Ergün, P. Wörsdörfer, S. R. Mekala, F. Kleefeldt, H. Bömmel)

The generation of induced pluripotent stem cells (iPSCs) and their directed differentiation into specific cell types such as vascular progenitors, neural progenitors or cardiomyocytes enables us to generate complex, vascularized organoid models *in vitro* (Fig.1 A). These models can be used as tools for basic developmental biology as well as disease modeling. Moreover, these organoids can be used as basis for the development of new cell or tissue replacement therapies. Besides using epigenetically reprogrammed iPSCs, we are interested in the adventitial stem cell niche of blood vessels. This niche was first described by our group as so-called "vasculogenic zone". It exists within the wall of mouse and human vessels and harbors a variety of different stem and progenitor cells. Recently, we could show that adventitial CD34$^+$ Sca$^-$ Flk1$^+$ stem cells can be differentiated into spontaneously beating cardiomyocytes without any genetic manipulation (Mekala et al., 2018) (Fig. 1B).

Endothelial barrier, vascular inflammation and atherosclerosis
(S. Ergün, U. Rückschloß, F. Kleefeldt, Wagner, H. Bömmel)

Cardiovascular diseases still represent the leading cause of death within industrial countries. Mostly, dysfunction of the endothelium that covers the inner surface of the vessel wall is the starting point for subsequent pathological alterations within blood vessels. Analyzing mechanisms contributing to endothelial dysfunction, our group focuses on the role of the adhesion molecule CEACAM1. Using endothelial cell lines, we were able to show severe impairment of endothelial function due to CEACAM1 deficiency. We found that the formation of the important anti-atherosclerotic factor nitric oxide (NO) is reduced, endothelial adhesiveness towards immune cells is increased and integrity of the endothelial barrier is compromised (Fig. 2; Ghavampour *et al.*, 2018). However, preliminary data obtained from the murine model suggest that the effect of CEACAM1 on endothelial function might be age-dependent. Therefore, we aim to identify the contribution of CEACAM1 to physiological vascular aging as well as to pathological alterations, i.e. atherosclerosis in vitro and in vivo using murine models (i.e. *Ldlr*-KO, *Ldlr/Ceacam1*-KO) (Fig. 2).

Tumor angiogenesis, lymph angiogenesis and tumor metastatic spreading
(S. Ergün, E. Henke, S. Hübner, M. Veyhl-Wichmann, V. Pfeiffer)

Tumors take second place in the cause of death-statistics worldwide. For growth and metastatic spreading, they need new vessels. "Tumor starvation", i.e. depriving the tumor of its own blood vessels, is one of the foremost aims in worldwide tumor research.

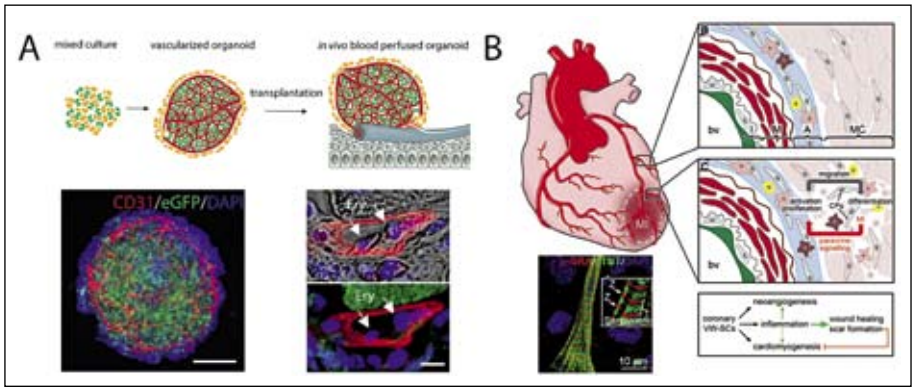


Fig. 1: A) Generation of vascularized organoids as exemplarily shown for tumor organoid. B) In vitro generation of spontaneously beating cardiomyocytes (figure panel with striated staining pattern in red and green) and activation of coronary vessel wall-resident stem cells after myocardial infarction.

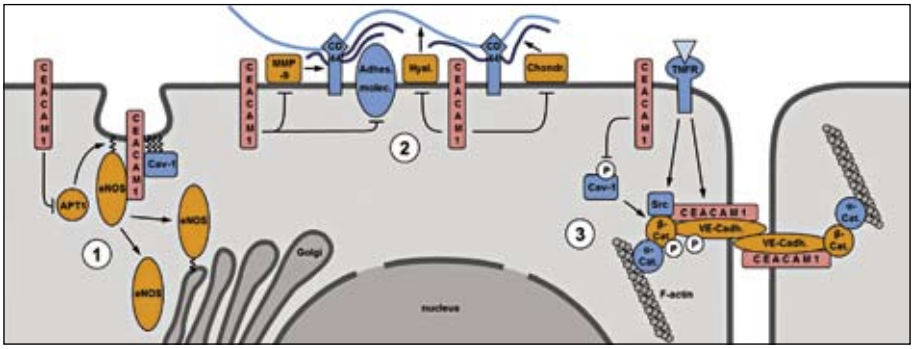


Fig. 2: Summarizing figure on the effects of CEACAM1 in endothelial cells. (1) CEACAM1 facilitates membrane localization of endothelial NO synthase and hence supports endothelial NO formation. (2) CEACAM1 facilitates anti-adhesive properties of the endothelium by suppressing the expression of adhesion molecules and glycocalyx-degrading enzymes (MMP-9, Hyaluronidase, Chondroitinase). (3) CEACAM1 facilitates basal endothelial barrier function by suppression of Caveolin-1 phosphorylation, but mediates TNF-α-induced barrier destabilization via Src kinase-dependent phosphorylation of adhesion junction proteins (VE-Cadherin, β-Catenin).

We are attempting, using in vitro, ex vivo and in vivo models, to characterize the molecular mechanisms of angiogenesis and postnatal vasculogenesis, to identify new cell types and factors contributing to tumor vascularization. One specific focus of our research is the role of the cell-celladhesion molecule CEACAM1 in tumor vascularization. In a DFG-funded project, we are additionally studying the role of this molecule in lymph angiogenesis and in the lymphogenic metastasis of prostate cancer. Furthermore, we could recently show that vessel remodeling under anti-angiogenetic therapy has a significant influence on the efficacy of tumor therapy. In particular, we study the role of vascular wall-resident stem cells in these processes.

Neuromorphology
(E. Asan)

Elucidation of the structural basis for complex nervous system functions is the main objective of research in the neuromorphology group. Analyses are focused on the central nervous processing of emotional stimuli, particularly in telencephalic areas such as the amygdala, and on the modulatory role of the monoaminergic and vegetative systems. Additionally, light and electron microscopic analyses of various regions and structures in the central and peripheral nervous system of different species ranging from *Drosophila* to mammals, and of different neural cell types *in situ* and *in vitro* are performed in cooperation with other research groups. These studies provide, for instance, functionally relevant information concerning structural alterations of specific, identified neural cells in genetically modified individuals and in animal models for disorders of the nervous system. These studies further contribute to the identification of the (sub)cellular localization of various molecules (e.g. neurotrophic factors, receptors for neurotransmitters and –modulators, adhesion proteins) which play central roles in developmental processes as well as for information processing within the nervous system.

The role of peroxisomes in cardiovascular biology
(S. Karnati)

Peroxisomes are very dynamic and metabolically active ubiquitous organelles that have the capacity to rapidly produce and scavenge ROS and thus play a central role in cellular redox signaling processes. However, the molecular mechanisms of how peroxisomes participate in cellular redox communication networks in cardiovascular diseases (CVDs) remain largely unknown. High levels of peroxisomal ROS may induce profound changes in gene expression and could initiate diverse cell signaling pathways leading to several cardiovascular disorders (endothelial dysfunction, ischemia-reperfusion injury, and atherosclerosis). Therefore, we are interested to develop the high-resolution microscopic imaging tools that allow tight spatial and temporal imaging of peroxisomal (site-specific) ROS and elucidate its functional role in the pathogenesis of CVDs. Further, peroxisomes control and regulate the inflammation process that aggravates fibrosis. Our recent study showed that in pulmonary fibrosis, peroxisomal function is impaired and that peroxisome induction attenuates the fibrotic response. Likewise, we are interested to dissect the peroxisomal contribution and its molecular mechanisms in the pathogenesis of cardiac fibrosis. We are starting a new field of science in cardiovascular biology, to provide updated insights into the mechanisms behind cardiovascular complications mediated by peroxisomal metabolism that possibly establishes novel diagnostic and therapeutic strategies to more effectively treat cardiovascular diseases.

Teaching

Courses in microscopic and macroscopic anatomy, neuroanatomy and cell biology are held for medical, biomedical and dentistry students (a total of about 420 students a year). Additionally, thesis work of medical and dentistry doctoral students, PhD students (biology), Bachelor and Master students of neurosciences and biomedicine is supervised. The Department II organizes a workshop of the Anatomical Society every two years (next event in the last week of September 2019).

SELECTED PUBLICATIONS

Ghavampour S, Kleefeldt F, Bömmel H, Volland J, Paus A, Horst A, Pfeiffer V, Hübner S, Wagner N, Rueckschloss U, Ergün S. (2018) Endothelial barrier function is differentially regulated by CEACAM1-mediated signaling. FASEB J 32:5612-5625.

Karnati S, Oruqaj G, Janga H, Tumpara S, Colasante C, Van Veldhoven PP, Braverman N, Pilatz A, Mariani TJ, Baumgart-Vogt E. (2018) PPARα-mediated peroxisome induction compensates PPARγ-deficiency in bronchiolar club cells. PLoS One 13:e0203466.

Mekala SR, Wörsdörfer P, Bauer J, Stoll O, Wagner N, Reeh L, Loew K, Eckner G, Kwok CK, Wischmeyer E, Dickinson ME, Schulze H, Stegner D, Benndorf RA, Edenhofer F, Pfeiffer V, Kuerten S, Frantz S, Ergün S. (2018) Generation of Cardiomyocytes from Vascular Adventitia-Resident Stem Cells. Circ Res 123:686-699.

Schampel A, Volovitch O, Koeniger T, Scholz CJ, Jörg S, Linker RA, Wischmeyer E, Wunsch M, Hell JW, Ergün S, Kuerten S. (2017) Nimodipine fosters remyelination in a mouse model of multiple sclerosis and induces microglia-specific apoptosis. Proc Natl Acad Sci U S A. 114:E3295-E3304.

Scholz N, Guan C, Nieberler M, Grotemeyer A, Maiellaro I, Gao S, Beck S, Pawlak M, Sauer M, Asan E, Rothemund S, Winkler J, Prömel S, Nagel G, Langenhan T, Kittel RJ. (2017) Mechano-dependent signaling by Latrophilin/CIRL quenches cAMP in proprioceptive neurons. Elife 6. pii: e28360.

Institute of Physiology, Chair of Vegetative Physiology

CONTACT DETAILS

Professor Dr. med. Michaela Kuhn (Head)

Röntgenring 9
97070 Würzburg
Phone: 0931/31-82721
Fax: 0931/31-82741
E-mail: sekretariat-kuhn@uni-wuerzburg.de
www.physiologie.uni-wuerzburg.de/vegetative-physiologie

Professor Dr. rer. nat. Andreas Friebe
Phone: 0931/31-88730

Professor Dr. rer. nat. Kai Schuh
Phone: 0931/31-82740

Mission and Structure

The Institute of Physiology comprises chairs for Vegetative Physiology and for Neurophysiology (Prof. Heckmann). The research at Vegetative Physiology is focused on Cardiovascular Physiology and four research groups are led by the University Professors Dr. Michaela Kuhn, Dr. Andreas Friebe and Dr. Kai Schuh as well as by the junior scientist Dr. Erick Miranda Laferte.

Major Research Interest

Our research focuses on the regulation and functions of the intracellular second messenger cyclic GMP (cGMP). This signaling molecule is synthesized by enzymes named guanylyl cyclases (GCs): transmembrane GCs, receptors for different peptide hormones; and cytosolic GCs, which are activated by nitric oxide/NO. Intracellular cGMP regulates many different cell functions such as growth and differentiation, migration, contraction, secretion and ion transport. To dissect the regulation, physiological functions and disease relevant alterations of hormone-receptor systems signaling via cGMP, we generate and characterize genetic mouse models with conditional, time- and cell-restricted deletions of specific GC receptors and/or of downstream cGMP-modulated regulatory proteins. Other projects dissect the cardiac functions of cytoskeleton-associated proteins containing EVH1 domains, such as SPRED, MENA and VASP, as well as of proteins forming part of being associated to cardiomyocyte´s LTCC channels. This research is supported by the DFG (SFB 688, TRR 166, etc.), the IZKF and the CHFC Würzburg. The University of Würzburg supports our teaching duties.

Natriuretic peptides have pleiotropic cGMP-mediated endocrine and paracrine cardiovascular and metabolic functions

(K. Špiranec Spes, W. Chen, F. Werner, N. Sivakumar, L. Bendz, J. Martin-Machado, H. M. Schrader, M. Rüsing, S. Tauscher, T. Potapenko, L. Krebes, K. Völker, M. Kuhn, and coworkers)

The heart is not only a „blood pump“ but also an important endocrine organ. Atrial myocytes are full of granules co-storing two hormones: atrial (ANP) and B-type natriuretic peptides (BNP). By activation of their shared guanylyl cyclase-A (GC-A) receptor, ANP and BNP lower arterial blood pressure and intravascular volume, and thereby reduce cardiac work load (Figure 1; Chen et al., 2016). Additionally, these peptides have important metabolic functions, improving the release and actions of insulin. Hence, the cGMP-producing GC-A receptor is expressed in pancreatic β cells, and also in target cells for insulin (adipocytes, skeletal muscle). Our research shows that in situations of enhanced metabolic demand, for instance in obesity and prediabetes, ANP/GC-A/cGMP signaling improves adaptative β cell proliferation, insulin secretion and sensitivity (Figure 1; Tauscher et al., 2018). However, clinical studies also demonstrated that at long-term obesity is accompanied by attenuation of ANP/GC-A activity in adipocytes which contributes to the development of insulin resistance and overt type 2 diabetes. In collaboration with the CHFC we are currently studying whether such metabolic effects/defects of ANP and BNP are involved in the cardiac and systemic metabolic alterations of patients with heart failure.

The third member of this peptide family, C-type natriuretic peptide (CNP), received its name because it shares a common amino acid core structure with previously isolated ANP and BNP. However, genetic studies later revealed that CNP´s major physiological function is not the regulation of renal natriuresis. Instead, CNP is most critical during bone development, stimulating physiological endochondral bone growth by autocrine activation of its specific cGMP-forming guanylyl cyclase-B (GC-B) receptor. In addition, CNP is constitutively released at low levels by endothelial cells. Since our cell culture studies revealed that both microcirculatory endothelial cells and pericytes express GC-B receptors, we applied the *Cre/loxP* system to dissect the role of microvascular endothelial versus mural, i.e. pericyte GC-B/cGMP signaling. Our studies revealed that the endothelial hor-

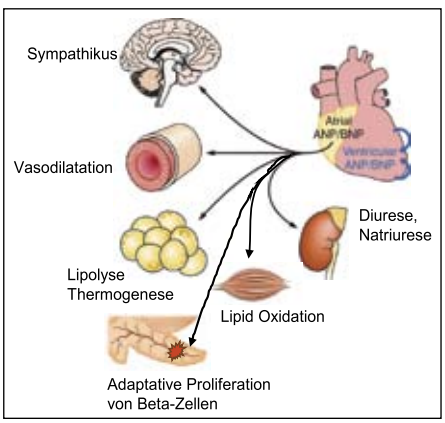


Fig. 1: Pleiotropic cGMP-mediated endocrine actions of ANP and BNP regulate blood pressure and confer metabolic protection (M. Kuhn, Physiol Rev 2016; 96:751-804).

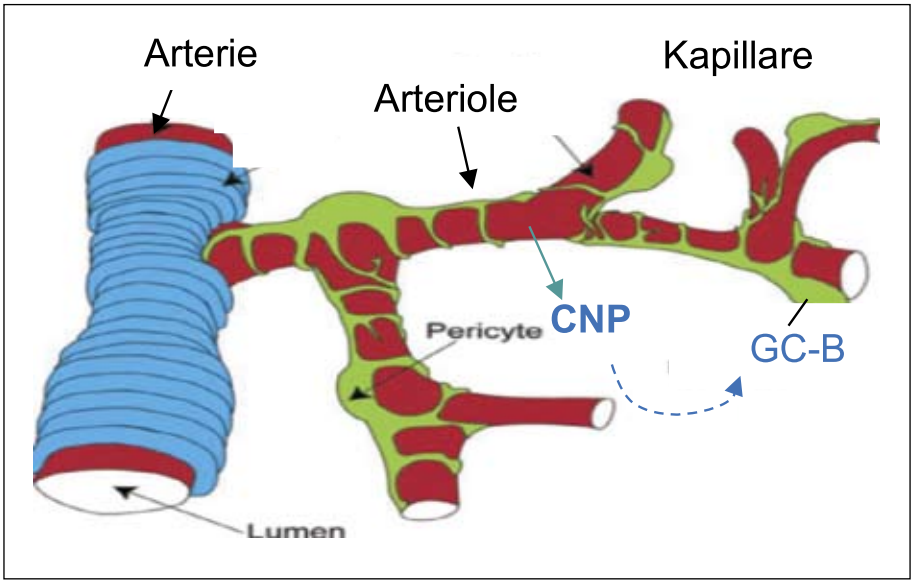


Fig. 2: In the microcirculation, endothelial CNP regulates neighboring pericytes. This cross-talk is critically involved in the regulation of microvascular tone and blood pressure (Spiranec et al., 2018).

mone acts on neighboring pericytes to diminish microcirculatory tone. Hence, paracrine acting CNP complements the homeostatic actions of local endothelial nitric oxide/NO and endocrine ANP/BNP in the moderation of peripheral resistance and thereby of blood pressure (Figure 2; Špiranec et al., 2018).

Role of NO/cGMP signaling in the gastrointestinal tract and in fibrosis
(A. Friebe, D. Groneberg, B. Voussen, K. Beck, A. Aue, F. Schwiering, N. Englert, B. Röger)

The NO-sensitive intracellular guanylyl cyclase (NO-GC) has a key function in the NO/cGMP cascade. As the most important NO receptor, NO-GC is involved in many physiological regulatory processes. We have generated transgenic mice with global deletion of NO-GC. These mice show increased blood pressure, gastrointestinal dysmotility, early postnatal lethality and shortened bleeding time. The identities of the individual cell types and tissues responsible for the respective phenotypes are not yet clear (Friebe et al., 2018). To characterize the role of NO-GC in gastrointestinal motility and organ fibrosis, we generated genetic mouse lines in which NO-GC is specifically ablated in smooth muscle cells or interstitial cells of Cajal or both. With these mice we were able to show a prominent role of NO-GC in the regulation of motor activity in murine colon and ileum (Beck et al., 2018). Currently, our focus is the role of NO/cGMP signaling during fibrotic processes in lung, liver and skin.

Cardiac roles of the β-subunit of L-type voltage-gated calcium channels (LTCCs)
(E. Miranda Laferte, S. Pickel, Y. Cruz Garcia, C. Heindl, M. Kuhn)

LTCCs are heteromultimeric proteins with a crucial role in cardiac electromechanical coupling. The cytosolic β-subunit ($Ca_v\beta$) regulates the trafficking and activity of the pore-forming α-subunit, and, in addition, possibly exerts LTCC-independent functions. To elucidate its role in cardiac hypertrophy we studied the impact of shRNA-mediated $Ca_v\beta_2$ silencing in cultured cardiomyocytes. $Ca_v\beta_2$ downregulation enhanced α_1-adrenoreceptor agonist-induced myocyte hypertrophy without involving changes in LTCC activity. Moreover, we observed that a fraction of $Ca_v\beta_2$ is targeted to the nucleus. Notably, overexpression of a nucleus-targeted $Ca_v\beta_2$ prevented cardiomyocyte hypertrophy. Quantitative proteomic analyses together with biochemical studies showed that $Ca_v\beta_2$ inhibits the activity of the calcium-dependent prohypertrophic protease calpain. Using mass-spectrometry-based analyses we are currently unmasking the interaction partners of $Ca_v\beta_2$ in cardiomyocytes, to dissect its possible participation in other LTCC-independent signaling pathways.

Teaching

The chairs of Vegetative Physiology and Neurophysiology offer a broad spectrum of lectures, integrative seminars and practical courses for students of Medicine, Dentistry, Pharmacy, Biology, and Biomedicine. A major focus is the intensive teaching of Vegetative Physiology and Pathophysiology to students of Medicine (3rd and 4th term).

SELECTED PUBLICATIONS

Beck K, Friebe A, Voussen B. (2018) Nitrergic signaling via interstitial cells of Cajal and smooth muscle cells influences circular smooth muscle contractility in murine colon. Neurogastroenterol Motil 30:e13300.

Chen W, Spitzl A, Mathes D, Nikolaev VO, Werner F, Weirather J, Špiranec K, Röck K, Fischer JW, Kämmerer U, Stegner D, Baba HA, Hofmann U, Frantz S, Kuhn M. (2016) Endothelial Actions of ANP Enhance Myocardial Inflammatory Infiltration in the Early Phase After Acute Infarction. Circ Res 119:237-248.

Friebe A, Voußen B, Groneberg D. (2018) NO-GC in cells 'off the beaten track'. Nitric Oxide 77:12-18.

Špiranec K, Chen W, Werner F, Nikolaev VO, Naruke T, Koch F, Werner A, Eder-Negrin P, Diéguez-Hurtado R, Adams RH, Baba HA, Schmidt H, Schuh K, Skryabin BV, Movahedi K, Schweda F, Kuhn M. (2018) Endothelial C-Type Natriuretic Peptide Acts on Pericytes to Regulate Microcirculatory Flow and Blood Pressure. Circulation 138:494-508.

Tauscher S, Nakagawa H, Völker K, Werner F, Krebes L, Potapenko T, Doose S, Birkenfeld AL, Baba HA, Kuhn M. (2018) β Cell-specific deletion of guanylyl cyclase A, the receptor for atrial natriuretic peptide, accelerates obesity-induced glucose intolerance in mice. Cardiovasc Diabetol 17:103-110.

Institute of Physiology, Chair of Neurophysiology

CONTACT DETAILS

Professor Dr. med. Manfred Heckmann (Head)

Röntgenring 9
97070 Würzburg
Phone: 0931/31-82730
Fax: 0931/31-82741
E-mail: heckmann@uni-wuerzburg.de
www.physiologie.uni-wuerzburg.de/en/neurophysiologie

Professor Dr. rer. nat. Erhard Wischmeyer
Phone: 0931/201-77531

Mission and Structure

Our research focuses on synaptic transmission, synaptogenesis and neuronal excitability from the molecular to the cellular and systems levels. We use the mouse and the fruit fly Drosophila melanogaster as prime model organisms and combine electrophysiological methods, molecular biological and genetic tools, with high-end microscopy.

Major Research Interests

Molecular physiology of active zones
(K. Lichter, A. Mrestani, J. Scherbel, M. Paul, M. Pauli, M. Heckmann)

At chemical synapses the transfer of information from a neuron to a postsynaptic target cell involves release of neurotransmitter substances. Excitation of the presynaptic terminal trigger's fusion of single synaptic vesicles with the presynaptic cell membrane and thus the release of the neurotransmitter that was stored in these vesicles. Synaptic release occurs preferentially at specialized presynaptic membrane compartments, so called active zones. Active zones regulate the presynaptic release of neurotransmitter and thus synaptic information processing. Active zones are complex and dynamic structures with a radius of about 50 to 500 nm. Active zones contain many different proteins and can be viewed as neuronal nanoprocessors. The organization of active zones is so far not well understood.

We investigate the structure and the dynamics of active zones in neuromuscular synapses, in the hippocampus and in the cerebellum (with Prof. Anna-Leena Sirén, Experimental Neurosurgery). Very fast high pressure freezing and electron microscopy (with Prof. Christian Stigloher, central facility for microscopy of the biocenter) in combination with electrophysiological, functional characterization allows organization and dynamics of active zones to be studied.

Super-resolution light microscopy, in particular localization microscopy and *d*STORM (direct Stochastic Reconstruction Microscopy, with Prof. Markus Sauer, Biotechnology and Biophysics) and new routines for fast, automated and reproduceable quantification of nanoscopic data are developed (with Prof. P. Kollmannsberger, Center for Computational and Theoretical Biology) and used to measure the position of proteins in active zones at the nanometre level. Modern genetic methods such as CRISPR/Cas9 in the model organism *Drosophila melanogaster* allow excellent targeted experimental manipulation down to the level of single amino acids in proteins of active zones.

Regulation of cellular excitability by potassium background currents
(E. Wischmeyer, F. Döring)

Two-pore domain K+ (K2P) channels give rise to time- and voltage-independent background currents that substantially control cellular excitability and K+ homeostasis. The activity of K2P channels is modulated by various physical and chemical stimuli as well as by G-protein coupled receptors. As some members of the K2P channel family (TREK, TRESK) are prominently expressed in neurons of the nociceptive system they most probably play an important role in pain reception. Under inflammatory conditions signalling substances are released that augment excitation of nociceptive neurons and thus pain perception. The same substances activate simultaneously TRESK potassium currents leading to inhibition of excitation. Peripheral nociceptive neurones thus exhibit a balanced system of excitation and inhibition to avoid over-excitation during inflammation.

Autoimmune synaptopathy
(C. Albert-Weißenberger, M. Heckmann)

Synaptic transmission in the central nervous system can be disturbed by autoantibodies against pre- and postsynaptic proteins. Synaptic autoantibodies can cause severe neuropsychiatric disease. We focus on the investigation of autoantibodies against the NR1-subunit of NMDA-type glutamate receptor channels. Recombinant monoclonal autoantibodies of different patients allow detailed comparisons of the effects of the different autoantibodies on the receptor channels. We investigate the interaction of the different autoantibodies with the aim to develop therapeutic tools.

Teaching

We teach physiology and pathophysiology to undergraduates enrolled in medicine, dentistry, biomedicine, pharmacy, psychology and neurobiology (lectures, practical and comprehensive courses, seminars). The clinical aspect of human physiology is conveyed in integrated seminar series, which are held in collaboration with clinicians, which co-lecture on physiological topics.

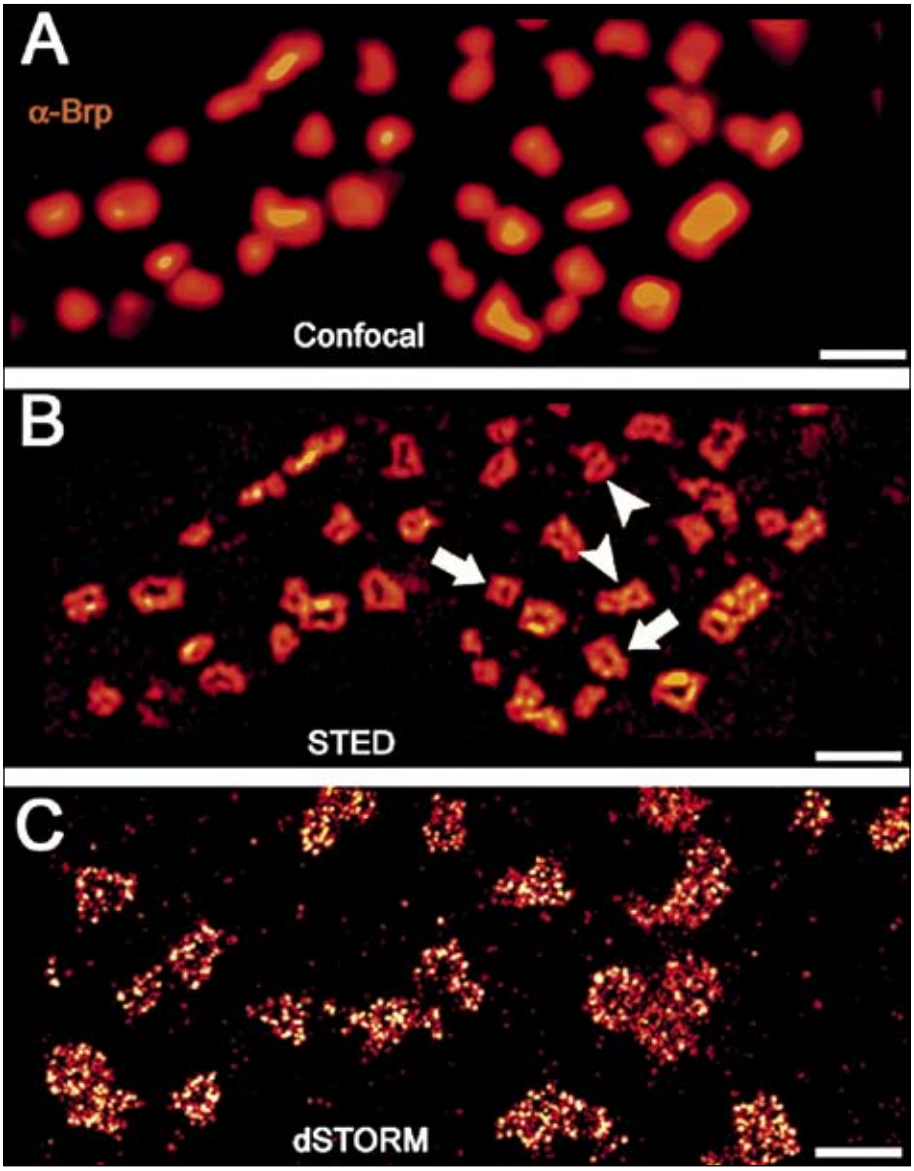


Fig.: Molecular Structure of Active Zones. Investigations by the Kittel Emmy-Noether group in collaboration with the Sauer laboratory (Department of Biotechnology and Biophysics) concerning the spatial distribution of the Bruchpilot (Brp) protein in active zones. Application of „Super-Resolution" light-microscopy (STED and dSTORM) permits the identification of ultrastructural details concealed in conventional confocal imaging. A and B from Kittel et al., 2006. Scale bar: 1 μm (A, B), 500 nm (C).

SELECTED PUBLICATIONS

Hofmann L, Hose D, Grießhammer A, Blum R, Döring F, Dib-Hajj S, Waxman S, Sommer C, Wischmeyer E, Üçeyler N. (2018) Characterization of small fiber pathology in a mouse model of Fabry disease. eLife 7 pii:e39300.

Hopp S, Nolte MW, Stetter C, Kleinschnitz C, Sirén AL, Albert-Weissenberger C. (2017) Alleviation of secondary brain injury, posttraumatic inflammation, and brain edema formation by inhibition of factor XIIa. J Neuroinflammation 14:39.

Kusch V, Bornschein G, Loreth D, Bank J, Jordan J, Baur D, Watanabe M, Kulik A, Heckmann M, Eilers J, Schmidt H. (2018) Munc13-3 Is Required for the Developmental Localization of Ca2+ Channels to Active Zones and the Nanopositioning of Cav2.1 Near Release Sensors. Cell Rep 22:1965-1973.

Schampel A, Volovitch O, Koeniger T, Scholz CJ, Jörg S, Linker RA, Wischmeyer E, Wunsch M, Hell JW, Ergün S, Kuerten S. (2017) Nimodipine fosters remyelination in a mouse model of multiple sclerosis and induces microglia-specific apoptosis. Proc Natl Acad Sci U S A 114:E3295-E3304.

Scholz N, Ehmann N, Sachidanandan D, Imig C, Cooper BH, Jahn O, Reim K, Brose N, Meyer J, Lamberty M, Altrichter S, Bormann A, Hallermann S, Pauli M, Heckmann M, Stigloher C, Langenhan T, Kittel RJ. (2019) Complexin cooperates with Bruchpilot to tether synaptic vesicles to the active zone cytomatrix. J Cell Biol 218:1011-1026.

Biocenter Würzburg, Chair of Physiological Chemistry

CONTACT DETAILS

Professor Dr. rer. nat. Dr.h.c. Manfred Schartl (Head)

Biozentrum
Am Hubland
97074 Würzburg
Phone: 0931/31-84148
Fax: 0931/31-84150
E-mail: phch1@biozentrum.uni-wuerzburg.de
www.pch1.biozentrum.uni-wuerzburg.de

Professor Dr. rer. nat. Stefan Gaubatz
Phone: 0931/31-84138

Professor Dr. rer. nat. Svenja Meierjohann
Phone: 0931/31-81348

Mission and Structure

In accordance with the global scientific approach at the Biocenter, the research interests at the department extend from functional molecular biology to questions concerning the development of organisms and their interactions with the environment. All research groups at this unit use molecular methods to understand problems in Biology and Medicine on all levels of the biological organization. The multi-faceted approach is reflected in the fact that scientists of the department are developmental biologists, molecular biologists, biochemists and biomedical researchers and that the head of the institute is a member of the Medical Faculty as well as of the Biological Faculty. The research focus is the molecular understanding of developmental processes and the pathobiochemistry of cancer.

Major Research Interests

Molecular analysis of melanoma formation
(M. Schartl)

Due to the enormous complexity and variety of human cancerous diseases, animal models are especially necessary because they are well suited to analyse basic mechanisms of tumor development and tumor progression at the genetic and molecular level. Our group is mainly interested in the processes and mechanisms of melanoma development, which is studied in several elaborate model systems, including laboratory fish and mouse models, in vitro cell culture systems and patient materials. Traditionally, one focus is the study of small aquarium model species, Xiphophorus and Medaka, which represent well-established and useful melanoma models. During the last two years, we have performed DNA high throughput sequencing transcriptome analyses of different types of melanoma, induced by the oncogenic receptor tyrosine kinase Xmrk in both model systems. We found a high level of similarity in expression regulation of known and novel tumor related genes in fish melanoma and human melanoma. These are now further investigated for their functional relevance to melanoma development. Functional studies are primarily done in transgenic fish, including genome editing by the CRISPR/Cas9 technology.
As small laboratory fish model species are particularly suited for high throughput approaches, we are conducting extensive pilot experiments for a chemical library screen to identify new molecules, which impact on melanomagenesis. At the beginning we started with the hypothesis that therapeutic effects become recognizable on the gene expression level much earlier than any phenotypic changes in tumor growth will be visible. We were able to confirm this by extensive RNA seq experiments and could define a "transcriptional disease signature". This should allow a most effective screening procedure and at the same time will reduce animal experiment load in the future. From RNA-seq data of human melanoma, obtained through a large national cooperation, we have been able to identify different transcriptional types and developmental trajectories from naevi to primary melanoma that are also relevant to diagnosis and therapy.

Phenotypic plasticity in melanoma and strategies for optimizing therapy
(S. Meierjohann)

The therapy of malignant melanoma is based on two main strategies: 1.) the inhibition of the melanoma oncogene BRAF-V600E with small molecule inhibitors directed against BRAF and MEK, and 2.) immune checkpoint inhibition, which enhances the immune response against the tumor. Due to their enormous phenotypic plasticity and adaptation mechanisms to cope with cellular stress, melanomas are frequently able to develop resistance mechanisms to both types of therapy. We are investigating mechanisms and factors, which enable phenotypic plasticity and have found that oxidative stress and the resulting changes in glutathione are potent inducers of transcriptional phenotypic adaptation. This results in dedifferentiation and the gain of invasive properties, leading to enhanced pro-metastatic potential. Similar stress adaptations also occur in vivo, and we are investigating the factors required for these adaptations with the aim of identifying novel potential targets for therapy.
In collaboration with the Departments of Dermatology, Pathology and the CCC Mainfranken, we are furthermore analysing germ-

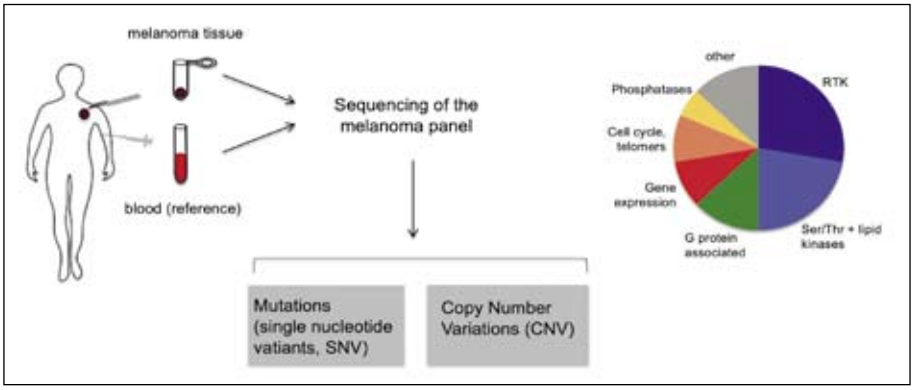


Fig. 1: Schematic presentation of the melanoma analyses by sequencing (left). The genes, which are analysed by panel sequencing, belong to different functional groups (right). RTK: receptor tyrosine kinases.

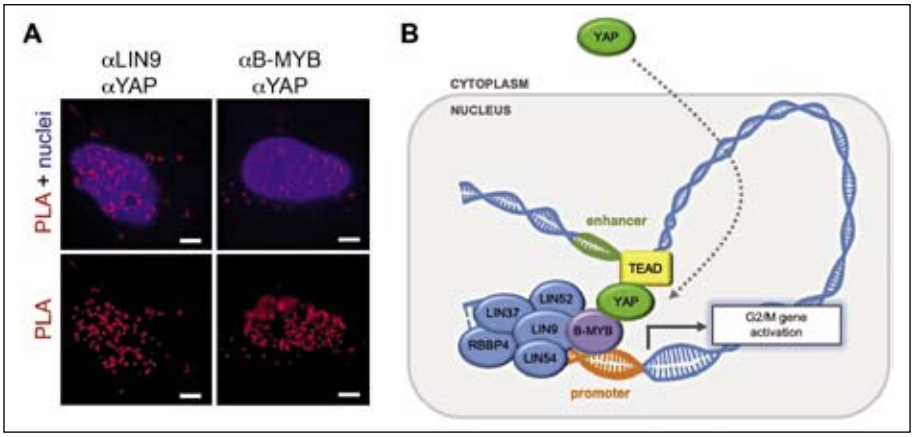


Fig. 2: A) The interaction between subunits of MMB and YAP was visualized by PLA (red dots). B) Model illustrating the crosstalk between YAP and B-MYB resulting in expression of mitotic cell cycle genes. (Scheme by Dr. G. Pattschull)

line and tumor-specific genomic alterations of melanoma patients, which enables us to identify genetic reasons for therapy resistance and therapy-relevant alterations (Figure 1). We could demonstrate that activating alterations in various receptor tyrosine kinases are particularly enriched in patients with BRAF/NRAS wildype melanomas. In contrast, specific genetic alterations in the nucleotide excision repair (NER) pathway are found in the rare heritable disease Xeroderma pigmentosum, which goes along with a strongly increased melanoma predisposition at young age. Together with colleagues from the Department of Structural Biology, we are using genetically manipulated cell line models of the NER mutations to better understand processes of early melanoma development and to exploit NER deficiencies in the therapeutic context.

The role of the pRB/E2F pathway in gene expression and cell cycle progression
(S. Gaubatz)

Our research focuses on transcriptional control of the cell cycle by E2F transcription factors and the retinoblastoma tumor suppressor protein (RB). These proteins play key roles in the regulation of cellular proliferation, differentiation and apoptosis and they have been implicated in tumorigenesis. We have recently identified a novel protein complex in human cells, called MuvB, that is related to similar complexes in invertebrates. MuvB, consists of the five proteins LIN9, LIN37, LIN52, LIN54 and RBBP4 and associates with the p130 retinoblastoma protein paralogue and with E2F4 to form DREAM, which represses cell cycle genes in quiescence and early G1. In contrast, during S phase of the cell cycle, the interaction of the MuvB core with p130/E2F4 is lost and MuvB now binds to the B-MYB oncogene to form the Myb-MuvB (MMB) complex. By carrying out genome wide studies by RNA-seq and ChIP-seq we found that MMB mediates the activation of a cluster of genes required for entry into mitosis, spindle assembly and cytokinesis. The functional importance of mitotic gene regulation by MMB is underlined by the observation that inactivation of MMB results in mitotic defects and G2/M arrest in vitro and in vivo. We have also demonstrated a requirement for MMB for tumorigenesis in a mouse model of lung cancer driven by oncogenic Ras and mutant p53. Disrupting the function of MMB may thus be a novel therapeutic strategy for the treatment of cancer. In our current work we are investigating the interplay between MMB and other cancer-related pathways such as the Hippo-YAP signalling pathway.
We are also interested in the function of novel target genes of DREAM such as GAS2L3, an actin and microtubule-interacting protein. In vivo, GAS2L3 plays a specific role in the heart. GAS2L3 deficient mice die shortly after birth because of heart failure. Mammalian cardiomyocytes lose the ability to proliferate shortly after birth, and further increase in cardiac mass is achieved by hypertrophy. The proliferation arrest of cardiomyocytes is accompanied by binucleation through incomplete cytokinesis. We observed that GAS2L3 deficiency leads to inhibition of cardiomyocyte proliferation and to cardiomyocyte hypertrophy during embryonic development. Furthermore, loss of GAS2L3 results in premature binucleation of cardiomyocytes accompanied by unresolved midbody structures. Together these results indicate a requirement for GAS2L3 in cardiomyocyte cytokinesis and proliferation during heart development.

SELECTED PUBLICATIONS

Appenzeller S, Gesierich A, Thiem A, Hufnagel A, Jessen C, Kneitz H, Regensburger M, Schmidt C, Zirkenbach V, Bischler T, Schilling B, Siedel C, Goebeler ME, Houben R, Schrama D, Gehrig A, Rost S, Maurus K, Bargou R, Rosenwald A, Schartl M, Goebeler M, Meierjohann S. (2019) Identification of patient-specific mutations reveals dual pathway activation in most melanoma patients and activated receptor tyrosine kinases in BRAF/NRAS wildtype melanomas. Cancer 125:586-600.

Iltzsche F, Simon K, Stopp S, Pattschull G, Francke S, Wolter P, Hauser S, Murphy DJ, Garcia P, Rosenwald A, Gaubatz S. (2017) An important role for Myb-MuvB and its target gene KIF23 in a mouse model of lung adenocarcinoma. Oncogene 36:110-121.

Kunz M, Löffler-Wirth H, Dannemann M, Willscher E, Doose G, Kelso J, Kottek T, Nickel B, Hopp L, Landsberg J, Hoffmann S, Tüting T, Zigrino P, Mauch C, Utikal J, Ziemer M, Schulze HJ, Hölzel M, Roesch A, Kneitz S, Meierjohann S, Bosserhoff A, Binder H, Schartl M. (2018) RNA-seq analysis identifies different transcriptomic types and developmental trajectories of primary melanomas. Oncogene 37:6136-6151.

Maurus K, Hufnagel A, Geiger F, Graf S, Berking C, Heinemann A, Paschen A, Kneitz S, Stigloher C, Geissinger E, Otto C, Bosserhoff A, Schartl M, Meierjohann S. (2017) The AP-1 transcription factor FOSL1 causes melanocyte reprogramming and transformation. Oncogene 36:5110-5121.

Stopp S, Gründl M, Fackler M, Malkmus J, Leone M, Naumann R, Frantz S, Wolf E, von Eyss B, Engel FB, Gaubatz S. (2017) Deletion of Gas2l3 in mice leads to specific defects in cardiomyocyte cytokinesis during development. Proc Natl Acad Sci USA: 114:8029-8034.

Biocenter Würzburg, Chair of Biochemistry and Molecular Biology

CONTACT DETAILS

Professor Dr. phil. Martin Eilers (Head)

Biozentrum
Am Hubland
97074 Würzburg
Phone: 0931/318-4111
Fax: 0931/318-4113
E-mail: martin.eilers@biozentrum.uni-wuerzburg.de
www.pch2.biozentrum.uni-wuerzburg.de

Professor Dr. rer. nat. Almut Schulze
Phone: 0931/318-3290

Mission and Structure

The department of Biochemistry and Molecular Biology (BMB) is part of the Biocenter founded in 1990, in which 10 institutions from the faculties of Biology, Chemistry and Medicine co-operate in teaching and research. The department for BMB teaches biochemistry for preclinical students in Medicine and Dentistry and coordinates the focus „Molecular Oncology“ within the MSc programm Biochemistry.

Beside the established groups of Professor Martin Eilers, Professor Peter Gallant and Professor Ernst Conzelmann, Professor Almut Schulze was recruited as a Professor in the “Leuchtturmprogramm” since the last report. Furthermore, two new junior groups could be established in addition to the junior group of Dr. Armin Wiegering – Dr. Markus E. Diefenbacher was recruited from Francis Crick London Research Institute and Dr. Elmar Wolf raised funds for the establishment of an Emmy-Noether research group from the DFG.

The research is focused on the molecular mechanisms during tumorigenesis. The major research aim of BMB is to understand the function of the Myc family of nuclear oncoproteins, which contribute to the majority of all human cancers. A second research aim is to use mouse models and functional genomic tools to identify novel strategies for the therapy of human cancers.

Major Research Interests

Function and Regulation of the Human Myc Proto-oncogene
(M. Eilers)

The *MYC* family of proto-oncogenes participates in the genesis of the majority of all human tumors. The three genes of this family encode transcription factors that are central regulators of cell growth and cell proliferation. They exert this control at least in part by binding to specific DNA sequences and affecting the transcription of multiple genes involved in protein synthesis, metabolism and cell proliferation. Many central questions about the basic function of Myc and the regulation of its multiple activities remain unanswered.
The aim of our research is to unravel how Myc functions and to devise strategies to use this knowledge for the treatment of human disease.

Metabolic Reprogramming in Cancer
(A. Schulze)

Metabolic reprogramming in cancer supports macromolecule biosynthesis and is a prerequisite for rapid growth and proliferation. It also enables cancer cells to survive conditions of limited nutrient and oxygen supply that are characteristic for the tumour microenvironment. The aim of our research is to uncover the mechanisms by which oncogenes drive metabolic reprogramming in cancer and how different metabolic processes contribute to cancer growth. We also aim to identify selective metabolic sensitivities in cancer cells that can be used for novel strategies for cancer therapy.

Control of Growth in Drosophila
(P. Gallant)

We are exploiting the fruit fly *Drosophila melanogaster* as a model system to investigate the molecular mechanisms governing cellular and organismal growth. On one hand we are characterizing the mechanism of action of the proto-oncogene and transcription factor Myc (defining Myc activated genes as well as the molecular mechanism of their activation), on the other hand we are identifying novel systemic growth signals.

Stem cells, protein stabilty, and cancer
(M. E. Diefenbacher)

Apart from mutations occurring in proto-oncogenes, deregulated protein stability is a common observation in human malignancies. Sequencing data available from cancer patients have shown that the ubiquitin machinery is frequently mutated or inactivated in lung and colorectal tumours. This includes the ubiquitin-ligase *KEAP1, CUL3, FBXW7* and *APC*.
By utilising murine intestinal organoid cultures or primary lung cancer cell lines, we aim to dissect the importance of the ubiquitin system and identify novel therapeutic avenues. Deregulating/suppressing deubiquitining enzymes (e.g. Usp28) has been demonstrated to be beneficial in the murine colorectal cancer model upon loss of the E3-ligase Fbxw7 by counteracting increased protein levels for potent oncogenes.

Colorectal Cancer
(A. Wiegering)

Colorectal cancer is the most common cancer of the gastrointestinal tract and accounts

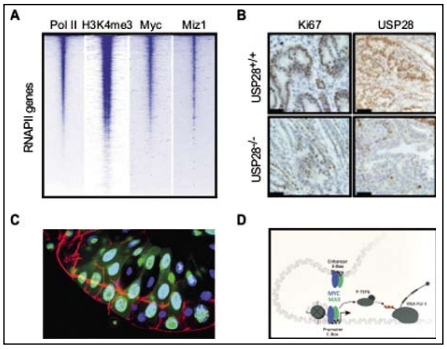


Fig.: MYC proteins are central regulators in the development and maintenance of normal tissue and in the process of tumorigenesis (A) Heatmap showing binding to all genes based on global analyses (ChIP-sequencing). Our experiments demonstrate, that MYC and the MYC interacting protein MIZ1 are global transcription factors, whose binding pattern cannot be discriminated from RNA polymerase (RNAPII) or marks of open chromatin (H3K4me3). Modified from Walz et al, Nature, 2014. (B) Histology of mouse colorectal cancer. USP28 could be identified as a protein, which regulates MYC stability. Here we show, that the gene knockout of USP28 (USP28-/-) strongly compromises the development of highly proliferative intestinal tumors (Ki67). Modified from Diefenbacher et al, Cancer Research, 2015. (C) Immunofluorescence of fly larvae. Cells which express increased amounts of the MYC protein (labeled in green) show enlarged cell nuclei, demonstrating elevated DNA sysnthesis rates (replication). Blue: Cell nuclei, red: Cell borders. (D) Model showing MYCs molecular mode of action. MYC is a transcription factor that binds to promoter and enhancer regions and changes the gene expression pattern of its target genes. Modified from Wolf et al, Trends Cell Biol, 2015.

for 80.000 new cases per year in Germany. Growth and metastasis is MYC dependent. We are working on new ways to reduce oncogene MYC level in CRC. For this we have deciphered to ways: A) An inhibition of protein translation specific helicases leads to a MYC reduction and growth arrest in CRC but not in normal mucosa. By using an shRNA screen we are searching for proteins that are only essential for growth of APC mutated tumors but not for the growth of normal tissue.

Targeting the oncogenic function of Myc for tumour therapy.
(E. Wolf)

The transcription factor Myc plays a central role in the development of human tumours but is also an essential protein. Proof-of-principle studies using a dominant negative allele of Myc in mice have demonstrated the dependency of established tumours on Myc function. One goal of our research is to develop strategies to target Myc function for cancer therapy. We have already discovered that promoters differ in their affinity for Myc and that these differences enable Myc to regulate functionally distinct genes at different nuclear concentrations (Lorenzin et al, eLife, 2016). The new notion that Myc regulates distinct sets of genes at physiological and oncogenic levels opens the compelling possibility to specifically target the oncogenic functions of Myc. We are exploring this concept in vivo and will identify and target crucial Myc target genes.

Teaching

The chair of Biochemistry and Molecular Biology in conjunction with the Chair of Physiological Chemistry and with the Chair of Developmental Biochemistry teaches Biochemistry and Molecular Biology to the more than 400 students of Medicine and Dentistry per year. He coordinates the focus „Molecular Oncology“ within the MSc program Biochemistry.

SELECTED PUBLICATIONS

Baluapuri A, Hofstetter J, Dudvarski Stankovic N, Endres T, Bhandare P, Vos SM, Adhikari B, Schwarz JD, Narain A, Vogt M, Wang SY, Düster R, Jung LA, Vanselow JT, Wiegering A, Geyer M, Maric HM, Gallant P, Walz S, Schlosser A, Cramer P, Eilers M, Wolf E. (2019) MYC Recruits SPT5 to RNA Polymerase II to Promote Processive Transcription Elongation. Mol Cell doi: 10.1016/j.molcel.2019.02.031. [Epub ahead of print]

Büchel G, Carstensen A, Mak KY, Roeschert I, Leen E, Sumara O, Hofstetter J, Herold S, Kalb J, Baluapuri A, Poon E, Kwok C, Chesler L, Maric HM, Rickman DS, Wolf E, Bayliss R, Walz S, Eilers M. (2017) Association with Aurora-A controls N-MYC-dependent promoter escape and pause release of RNA polymerase II during cell cycle. Cell Rep 21:3483-3497.

Dejure FR, Royla N, Herold S, Kalb J, Walz S, Ade CP, Mastrobuoni G, Vanselow J, Schlosser A, Wolf E, Kempa S, Eilers M. (2017) The 3'-UTR of MYC couples RNA polymerase II function to ribonucleotide levels. EMBO J 36:1854-1868.

Gerlach JM, Furrer M, Gallant M, Birkel D, Baluapuri A, Wolf E, Gallant P. (2017) PAF1 complex component Leo1 helps recruit Drosophila Myc to promoters. Proc Natl Acad Sci U S A 114:E9224-E9232.

Herold S, Kalb J, Büchel G, Ade CP, Baluapuri A, Xu J, Koster J, Solvie D, Carstensen A, Klotz C, Rodewald S, Schülein-Völk C, Dobbelstein M, Wolf E, Molenaar J, Versteeg R, Walz S, Eilers M. (2019) Recruitment of BRCA1 limits MYCN-driven accumulation of stalled RNA polymerase. Nature 567:545-549.

Biocenter Würzburg, Chair of Developmental Biochemistry

CONTACT DETAILS

Professor Dr. med. Manfred Gessler (Head)

Theodor-Boveri-Institut
Am Hubland
97074 Würzburg
Phone: 0931/31-84159
Fax: 0931/31-87038
E-mail: gessler@biozentrum.uni-wuerzburg.de
www.ebch.biozentrum.uni-wuerzburg.de

Mission and Structure

The research interests of the Chair of Developmental Biochemistry range from the elucidation of the molecular control of developmental and differentiation processes to diseases caused by the misregulation of these mechanisms. Special attention is paid to pediatric kidney tumors, such as nephroblastomas (Wilms tumors), clear cell sarcomas, or mesoblastic nephromas, which are investigated using high-throughput methods. Tumor-typical gene alterations are functionally characterized and examined for their role during normal development of the kidneys and their corresponding malfunction. We also focus on the development of the cardiovascular system during embryogenesis.
The chair is involved in the education of Medical and Dentistry students, Biologists, Biochemists and especially in the study programs Biomedicine and Translational Medicine.

Major Research Interests

Pediatric kidney tumors / Wilms tumors

Wilms tumors (nephroblastomas) are early childhood kidney cancers that originate from a failure of embryonic precursor cells to fully differentiate. Within the framework of the German Wilms tumor study, we have established a biobank that now comprises more than 1500 tumors with control tissues. These are routinely examined for chromosomal changes and mutations in known tumor genes such as WT1, CTNNB1, DROSHA, DGCR8 or SIX1/2 and used to identify further biomarkers and target structures in order to improve diagnosis and therapy. This work is part of an international network, for which the chair has a coordinating function (Vujanic et al., 2018).
A major obstacle to in vitro investigations into the biology of Wilms tumors has so far been the lack of appropriate cell culture systems. We have established and functionally characterized a number of primary cultures of these tumors. The individual cultures represent important aspects of the tumors, namely the stroma and epithelial components, whereas blastema cannot be detected under these conditions. By expression of telomerase, primary cultures could be immortalized and established as permanent, stable lines. In the meantime, propagation of blastemal cells in so-called spheroid cultures has also been successful (Fig. 1). For the first time, functional in vitro studies are now possible on standardized cells that represent all components of typical Wilms tumors and these can be genetically manipulated.
In cooperation with the Heidelberg Initiative for Personalised Oncology (hipo), we were able to identify a number of completely new candidate genes for the high-risk group of Wilms tumors that are currently under investigation. The impairment of the processing of miRNAs by the DROSHA/DGCR8 microprocessor complex and the deregulation of a network of growth genes consisting of SIX1/2, MYCN, LIN28B and others appear to act as new triggers for these tumors. By further bioinformatic network analyses in cooperation with the Center for Bioinformatics of Saarland University, new candidates for the orchestration of the oncogenic phenotype could be defined.
The targeted analysis of TP53 changes showed that these, together with anaplasia, represent an important risk factor for relapses and reduced chances of survival (Wegert et al., 2017).

Functional analysis of Wilms tumor genes

We have established cell culture and mouse models for some of the genetic alterations in Wilms' tumors, in which the function of the defective alleles can be studied in vivo. It was shown that DROSHA changes due to lack of miRNA processing can lead to dramatic disturbances of kidney development up to renal failure, whereas DGCR8 mutations are more selective for groups of miRNA species. (Fig. 2) (Kruber et al, 2018).

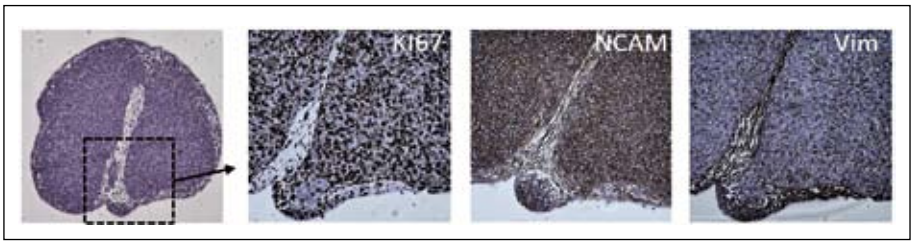


Fig. 1: Wilms' tumor spheroid culture. Histological sections show proliferation (KI67) and expression of differentiation markers (NCAM, vimentin).

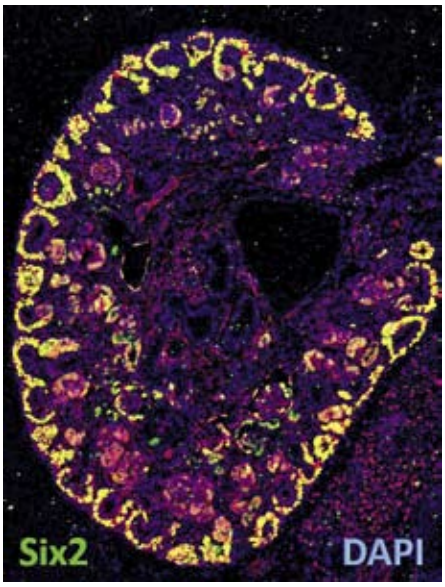


Fig. 2: Expression of the differentiation marker Six2 in the proliferation zone of a mutant embryonic kidney with counterstaining of all cell nuclei using DAPI.

CCSK and CMN

For another pediatric kidney tumor, the clear cell sarcoma of the kidney (CCSK), we were able to show that about 85% of these tumors have small duplications within the BCOR gene, the functional effect of which we are currently analyzing using various in vitro methods. The remaining cases could define diagnostically and therapeutically relevant subgroups in the future.
In the similarly rare congenital mesoblastic nephroma (CMN), only an ETV6-NTRK3 translocation was known as trigger, which characterizes the cellular subtype. In cooperation with the group of Sam Behjati at the Sanger Center in Cambridge, we identified an internal duplication of the EGFR tyrosine kinase domain as a typical change in classical and mixed CMN. Rarely, changes in the BRAF gene were also present. Thus, CCSK and CMN can be functionally explained as relatively homogeneous, genetically defined tumor entities and in the case of CMN there are direct therapeutic targets which are already being used successfully.

Regulation of Angiogenesis

Endothelial cells line the inside of blood vessels, regulate the exchange of substances between blood and surrounding tissues and communicate with various other cell types. Depending on the organ system and vascular calibre, these tasks can be very different. Using a genetic trick, we were able to isolate and sequence mRNAs from embryonic tissues that were actively translated into proteins. This resulted in tissue-specific patterns of gene activity that reflect the different functions of the respective organs. By sequencing the RNA repertoire of single sorted endothelial cells this could be further refined. This resulted in a first compendium of the temporally and spatially controlled gene activity in endothelial cells in the course of embryonic angiogenesis, which can be refined in the future and represents an important basis for functional analyses (Hupe et al., 2017).

Teaching

Together with the Chairs of Physiological Chemistry and Biochemistry and Molecular Biology we offer a wide range of lectures, seminars and courses. This includes above all the theoretical and practical training of more than 400 students of human and dental medicine in biochemistry and molecular biology every year. In addition, students of the B.Sc./M.Sc. Biomedicine program are taught a series of courses in biochemistry, molecular biology and developmental biology. Modules with biochemical, developmental and tumor biological focus are offered for biology students and biochemistry students. Furthermore, the chair is involved in the education of PhD students within the Graduate School of Life Sciences (GSLS).
In 2018, the chair, together with the Chair of Clinical Epidemiology and Biometry, received funding for the degree course Translational Medicine (additional studies and M.Sc.) within the framework of the Bavarian Elite Network. In addition to individual teaching modules, we are also responsible for the organization and coordination of the course offerings.

SELECTED PUBLICATIONS

Hupe, M, Li MX, Kneitz S, Davydova D, Yokota C, Kele-Olovsson J, Hot B, Stenman JM, Gessler M. (2017) Gene expression profiles of brain endothelial cells during embryonic development at bulk and single-cell levels. Sci Signal 10:pii:eaag2476.

Kruber P, Angay O, Winkler A, Bosl MR, Kneitz S, Heinze KG, Gessler M. (2018) Loss or oncogenic mutation of DROSHA impairs kidney development and function, but is not sufficient for Wilms tumor formation. Int J Cancer 144:1391-1400.

Vujanic GM, Gessler M, Ooms A, Collini P, Coulomb-l'Hermine A, D'Hooghe E, de Krijger RR, Perotti D, Pritchard-Jones K, Vokuhl C, van den Heuvel-Eibrink MM, Graf N, International Society of Paediatric Oncology-Renal Tumour Study Group. (2018) The UMBRELLA SIOP-RTSG 2016 Wilms tumour pathology and molecular biology protocol Nat Rev Urol 15:693–701.

Wegert J, Vokuhl C, Collord G, Del Castillo Velasco-Herrera M, Farndon SJ, Guzzo C, Jorgensen M, Anderson J, Slater O, Duncan C, Bausenwein S, Streitenberger H, Ziegler B, Furtwangler R, Graf N, Stratton MR, Campbell PJ, Jones DT, Koelsche C, Pfister SM, Mifsud W, Sebire N, Sparber-Sauer M, Koscielniak E, Rosenwald A, Gessler M, Behjati S. (2018) Recurrent intragenic rearrangements of EGFR and BRAF in soft tissue tumors of infants. Nat Commun 9:2378.

Wegert J, Vokuhl C, Ziegler B, Ernestus K, Leuschner I, Furtwangler R, Graf N, Gessler M. (2017) TP53 alterations in Wilms tumour represent progression events with strong intratumour heterogeneity that are closely linked but not limited to anaplasia. J Pathol Clin Res 3:234-248.

Institute for Hygiene and Microbiology, Chair of Hygiene and Microbiology

CONTACT DETAILS

Professor Dr. med. Matthias Frosch (Head)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-46160
Fax: 0931/31-46445
E-mail: secretary@hygiene.uni-wuerzburg.de
www.hygiene.uni-wuerzburg.de
www.meningococcus.de
www.haemophilus.uni-wuerzburg.de
www.echinococcus.de

Professor Dr. rer. nat. Klaus Brehm
Phone: 0931/31-46168

Professor Dr. med. Alexandra Schubert-Unkmeir
Phone: 0931/31-46721

Professor Dr. med. Ulrich Vogel
Phone: 0931/31-46802

Mission and Structure

The activities of the Institute for Hygiene and Microbiology comprise the laboratory diagnosis of infectious diseases caused by bacteria, fungi and parasites, advising clinicians with respect to diagnosis, therapy and prevention of infectious diseases, the research into infectious diseases and their causative agents, hospital hygiene and infection control as well the education of students in medicine, dentistry and related subjects.
In addition to the comprehensive range of diagnostic tools routinely employed the Institute also provides special molecular and serological test systems. Our commitment to patient care also includes the development of strategies toward the prevention of hospital infections and the monitoring of hospital hygiene. The Institute performs approximately 90, 000 microbiological analyses annually. The research activities of the Institute mainly focus on the elucidation of molecular mechanisms in the pathogenesis of infectious diseases. Using tools from molecular genetics, cell biology, immunology and genome research, we investigate the pathogenicity of bacteria and parasites and develop novel strategies toward the diagnosis, therapy, and prevention of infectious diseases. The Institute also hosts the infection control unit of the University Hospital.
The Robert-Koch-Institute established the National Reference Center for Meningococci and *Haemophilus influenzae* (NRZMHi) at the Institute. The activities of the NRZMHi include the molecular characterization of pathogens, an advisory service in case management and the counselling of public health departments in the epidemiological monitoring of outbreaks of meningococci diseases. The Institute is a member of the pan-European network of reference centers, the European Meningococcal and Haemophilus Disease Society (EMGM). In cooperation with the European Center for Disease Prevention and Control (ECDC) the "Laboratory surveillance and external quality assurance of invasive bacterial diseases in in EU" (IBD-labnet) project is coordinated by the Institute for Hygiene and Microbiology which focuses on the establishment of a European laboratory network for the surveillance of invasive infections caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* und *Haemophilus influenzae*. Moreover, on behalf of the Robert-Koch-Institute, the Institute also functions as consiliary laboratory for echinococcosis, employing special diagnostic tests and providing advice on diagnosis, therapy, prevention, and epidemiology.

Major Research Interests

Infection biology of meningococcal disease

(A. Schubert-Unkmeir)

Meningococci, an important cause of septicaemia and meningitis in infants and adolescents, are in the focus of research on infection biology. The molecular basis of transmission across specialized endothelial cells underlining the blood-brain barrier is a major point of interest in our research. The group works on analysing of bacterial factors as well as host cell receptors that determine the interaction, and the characterization of major signalling pathways resulting in cytoskeletal remodelling and bacterial engulfment.

Meningococcal host interaction during colonisation and sepsis

(K. Johswich)

Although it is the causative agent of severe sepsis and meningitis, meningococci are a common component of the human nasopharyngeal flora. Using a novel humanized mouse model, we characterise the factors that allow for *N. meningitidis* colonization of the nasopharyngeal mucosa. Of particular interest is whether and how the complement system affects mucosal colonisation, as the complement system is pivotal during invasive meningococcal disease. During sepsis, the complement system is strongly activated in blood, liberating highly potent inflammatory mediators C3a and C5a. Since these so-called anaphylatoxins may aggravate systemic hyper-inflammation, we analyse their contribution to the pathophysiology of meningococcal sepsis using an experimental sepsis model.

Genome research on pathogenic bacteria

(C. Schoen, M. Frosch)

The still unfolding revolution in DNA sequencing and DNA sequence-based technologies has already transformed the fields of basic and diagnostic medical microbiology. Work in our group therefore focuses on the application of molecular technologies to improve the diagnosis of infectious diseases and to better understand how microorganisms, and in particular commensal bacteria, can sometimes cause invasive diseases in humans. *Neisseria meningitidis* is a prime example that colonizes the nasopharynx of up to 30% of the healthy human population. Whereas most isolates from healthy carriers are considered non-pathogenic, a small number of strains belonging to hyperinvasive lineages can cause invasive meningococcal disease such as

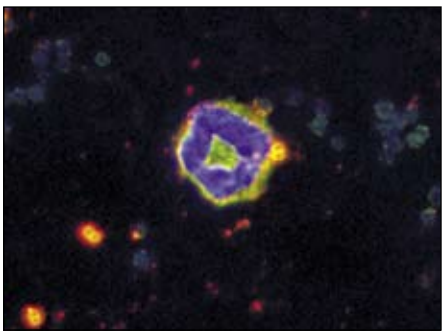


Fig. 1: N. meningitidis associated with neutrophil granulcyte in whole blood. Bacteria are stained in red, neutrophil surface stained in green and DNA in blue.

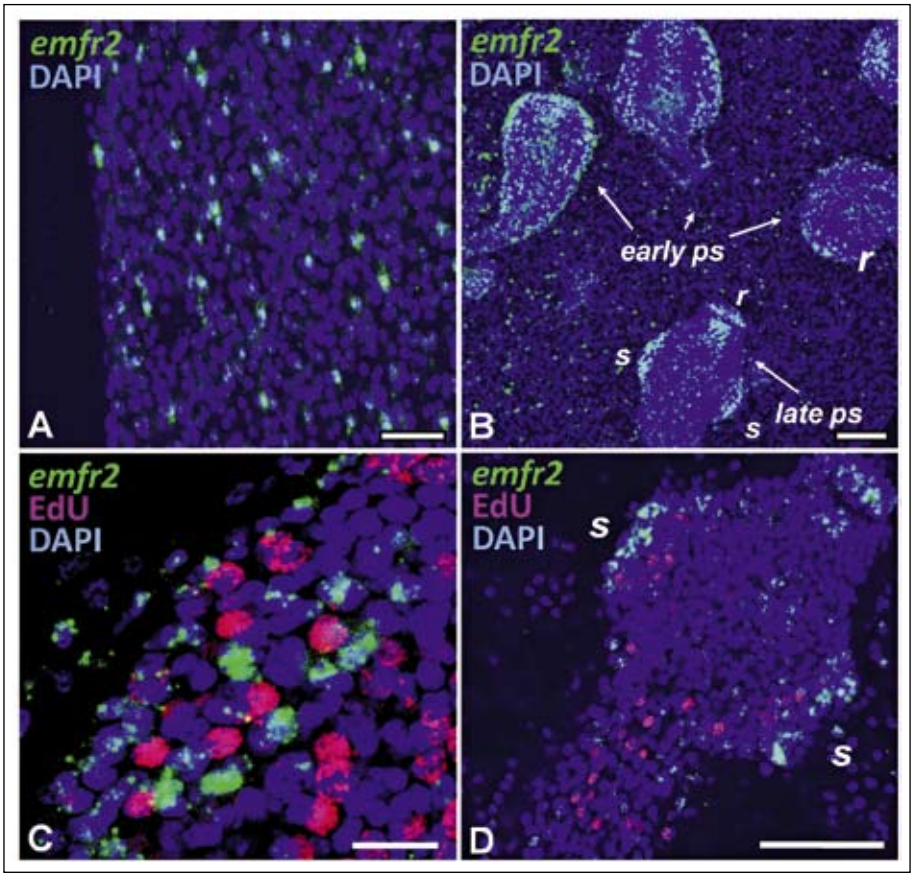


Fig. 2: The Echinococcus multilocularis Fibroblast Growth Factor receptor EmFR2 is expressed in muscle cells of the metacestode and protoscolex stages. Whole mount in situ hybridization for the expression of emfr2 (green) in metacestode tissue (A), during protoscolex developemt (B), and in mature protoscoleces (C,D). Pink staining (EdU incorporation) marks parasite stem cells during proliferation. Note emfr2 expression in sucker muscle cells but not in parasite stem cells.

acute bacterial meningitis or sepsis. Genomic comparison of hyperinvasive and apathogenic lineages did so far not reveal unambiguous hints towards indispensable virulence factors. Our group thus employs a variety of molecular biological and genomic techniques, including comparative whole-genome sequencing, microarrays and RNA-sequencing to search for the genetic basis of meningococcal virulence with a particular emphasis on the role of small non-coding RNAs and RNA chaperones.

Infection epidemiology of invasive and nosocomial pathogens
(U. Vogel, H. Claus)

The molecular epidemiology of *N. meningitidis* and *Haemophilus influenzae* is analysed by bacterial finetyping. Representative strain collections continuously assembled at the National Reference Laboratory are used. Laboratory surveillance also comprises the monitoring of resistance to antibiotics. Furthermore, the group analyses the epidemiology of nosocomial pathogens in the frame of its hospital infection control activities.

Fox-tapeworm and alveolar echinococcosis
(K. Brehm)

Alveolar echinococcosis, caused by the cancer-like growth of the metacestode larva of the fox-tapeworm *Echinococcus multilocularis*, is a life-threatening human parasitosis that leads to liver tissue destruction and metastasis formation in secondary organs. We have recently characterized the whole genome sequence of this parasite and thus gained valuable information on novel drug targets and molecules that govern host-parasite interaction. These studies are currently complemented by extensive transcriptomic and proteomic analyses on in vitro cultivation systems for parasite larvae and stem cells that we have developed. We demonstrated that hormonal host-parasite cross communication via evolutionarily conserved signalling systems occurs during alveolar echinococcosis and that totipotent somatic stem cells play a central role in host-induced parasite development. Current analyses concentrate on the integration of host-controlled parasite signalling systems into stem cell signalling and differentiation, as well as on excretory/secretory products of parasite larvae as immune-modulators that ensure the long-term persistence of *Echinococcus* in the host.

Teaching

Student courses are organised for students of medicine, dentistry, biomedicine, pharmacy, and food chemistry. Scientists at the institutes participated in the organization of several scientific and medical meetings.

SELECTED PUBLICATIONS

Burgert A, Schlegel J, Bécam J, Doose S, Bieberich E, Schubert-Unkmeir A, Sauer M. (2017) Characterization of Plasma Membrane Ceramides by Super-Resolution Microscopy. Angew Chem Int Ed Engl 56:6131-6135.

Förster S, Koziol U, Schäfer T, Duvoisin R, Cailliau K, Vanderstraete M, Dissous C, Brehm K. (2019) The role of fibroblast growth factor signalling in Echinococcus multilocularis development and host-parasite interaction. PLoS Negl Trop Dis, in press.

Heidrich N, Hagmann A, Bauriedl S, Vogel J, Schoen C. (2018) The CRISPR/Cas system in N. meningitidis affects bacterial adhesion to human nasopharyngeal epithelial cells. RNA Biol 30:1-7.

Herrmann JB, Muenstermann M, Strobel L, Schubert-Unkmeir A, Woodruff TM, Gray-Owen SD, Klos A, Johswich KO. (2018) Complement C5a receptor 1 exacerbates the pathophysiology of Neisseria meningitidis sepsis and is a potential target for disease treatment. mBio 9:e01755-17.

Moremi N, Claus H, Rutta L, Frosch M, Vogel U, Mshana SE. (2018) High carriage rate of extended-spectrum beta-lactamase-producing Enterobacteriaceae among patients admitted for surgery in Tanzanian hospitals with a low rate of endogenous surgical site infections. J Hosp Infect 100:47-53.

Institute for Hygiene and Microbiology, Chair of Medical Microbiology and Mycology

CONTACT DETAILS

Professor Dr. med. Oliver Kurzai
(Head)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-88007
Fax: 0931/31-46445
E-mail: sekretariat-kurzai@hygiene.uni-wuerzburg.de
www.hygiene.uni-wuerzburg.de
www.septomics.de
www.leibniz-hki.de.de
www.nrz-myk.de.de

Mission and Structure

The Chair for Medical Microbiology and Mycology jointly with the Chair for Hygiene and Microbiology is responsible for the laboratory diagnostics of infectious diseases caused by bacteria, fungi and parasites. Based on our lab results we are engaged in consultation of treating physicians for diagnosis, treatment and prevention of infectious diseases. Prof. Oliver Kurzai is head of the German National Reference Center for invasive fungal infections (NRZMyk) appointed by the federal Ministry for Health and the Robert Koch-Institute. The NRZMyk is located at the Leibniz Institute for Natural Product Research and Infection Biology – Hans-Knoell-Institute in Jena and is the major point of contact in Germany for all questions regarding diagnostics and clinical management of invasive fungal infections. In addition, the NRZMyk participates in clinical and epidemiological studies, the evaluation of new diagnostic tools and the establishment of guidelines for diagnosis and treatment of fungal infections.

Invasive fungal infections are also the focus of our research. These life-threatening infections mainly occur in hospitalized patients suffering from impaired immunity. With increasing numbers of at-risk patients, the frequency of invasive fungal infections has steadily been on the rise. Yeasts of the genus *Candida* are the most frequent pathogens causing invasive fungal infections in Germany, followed by moulds in the genus *Aspergillus*. In addition, a large number of rare and extremely rare fungal species can cause human infection. Pathogens within the Mucorales as well as *Fusarium* spp. are most difficult to manage because of a plethora of resistance phenotypes against common antifungal drugs. Invasive fungal infections are related to disturbances in host immunity, which can also be caused by genetic variants that result in impaired responses. Research on protective immunity and genetic risk factors at the Chair for Medical Microbiology and Mycology is integrated into leading national consortia. Funded by the Federal Ministry for Education and Science, the research consortium InfectControl 2020 (scientific administrator: Prof. O. Kurzai) aims to develop interdisciplinary approaches to combatting infectious diseases. Within the collaborative research center / Transregio FungiNet (TR124) funded by the German Research Foundation (DFG) we uses systems biology based approaches to analyse pathogen-host interaction in invasive fungal infection

Major Research Interests

Virulence Determinants of *Candida* spp.
(O. Kurzai)

Yeast Fungi of the genus Candida, mainly *Candida albicans* and *Candida glabrata* are the most frequent pathogens causing invasive fungal infections in Germany. *C. albicans* can respond to changing environmental conditions by a morphological switch between yeast and filamentous growth. This morphological plasticity is a major virulence factor. In our work, we analyse genetic regulation of the yeast-to-filament transition in *C. albicans*. In contrast to *C. albicans, C. glabrata* is a monomorphic yeast unable to form filaments. Consequently virulence traits of both species are largely different. By performing comparative analyses in diverse infection models, the differing virulence determinants of both species are characterised.

Immune Response in Invasive Fungal Infection
(O. Kurzai)

Manifestation of invasive fungal infections is in most cases based on underlying defects in the host immune response. To address the role of different immune effector mechanisms in the antifungal response we use infection models for primary human immune cells as well as a human whole blood infection model. In combination with biomathematical modelling, we can characterize protective immune activation during invasive fungal infection. However, the clinical course of infection is also determined by genetic variants in the host genome. We aim to characterise genetic variants that are associated with invasive fungal infection and establish models for the functional implications of these genetic variations.

Virulence and Antifungal Drug Resistance in *Aspergillus fumigatus*
(J. Wagener)

Currently, the number of antifungal drugs available fot he treatment of invasive fun-

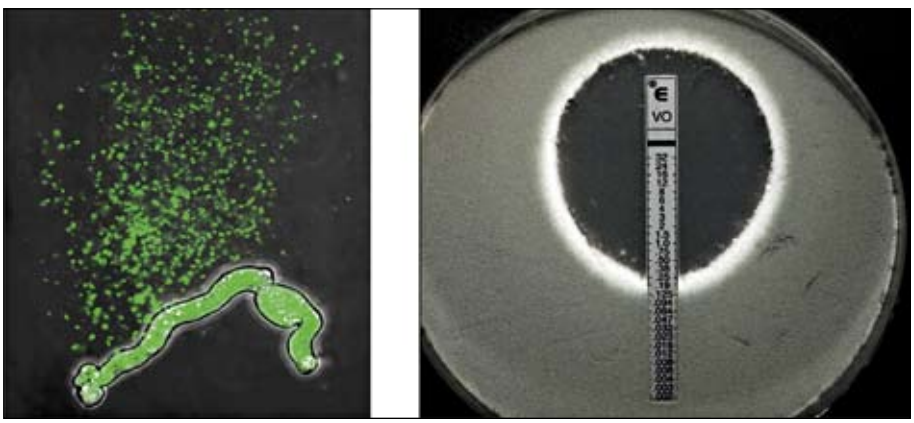


Fig. 1: Azoles act fungicidal on the pathogenic mould Aspergillus fumigatus. (left) hyphae of A. fumigatus after azol-exposure. Fungal mitochondria are stained green. Contact with the antifungal drug triggers loss of cellular integrity, bursting hyphae and release of intracellular content. (right) Susceptibility testing of A. fumigatus against voriconazol.

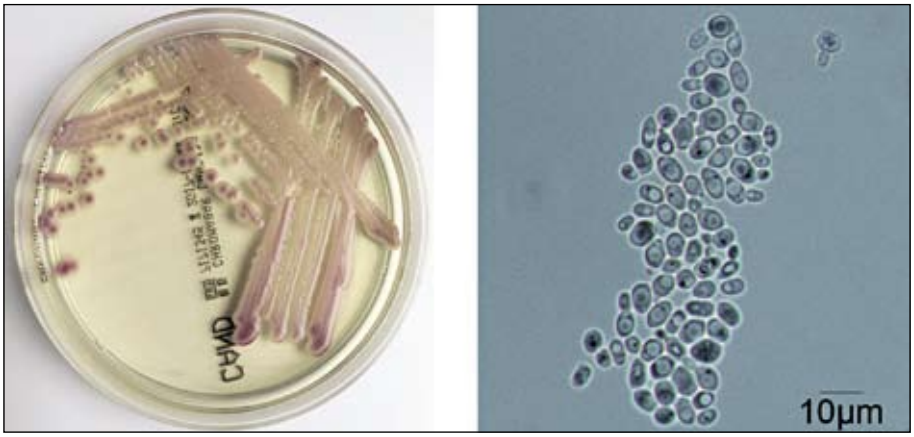


Fig. 2: The species Candida auris (left: agar-culture, right: microscopy) was initially described in 2009. Since then, it has spread worldwide. In contrast to other Candida spp. it can readily spread from human to human, leading to hospital outbreaks. First cases of C. auris infections in Germany have been confirmed and analyzed at the NRZMyk.

gal infections is limited. Furthermore, emergence of antifungal drug resistance further impairs choices for antifungal therapy. We aim to achieve a molecular understanding of the mode of action of antifungal drugs. For this, we analyse the exact mechanisms that result in growth inhibition or fungal cell death. These mechanisms can differ dependent on the fungal organism. Azole antifungals, for example, excert fungistatic activity against *Candida*, but are fungicidal for *Aspergillus*. Vice versa, echinocandins are fungicidal for *Candida* but only fungistatic for *Aspergillus*. By analysing these different action principles as well as the interplay between fungal pathogens, antifungal drugs and human immunity, we aim to identify new targets to improve antifungal therapy.

National Reference Center for Invasive Fungal Infections NRZMyk
(O. Kurzai)

The NRZMyk is a central point of contact in Germany for all questions related to diagnosis and clinical management of invasive fungal infections. In the past years, diagnostic activities (currently >600 samples per year) as well as availability for consiliary advice could be further extended. One major focus is the determination of genus and species for rare and unknown fungal pathogens isolated from clinical samples. In addition, the NRZMyk has developed a broad range of molecular tests for detection of fungal pathogens in clinical samples. We participate in clinical and epidemiological studies addressing the diagnosis of invasive fungal infections in intensive care units or the worldwide emergence of the new pathogenic species *Candida auris*. In cooperation with the Department of Ohthalmology at the University Hospital in Düsseldorf the NRZMyk has established a National Registry for Fungal Keratitis. Besides these projects, the NRZMyk participates in national and international standardization committees like the Antifungal Susceptibility Testing Subcommittee of the EUCAST and the National Antibiotic-Susceptibility Testing Committee (NAK).

New diagnostic Tools to detect Invasive Fungal Infections
(J. Wagener, O. Kurzai)

Successful treatment of invasive fungal infection is mainly based on early and reliable diagnosis. Thus we aim to improve diagnostic tools for early detection. Currently we rely on a limited portfolio of tests, mainly including mycological culture, molecular detection and antigen detection in blood. In severely ill patients with a high risk for fungal infection (e.g. patients after allogeneic stem cell transplantation) these tests are the major microbiological tools. Together with partners from diagnostics companies we aim to improve these tests and evaluate new test systems for early detection of fungal infection and testing for antifungal drug resistance.

Teaching

Student's courses are organised for students of medicine, dentistry, experimental and translational medicine, pharmacy and food chemistry. Scientists at the institutes participated in the organization of several scientific and medical meetings.

SELECTED PUBLICATIONS

Barber AE, Weber M, Kaerger K, Linde J, Gölz H, Duerschmied D, Markert A, Guthke R, Walther G, Kurzai O. (2019) Comparative genomics of serial Candida glabrata isolates and the rapid acquisition of echinocandin resistance during therapy. Antimicrob Agents Chemother 63. pii:e01628-18.

Cunha C, Gonçalves SM, Duarte-Oliveira C, Leite L, Lagrou K, Marques A, Lupiañez CB, Mesquita I, Gaifem J, Barbosa AM, Pinho Vaz C, Branca R, Campilho F,Freitas F, Ligeiro D, Lass-Flörl C, Löffler J, Jurado M, Saraiva M, Kurzai O, Rodrigues F, Castro AG, Silvestre R, Sainz J, Maertens JA, Torrado E, Jacobsen ID, Lacerda JF, Campos A Jr, Carvalho A. (2017) IL-10 overexpression predisposes to invasive aspergillosis by suppressing antifungal immunity. J Allergy Clin Immunol 140:867-870.

Dichtl K, Seybold U, Wagener J. (2018) Evaluation of a Turbidimetric β-d-Glucan Test for Detection of Pneumocystis jirovecii Pneumonia. J Clin Microbiol 56. pii:e00286-18.

Geißel B, Loiko V, Klugherz I, Zhu Z, Wagener N, Kurzai O, van den Hondel CAMJJ, Wagener J. (2018) Azole-induced cell wall carbohydrate patches kill Aspergillus fumigatus. Nat Commun 9:3098.

Pohlers S, Martin R, Krüger T, Hellwig D, Hänel F, Kniemeyer O, Saluz HP, Van Dijck P, Ernst JF, Brakhage A, Mühlschlegel FA, Kurzai O. (2017) Lipid Signaling via Pkh1/2 Regulates Fungal CO_2 Sensing through the Kinase Sch9. MBio 8. pii: e02211-16.

Institute of Molecular Infection Biology, Chair of Molecular Infection Biology I

CONTACT DETAILS

Professor Dr. rer. nat. Jörg Vogel (Head)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-82575
Fax: 0931/31-82578
E-mail: joerg.vogel@uni-wuerzburg.de
www.imib-wuerzburg.de

Professor Dr. rer. nat. Dr. med. habil. Heidrun Moll
Phone: 0931/31-82627

Professor Dr. rer. nat. Joachim Morschhäuser
Phone: 0931/31-82152

Mission and Structure

The Institute of Molecular Infection Biology (IMIB) is an interdisciplinary institution within the Medical Faculty of the University of Würzburg and part of the Research Center for Infectious Diseases (ZINF). It also accommodates the young investigator groups of the ZINF. Research at the institute focuses on elucidating fundamental principles of infection processes. Its members study the molecular aspects of infections caused by a variety of bacteria, parasites and fungi, to identify common strategies employed by these pathogens to interact with host cells, the microbiota and the immune system. While the majority of projects at the institute focus on basic research, several important clinically related projects are performed in collaboration with the University Hospital, ZINF and Interdisciplinary Center for Clinical Research (IZKF).

Major Research Interests

The main research interests at the institute relate to understanding the biology of the pathogens and their interaction with host cells, the microbiota and the immune response. This is primarily achieved by using molecular and cell biological methods, global high-throughput approaches, including genomics, transcriptomics, proteomics, and complimented by structural biology and advanced infectious disease models to understand the infection process from a new global perspective.

RNA biology of bacterial infections
(J. Vogel)

Despite considerable advances in our understanding of RNA Biology in model bacteria, the diversity of RNA molecules and the proteins with which they associate are unknown in the vast majority of medically important species. The Vogel lab strives to chart the full cosmos of noncoding RNA functions and RNA-binding proteins in major bacterial pathogens and the thousand different bacteria that make up the human microbiome. They develop new RNA-seq based techniques to rapidly capture the RNA world of any microbe, ideally at the level of single cells, and understand how and why bacteria use RNA as a regulator as they infect humans. Studies include basic mechanistic questions relating to RNA Biology and apply this knowledge for an RNA-centric manipulation of the microbiota.

Immunological and cell biological studies of *Leishmania* pathogenicity
(H. Moll)

Leishmania cause a spectrum of different diseases, depending on the parasite species and the type of the host's immune response. This model allows the analysis of the mechanisms involved in host resistance or susceptibility to a microbial pathogen. The development of new strategies for immunotherapy and vaccination based on the use of dendritic cells and the identification and characterization of leishmanicidal compounds are the major research topics of this group.

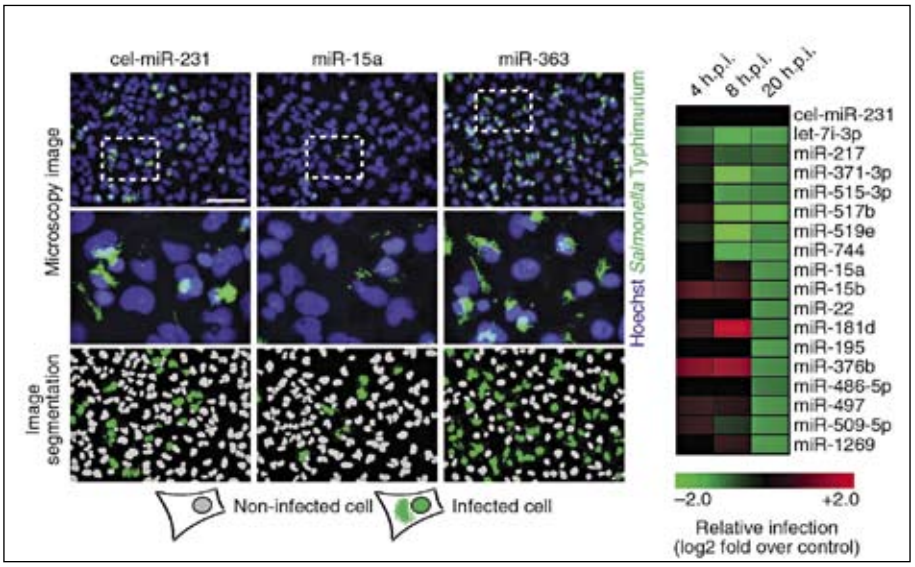


Fig.: A: Analysis of HeLa-cells infected with salmonella after treatment with microRNAs. B: microRNAs are able to influence the level of infection with salmonella (modified, Maudet et al. 2014, Nature Communications 5:4718).

Biology and Pathogenicity of *Candida albicans*
(J. Morschhäuser)

The yeast *Candida albicans* is a harmless commensal in the digestive tract of most healthy people, but it can also cause superficial infections of the mucosae as well as life-threatening systemic infections, especially in immunocompromised patients. The Morschhäuser group is investigating how *C. albicans* adapts to different host niches and changes in its environment. They are especially interested in the elucidation of signalling pathways that control morphological switches and virulence gene expression and of genetic alterations that are responsible for the evolution of variants with novel phenotypic traits.

Pathogenic enterobacteria and probiotic *Escherichia coli*
(T. Ölschläger)

An early and often essential step in the establishment of a bacterial infection is the adhesion of the pathogen to host cells. The Ölschlaeger group focuses on identifying bacterial adhesins and their corresponding eukaryotic receptors. Additionally, substances including phytopharmaceuticals with unknown modes of action are being tested for their ability to inhibit bacterial adherence and invasion of host cells. The probiotic *E. coli* strain Nissle 1917 has been licensed as a drug and the group has shown that it interferes with the adhesion and invasion of pathogenic bacteria. Current work focuses on the elucidation of the causative molecular mode(s) of action of this probiotic *E. coli* strain.

Virulence and resistance mechanisms of pathogenic staphylococci
(K. Ohlsen)

Staphylococcus aureus is currently one of the most important nosocomical pathogens. The Ohlsen group is interested in understanding the molecular mechanisms involved in its virulence and resistance to antibiotics. One focus is the elucidation of the function of protein kinases and corresponding phosphatases. In addition, they are developing *in vivo* imaging technologies to visualise the infection process and host defense mechanisms *in situ*. Furthermore, they are developing strategies to combat this pathogen including antibody-based therapy approaches and the search for new targets and drugs.

Molecular biology of pathogenic staphylococci
(W. Ziebuhr)

Staphylococcus aureus and *Staphylococcus epidermidis* are common causes of health care-associated (nosocomial) infections that often affect immunocompromised patients carrying medical devices. The Ziebuhr group works on factors and processes contributing to the establishment of staphylococci as pathogens in the hospital environment. Their main interest is to team basic research with public health by covering epidemiology, genetics and the molecular biology of staphylococci.

RNA metabolism in host cells
(A. Eulalio)

RNA metabolism is essential for a number of host cell functions. It is therefore not surprising that pathogens have evolved sophisticated mechanisms to subvert these pathways for their own benefit. The research within the Eulalio group focuses on determining the impact of bacterial infections on the RNA metabolism of the host cell, and the reciprocal effect of host RNA regulation on the life cycle of pathogenic bacteria. A major research focus has been on the roles of human and mouse microRNAs using automated microscopy coupled with high-throughput screening approaches of RNA libraries, as well as RNA-seq.

Structural biology of mycobacteria
(S. Geibel)

Tuberculosis is a highly infectious respiratory disease caused by various strains of mycobacteria. Mycobacteria use a variety of type VII secretion systems to manipulate the host cell and to evade its immune response. The Geibel group is using a variety of structural approaches, including X-ray crystallography and cryo-electron microscopy to obtain a molecular and functional understanding of the type VII secretion machines.

Host-pathogen-microbiota transcriptomes
(A. Westermann)

The interaction of bacterial pathogens with mammalian hosts and their resident microbiota represents an incredibly intricate biological process, involving numerous organisms from different kingdoms of life, all actively contributing to the balance between pathogenesis and clearance. The group applies high-throughput RNA-seq approaches to complex infection settings comprising of enteric bacterial pathogens, including *Salmonella*, their mammalian hosts and the resident gut microbiota, with a focus on anaerobic *Bacteroides thetaiotaomicron*. The aim is to identify and molecularly characterize novel noncoding RNAs and RNA-binding proteins with potential roles in bacterial virulence or protection against pathogenic attack.

Teaching

The IMIB scientists teach undergraduate and master students from biomedicine, biology, biochemistry and food chemistry, which include both lecture-based and practical courses. A major part of the teaching activities are dedicated to the training of biomedicine students. These activities include practical courses on Molecular Infection Biology, Molecular Microbiology and Mycology as well as lectures in general microbiology, pathogenicity and immunology and seminars on current topics in Infection Biology. Furthermore, lectures and seminars are provided for medicine students of the study program “Translational Medicine”. The institute also organises lectures, courses, seminars and summer schools for the members of the Graduate College ’Infectiology‘ in association with the International Graduate School of Life Sciences at the University of Würzburg as well as hosting several internships.

SELECTED PUBLICATIONS

Dugar G, Leenay RT, Eisenbart SK, Bischler T, Aul BU, Beisel CL, Sharma CM. (2018) CRISPR RNA-Dependent Binding and Cleavage of Endogenous RNAs by the Campylobacter jejuni Cas9. Mol Cell 69:893-905.

García-Fernández E, Koch G, Wagner RM, Fekete A, Stengel ST, Schneider J, Mielich-Süss B, Geibel S, Markert SM, Stigloher C, Lopez D. (2017) Membrane Microdomain Disassembly Inhibits MRSA Antibiotic Resistance. Cell 171:1354-1367.

Michaux C, Holmqvist E, Vasicek E, Sharan M, Barquist L, Westermann AJ, Gunn JS, Vogel J. (2017) RNA target profiles direct the discovery of virulence functions for thecold shock proteins CspC and CspE. Proc Natl Acad Sci U S A 114:6824-6829.

Stapels DAC, Hill PWS, Westermann AJ, Fisher RA, Thurston TL, Saliba AE, Blommestein I, Vogel J, Helaine S. (2018) Salmonella persisters undermine host immune defenses during antibiotic treatment. Science 362:1156-1160.

Tawk C, Nigro G, Rodrigues Lopes I, Aguilar C, Lisowski C, Mano M, Sansonetti P, Vogel J, Eulalio A. (2018) Stress-induced host membrane remodeling protects from infection by non-motile bacterial pathogens. EMBO J 37: e98529.

Institute of Molecular Infection Biology, Chair of Molecular Infection Biology II

CONTACT DETAILS

Professor Dr. rer. nat. Cynthia Sharma (Head)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-82560
Fax: 0931-/31-82578
E-mail: cynthia.sharma@uni-wuerzburg.de
www.imib-wuerzburg.de/research/sharma

Mission and Structure

The Chair of Molecular Infection Biology II was established in 2016 as part of the Institute of Molecular Infection Biology (IMIB). The IMIB is an interdisciplinary research institution within the Medical Faculty of the University of Würzburg and part of the Research Center for Infectious Diseases (ZINF). The scientists at IMIB aim to elucidate fundamental principles of infection processes and host-pathogen interactions in a variety of bacterial or eukaryotic pathogens. The Chair of Molecular Infection Biology II focuses on mechanisms and functions of post-transcriptional gene expression control in bacterial gastrointestinal pathogens, such as the Epsilonproteobacteria *Helicobacter pylori* and *Campylobacter jejuni*. We are especially interested in the identification and characterization of small regulatory RNAs and associated RNA binding proteins involved in stress response and virulence control. We have been developing and employing diverse deep-sequencing approaches to study transcriptomes, translatomes, and RNA-protein complexes on a genome-wide scale. These approaches are combined with genomics, genetics, and biochemistry methods to identify novel RNA or protein factors and to characterize how they regulate genes at the post-transcriptional level. Our research will not only shed light on the role of RNA-based regulation in the virulence of Epsilonproteobacteria, but also in other bacterial pathogens.

Major Research Interests

Post-transcriptional regulation in bacterial pathogens

Posttranscriptional regulation represents a central level of gene expression control in the cell, in which small RNAs (sRNAs), RNA-binding proteins (RBPs), and ribonucleases (RNases) play a key role. In bacteria, the 50- to 400-nt-long sRNAs represent a heterogeneous class of molecules that regulate gene expression in response to adverse growth and environmental stress conditions and have also been implicated in controlling virulence. Genome-wide approaches have revealed hundreds of sRNAs in diverse bacteria, including many pathogens. However, the functions and cellular targets of most of these sRNAs are still elusive. The model organisms in our lab are the gastric pathogen *Helicobacter pylori*, the causative agent of gastric cancer, and the related food-borne pathogen *Campylobacter jejuni,* which is currently the most common cause of bacterial food-borne disease (Fig. 1). Using diverse deep-sequencing techniques, we have annotated the transcriptomes of *H. pylori* and *C. jejuni* and have identified many conserved and strain-specific sRNAs. Using genomics, biochemical, molecular biology, and genetics approaches, we are now elucidating the physiological roles and underlying molecular mechanisms of sRNAs and RBPs in stress responses and virulence control. For example, we could show that the conserved and abundant sRNA RepG directly targets a phase-variable homopolymeric G-repeat in an *H. pylori* chemotaxis receptor mRNA. Length variation of this G-repeat determines the outcome of post-transcriptional regulation by the sRNA and thereby influences strain-specific gene regulation. This represents an unexpected connection between sRNA-mediated regulation and phase variation, which is often associated with bacterial virulence. Besides RepG, we have been characterizing several other sRNAs in *H. pylori* and *C. jejuni* and have identified several mRNAs encoding colonization or virulence factors as sRNA targets.

Identification and characterization of RNA protein complexes

The RNA binding protein Hfq plays a key role in sRNA-mediated regulation in enterobacteria, such as *Escherichia coli* or *Salmonella*. Because Epsilonproteobacteria, like 50% of all bacteria, lack a homolog of Hfq, we are interested in discovering alternative auxiliary protein factors that are involved in post-transcriptional regulation in these bacteria. Using biochemical and genomics approaches to capture and analyze RNA-protein complexes, we aim to identify and study RNA binding proteins. For example, using co-immunoprecipitation combined with RNA-seq (RIP-seq) we have determined the direct RNA binding partners of the translational regulator CsrA in *C. jejuni* on a genome-wide scale. This has

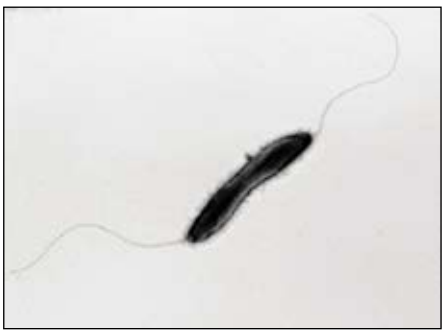


Fig. 1: Transmission electron microscopy image of the food-borne pathogen Campylobacter jejuni at 3,000x magnification.

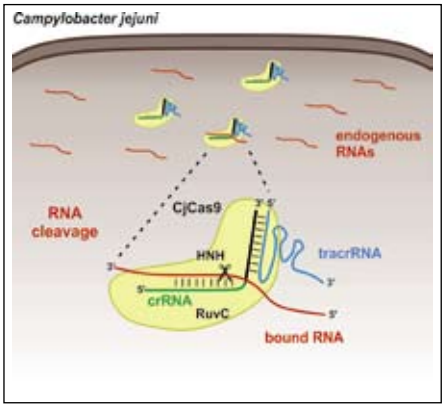


Fig. 2: Targeting of endogenous RNAs by the CRISPR-Cas9 nuclease of C. jejuni. The crRNA-guided CRISPR-Cas9 nucleases typically target double-stranded DNA targets. C. jejuni Cas9 can also target endogenous RNAs through imperfect complementarity with native crRNA guides bound to tracrRNA, followed by cleavage by the HNH domain of CjCas9. Figure adapted from Dugar et al. (2018) Molecular Cell.

revealed many flagellar mRNAs to be direct CsrA targets, and has identified the mRNA encoding the major flagellin as both the main target of CsrA repression and an RNA antagonist of CsrA activity (Dugar *et al*., 2016, Nature Communications). Moreover, we observed that the flagellin mRNA localizes to the cell poles in a cell division-dependent manner, and that CsrA and its protein antagonist FliW regulate flagellin mRNA localization. This suggests that post-transcriptional networks in bacteria employ a high temporal and spatial complexity.

Mechanisms and functions of CRISPR-Cas9 beyond genome defense

CRISPR-Cas systems are RNA-based prokaryotic immune systems that employ CRISPR-RNA (crRNA) guides and diverse nucleases to target and destroy invading foreign nucleic acids. Components of these systems, such as the Cas9 nuclease, have recently revolutionized genome editing in eukaryotes, and are nowadays widely exploited for diverse biotechnological applications. The study of CRISPR-Cas systems in diverse prokaryotes is continually uncovering new classes and subtypes with novel protein components and mechanisms of action that could be adapted for specialized engineering approaches. The Cas9 nuclease typically targets double-stranded DNA. Using co-immunoprecipitation combined with RNA-sequencing, we recently revealed that the CRISPR-Cas9 nuclease of *C. jejuni* (CjCas9) can bind and cleave endogenous bacterial RNAs in a crRNA-guided manner (Fig. 2). Moreover, we showed that RNA targeting by CjCas9, the smallest Cas9 used for genome editing so far, can be programmed to target different sequences *in vitro*. This provides new opportunities for biotechnological applications of CjCas9, such as parallel targeting of RNA and DNA. We are now interested in the potential roles of RNA targeting beyond genome defense, such as virulence control or endogenous gene regulation.

3D-Infection models to study host-pathogen interactions

To study the roles of bacterial sRNAs during infection and to identify factors important for host-pathogen interactions, we have been developing and applying novel three-dimensional (3D) infection models based on tissue engineering. Such complex multicellular 3D tissue cultures can mimic the complexity and microenvironment of human tissues more closely than classical 2D cell line monolayers. We have successfully established infection conditions with *C. jejuni* and a human small intestine model and have started to develop a new stomach model for *H. pylori*. To identify genes relevant for host-pathogen interactions during infections of these novel models, we have been employing deep-sequencing analysis of high-density bacterial transposon mutant libraries before and after infection, as well as dual RNA-seq to monitor host and pathogen transcriptomes in parallel. Using our novel 3D infection models, we aim to identify new regulatory and physiological paradigms that govern virulence in these major human pathogens.

Identification and characterization of small proteins

Understanding the biology of an organism requires a complete catalog of its expressed proteins. Ribosome profiling (Ribo-seq; identification of translated transcripts by deep sequencing of so-called mRNA footprints protected by ribosomes) has provided a sensitive proxy for discovering cellular proteins by determining their open reading frames (ORFs). Recent studies of the "translatome" of diverse organisms using Ribo-seq have identified unannotated small ORFs (smORFs) that could encode for small proteins with diverse cellular functions. We have established Ribo-seq in *H. pylori* and *C. jejuni*, which has revealed several small mRNAs encoding smORFs < 70 codons. In addition to ORF mapping, we also use ribosome profiling to study post-transcriptional regulation in *C. jejuni* and *H. pylori* on a global scale. We are now also investigating the functions of selected small proteins that we have identified in *C. jejuni*, and have discovered first phenotypes for some of them, such as roles in motility.

Teaching

The Chair of Molecular Infection Biology II is involved in the teaching of students in the Bachelor and Master study programs in biomedicine, biology, and biochemistry. Our teaching activities comprise both lecture-based and practical courses, and we supervise Bachelor's and Master's students' research internships and thesis projects. All of our doctoral students are members of the section "Infection and Immunity" of the Graduate School of Life Sciences (GSLS) and the chair is involved in graduate supervision and training, such as organization of workshops, *e.g.,* within the framework of the GRK2157 (3D-Infect).

SELECTED PUBLICATIONS

Bischler T, Hsieh PK, Resch M, Liu O, Tan HS, Foley PL, Hartleib A, Sharma CM, Belasco JG. (2017) Identification of the RNA pyrophosphohydrolase RppH of Helicobacter pylori and global analysis of its RNA targets. J Biol Chem 292:1934-1950.

Dugar G, Leenay RT, Eisenbart SK, Bischler T, Aul BU, Beisel CL, Sharma CM. (2018) CRISPR RNA-dependent binding and cleavage of endogenous RNAs by the Campylobacter jejuni Cas9. Mol Cell 69:893-905.e7.

Dugar G, Svensson SL, Bischler T, Wäldchen S, Reinhardt R, Sauer M, Sharma CM. (2016) The CsrA-FliW network controls polar localization of the dual-function flagellin mRNA in Campylobacter jejuni. Nat Commun 7:11667.

Fei J, Sharma CM. (2018) RNA Localization in Bacteria. Microbiol Spectr doi:10.1128/microbiolspec.RWR-0024-2018.

Svensson SL, Sharma CM. (2016) Small RNAs in Bacterial Virulence and Communication. Microbiol Spectr doi:10.1128/microbiolspec.VMBF-0028-2015.

Institute of Clinical Epidemiology and Biometry (ICE-B)

CONTACT DETAILS

Professor Dr. med. Peter U. Heuschmann, MPH (Head)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/201-47308
Fax: 0931/201-647310
E-mail: peter.heuschmann@uni-wuerzburg.de
www.epidemiologie.uni-wuerzburg.de

Professor Dr. rer. nat.
Dr. rer. med. Götz Gelbrich
Phone: 0931/201-47312

Professor Dr. med. Thomas Keil, MScPH
Joint professorship with the Bavarian Health and Food Safety Authority (LGL)
Phone: 0931/201-647308

Mission Statement and Structure

The Institute of Clinical Epidemiology and Biometry (ICE-B, Chair: Univ.-Prof. Dr. P. U. Heuschmann) was newly established at the University of Würzburg in October 2011. The ICE-B represents the disciplines epidemiology and biometry in research and teaching at the medical school of the University of Würzburg. The main research focus of the institute is clinical epidemiology including the investigation of causes and risk factors of diseases; therapy and prevention; prognosis and outcome; diagnostics and screening; as well as adequacy and quality of medical care.
In 2012, a professorship for biometry was established (Univ.-Prof. Dr. Dr. G. Gelbrich). In 2018, a professorship for prevention and health promotion (Univ.-Prof. Dr. T. Keil) was created as joint professorship with the Bavarian Health and Food Safety Authority (LGL), that includes chairing the Institute for Health Resort Medicine and Health Promotion in Bad Kissingen.

Research Foci

The research focus of the institute comprises independent interdisciplinary research projects at the interface between clinical medicine and epidemiology in the three main research areas: clinical research; prognostic studies; and health services research. Research projects are conducted in close collaboration with various departments and institutes of the University Würzburg and the University Hospital Würzburg including the Comprehensive Heart Failure Center (CHFC) of the University of Würzburg and the Clinical Trial Center of the University Hospital Würzburg (CTC), as well as with external national and international cooperation partners. In the future, these areas will be complemented by prevention and health promotion research in collaboration with the Institute for Health Resort Medicine and Health Promotion in Bad Kissingen.

Clinical research

Main focus of the area “clinical research” is the development of new methods for designing and analysing clinical studies of different phases. This also includes the support of clinical studies being planned or conducted by institutions within the University Hospital and the University of Würzburg as well as with external partners. The ICE-B is closely collaborating with the Clinical Trial Center of the University Hospital Würzburg, especially in the area of biometry represented by Prof. Dr. Dr. Gelbrich.

The projects of the ICE-B in this area comprise for example the biostatistical support of national multicentre trials to improve detection of atrial fibrillation after stroke (e.g. FIND AF randomized, MONDAFIS).

Prognostic studies

The research area “prognostic studies” includes planning, conducting and analysing of cohort studies in high risk groups of the general population as well as in patients with specific diseases. One specific research focus of the ICE-B comprises investigating the natural course of diseases as well as identifying high risk groups for clinically relevant endpoints such as complications, comorbidities or survival in populations from the clinical routine.

As an example for this thematic area, the „PREvention of STroke in Intracerebral haemorrhaGE survivors with Atrial Fibrillation“ (PRESTIGE-AF) study was recently initiated that receives funding within the „European Union Research and Innovation Programme Horizon 2020“ (http://www.prestige-af.org). PRESTIGE-AF is an European multicentre open prospective randomized clinical trial headed by Prof. Roland Veltkamp, Imperial College, London. The study will be conducted in 8 European countries to investigate if treatment with direct oral anticoagulants (DOAC) is an effective and safe option for stroke prevention in patients with intracerebral haemorrhage (ICH) with concomitant atrial fibrillation. The ICE-B develops within the substudy „predictive modelling“ new ap-

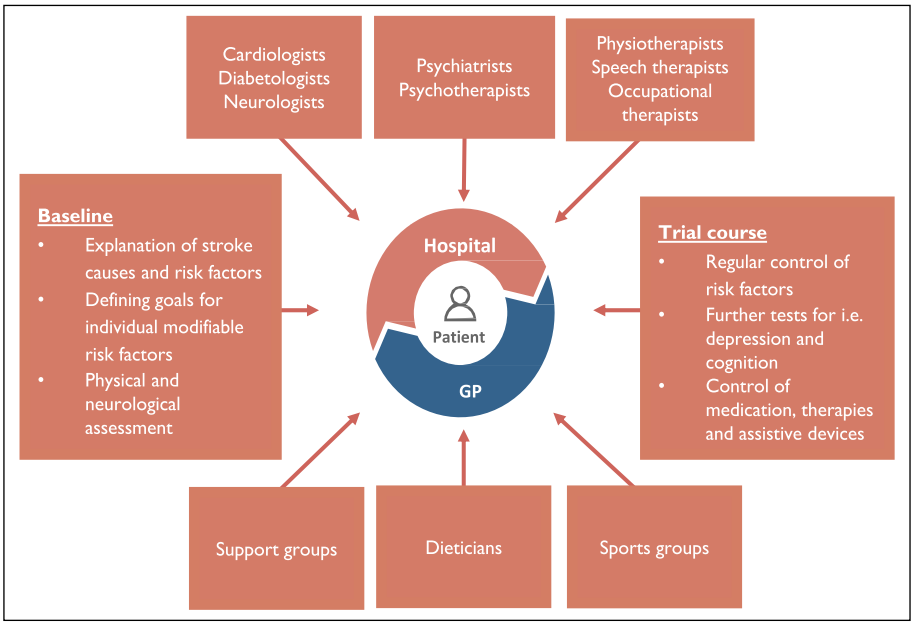


Fig.: Planned post-care stroke network.

proaches for predicting risk of recurrent strokes based on comprehensive clinical information. Within a second step, improvement of predictive properties will be investigated by adding additional biological information to the model such as blood-based biomarkers, genetic or neuroimaging information. As the final deliverable a comprehensive risk prediction tool shall be proposed to tailor individual prevention in ICH patients with concomitant atrial fibrillation.

Health services research

The thematic area "health services research" addresses research questions related to adequacy and quality of medical care within the population. In this research area, a number of register and cohort studies on coronary heart disease (e.g. EUROASPIRE) as well as stroke (e.g. ADSR, RASUONA-prime) were performed. In addition, the ICE-B participates as the evaluating institution in a number of projects to improve health care or to develop new health care concepts for different disease conditions (e.g. SANO, OVERBEAS, ZSE-DUO).

As an example, the project „structured ambulatory post-stroke care program - strukturierte ambulante Nachsorge nach Schlaganfall (SANO)" will be presented funded by the Federal Joint Committee (G-BA) within the Innovationfond (01NVF17032). SANO is a cluster-randomised study in 30 regions in Germany coordinated by Prof. Dr. Armin Grau, Department of Neurology, Klinikum Ludwigshafen and being evaluated by the ICE-B. SANO aims to improve care as well as diagnosis and therapy of complications after hospital discharge in ischemic stroke patients. For this purpose, a multidisciplinary post-stroke care network will be established in the intervention regions (figure 1). After inclusion in the study, patients receive detailed counselling, motivational interviews as well as definition of individual treatment targets together with their relatives. During regular visits to the hospital as well as to general practitioners, appropriate treatment of individual risk factors can directly be initiated, and potential complications being monitored. After the program, a potential reduction of complications as well as repeated hospital admissions by the intervention will be evaluated. For this purpose, about 1400 ischemic stroke patients from 15 regions offering the intervention will be compared with about 1400 patients from control regions, receiving usual care.

Prevention and health promotion

Since 2016, the new German prevention law requires a stronger engagement especially of the federal states, communities and social security institutions in prevention and health activities. The ICE-B and the Institute of Health Resort Medicine and Health Promotion intend to develop and evaluate preventive strategies for common chronic diseases. They will focus on potentially vulnerable groups such as the increasing number of lay carers in family settings (caring relatives) as well as employees of small enterprises and free-lancers who are often lacking sufficient resources for occupational health promotion.

Teaching

In teaching activities, the ICE-B put specific emphasis in improving the education and training of medical students, young physicians and scientists in epidemiology and biometry at the University of Würzburg.
Teaching activities for undergraduate training of medical students include for example specific lectures and practical small group courses in epidemiology and biometry as well as in evidence-based medicine. In addition, extended modules for medical students on epidemiological and biometrical topics were implemented.
Since October 2014, the ICE-B also offers statistical consulting for medical students performing their medical thesis at the University of Würzburg. In this context, statistical consulting provides "help for self-help" to support the students regarding planning, performing, analysing and interpreting their thesis project. In total, over 930 consultancies have been performed (by December 2018). The close interaction between training and consultancy activities is also contributing to improve the quality of the medical theses.
The ICE-B is also actively contributing together with Prof. Manfred Gessler and other colleagues to further develop the "clinical research and epidemiology" program for medical students existing since 2012 into a program and master course "translational medicine". Since 2018, this program receives funding as part of the Elite Network Bavaria. Within this elite course, medical students have the opportunity to assemble their individual study profile by choosing from specific modules covering the entire spectrum of translational medicine from experimental medicine to clinical research and epidemiology.

SELECTED PUBLICATIONS

Korompoki E, Filippidis FT, Nielsen PB, Del Giudice A, Lip GYH, Kuramatsu JB, Huttner HB, Fang J, Schulman S, Martí-Fàbregas J, Gathier CS, Viswanathan A, Biffi A, Poli D, Weimar C, Malzahn U, Heuschmann P, Veltkamp R. (2017) Long-term antithrombotic treatment in intracranial hemorrhage survivors with atrial fibrillation. Neurology 89:687-696.

Morbach C, Gelbrich G, Tiffe T, Eichner F, Wagner M, Heuschmann PU, Störk S; STAAB consortium, Frantz S, Maack C, Ertl G, Fassnacht M, Wanner C, Leyh R, Volkmann J, Deckert J, Faller H, Jahns R. (2018) Variations in cardiovascular risk factors in people with and without migration background in Germany - Results from the STAAB cohort study. Int J Cardiol pii: S0167-5273(18)34130-5.

Rücker V, Wiedmann S, O'Flaherty M, Busch MA, Heuschmann PU. (2018) Decline in regional trends in mortality of stroke subtypes in Germany from 1998 to 2015. Stroke 49:2577-2583.

Wachter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, Seegers J, Wasser K, Schulte A, Jürries F, Messerschmid A, Behnke N, Gröschel S, Uphaus T, Grings A, Ibis T, Klimpe S, Wagner-Heck M, Arnold M, Protsenko E, Heuschmann PU, Conen D, Weber-Krüger M; Find-AF(randomised) Investigators and Coordinators. (2017) Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial. Lancet Neurol 16:282-290.

Wagner M, Wanner C, Kotseva K, Wood D, De Bacquer D, Rydén L, Störk S, Heuschmann PU; EUROASPIRE IV investigators. (2017) Prevalence of chronic kidney disease and its determinants in coronary heart disease patients in 24 European countries: Insights from the EUROASPIRE IV survey of the European Society of Cardiology. Eur J Prev Cardiol 24:1168-1180.

Institute of Forensic Medicine

CONTACT DETAILS

Professor Dr. med. Michael Bohnert
(Head)

Versbacher Str. 3
97078 Würzburg
Phone: 0931/31-47020
Fax: 0931/31-47000
E-mail: i-rechtsmedizin@uni-wuerzburg.de
www.med.uni-wuerzburg.de/rechtsmedizin

Mission and Structure

The Institute of Legal Medicine of the University of Würzburg provides services in legal medicine on behalf of courts of justice, public prosecutors and police departments for the region of Lower Franconia as well as adjacent regions in Upper Franconia and Baden-Württemberg. Key responsibilities are the investigation of deaths, post-mortems, clinical forensic medicine, assessing fitness to drive, forensic trace analysis, paternity testing and forensic-toxicological analysis of body fluids and pieces of evidence.

Apart from the Board Director, in 2018 the academic staff of the University of Würzburg Institute of Legal Medicine consisted of 2 consultants (Oberärzte), 4 senior house officers (Assistenzärzte), 2 biologists and 1 toxicologist. 11 of the 20 employees of the institute are paid from the institute's own resources. The other posts are financed on the basis of the Institute's tasks in research and teaching.

Major Research Interests

Legal medicine is defined as a medical specialty applying medical and scientific knowledge and techniques to the administration of justice. It is a strongly application-oriented and interdisciplinary subject with research activities geared to the requirements of the police and the judiciary. As in any other practice-oriented medical field, the daily activities and tasks determine the scientific issues to be addressed. Scientific forensic research concentrates on the assessment of findings, the evaluation of evidence, the reconstruction of events and the development of valid assessment criteria. Thus, our subject plays a special role among the other medical fields, because its scientific focus can neither be defined as basic research nor is it primarily oriented to patient care. It is much more concerned with the individual case than other subjects.

Current key research areas are forensic neuropathology, forensic osteology and death by heat exposure.

Forensic Neuropathology

(S. Bohnert, M. Bohnert)

The research group Forensic Neuropathology examines the effects of mechanic, toxicologic or hypoxic trauma on human brain. Main topics are the possibilities and limitations of post-mortem examination of cerebrospinal fluid, the histological and immunohistochemical examination of early reactions in traumatic brain injuries as well as in drug deaths and the development of brain edema.
Cooperation partners are the Section Neuropathology at the Institute of Pathology oft

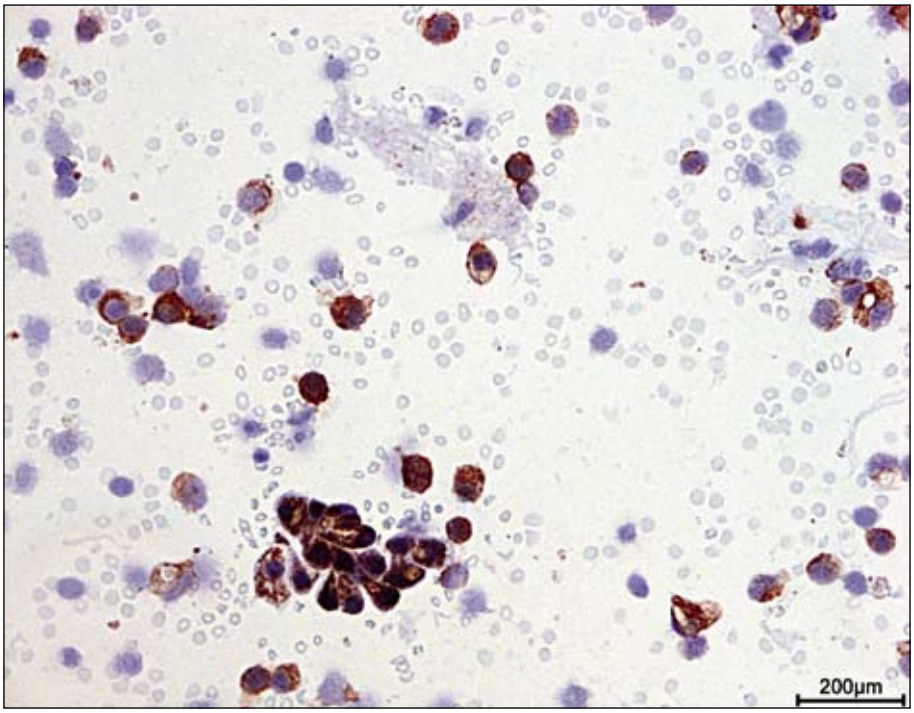


Fig. 1: Immunocytochemistry: Staining with antibody to TMEM 119, post-mortem interval 4 days, 200x magnification dilution 1:1000.

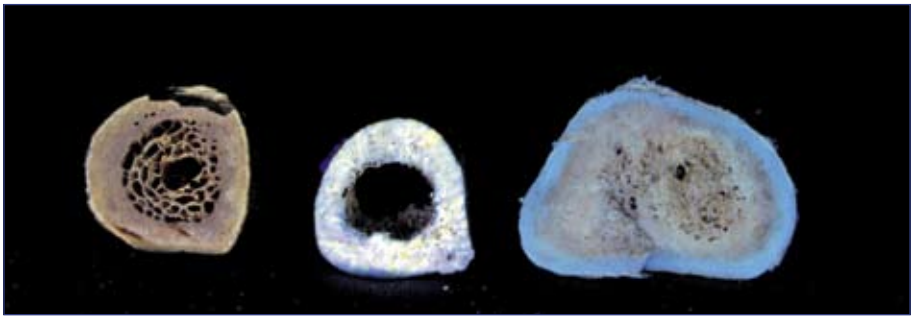


Fig. 2: UV-reflection of a cross cut bone sample (middle) with negative control (left) positive control (right).

he University of Würzburg, the Institute of Virology, the Department of Neurology, University Hospital Würzburg und the Institutes of Legal Medicine of the Universities Leipzig, Rostock and Heidelberg.

Determination of the post-mortem interval of bones
(K. Jellinghaus, M. Bohnert)

The forensic and anthropological assessment of bone finds is not only concerned with questions such as sex, age, presence of trauma and individual features but also the time since death. This is of significant importance under legal aspects, as apart from genocide and murder a crime becomes barred by the statute of limitation and can no longer be prosecuted after 3, 5, 10, 20 or 30 years depending on the punishment provided for in the law (Section 78 Criminal Code). Usually the Criminal Investigation Department investigates bones up to a post-mortem interval of 30 years or less. However, due to the different preservation state of bones or bone parts it is often difficult to make a precise statement with regard to the post-mortem interval. A bone's state of preservation is essentially influenced by the ambient conditions, which are ultimately more important for the condition of a bone than the time since death itself. Due to these diagnostic uncertainties the age of bone finds is often over- or underestimated. This in turn has consequences for the investigations. The aim of the present study is to extend and improve the methodological spectrum to estimate the post-mortem interval of human bones. For this purpose, the conventional methods to estimate the post-mortem interval are checked by means of bones with an exactly known post-mortem interval and used together with new techniques (fluorescence, histology, molecular degradation, densitometry) to develop low-cost routine parameters for the medico-legal routine which can be used for unknown bone finds. Collaboration partners are the Institute of Anthropology of Freiburg University (Prof. Dr. Wittwer-Backofen), the Landesamt für Geologie Baden-Württemberg, the Reiss-Engelhorn-Museum Mannheim, and the Forensic Anthropology Center der University of Tenneseee, Knoxville.

Traumatomorphology of burn deaths
(M. Bohnert)

The possible findings in burned bodies cover a broad spectrum, ranging from minor, local, superficial burns of the skin to calcined skeletal remains without any soft tissue left and total incineration. The extent of the tissue changes depends on the temperature actually applied to the body, the time for which it is applied, the kind of transmission of the heat to the body and other prevailing conditions. In most cases, the heat acts on the body beyond death. Consequently, the changes found are largely of postmortem origin. The effects of the heat on the body are burns of the exposed tissue, changes in the content and distribution of tissue fluids, fixation of the tissue and shrinking processes.

Burn deaths are critical cases from a forensic viewpoint, especially if the body is heavily destroyed or if the classical signs of vitality are missing. We examine the following main topics:

- New parameters for proving a peracute fire death
- Parameters for proving a vital fire exposure
- Correlation between dynamics of the fire, burn morphology and duration of fire exposure

Teaching

Forensic science is taught to students of medicine in a main lecture held over 2 semesters, a laboratory course and a compulsory optional subject. In the 6th semester, fundamentals are taught, in the 7th semester special topics are addressed and students do a course on post-mortems. Fundamentals include the fields of thanatology, forensic traumatology, medical law, forensic alcohology, forensic genetics and forensic toxicology. In the 7th semester, the post-mortem examination, traffic medicine, clinical forensic medicine and forensic case work are covered. In the laboratory course, students learn how to perform a post-mortem examination. An aspect regarded as especially important in teaching is to make students aware of forensic aspects in their clinical work. Those particularly interested in the field can attend the compulsory optional subject "Medical Criminalistics".

In a well-attended lecture, legal medicine is also presented to students of law and biomedicine. Junior lawyers (between the first and second state examination) are regularly instructed on the effect of alcohol and drugs in road traffic with a scientifically monitored drinking test. Regular training courses are also held for the police and the German Armed Forces.

SELECTED PUBLICATIONS

Jellinghaus K, Hachmann C, Höland K Bohnert M, Wittwer-Backofen U. (2018) Collagen degradation as a possibility to determine the post-mortem interval (PMI) of animal bones: a validation study referring to an original study of Boaks et al. (2014). Int J Legal Med 132:753-763.

Jellinghaus K, Höland K, Hachmann C, Prescher A, Bohnert M, Jantz R. (2018) Cranial secular change from the nineteenth to the twentieth century in modern German individuals compared to modern Euro-American individuals. Int J Legal Med 132:1477-1484.

Lang J, Stiller D, Lessig R, Sterzik V, Bohnert M. (2017) Mordbrand Arch Kriminol 240:1-16.

Oerter S, Förster CY, Bohnert M. (2018) Validation of sodium/glucose cotransporter proteins in human brain as a potential marker for temporal narrowing of the trauma formation. Int J Legal Med doi:10.1007/s00414-018-1893-6. [Epub ahead of print].

Sterzik V, Hinderberger P, Panzer S, Bohnert M. (2018) Visualizing old biological traces on different materials without using chemicals. Int J Legal Med 132:35–41.

Institute of Pathology

CONTACT DETAILS

Professor Dr. med. Andreas Rosenwald (Head)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-81199
Fax: 0931/31-81224
E-mail: Rosenwald@mail.uni-wuerzburg.de
www.pathologie.uni-wuerzburg.de

Professor Dr. med. Eva Geissinger
Phone: 0931/31-81259

Mission and Structure

The Institute of Pathology is an academic center with more than 100 employees including 20 pathologists and more than 20 scientists. The institute delivers clinical care for the university hospital and outside health care providers including histological, cytological and molecular diagnostic assessments of surgical biopsies and specimens, as well as autopsies. Specialized departments, e.g. for Neuropathology or Molecular Pathology, concentrate on specific diagnostic and scientific topics. The Institute of Pathology has a particular focus on diagnostic and scientific aspects of hematological malignancies and constitutes one of several German reference centers which are responsible for the diagnostic and scientific work-up of lymphoma specimens from patients included in German and European prospective clinical trials. The diagnostic expertise in this field and the scientific achievements are internationally visible.

Major Research Interests

Research in Hematopathology and Consultation Center for Hematological Malignancies
(A. Rosenwald, E. Geissinger)

The Reference Center for hematological malignancies operates as a national consultation center and coordinates research activities associated with prospective clinical lymphoma trials including trials of the 'German study group for high-grade non-Hodgkin lymphomas'. Research interests include the molecular pathogenesis of malignant B- and T-cell lymphomas as well as of multiple myeloma and cutaneous lymphomas. The molecular definition of biologically and clinically relevant lymphoma subtypes in the era of targeted treatment approaches is one of the major goals.
Recently, a molecular subgroup of aggressive B-cell lymphomas that harbour simultaneous translocations of the MYC and BCL2 oncogenes could be characterized. The group plays a major role in several national and international research networks, including the Leukemia and Lymphoma Molecular Profiling Project (National Cancer Institute, USA).

Molecular Pathogenesis of Hematological Malignancies
(E. Leich)

This research group focuses on the molecular and clinical characterization of t(14;18)-negative follicular lymphomas (FL) and multiple myeloma (MM). Hypothesis driven approaches include high throughput technologies such as "Next Generation Sequencing" (NGS) and microarrays. In collaboration with the 'Leukemia and Lymphoma Molecular Profiling Project' and the 'International Cancer Genome Consortium', we were able to show that t(14;18)-negative FL show a late germinal center B-cell phenotype and acquire less frequently novel N-glycosylation motives in the variable regions of their immunoglobulin gene loci. Moreover, in the context of the "Klinische Forschergruppe 216" and the "Sandertherapieeinheit Multiples Myelom" we defined a signalling network of receptor tyrosine kinases (RTKs), adhesion molecules and their downstream effectors that is affected by somatic mutations in almost all MM-patients. Retrospective NGS-analyses in study cohorts of the "Deutsche Studiengruppe Multiples Myelom" moreover showed that mutations in RTKs are associated with an inferior outcome. The functional characterization of RTKs and their effectors are part of our current research approaches.

Molecular and Cellular Immunology
(F. Berberich-Siebelt)

Within the field of 'Molecular and Cellular Immunology' the major research focuses on $CD4^+$ T cells. For some time, we particularly analyze the role of the family of NFAT transcription factors as well as individual family members and their isoforms for the activation and function of conventional T cells (Tcon) and regulatory T cells (Treg). On one hand, the importance of NFAT factors for Tcons could be proven in various models for autoimmune diseases, but on the other hand it got clear that Tregs are hardly NFAT-dependent in their function. This opens up the option to specifically inhibit NFAT in contrast to a general immunosuppression and thus to preserve the functionality of Tregs. An exception to the dichotomy between Tcons and Tregs in relation to the NFAT-dependence represent such Tregs, which migrate into the follicles to control the germinal center reaction. Here NFATc1 is essential for the migration process. In the absence of NFATc1 autoantibodies develop as they are known from lupus erythematosus. Thus, in some circumstances, it might be useful to turn off only individual NFAT members therapeutically. To this end, pre-clinical models with our different NFAT-deficient mice provide directions and, accordingly, pharmacological inhibitors and genome editing strategies are tested. These experiments are performed in cooperation with the reference center for hemato-

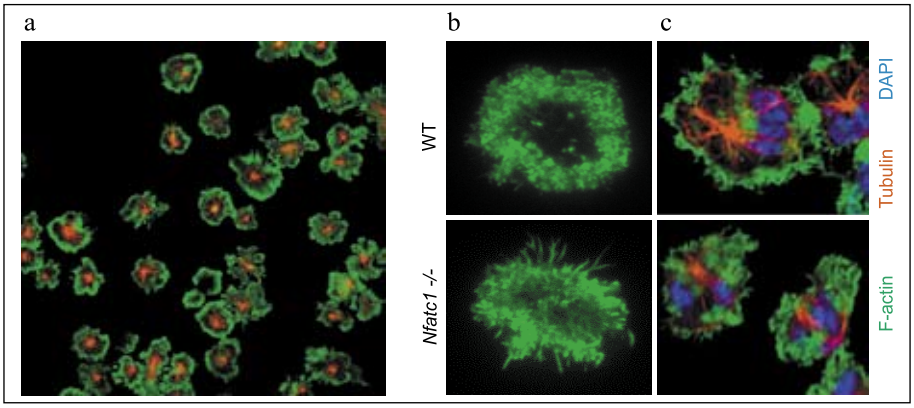


Fig.: The transcription factor NFATc1 controls the re-organization of cytoskeleton at the immunological synapse upon activation of cytotoxic T cells (CTLs). TIRF (total-internal-reflection-fluorescence microscopy). (Photography: Dr. Nora Müller) (a) Formation of F-actin rings and appearance of microtubule organizing center (MTOC) upon CD3/CD28 activation of CTLs within 5 minutes. (b and c) Defective F-actin formation in CTLs in which NFATc1 was ablated (see also Klein-Hessling et al., Nature Comm. 2017).

logical malignancies and funded by the DFG, the Wilhelm Sander-, Fritz Thyssen- and Else Kröner-Fresenius-Foundation as well as by Roche und Pfizer.

Transcriptional Control by NFAT Factors in T-Lymphocytes
(E. Serfling)

The members of 'genuine' NFATc ('Nuclear Factors of Activated T Cell') transcription factors control immune reactions. This is reflected by the inhibitory effect of immune suppressants Cyclosporin A (CsA) and FK506 on the activation of NFATs. Both CsA and FK506 are used worldwide in transplant patients to suppress the rejection of transplanted organs. In a collaboration with the Department of Surgery we showed recently that the activity of NFATc1 rejects allogenic heart transplants in mice. The crucial role of NFATc1 in the control of immune reactions is also reflected by our studies on the genome-wide gene control in $CD8^+$T cells by NFATc1. Using transgenic mice expressing a biotin-tagged version of NFATc1 we were able to determine in Chip-Seq assays the binding of NFATc1-bio to its target genes upon activation of $CD8^+$T cells. Among the target genes in $CD8^+$T cells are numerous lymphokine and chemokine genes, and, in addition, the PD1/*Pdcd1* and *Ctla4* genes that code for two checkpoint inhibitor proteins. These and further findings prompted us to start a project on the role of NFATc factors in the generation of melanomas in mice.
A second research project of our laboratory deals with the role of NFAT5 on the differentiation of keratinocytes in skin epidermis. Our experimental data that were obtained in collaboration with the Department of Dermatology indicate a crucial role for NFAT5 in the terminal differentiation of keratinocytes to corneocytes. It is likely that defects in NFAT5 cause numerous skin diseases that are characterized by a thickening of epidermis.

Neurodegeneration and Neuroinflammation
(C. Monoranu)

The research focus in the Department of Neuropathology is on neurodegenerative diseases, especially on Alzheimer dementia. Beside gene expression analysis of human *post mortem* brain tissue from patients with Alzheimer's disease at different stages, cell-type specific mitochondrial DNA deletion levels as marker for oxidative stress were assessed based on the concept of selective vulnerability of different brain regions, which is not yet fully understood. Microscopically early affected regions such as the hippocampus show differences also on molecular level compared to more resistant regions such as the cerebellum. This also applies to other obviously involved cell types such as astrocytes and microglia.
Due to the increasing relevance of neuroinflammation for the pathogenesis and progression of neurodegenerative diseases and forensic neuropathology a new research focus was recently developed in cooperation with the Institute of Legal Medicine. Analysis of the time-dependent flow of microglia, macrophages and astroglia from the damaged brain tissue after mechanical brain injury into the cerebrospinal fluid compartment seems to be a promising tool to estimate the posttraumatic interval.

Teaching

The Institute of Pathology is responsible for teaching pathology as part of the medical curriculum of the Würzburg Medical School. Specifically, 3 professors and additional teaching staff conduct lectures, seminars, practical classes (histology) and macropathologic case demonstrations (autopsies). Additional courses for graduate students cover a wide range of specific subjects, techniques, and skills. Pathology lecturers also participate in interdisciplinary teaching projects (e.g. interdisciplinary oncology) and clinico-pathologic conferences for several hospitals and clinical departments. According to the hemato-pathological focus as well as the reference center for haematological malignancies, scientific staff of the institute additionally takes part in the immunological education of medical and natural science students.

SELECTED PUBLICATIONS

Klein-Hessling S, Muhammad K, Klein M, Pusch T, Rudolf R, Floter J, Qureischi M, Beilhack A, Vaeth M, Kummerow C, Backes C, Schoppmeyer R, Hahn U, Hoth M, Bopp T, Berberich-Siebelt F, Patra A, Avots A, Muller N, Schulze A, Serfling E. (2017) NFATc1 controls the cytotoxicity of CD8+ T cells. Nat Commun 8:511-526.

Scott DW, King RL, Staiger AM, Ben-Neriah S, Jiang A, Horn H, Mottok A, Farinha P, Slack GW, Ennishi D, Schmitz N, Pfreundschuh M, Nowakowski GS, Kahl BS, Connors JM, Gascoyne RD, Ott G, Macon WR, Rosenwald A. (2018) High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with diffuse large B-cell lymphoma morphology. Blood 131:2060-2064.

Strobel S, Grünblatt E, Heinsen H, Riederer P, Espach T, Meder M, Monoranu CM. (2019) Astrocyte and microglia-specific mitochondrial DNA deletions levels in sporadic Alzheimer's disease. J Alzheimers Dis 67:149-157.

Wobser M, Maurus K, Roth S, Appenzeller S, Weyandt G, Goebeler M, Rosenwald A, Geissinger E. (2017) Myeloid differentiation primary response 88 mutations in a distinct type of cutaneous marginal-zone lymphoma with a nonclass-switched immunoglobulin M immunophenotype. Br J Dermatol 177:564-566.

Zamò A, Pischimarov J, Schlesner M, Rosenstiel P, Bomben R, Horn H, Grieb T, Nedeva T, López C, Haake A, Richter J, Trümper L, Lawerenz C, Klapper W, Möller P, Hummel M, Lenze D, Szczepanowski M, Flossbach L, Schreder M, Gattei V, Ott G, Siebert R, Rosenwald A, Leich E. (2017) Differences between BCL2-break positive and negative follicular lymphoma unraveled by whole-exome sequencing. Leukemia 32:685-693.

Institute of Pharmacology and Toxicology, Chair of Pharmacology

CONTACT DETAILS

Professor Dr. rer. nat. Antje Gohla
(acting Head until 1/2019)

Professor Dr. rer. nat. Kristina Lorenz
(Chair of Pharmacology and Toxicology since 2/2019)

Versbacher Str. 9
97078 Würzburg
Phone: 0931/31-48400
Fax: 0931/201-48411
E-mail: i-pharm@toxi.uni-wuerzburg.de
www.pharmakologie.uni-wuerzburg.de

Professor Dr. rer. nat. Carsten Hoffmann
(with Bio-Imaging Center, until 4/2017)

Mission and Structure

The Institute of Pharmacology and Toxicology comprises the Chairs of Pharmacology and of Toxicology. The Institute is also home to several research groups of the Rudolf Virchow Center that was founded in 2001. The chair employs ca. 35 staff members (about half of them grant-funded). All research groups focus on the molecular mechanisms of cellular communication, their role in physiological functions and their potential to serve as targets for therapeutic drugs. In addition to standard biochemical and molecular biology equipment, the chair has equipment for rapid microscopic imaging, for confocal, 2-photon and TIRF microscopy, and for phenotyping of transgenic mouse models. The chair also provides a drug information service for the University Hospital and Medical Faculty as well as for outside physicians and pharmacists. The Ethics Committee of the Medical Faculty is also based at the Institute.

Major Research Interests

A major research focus of the Chair of Pharmacology is on G protein-coupled receptors. They transmit the effects of hormones and neurotransmitters, but also of therapeutic drugs such as opiates, beta blockers against high blood pressure and anti-allergic antihistamines. These receptors are investigated with a large array of methods to answer questions ranging from the structure of receptors and ligands to transgenic disease models and studies on patient samples. Another major research effort focuses on heart failure and the development of new therapeutic strategies. A third focus is on mechanisms of cellular lipid metabolism and co-factor homeostasis. Our research is funded by grants from the DFG, the Rudolf Virchow Center for Experimental Biomedicine, the SFB688 and the TR166, the European Union, the BMBF (Federal Ministry of Education and Research), the NIH, the Elitenetzwerk Bayern and others.

Mechanisms und Functions of G Protein-coupled Receptors

(C. Hoffmann; also Bio-Imaging Center/ Rudolf Virchow Center)

Communication between cells occurs through signaling molecules like hormones or neurotransmitters that are recognized by specific receptors, which constitute the primary class of drug targets. We investigate their function and regulation in various model systems to explore general mechanisms and functional principles. Over the last few years, we have developed a variety of techniques to visualize receptor activation, inactivation and the resulting signals by means of new fluorescent sensors and fluorescence microscopy. This allows us to directly observe receptors and signaling mechanisms „at work“. Recently, we were able to demonstrate the similarity of the molecular activation mechanisms between class A GPCRs and Frizzled receptors, and we also provided evidence for G protein coupling of Frizzled 5 receptors. Furthermore, together with pharmaceutical chemists, we were able to describe the first M1 selective muscarinic receptor ligand that can be isomerized by light between an agonist or an antagonist. Such “photo-switchable” ligands offer a way to control receptor activity by light, and open a new area of photopharmacology.

Signal Transduction by G Protein-coupled Receptors

(D. Calebiro, M. Lohse; also Bio-Imaging Center/Rudolf Virchow Center)

We have developed single-molecule techniques to visualize receptors and their resulting signals using new sensors and advanced fluorescence microscopy methods. These approaches enable us to analyze the speed and localization of signals and receptors even at the level of single molecules in isolated cells. We have recently succeeded in precisely characterizing the dynamics and localization of receptors and their signals. This has allowed us to discover a sequence of distinct receptor-triggered “signaling waves”. These findings have important implications for drug discovery and provide the basis to develop new drugs with improved efficacy and tolerability. Moreover, we have developed an innovative single-molecule microscopy approach to investigate receptor interactions on the

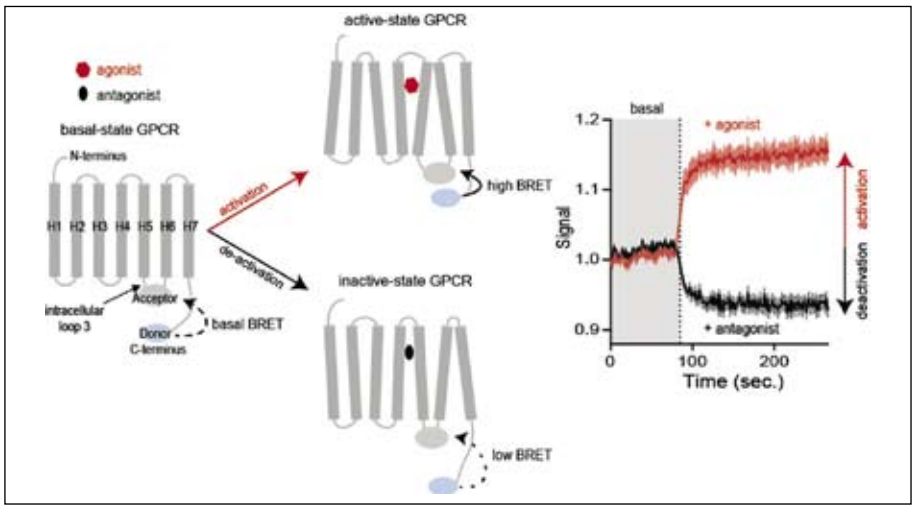


Fig. 1: Design of novel GPCR probes for high-throughput screening. (Schihada et al., Commun Biol, 2018)

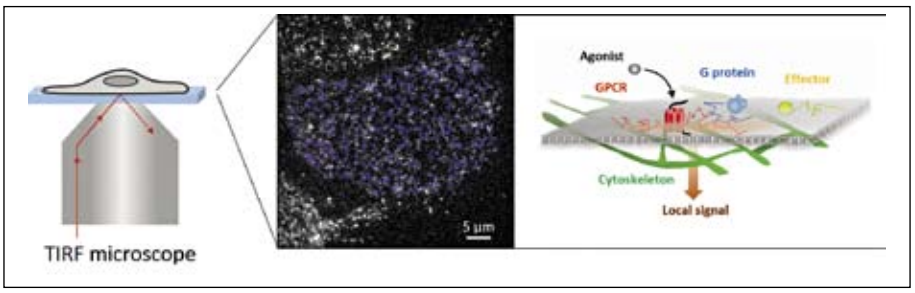


Fig. 2: Fluorescence resonance energy transfer (FRET) and single-molecule microscopy to analyze receptor signaling in single living cells. (Sungkaworn et al., Nature, 2017)

plasma membrane with unprecedented spatiotemporal resolution. Using this approach, we succeeded for the first time to directly visualize individual receptors and G proteins as they interact and signal in living cells. This has revealed hot spots for G protein signaling on the plasma membrane, which might confer speed and specificity to GPCR signaling.

Optical Sensors for High-Throughput Analyses of G Protein-coupled Receptors
(I. Maiellaro, M. Lohse; also Bio-Imaging Center/Rudolf Virchow Center)

Numerous currently employed drugs target G protein-coupled receptors. The detailed understanding of receptor function has greatly affected modern medicine and drug discovery programs. We develop optical probes that allow the investigation of receptor activation in high-throughput formats. Furthermore, we use these probes to elucidate the interactions of receptors with endogenous modulators. These approaches generate time- and cost-effective tools to monitor receptor function inside living cells. In addition to facilitating drug development, they might pave the way towards studying currently unexplored receptors.

Receptor-Antibodies in Heart Failure/ Myocarditis
(R. Jahns, together with Comprehensive Heart Failure Center and Rudolf Virchow Center)

Stimulating auto-antibodies against the β1-adrenergic receptor can be detected in about a third of patients with dilated or inflammatory heart muscle damage; the cardiovascular mortality-risk of antibody-positive patients is increased about 3-fold (Boivin-Jahns V & Jahns R, Front Biosci 2018; Boivin-Jahns V et al., Front Biosci 2018). By immunization of rats we have generated corresponding animal models. In several BMBF-funded projects, we investigate whether formation of such antibodies in patients is triggered by ischemic (myocardial infarction) or inflammatory heart muscle injury (acute myocarditis), and how such stimulating antibodies can be therapeutically neutralized with cyclic peptides. For further development and clinical phase I and II studies we have founded the Biotech company Corimmun. First results suggest that the immunomodulatory cyclopeptide COR-1 offers promise in the treatment of immune-mediated cardiac diseases (Boivin-Jahns V et al., PLoS One, 2018).

MicroRNAs in Neuropsychiatric and Cardiovascular Diseases
(L. Hommers, also Department of Psychiatry and Interdisciplinary Center for Clinical Research)

Comorbidity of cardiovascular and neuropsychiatric diseases results in a significant excess mortality. We aim to identify microRNAs regulating candidate genes of neuropsychiatric diseases, predominantly those in G-Protein coupled pathways, and investigate their mechanisms of action and test their relevance in on-going clinical studies of the Comprehensive Heart Failure Center.

Phosphatases and Metabolism
(A. Gohla)

We have identified a phosphatase that regulates cellular amino acid and neurotransmitter metabolism by controlling the homeostasis of a central cofactor. By analyzing gene-targeted mice, we showed that the phosphatase affects the balance between stimulatory and inhibitory neurotransmission. Loss of phosphatase activity improved spatial learning and memory. Hence, this enzyme might represent a novel target for the development of neuropsychiatric drugs. Using biochemical and cell biological methods, we investigate the regulation of phosphatase activity by endogenous mechanisms and small molecular weight compounds.

Teaching

The institute is responsible for teaching pharmacology and toxicology to students of medicine, dentistry, pharmacy, biology and biomedicine. The focus is on general and clinical pharmacology for medical students (5th, 6th and 8th term) and pharmacy students (5th-8th term). We also play a key role in the conception of the new research oriented BSc/ MSc curriculum in Biomedicine and participate in the MSc curriculum in Experimental Medicine.

SELECTED PUBLICATIONS

Hommers LG, Richter J, Yang Y, Raab A, Baumann C, Lang K, Schiele MA, Weber H, Wittmann A, Wolf C, Alpers GW, Arolt V, Domschke K, Fehm L, Fydrich T, Gerlach A, Gloster AT, Hamm AO, Helbig-Lang S, Kircher T, Lang T, Pané-Farré CA, Pauli P, Pfleiderer B, Reif A, Romanos M, Straube B, Ströhle A, Wittchen HU, Frantz S, Ertl G, Lohse MJ, Lueken U, Deckert J. (2018) A functional genetic variation of SLC6A2 repressor hsa-miR-579-3p upregulates sympathetic noradrenergic processes of fear and anxiety. Transl Psychiatry 8:226.

Jeanclos E, Albersen M, Ramos RJJ, Raab A, Wilhelm C, Hommers L, Lesch KP, Verhoeven-Duif NM, Gohla A. (2018) Improved cognition, mild anxiety-like behavior and decreased motor performance in pyridoxal phosphatase-deficient mice. Biochim Biophys Acta 1865:193.

Schihada H, Vandenabeele S, Zabel U, Frank M, Lohse MJ, Maiellaro I. (2018) A universal bioluminescence resonance energy transfer sensor design enables high-sensitivity screening of GPCR activation dynamics. Commun Biol 1:105.

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

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

Institute of Pharmacology and Toxicology, Chair of Toxicology

CONTACT DETAILS

Professor Dr. rer. nat. Helga Stopper
(acting Head until 1/2019)

Versbacher Str. 9
97078 Würzburg
Phone: 0931/31-48427
Fax: 0931/201-48446
E-mail: stopper@toxi.uni-wuerzburg.de
www.toxikologie.uni-wuerzburg.de

Mission and Structure

The departments of Pharmacology (acting head Prof. Dr. Antje Gohla), and Toxicology constitute the Institute of Pharmacology and Toxicology. The building accommodates the research laboratories and offices, a lecture hall seating 300 students, course laboratories, a seminar room, and a library for pharmacology and toxicology. Facilities for work with high levels of radioactive isotopes, a repair shop, and computer facilities for medical students are also available.

The workforce of the department of Toxicology comprises about 30 members. Four research groups are led by the University Professor Dr. Helga Stopper, the Associate Professor Dr. Wolfgang Dekant, the Associate Professor Dr. Angela Mally, and Dr. Henning Hintzsche. Postdocs and Ph.D. students with degrees in chemistry, food chemistry, biology, pharmacy, and medicine accomplish the experimental work, supported by technicians.

Major Research Interests

Chemical Carcinogenesis

Our research focuses on elucidating the first-line interactions of mutagenic and carcinogenic chemicals with biological targets, with the aim of a mechanistically supported risk characterization of chemically induced cancer in humans. We investigate the kinetics and metabolism of chemicals in vitro, in cells, animals and humans, paying special attention to the metabolic activation to chemically reactive intermediates, their interaction with biological macromolecules such as DNA and protein, and their detoxification. We study genotoxicity by analyzing covalent DNA binding, induction of other types of DNA damage (see Figures) and the course of events leading to mutations. Epigenetic mechanisms include modulation of DNA methylation and histone acetylation, hormonal effects, changes in the cell cycle and disturbance of cell differentiation.

Biomarkers

A second research focus are biomarkers in both animals and humans. Biomarkers of exposure are based mainly on the analysis of metabolites in urine and on cytogenetic alterations, for example in peripheral lymphocytes and buccal mucosa cells in humans. In animal models, early molecular and cellular alterations are also investigated in the search of early biomarkers of toxicity and carcinogenicity in kidney and liver, including idiosyncratic reactions. Biomarkers of individual susceptibility are studied in connection with side effects of radiotherapy and differences in metabolism due to genetic polymorphisms or inhibition of enzymes involved in resorption, metabolism and excretion.

Alternatives to Animal Testing

A further aim is to accelerate the transition of chemical safety testing from animal-based approaches with limited predictivity for human risk to more predictive, animal-sparing solutions by developing new mechanism-based in vitro methods and assessing the confidence in risk assessment based on in vitro data.

Risk Assessment

Knowledge on the mode of toxic action is a prerequisite for biologically based extrapolation from cells in culture or laboratory animals to humans, from high dose to low dose, and from the reproducible situation of experimental systems to the heterogeneity of a

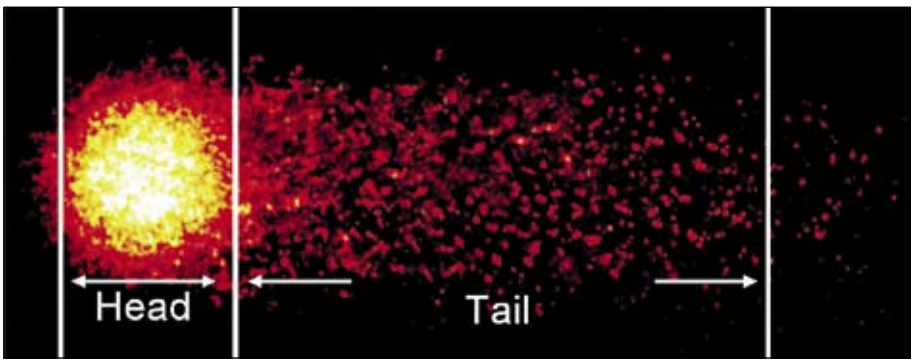


Fig. 1: "The Comet Assay": DNA fragments induced by a genotoxic agent migrate in an electric field out of the cell nucleus (Head) into a Tail.

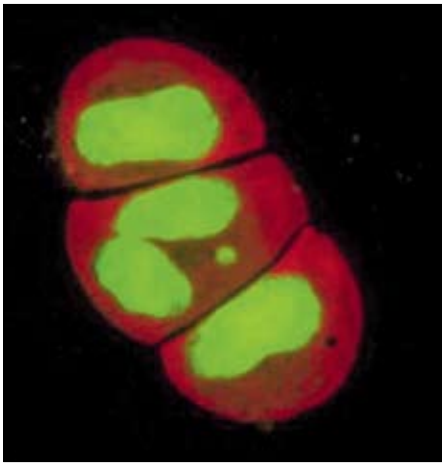


Fig. 2: "The Micronucleus Test": Chromosome damage is indicated by the presence of a DNA-containing fragment in the cytoplasm of the bi-nucleated cell in the middle of the three cells.

human population. Efforts on dose-response relationships and mixture effects are based on experimental data but include elaborate statistical analysis as well as kinetic modeling.

Investigated Compounds

The list of investigated compounds comprises a variety of chemical classes and sources. Exposure at the work place and in the environment include aromatic hydrocarbons and substituted derivatives, as well as chlorinated and fluorinated chemicals. Dietary exposure includes mycotoxins (ochratoxin A, fumonisin B_1), heat-derived products (acrylamide, furan), migrants from polymers and phytoestrogens. For drugs, we focus on agents for which the probability of side effects is modulated by environmental factors, pharmacogenetic differences and/or enzyme inhibition. Compounds with estrogenic and antiestrogenic activity are used primarily in connection with the investigation of epigenetic effects. Endogenous (insulin) and unavoidable DNA-damaging agents and processes that contribute to "spontaneous" tumor formation are also of interest. Oxidative stress is considered a major factor in this respect.

Teaching

Our staff covers all aspects of toxicology and shares the responsibility with the Pharmacology Department for teaching general and systematic pharmacology for students of medicine and biomedicine, pharmacy, dentistry, and biology. For chemistry students, a special course meets the legal requirements according to the "Gefahrstoffverordnung" to allow graduates to do business in chemical manufacture and sale. Prof. Stopper is speaker of the class "Biomedicine" of the Graduate School of the University. The working group leaders contribute to the postgraduate courses organized by the Society of Toxicology of the DGPT to register as DGPT and EUROTOX-certified Toxicologist. The institute offers advanced education for the degree of Pharmacist for Toxicology and Ecology. Editing and reviewing for scientific journals, membership in national and international scientific committees and consulting of political and governmental bodies is another part of our activities in the field. For the chemical and pharmaceutical industry, we offer both theoretical and experimental expertise for cooperations.

SELECTED PUBLICATIONS

Bankoglu EE, Arnold C, Hering I, Hankir M, Seyfried F, Stopper H. (2018) Decreased Chromosomal Damage in Lymphocytes of Obese Patients After Bariatric Surgery. Sci Rep 8:11195.

Colnot T, Dekant W. (2017) Approaches for grouping of pesticides into cumulative assessment groups for risk assessment of pesticide residues in food. Regul Toxicol Pharmacol 83:89-99.

Hintzsche H, Montag G, Stopper H. (2018) Induction of micronuclei by four cytostatic compounds in human hematopoietic stem cells and human lymphoblastoid TK6 cells. Sci Rep 8:3371.

Limbeck E, Vanselow JT, Hofmann J, Schlosser A, Mally A. (2019) Linking site-specific loss of histone acetylation to repression of gene expression by the mycotoxin ochratoxin A. Arch Toxicol 92:995-1014.

Lorenz N, Dänicke S, Edler L, Gottschalk C, Lassek E, Marko D, Rychlik M, Mally A. (2018) A critical evaluation of health risk assessment of modified mycotoxins with a special focus on zearalenone. Mycotoxin Res. 35:27-46.

Institute of Virology and Immunobiology, Chair of Immunology

CONTACT DETAILS

Professor Dr. med. Wolfgang Kastenmüller (acting Head)

Professor Dr. rer. nat. Thomas Hünig (Head until 9/2017)

Versbacher Str. 7
97078 Würzburg
Phone: 0931/31-89796
Fax: 0931/31-81619
E-mail: wolfgang.kastenmueller@uni-wuerzburg.de
www.virologie.uni-wuerzburg.de/immunologie

Professor Dr. rer. nat. Ingolf Berberich
Phone: 0931/31-81528

Professor Dr. rer. nat. Thomas Herrmann
Phone: 0931/31-81538

Professor Dr. rer. nat. Manfred Lutz
Phone: 0931/31-81553

Mission and Structure

The working groups of the Department of Immunology work on topics from basic research such as the interaction of the immune system with the organism, in particular the interaction of different cells of the immune system in local networks and with cells of other organ systems. This includes questions on the mechanisms by which regulatory T-cells and myeloid-derived suppressor cells control pathologic immune responses, the control of B-cell growth and survival, and the function and specificity of non-conventional T-cells in recognizing tumors and infectious agents. In a number of translational projects, they are working on the manipulation of the immune system by monoclonal antibodies and application of dendritic cells and myeloid-derived suppressor cells. Funding for research at the Chair of Immunology is provided by the Deutsche Forschungsgemeinschaft via individual project and collaborative research grants, and by foundations, which invest into medical progress. In addition, the research groups are active as cooperation partners in research projects funded by the Interdisciplinary Center for Clinical Research (IZKF). Another important activity of the Chair of Immunology is the laboratory diagnostics for patients with autoimmune diseases at the University Clinic (headed by Prof. Dr. T. Kerkau and PD Dr. N. Beyersdorf).

Major Research Interests

Migration and interaction of leukocytes between and within organs
(W. Kastenmüller)

Our lab focuses on cell-cell interactions, cellular localization and migration between and within tissues. To address such questions we combine classical immunological assays like multicolor flow cytometry with cutting edge microscopy including 2-photon imaging of live animals, confocal analysis of tissue section and whole mount preparations to study cellular immune responses in the context of infections. Central questions currently addressed in our lab include, function and development of cytotoxic CD8+ T cells, migration and dynamics of Dendritic Cells within tissues, immune defense against viral and bacterial infections, interface between innate and adaptive immune system, intercellular communiction.

Phosphoantigen-specific γδ cells: Molecular basis, evolution und therapeutic potential
(T. Herrmann)

γδ T cell antigen receptor (γδ TCR)-expressing lymphocytes are phylogenetically at least as old as B-lymphocytes and 'conventional' MHC-restricted αβ T lymphocytes. A population of γδ cells, which so far has been found only in higher primates, are the Vγ9Vδ2T-cells. Their γδ TCRs recognize the so-called phosphoantigens (PAgs). These are products of microbial isoprenoid synthesis such as the (E)-4-Hydroxy-3-methyl-but-2-enyl-pyrophosphate (HMBPP) or the universal metabolite isopentenyl-pyrophosphate (IPP), which is accumulated in some tumor cells. Newly generated reagents allowed us to identity the new world camelid alpaca (Vicugna pacos) as the first non-primate species possessing Vγ9Vδ2 T-cells and to better understand the molecular mechanisms of PAg-recognition. We also demonstrated a special role of the CDR3 regions of the TCR for PAg-recognition. Currently, we try to identify chromosome 6 located genes, which are mandatory for PAg-mediate recognition, with the final aim to generate mouse models with functional Vγ9Vδ2 T cells.

Cooperation between dendritic cells in Th1 polarization
(M. Lutz)

The success of vaccine dendritic cells (DCs) depends on the quality of antigen presentation, costimulation, lymph node migration, and the release of IL-12 in the case of Th1 priming. Our recent work shows that interaction between the injected vaccine DCs with endogenous migrating DCs is necessary for Th1 induction. Injected lymph node-migrating DCs, although directing T-cell priming and novel bystander DC activation, are not involved in Th1 polarization. This is mediated by IL-12 production of endogenous $XCR1^+$ bystander DCs. Our findings are important for clinical trials of DC vaccinations in which endogenous DCs may be functionally impaired by chemotherapy.

Inoculation with Mycobacterium tuberculosis induces myeloid suppressor cells (MDSCs)
(M. Lutz)

Tuberculosis (TB) vaccines based on Mycobacterium tuberculosis (Mtb) have so far failed. Since myeloid-derived suppressor cells (MDSCs) accumulate in patients with TB, we hypothesized that Mtb vaccines can also induce MDSCs that impair vaccination success. Indeed, repeated immunizations of mice with heat-inactivated Mtb increase the number of MDSCs in the spleen. Mechanistically, the Mtb-induced Nos2-dependent NO release by the subset of monocytic MDSCs is responsible for apoptosis induction of spleen dendritic cells (DCs). Taken together, these data demonstrate that Mtb booster vaccines induce MDSCs in the spleen that restrict T cell immune protection through NO-dependent DC killing.

B cell maturation
(I. Berberich)

B cells recognize invading microbes, viruses and foreign substances (antigens) with their antigen receptors (BCRs) and Toll-like recep-

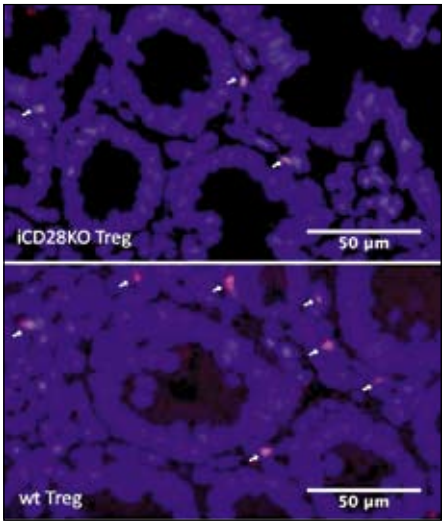


Fig.: from Uri et al. 2017: Only CD4⁺ Foxp3⁺ T cells (Treg, pink) expressing the CD28 molecule are capable of protecting mice from acute Graft versus Host Disease (aGvHD) over more than three weeks. After genetic deletion of CD28 in Treg (top, iCD28KO) their numbers in the gut of mice with aGvHD are substantially reduced compared to CD28-expressing Treg (bottom, wt).

tors (TLRs). After contact with these antigens, B cells proliferate and differentiate to antibody-producing "factories" (plasma cells). Currently, we are trying to understand by in vivo and in vitro experiments how the E3 ubiquitin ligase HectD1 and the NFAT transcription factors impact on the development and differentiation of B cells.

Role of CD28 costimulation in the activation of memory CD4⁺ T helper cells
(N. Beyersdorf)

The role of CD28 costimulation in the reactivation of memory CD4⁺ T helper cells is not well documented. Using blocking reagents and genetic deletion we could recently show that CD28 costimulation is critically required for cytokine release from CD4⁺ T helper 1 cells of mice and humans. CD28 is, thus, a therapeutic target for the manipulation of these cells *in vivo*.

Regulation of misguided immune reactions
(T. Kerkau, N. Beyersdorf)

The team is working on the pathophysiology of and novel immunotherapeutic for pathological immune reactions. For this, we are studying, among others, animal models of acute Graft-versus-host-disease (aGvHD), a major complication after allogeneic bone marrow transplantation. Here we discovered that CD28 costimulation of CD4⁺ regulatory T cells is critical for long-term protection from aGvHD. CD4⁺ T helper cells, further, require CD28 costimulation to be able to provide sufficient help to CD8⁺ T cells for leukemia cell killing.

The role of CD4⁺ T cells in myocardial wound healing
(T. Kerkau, N. Beyersdorf)

In collaboration with Prof. Dr. S. Frantz, PD Dr. Anna Frey and Prof. Dr. U. Hofmann, Internal Medicine I, the group has recently identified CD4⁺ regulatory T cells to improve wound healing after myocardial infarction (MI). Currently we are testing whether similarly beneficial effects can be observed in pigs after MI. This could be a major step towards novel forms of immunotherapy for patients after MI.

Modulation of T cell responses against *Candida albicans*
(N. Beyersdorf)

T cells crucially contribute to immunity against opportunistic pathogens like *Candida albicans*. In our joint project with Prof. Dr. P. Zipfel, Jena, we observed binding of a number of proteins secreted by *C. albicans* directly to the surface of T cells modulating T cell function. We are following up on these observations to develop new therapeutic options for infections with *C. albicans*.

Role of sphingolipids in T cells and immunity against the Measles virus
(N. Beyersdorf)

Within the DFG research group 2123 'Sphingolipids in infection control' we are studying together with Prof. Dr. J. Schneider-Schaulies the impact function of sphingolipids on the balance of CD4⁺ conventional and Foxp3⁺ regulatory T cells. In a prospective clinical study we are now validating our findings from the mouse system in humans, which might lead to increased use of pharmacological modulators of sphingolipid metabolism as immunotherapeutics.

Teaching

Various theoretical and practical courses are provided to students. These include basic immunology lectures for medical, biomedical, biochemistry and biology students, which are complemented by a series of seminars for advanced students together with practical courses of 8 weeks per year.

SELECTED PUBLICATIONS

Borst J, Ahrends T, Babała N, Melief CJM, Kastenmüller W. (2018) CD4+ T cell help in cancer immunology and immunotherapy. Nat Rev Immunol 18:635-647.

Ribechini E, Hutchinson JA, Hergovits S, Heuer M, Lucas J, Schleicher U, Jordán Garrote AL, Potter SJ, Riquelme P, Brackmann H, Müller N, Raifer H, Berberich I, Huber M, Beilhack A, Lohoff M, Bogdan C, Eyrich M, Hermanns HM, Geissler EK, Lutz MB.(2017) Novel GM-CSF signals via IFN-γR/IRF-1 and AKT/mTOR license monocytes for suppressor function. Blood Adv 1:947-960.

Starick L, Riano F, Karunakaran MM, Kunzmann V, Li J, Kreiss M, Amslinger S, Scotet E, Olive D, De Libero G, Herrmann T. (2017) Butyrophilin 3A (BTN3A, CD277)-specific antibody 20.1 differentially activates Vg9Vd2 TCR clonotypes and interferes with phosphoantigen activation. Eur J Immunol 47:982-992.

Uri A, Werner S, Lühder F, Hünig T, Kerkau T, Beyersdorf, N. (2017) Protection of mice from actute Graft-versus-Host-Disease requires CD28 costimulation on donor CD4+ Foxp3+ regulatroy T cells. Front Immunol 8:721.

Welz M, Eickhoff S, Abdullah Z, Trebicka J, Gartlan KH, Spicer JA, Demetris AJ, Akhlaghi H, Anton M, Manske K, Zehn D, Nieswandt B, Kurts C, Trapani JA, Knolle P, Wohlleber D, Kastenmüller W. (2018) Perforin inhibition protects from lethal endothelial damage during fulminant viral hepatitis. Nat Commun 9:4805.

Institute for Virology and Immunobiology, Chair of Virology

CONTACT DETAILS

Professor Dr. med. Lars Dölken (Head)

Versbacher Str. 7
97078 Würzburg
Phone: 0931/31-89781
Fax: 0931/31-81611
E-mail: virologie@vim.uni-wuerzburg.de
www.virologie.uni-wuerzburg.de

Professor Dr. rer. nat. Florian Erhard
Phone: 0931/31-86523

Professor Dr. med. Michael Klein
Phone: 0931/31-81517

Mission and Structure

Research within the Chair of Virology is focused on basic mechanisms of viral pathogenesis, regulation of cellular and viral gene expression and immune evasion, as well as the development of drug resistance. Within the diagnostic unit serological and molecular biology techniques are available for qualitative and quantitative analyses as well as established cell culture systems for all relevant human viruses. We host approx. 65 scientific, administrative and technical staff. Sibylle Schneider-Schaulies is speaker of the DFG research unit 2123 'Sphingolipid Dynamics in Infection Control', which was established in 2014. Lars Dölken has held an ERC Consolidator Award since 2017.

Major Research Interests

Systems biology of herpes virus infections

(L. Dölken)

Herpesviruses cause a broad spectrum of diseases ranging from common cold sores to cancer. We employ a systems biology approach to study how herpes simplex virus 1 (HSV-1) and cytomegaloviruses (CMV) reprogram their host cells and escape the immune system. In the frame of the ERC Consolidator Award "HERPES", we are studying herpesvirus effectors of RNA synthesis, processing, export and stability in productive HSV-1 infection. This revealed host-selective disruption of transcription termination and impaired histone repositioning in the wake of RNA polymerase II. Moreover, we are studying translational regulation by upstream open reading frames (uORFs) and altered usage of non-canonical start codons during the course of infection. In collaboration with Prof. Florian Erhard and Dr. Emmanuel Saliba (HIRI), we developed a new single cell RNA-seq approach (scSLAM-seq), which illustrates real-time transcriptional activity for thousands of cellular genes at single cell level.

Computational systems virology

(F. Erhard)

The advent of "next-generation-sequencing" and other high-throughput techniques has revolutionized research in all life sciences. We develop new approaches and tools to make use of the large variety of high-throughput data to study virus host interactions. We developed a new statistical method (PRICE) to identify the full complement of open reading frames (ORFs) translated in the cells based on ribosome profiling data. This identified hundreds of novel viral gene products in human cytomegalovirus infection. Moreover, it revealed efficient presentation of peptides derived from cellular short ORFs (sORFs) by major histocompatibility class I (MHC-I) molecules on the cell surface. We thereby provide the first experimental validation of these cryptic gene products and highlight their potential relevance in adaptive immune responses. We also developed new computational methods (GRAND-SLAM) to quantify newly synthesized RNA from metabolic labelling experiments in single cells (scSLAM-seq). This revealed the earliest changes induced by cytomegalovirus infection in single cells. We will now expand our computational methods and apply them to new biological models.

Small non-coding RNAs during virus infection

(S. Backes)

We discovered that the poxviral poly(A) polymerase VP55 specifically induces the global and rapid degradation of miRNAs by a poorly characterized cellular pathway. In addition to determining the physiological relevance of poxviral miRNA antagonism for virus replication, we are establishing approaches to exploit VP55-induced global and synchronized miRNA degradation as a tool to investigate miRNA decay pathways.
A second major aim of our group is to determine the biogenesis and functions of a class of recently discovered small non-coding RNA species generated by Influenza A viruses (IAV). These small viral RNAs (svRNAs) directly associate with the viral RNA polymerase. We propose a new model in which svRNAs modulate the viral polymerase to switch from an mRNA-producing transcriptase to a genome-producing RNA replicase.

Measles virus immunomodulation

(S. Schneider-Schaulies)

Interaction with cells of hematopoietic origin is of crucial importance for measles virus (MV) dissemination. One focus of the group addresses parameters governing transmission of infectious virus from immune donor cells to respiratory tract epithelial cells in 3D environments involving suitable tissue models (GRK 2157). Dynamic repatterning of T cell receptor signalosome components into membrane microdomains is crucial for efficient T cell activation.
A second focus of the group addressed the role of sphingomyelinases both in T cell metabolism and activation and in MV-induced T cell suppression (‚Sphingolipid dynamics in infection control' FOR2123). Molecular targets of sphingomyelinase-catalysed membrane restructuring are currently being identified using functionalized sphingolipids in bioorthogonal click reactions (collaboration with J. Seibel, Organic Chemistry, Z01 FOR2123) as are membrane proximal effectors of MV essential for T cell silencing using a phosphoproteomic approach (collaboration with L. Jänsch, Helmholtz, Braunschweig).

Pathogenesis of Measles: Virus-Host-Interactions

(J. Schneider-Schaulies)

Acute measles infection results in transient immunosuppression. The virus sometimes persists in the central nervous system (CNS), which may lead to subacute sclerosing panencephalitis (SSPE) many years later. Genetic ablation or pharmacological inhibition of the acid sphingomyelinase (ASM) increases the frequency and activity of regulatory T cells and the CNS infection with measles virus in a mouse model. Our data suggest that ASM inhibiting drugs such as amitriptyline should be considered as potential immunomodulatory drugs for the treatment of inflammatory and autoimmune diseases. Other enzymes of the sphingolipid metabolism are

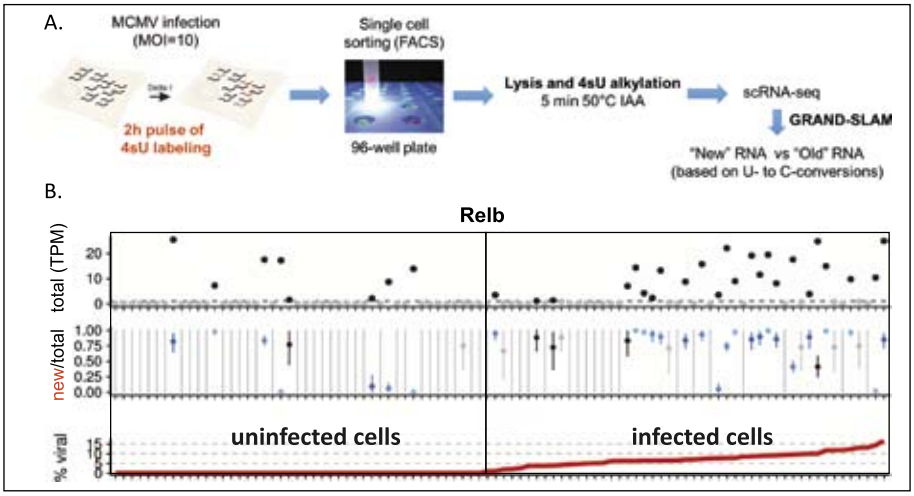


Fig.: Visualization of transcriptional activity in single cells A. Single cell SLAM-seq (scSLAM-seq) combines metabolic RNA labelling, chemical nucleoside conversion and single cell RNA sequencing. B. Transcriptional activity of an exemplary gene (Relb) in a total of 94 single cells following 2h of CMV infection. (Erhard et al., in revision)

also promising to inhibit viral infection. Various candidate host factors and pathways are under investigation.

Pathogenesis of Pneumoviruses
(C. Krempl)

Respiratory Syncytial virus (RSV) is a major viral cause of serious lower respiratory tract disease in children, the elderly as well as immunocompromised patients. We combine model systems for RSV with the surrogate in vivo model of the RSV-mouse homolog, the pneumonia virus of mice (PVM), to investigate pathogenicity factors of virus and host with a focus on virus-induced immunopathology. PVM-reporter viruses permit the spatio-temporal analysis of infection and the immune response in transgenic mouse models. RSV infections are investigated using human respiratory 3D-tissue models in close collaboration with the Department of Tissue Engineering and Regenerative Medicine. The aim of these studies is a better understanding of the mechanism of RSV-induced disease and the development of targeted therapy approaches.

Pathogenesis of HIV infection and HIV/AIDS in Africa
(C. Scheller)

HIV infection triggers a chronic immune activation that correlates with the progression to AIDS. Despite antiretroviral therapy, some patients still exhibit elevated immune activation, which is associated with increased morbidity. Substances that dampen this activation may have a therapeutic benefit. We investigate the effects of immunomodulators on disease progression in clinical studies. In addition, we conduct epidemiological studies to assess the prevalence of drug-resistant HIV strains in Sub-Saharan Africa (South Africa, Tanzania, Malawi).

Pathogenesis of HIV-associated neurocognitive disorders (HAND)
(E. Koutsilieri, C. Scheller)

Antiretroviral treatment provides a normal life expectancy for patients with HIV infection. However, the infection is associated with neuropsychiatric complications ("HIV-associated neurocognitive disorders", HAND) in about 30% of the patients. We study the role of the neurotransmitter dopamine and the influence of genetic polymorphisms at the dopaminergic synapse on HAND in patients in Germany, South Africa and Tanzania. In a randomized controlled trial, we analyse efficacy, safety and tolerability of lithium in the treatment of HAND. A particular focus is on the influence of lithium on central and peripheral dopaminergic neurotransmission (EDCTP; SP2011.41304.065/BMBF01KA1306).

Development of new antiviral protease inhibitors and retroviral splicing
(J. Bodem)

Dengue viruses (DENV) are human pathogenic RNA viruses endemic in more than 100 countries. No specific therapy or vaccine is currently available. In cooperation with the group of Prof. Tanja Schirmeister (University of Mainz), we identified and optimised novel antiviral agents, which inhibit viral replication at submicromolar concentrations. Moreover, we identified new lead compounds targeting herpesviral proteases, which we are currently improving by rational and structure-guided drug design.
Complex retroviruses control gene expression by extensive alternative splicing involving specific regulatory elements. We found that a positive acting splice regulator is used by retroviruses to inhibit splicing of viral RNAs. This effect is position dependent and we were able to elucidate the molecular mechanism.

Clinical Virology
(B. Weißbrich, C. Prifert, K. Knies)

The clinical diagnostic unit of the Institute provides the virological diagnostic services for the University Hospital of Würzburg. Clinical virology research focuses on the epidemiology of respiratory viruses. In this area, there is an intensive collaboration with the Department of Infectious Diseases of the Pediatric University Hospital.

Teaching

Staff members at the department of virology offer a variety of lectures, seminars and lab training for Bachelor-, Master-, and medical students of the Faculty of Medicine and Natural Sciences. Students from other faculties are welcome to attend.

SELECTED PUBLICATIONS

Boertlein C, Draeger A, Schoenauer R, Kuhlemann A, Sauer M, Schneider-Schaulies S, Avota E. (2018) The neutral sphingomyelinase is required to polarize and sustain T cell receptor signaling. Front Immunol 9:815.

Erhard F, Halenius A, ..., Zimmer R, Dölken L. (2018) Improved Ribo-seq enables identification of cryptic translation events. Nat Methods 15:363-366.

Horn A, Scheller C, du Plessis S, Burger R, ..., Koutsilieri E. (2017) The dopamine-related polymorphisms BDNF, COMT, DRD2, DRD3, and DRD4 are not linked with changes in CSF dopamine levels and frequency of HIV infection. J Neural Transm 124:501-509.

Jürges C, Dölken L, Erhard F. (2018) Dissecting newly transcribed and old RNA using GRAND-SLAM. Bioinformatics 34:i218-i226.

Moschall R, Denk S, Erkelenz S, Schenk C, Schaal H, Bodem J. (2017) A purine-rich element in foamy virus pol regulates env splicing and gag/pol expression. Retrovirology 14:10.

Institute of Systems Immunology, Chair of Systems Immunology I and II

CONTACT DETAILS

Professor Dr. med. Wolfgang Kastenmüller
(Head, Chair of Systems Immunology I)

Professor Dr. med. Georg Gasteiger
(Head, Chair of Systems Immunology II)

Versbacher Str. 9
97078 Würzburg
Phone: 0931/31-89740
E-mail: systemimmunologie@uni-wuerzburg.de
www.med.uni-wuerzburg.de/systemimmunologie

Mission and Structure

The Institute of Systems Immunology was founded at the end of 2017 and is momentarily in the set-up and recruitment phase. Starting January 2020 the institute will commence to function as Max-Planck Research Group. Supported by the Max-Planck Society and the State of Bavaria the research groups will focus on studying the interplay of the immune system with the organism as a whole, especially the interaction of different cells of the immune system within local networks as well as the interaction with cells of other organ systems. The aim is to understand the regulatory mechanisms of the immune system in order to develop new approaches to generate effective immune responses against e.g. infectious agents and tumors or a therapy for inflammatory diseases.

The Institute of Systems Immunology mainly focuses on basic research and is active in the training of PhDs and Post-Docs. The research is supported through third-party funding projects of the ECR (Consolidator Grant 2019 - Prof. Kastenmüller, Starting Grant 2018 – Prof. Gasteiger) and the DFG (Emmy-Noether Program - Prof. Gasteiger) and is part of consortia, e.g. the DFG priority program 1937 ”Innate Lymphoid Cells”.

Research Foci

The regulation of the immune system requires complex mechanisms to efficiently fight invasion by pathogens and malignant cells while preventing harmful reactions against the body’s healthy tissue or symbiotic microbiota. If this intricate balance is not achieved, it can lead to an increased susceptibility to infections and tumors or to the development of autoimmune diseases. The researchers at the Institute of Systems Immunology examine the mechanisms of the immune system at multiple scales, investigating, for example, the influence of external and environmental factors (e.g. diet, microbiome, infection), the mechanisms of cellular interactions in different tissues as well as the role of single molecules and metabolic pathways in homeostasis and disease.

Leukocyte Dynamics
(W. Kastenmüller)

Similar to the nervous system the immune system represents an interactive cellular network, which gets locally activated in order to induce systemic changes. There is, however, one major difference between these two systems. In contrast to the nervous system the immune system is comprised of a dynamic network in the sense that its cellular elements (leukocytes) travel through the body. When the immune system gets activated, different cells must work together to induce and organize an efficient immune response. Therefore, the cellular migration between and within organs is a key feature of the immune system. In the research group Leucocyte Dynamics we want to find out when, where and how different immune cells work together to induce an immune response and efficiently eliminate pathogens. A main focus is cell-cell interactions and associated cellular migration induced by cytokines and chemokines. In order to get answers to these questions as well as for the analysis of cellular immune responses in the context of infections we combine classical immunological methods like multicolor flow-cytometry with the latest microscopy including 2-photon imaging and confocal analysis of tissue sections and entire tissues. Our lab works on the following topics:

- Function and development of cytotoxic CD8+ T cells
- Migration and dynamics of dendritic cells in the tissue
- Immune defense to viral and bacterial infections
- Interface between innate and adaptive immune system
- Intercellular communication within the tissue

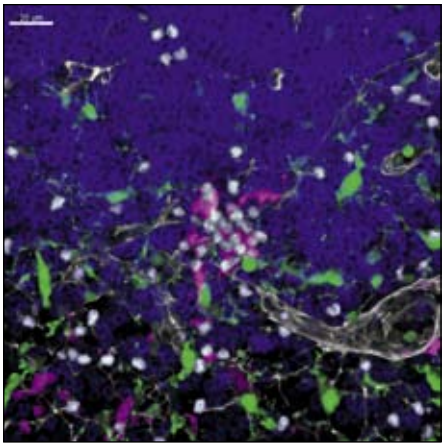


Fig. 1: CD8+ T cells interact with a group of myeloid cells in the lymph node. Depicted is a section through the lymph node 8h after a viral infection in the skin (vaccinia virus). Immunohistochemical dyeing for macrophages (green), dendritic cells (purple), antigen specific CD8+ T cells (white), B cells (blue) and cells of the connective tissue (grey).

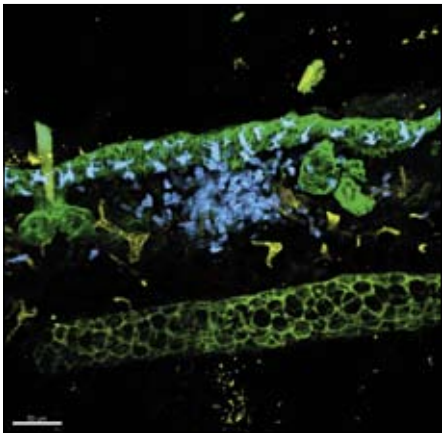


Fig. 2: Memory T cells populate niches in the non-lymphoid organs. Depicted is a section through the skin in the memory-phase after a local viral infraction (vaccinia virus). Immunohistochemical dyeing for E-Cadherin (green) mark the epidermis and CD3+ T cells (turquois).

Tissue-resident Lymphocytes
(G. Gasteiger)

Nearly all organs and anatomic compartments "accommodate" tissue-resident lymphocytes, which create a local network. Therefore, these cells are strategically positioned in different physiological barriers like e.g. the skin, lung and intestine to support the immune surveillance and the microbial defense at the front line of our body. In addition to the immediate immunological effector function these lymphocytes interact locally with hematopoietic and non-hematopoietic cells and in this respect support physiological mechanisms of the tissue hemostasis, tissue repair and barrier function. Recently discovered innate lymphoid cells (ILCs) appear to seed and integrate into different organs as a part of their default developmental program early during life. Tissue resident memory T cells, on the other hand, can be generated in the adult organism in response to infection or vaccination. The microanatomical niches, the numbers and the specific kind of cell types differ very much between the local lymphocyte networks in different organs already under physiological conditions. In the research group Tissue-resident Lymphocytes we investigate how and where local lymphocyte networks are generated and positioned in different tissue-contexts and which organ-specific functions they have. We also examine the mechanisms of cellular communication with non-hematopoetic cells or other cells of the immune system that are recruited from the blood e.g. during infection. Our aim is to understand the role of tissue resident lymphocytes for balanced tissue function and in immune responses, inflammatory diseases and tumor development at barrier tissues.

Metabolism and Immune Cell Signaling
(M. Vaeth)

The research group Metabolism and Immune Cell Signaling aims to understand the regulatory circuits of lymphocyte activation and function at the molecular level. We investigate the signals and regulatory hubs in the context of complex inflammatory reactions. In addition to 'classical' signal transduction (e.g. through Ca^{2+} ions) and the control of gene expression of immune cells (e.g. through transcription factors of the NFAT protein family) we are especially interested how metabolic adaptions of lymphoid cells regulate local immune responses. As immune cells migrate and populate virtually all tissues of the body they must adapt to the local microenvironment and nutrient availability. This is especially interesting in the context of cancerous diseases because the specific microenvironment of tumors often represents a 'metabolic barrier' that impedes the function of cytotoxic T cells and promotes their dysfunction thus disabling efficient anti-tumor immunity. We aim to understand and exploit the mechanisms of immune cell regulation in tissues at the molecular level to identify promising targets for the development of novel immune therapies, for example for the treatment of cancer and autoimmune diseases.

Host Microbial Interactions
(M. Gomez de Agüero)

In the human organism billions of different microorganisms like bacteria, archaeas, fungi, parasites and viruses can be found. Most of these microorganisms are part of the commensal microflora that provides essential vitamins and different nutrients and they protect us against microbial attack from pathogens. In addition to that the microbiome and its metabolic products stimulate our immune system directly as well as indirectly and therefore contributes to its protective function. Based on the latest research results the microbiome stimulates the immune system already at the first day of life and promotes its functional development. We could recently demonstrate that already during pregnancy the microbiome of the mother influences the immune system of the unborn child and prepares it to optimally deal with infections after birth. In our projects we study these functions of the microbiome and want to elucidate the underlying molecular mechanisms. Further, we want to understand how changes of the microbiome of the mother impact the child's health after birth and long-term during the course of life. We study how the interactions with the microbiome modulate different elements of the immune system and thus influence the immune response in the context of different infectious diseases, inflammatory and autoimmunological processes.

Teaching

Different theoretical and practical events for the students will be offered. They include basic lessons, seminars and internships in immunology for medical, biomedical, biochemistry and biology students. The PhD students at the Institute of Systems Immunology participate in the section biomedicine of the graduate school of Life Sciences (GSLS) of the University of Würzburg or the IMPRS graduate school of the Max-Planck Society.

SELECTED PUBLICATIONS

Borst J, Ahrends T, Bąbała N, Melief CJM, Kastenmüller W. (2018) CD4+ T cell help in cancer immunology and immunotherapy. Nat Rev Immunol 18:635-647.

Gomez de Agüero M, Ganal-Vonarburg SC, Fuhrer T, Rupp S, Uchimura Y, Li H, Steinert A, Heikenwalder M, Hapfelmeier S, Sauer U, McCoy KD, Macpherson AJ. (2016) The maternal microbiota drives early postnatal innate immune development. Science 351:1296-1302.

Muschaweckh A, Buchholz VR, Fellenzer A, Hessel C, König PA, Tao S, Tao R, Heikenwälder M, Busch DH, Korn T, Kastenmüller W, Drexler I, Gasteiger G. (2016) Antigen-dependent competition shapes the local repertoire of tissue-resident memory CD8+ T cells. J Exp Med 213:3075-3086.

Vaeth M, Maus M, Klein-Hessling S, Freinkman E, Yang J, Eckstein M, et al. (2017) Store-Operated Ca2+ Entry Controls Clonal Expansion of T Cells through Metabolic Reprogramming. Immunity 47:664-679.

Welz M, Eickhoff S, Abdullah Z, TrebickaJ, GartlanKH, SpicerJA, Demetris AJ, H. Akhlaghi H, Anton M, Manske K, Zehn D, Nieswandt B, Kurts C, Trapani JA, Knolle P, Wohlleber D, Kastenmüller W. (2018) Perforin inhibition protects from lethal endothelial damage during fulminant viral hepatitis. Nat Comm 9:4805.

Institute of Human Genetics

CONTACT DETAILS

Professor Dr. med. Thomas Haaf
(Head)

Biozentrum
Am Hubland
97074 Würzburg
Phone: 0931/31-88738
Fax: 0931/31-87398
E-mail: thomas.haaf@uni-wuerzburg.de
www.biozentrum.uni-wuerzburg.de/humangenetik

Professor Dr. rer. nat. Eva Klopocki
Phone: 0931/31-89779

Mission and Structure

Human Genetics is an important area of biomedicine with increasing impact on the practice of medicine. Human Genetics investigates evolution, structure, function, inheritance, and disorders of the human genome. Results of these studies are applied to genetic diagnosis, genetic counselling and patient care. The Institute is represented by different, both basic science and clinically oriented groups. It provides genetic services for patients and teaches students in the fields of medicine, biomedicine, biochemistry, and biology. Located in the Würzburg Biocenter, the Institute belongs to the University of Würzburg School of Medicine.

Major Research Interests

Medical genetics

As an application of human genetics, medical genetics translates scientific insights from basic human genetic research into the clinics. Preventive and predictive medicine are an important focus. Medical genetics deals with a large spectrum of inherited syndromatic disorders and familial predispositions. Interactions with patients and their families are established during genetic counselling sessions. In addition, medical genetics assures access to genetic testing for an ever increasing number of inherited disorders and disease susceptibilities. The genetic counsellor is responsible for the correct communication and interpretation of genetic test results. The Center for Muscular Disorders of the German Society of Muscular Diseases (together with the Department of Neurology) provides diagnostic, counselling, and social services for patients and families affected by muscle disease. The Center for Familial Breast and Ovarian Cancer (together with the Department of Gynecology) takes care of patients and families affected by or at risk of familial breast and ovarian cancer. Services include genetic counselling and testing as well as provision of medical and preventive care. In addition to neuromuscular, neurodegenerative, and familial cancer diseases, the medical genetics group studies the molecular pathology of craniosynostoses, congenital deafness, and developmental disorders.

Molecular human genetics

(S. Rost)

The group has a long standing interest in the genetics of bleeding disorders and of inherited muscle disorders, including the muscular dystrophies, the myotonias, and malignant hyperthermia. Next-generation-sequencing (NGS) techniques have greatly expanded the possibilities to identify the genomic alterations underlying heritable disorders. The technical facilities for NGS (Illumina NextSeq and MiSeq) were established in the department and software for efficient data analysis was implemented. The current challenge is to understand the biological significance of the great many variants identified by NGS assays.

Molecular genomics

(E. Klopocki)

The research focus is on pathogenesis of congenital malformations. In recent years genomic copy number variations (CNVs) were shown to be responsible for phenotypic variability and furthermore to be causal for congenital malformations. Clinically relevant

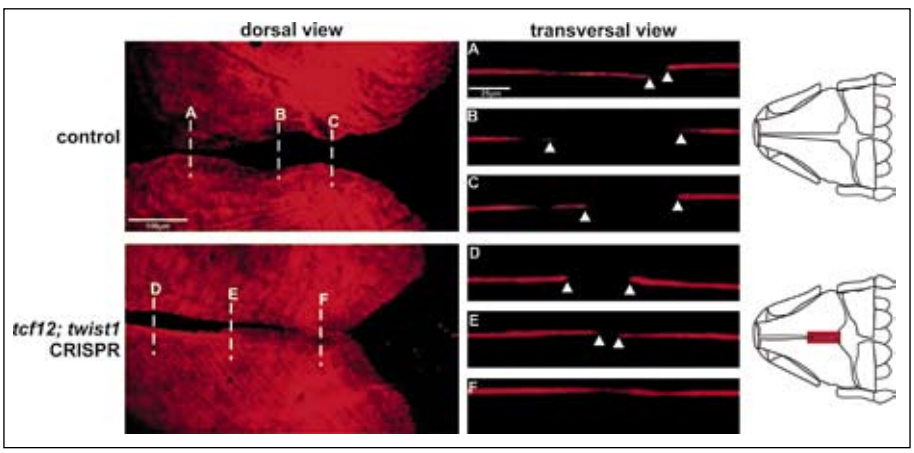


Fig. 1: Combined mutations in tcf12 and twist1a/b genes result in suture fusion and craniosynostosis in zebrafish (right panel: sketch of zebrafish skull). Alizarin red staining of calcified skull tissue.

CNVs affect coding regions (genes) as well as non-coding sequences with regulatory functions. In addition to congenital limb malformations the group investigates congenital craniofacial malformations like craniosynostosis. A broad range of methods is applied, including high-resolution microarray-based comparative genomic hybridization (array CGH) and NGS to detect CNVs, point mutations, and small insertion/deletions, respectively. For further functional characterization of candidate genes and the phenotypic consequences of novel variants zebrafish (*Danio rerio*) was established as model organism. The CRISPR/Cas technology is applied as a tool for genome editing to create knock-out and knock-in lines in zebrafish and thereby model human disorders (Fig. 1). Collaborations with the Departement of Cardiovascular Genetics (Prof. Gerull) at the Comprehensive Heart Failure Center Würzburg (CHFC) and the Orthopedic Center for Musculoskeletal Research (Prof. Jakob) at the König-Ludwig-Haus use the zebrafish as *in vivo* model for cardiomyopathies and rare bone disorders, respectively.

Somatic cell genetics
(R. Kalb)

Genes that ensure genomic stability of somatic cells and thus safeguard against cell death, premature ageing, and malignant transformation are of key interest to this group. These so-called caretaker genes are involved in the recognition and reversal of DNA damage. One focus is on genes of the FA/BRCA pathway which is crucial for efficient repair of DNA-interstrand crosslinks. Biallelic mutations result in Fanconi Anemia (FA) characterized by congenital abnormalities, bone marrow failure, and increased risk for developing cancer. To date, 23 FA-associated genes have been identified. Some of them, in particular *BRCA1*, *BRCA2*, *PALB2*, *XPF*, *RFWD3*, and *FANCJ* are also associated in other DNA repair pathways, however their exact molecular functions still remain elusive. Together with national and international collaborators, we want to decipher the molecular networks using genetic and cellular studies. Clinical and genetic data of patients with defects in caretaker genes support functional studies. Patient-derived cell lines are therefore a very powerful tool to analyse the effect of mutations on DNA, RNA, and protein level including signal transduction within the original genetic background. Subject of current research is the identification and functional characterization of genes required for genomic maintenance within the available patient cohort.

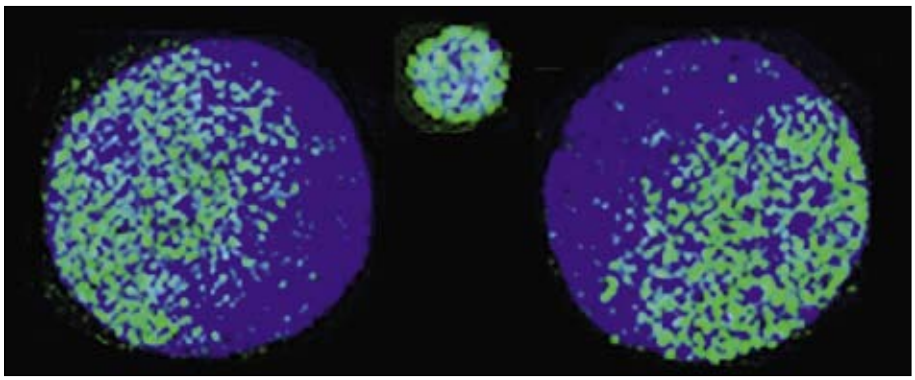


Fig. 2: Methylcytosine staining of mouse two-cell embryo. The already demethylated maternal genome (blue DAPI staining) and the not yet demethylated maternal genome (green anti-MeC immunofluoresescence) are spatially separated, occupying opposing nuclear territories. The second polar body which is still attached to the embryo remains methylated.

Epigenetics
(T. Haaf)

Epigenetic information is not encoded by the DNA sequence itself but by reversible modifications of DNA (in particular methylation of CpG dinucleotides) and/or histones. In mammals, the paternal and maternal genomes undergo parent-specific methylation reprogramming in the germ line and during early embryogenesis (Fig. 2). Stochastic and/or environmentally induced errors (epimutations) in this highly coordinated process may contribute to human disease. The group analyzes the effects of assisted reproductive technologies on epigenetic reprogramming in murine and bovine germ cells/embryos as well as in human miscarriages and newborns. Aberrant programming of the fetal metabolism in utero (i.e. by maternal malnutrition or overnutrition) increases the risk for many complex civilization diseases later in life. In addition, we analyse the effects of paternal factors, in particular age and body mass index on the sperm epigenome and the conceived children. Another project searches for epigenetic differences in the regulation of gene expression in human and non-human primate brains. DNA sequence variations alone cannot account for the enormous differences between human and primate brain structure/function and their cognitive abilities. Epigenetic factors may form a main source of phenotypic variation between individuals and between species.

Teaching

The medical school curriculum includes a lecture course entitled "Clinical Human Genetics" which is taught in the 6th semester, together with an interdisciplinary course on "Disease prevention". Medical students can choose human genetics as an elective during their rotating internships, with emphasis on genetic diagnosis, dysmorphology, and genetic counselling. In addition to teaching medical students, the Institute also offers courses to students of biomedicine, biochemistry, and biology, including laboratory courses in human cytogenetics and human molecular genetics. Undergraduate biology students can choose human genetics as one of the major subjects. Graduate students can obtain their M.Sc. or Ph.D. degrees within one of the research groups of the Department.

SELECTED PUBLICATIONS

Böck J, Remmele CW, Dittrich M, Müller T, Kondova I, Persengiev S, Bontrop RE, Ade C, Kraus TJF, Giese A, El Hajj N, Schneider E, Haaf T. (2018) Cell type and species-specific methylation patterns in neuronal and non-neuronal cells of human and chimpanzee cortex. Cereb Cortex 28:3724-3739.

El Hajj N, Haertle L, Dittrich M, Denk S, Lehnen H, Hahn T, Schorsch M, Haaf T. (2017) DNA methylation signatures in cord blood of IVF/ICSI children. Hum Reprod 32:1761-1769.

Knies K, Inano S, Ramírez MJ, Ishiai M, Surrallés J, Takata M, Schindler D. (2017) Biallelic mutations in the ubiquitin ligase RFWD3 cause Fanconi anemia. J Clin Invest 127:3013-3027.

Will AJ, Cova G, Osterwalder M, Chan WL, Wittler L, Brieske N, Heinrich V, de Villartay JP, Vingron M, Klopocki E, Visel A, Lupiáñez DG, Mundlos S. (2017) Composition and dosage of a multipartite enhancer cluster control developmental expression of Ihh (Indian hedgehog). Nat Genet 49:1539-1545.

Zaum AK, Stüve B, Gehrig A, Kölbel H, Schara U, Kress W, Rost S. (2017) Deep intronic variants introduce DMD pseudoexon in patient with muscular dystrophy. Neuromuscul Disord 27:631-634.

Institute for Medical Radiation and Cell Research (MSZ)

CONTACT DETAILS

Professor Dr. rer. nat. Albrecht Müller (acting Head)

Zinklesweg 10
97078 Würzburg
Phone: 0931/201-45848
Fax: 0931/201-45148
E-mail: albrecht.mueller@uni-wuerzburg.de
www.strahlenkunde.uni-wuerzburg.de

Professor Dr. rer. nat. Thomas Raabe
Phone: 0931/31-88548

Mission and Structure

The institute is proviosionally headed by Prof. Dr. Müller and consists of two groups which are working on different aspects of regenerative cell biology. Prof. Müllers group (housed in the ZEMM, building E7) is analyzing gene expression programs in mammalian embryonic and adult stem cells with a special emphasis on chromatin regulation. Prof. Raabe´s group (Biocenter) analyses neural progenitor cells, neural circuit formation and function in the model system *Drosophila*. Prof Müller is member of the bioethics commission of the state of Bavaria, of the DFG permanent senate commission on genetic research, and of the Leopoldina working group on genome editing. The MSZ is working together with several institutes of the faculties of medicine, biology and chemistry and is part of several national research collaborations.

Stem Cell Biology

(A. Müller)

Stem cells are rare but essential cell types for development and tissue regeneration. Research on stem cell biology and cellular pluripotency is one of the most promising research fields in human medicine. Of central importance to our studies is the question how global chromatin states guide stem cell behaviour. In the course of a project within the DFG priority program 1356 (*Pluripotency and cellular reprogramming)* funded until 2014, we identified the chromatin-associated polycomb group (PcG) protein PCGF6 as a crucial factor for the maintenance of embryonic stem cell (ESCs). In a DFG funded follow-up project we now aim at the elucidation of the precise molecular function of PCGF6 for the maintenance of pluripotency and at the end of pluripotency, when ESCs enter differentiation. In a further project funded until 2018 by the DFG priority programme 1463 (*Epigenetic regulation of normal haematopoiesis and its dysregulation in myeloid neoplasia*) we analyse the function of histone demethylases which belong to the KDM6 family and counteract the function of PcG proteins. Our results show that inhibition of KDM6 in differentiating embryonic stem cells leads to a DNA damage response. We therefore hypothesise that KDM6 demethylases in addition to their function in the regulation of gene transcription may also be involved in the maintenance of genomic stability. More recent research on the function of the KDM6 paralog KDM6A show that KDM6A is an important molecular player for the function of hematopoietic stem and progenitor cells. A further key aspect of our work is the elucidation of epigenetic mechanisms during neural ESC differentiation (Fig. 1). In this connection we are analysing the role of microRNA-26 (miR-26) during mammalian neural development. Our results show that miR-26 is an important factor at the beginning of neural differentiation. Our current work aims at the identification of the molecular machinery that controls the maturation of miR-26 at the start of neural differentiation. We hope that this way we will get further insight in the molecular regulation at the beginning of neurogenesis. These studies are performed in collaboration with the Department of Biochemistry (Prof. Utz Fischer) as part

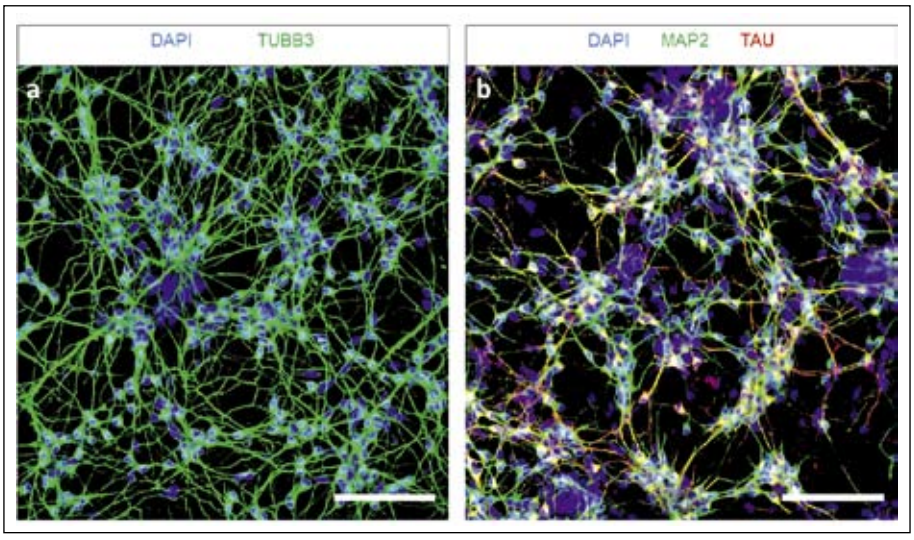


Fig. 1: Shown are ESC-derived neurons at day 15 of differentiation. Cells were stained with antibodies against the neuronal markers TUBB3 (a) or MAP2 and TAU (b). DAPI was used to stain the nuclei (a) and (b). Sacle bars: 100µm.

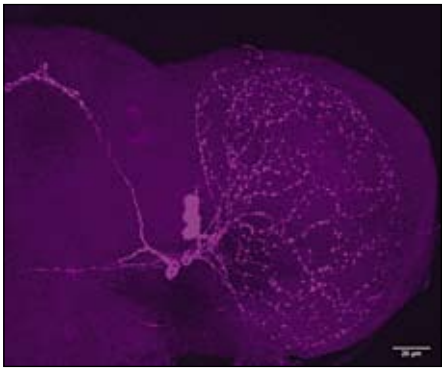


Fig. 2: Shown is a brain hemisphere of an adult Drosophila brain stained with an antibody against the neuropeptide PDF. PDF expression is seen in a subset of clock neurons, which among others control circadian activity and metabolism. Loss of RSK function does not affect architecture of clock neurons, but shortens periodicity of the circadian clock under constant darkness.

of the DFG priority programme 1738 (*Emerging roles of non-coding RNAs in the nervous system*).

Molecular Genetics
(T. Raabe)

The main focus of our research is the characterization of molecular mechanisms controlling development and function of neural networks in the model system *Drosophila*. Indeed, more than two-third of human disease-associated genes are conserved in *Drosophila*. In this context, we are interested in the protein kinase RSK2. Loss of RSK2 function in humans causes among others severe mental disabilities (Coffin-Lowry syndrome, CLS). In collaboration with the Department of Psychiatry (Dr. Dr. Fischer) and the Department of Neurophysiology (Prof. Dr. Kittel) we could establish a function of this kinase for synaptic transmission and axonal transport in the fly system. Funded until 2017 by the collaborative research center SFB1047 ("Insect timing") we were recently able to uncover a function of RSK in regulation of the circadian clock (Fig. 2). Our current research efforts aim to elucidate a potential link between RSK, synaptic plasticity and time-dependent learning and memory processes. Our research will hopefully contribute to better understand the pathophysiology of CLS. In a further project, we are analysing a number of mutations interfering with proliferation potential of neural progenitor cells, which finally lead to hypo- or hypertrophy of the adult nervous system. In particular, we are interested in cell cycle and growth control of neural progenitor cells. The question whether and how daytime dependent cellular metabolism affects proliferation of progenitor cells is addressed in a project funded by the PostDoc Plus programme of the GSLS. Finally, we are interested in the family of p21-activated kinases (PAK) and their role in regulation of cell morphogenesis in tissues through modulation of Cadherin-mediated cell adhesion. Based on first findings in vertebrates, we want to establish a link between PAK proteins, the dopaminergic system and neurodegenerative processes.

Teaching

The teaching activities relate to the research activities of the MSZ groups. Practical courses are offered for medical, biomedical, biochemical and biological students. Our main emphasis lies on teaching principles of cell biology. Practical courses on cell biology and on model organisms introduce students of biomedicine and biochemistry to modern techniques in cell biology, biochemistry and microscopy. Of particular interest to students is the interdisciplinary lecture series "stem cell biology and regenerative medicine" which covers current research topics of stem cell biology and their potential clinical applications. Biologists have the opportunity to gather insight in specific questions of molecular biology in a laboratory course. Further the MSZ takes part in various practical courses and lectures of the medical and biological faculty, for example in neurodevelopment. Albrecht Müller is the Study Responsible for the Accompanying and Master Study programme "Experimental Medicine".

SELECTED PUBLICATIONS

Beck K, Hovhanyan A, Menegazzi P, Helfrich-Förster C, Raabe T. (2018) RSK influences the pace of the circadian clock by negative regulation of protein kinase Shaggy activity. Front Mol Neurosci 11:122.

Blumröder R, Glunz A, Dunkelberge, BS, Serway CN, Berger C, Mentzel B, de Belle JS, Raabe T. (2016) Mcm3 replicative helicase mutation impairs neuroblast proliferation and memory in Drosophila. Genes Brain Behav 15:647-659.

Fischer M, Raabe T. (2018) Animal models for Coffin-Lowry Syndrome: RSK2 and nervous system dysfunction. Front Behav Neurosci 12:106.

Hofstetter C, Kampka JM., Huppertz, S, Weber H, Schlosser A, Müller AM, Becker M. (2016) Inhibition of KDM6 activity during murine ES cell differentiation induces DNA damage. J Cell Sci 129:788-803.

Müller AM, Strack S. (2017) Neue Genome-Editing-Techniken: Von den Grundlagenwissenschaften zur Konsensbildung in Wissenschaft und Gesellschaft. Kritisches Jahrbuch der Philosophie: Genome Editing- Quo Vadis? Ethische Fragen zur CRISPR/Cas-Technik. (Ranisch R, Müller AM, Hübner C, Knoepffler N, Eds.) ISBN 978-3-8260-6499-9.

Institute for the History of Medicine

CONTACT DETAILS

Professor Dr. med. Dr. phil. Michael Stolberg (Head)

Oberer Neubergweg 10a
97074 Würzburg
Phone: 0931/31-83093
E-mail: gesch.med@uni-wuerzburg.de
www.medizingeschichte.uni-wuerzburg.de

Mission and Structure

The origins of the Institute for the History of Medicine reach back to the nineteenth century when medical history became an established part of the medical curriculum in Würzburg. In the 1920s, the University boasted one of the first institutes of medical history in Germany, directed by Georg Sticker. The Institute was closed under National-Socialist rule but brought back to life after 1945. Since the 1990s, it has been housed in a former private ENT-clinic that was generously donated for this purpose by the late Würzburg professor Horst Wullstein and his wife Sabina. It occupies additional rooms in the former Zoology building in the city center. The Institute has one of the largest medico-historical libraries in the German-speaking area as well as a growing collection of old surgical and obstetrical instruments and wax models.

Major Research Interests

Research at the Institute has a major focus on the history of early modern medicine but its members also study various aspects of the more recent history of medicine and the body such as the history of obesity and palliative care and historical medical objects and films. Various projects with third-party funding are based at the Institute (see below). In addition, the Institute cooperates with other historical collections at the University of Würzburg in the project „INSIGHT. Signaturen des Blicks – Facetten des Sehens“ (K. Nolte; M. Weber), which studies the perception and uses of historical objects, and in a collaborative project that examines the works and manuscripts of Joachim Camerarius (U. Schlegelmilch; M. Huth).

Early Modern Physicians' Correspondence
(M. Stolberg, U. Schlegelmilch, T. Walter, A. Rappert-Sälzer)

Under the auspices of the Bayerische Akademie der Wissenschaften, this workgroup, which was established in 2009, is undertaking a systematic survey of the thousands of letters written by and to 16th- and 17th-century physicians in the German-speaking area. These letters have come down to us in libraries and archives all over Europe and are valuable sources for the study of a wide range of topics, from epistolary networks and the dissemination of new medical findings and theories to ordinary medical practice and the private lives of the early modern upper classes in general. Data on the individual letters and in many cases also detailed summaries of the letters' contents are entered into a database that is freely accessible to the international research community via internet (www.aerztebriefe.de).

History of Corpulence, 1500-1900
(M. Stolberg, A. Pyrges)

The negative ideas and images associated with corpulence in medicine and society are widely taken to be a fairly recent phenomenon. Already in the Middle Ages, corpulence was described as the of cause of apoplexy, putrid fevers and other deadly diseases however. With funding by the Deutsche Forschungsgemeinschaft (DFG) this project examined the long-term development of medical ideas about the dangers of corpulence and their impact on the esthetic, moral and economic judgments about corpulence in the media and among the population at large.

Anatomical teaching and practice in Padua (1540-1600)
(M. Stolberg, F. Bigotti)

Based on hitherto unknown and very detailed notes taken by German medical students in Padua, this DFG-funded project examines the approaches and methods that the leading post-Vesalian anatomists in Padua developed and passed on to their students and traces the application of anatomical knowledge to clinical and surgical practice.

Fig. 1: Doctor's visit. (Egbert van Heemskerk III, ca. 1725)

Fig. 2: Trepans, Würzburg, first half of the 19th century, before restauration.

Historical Collections of the Medical Faculty in Würzburg
(S. Schlegelmilch)

The Institute is undertaking a systematic survey of the collections of historical medical instruments, objects, films and documents at the Medical Faculty and of their condition of preservation. It is also doing research on them, currently with a focus on the history of surgery (16th-19th centuries) and of the history of didactic medical films. The collections were shown to a larger public in an exhibition at the Landesgartenschau Würzburg and on German television (Terra X).

Teaching

The Institute offers about a dozen compulsory courses in medical terminology and professional orientation every term, for students of medicine and of dentistry, as well as two elective seminars on medical history and one on medical history and medical ethics for medical students. In addition, it has developed online-courses in medical terminology that are accessible via the "Virtuelle Hochschule Bayern". The Institute is also responsible for organizing the compulsory transdisciplinary course on the history, theory and ethics of medicine for medical students in their third year, which combines a series of lectures with about 15 seminars on medical ethics for smaller groups of students. By ministerial agreement, the Institute is also responsible for the teaching of medical history and medical theory at the University of Regensburg. Furthermore, a wide variety of elective courses and seminars is offered, in Würzburg, ranging from medical English and courses in bibliography and paleography to seminars dealing with specific topics of medico-historical interest. The Institute's collection of historical objects is also used in the teaching of nurses at the University Hospital and in the interdisciplinary training of museologists in Würzburg.

SELECTED PUBLICATIONS

Schlegelmilch S. (2018) Ärztliche Praxis und sozialer Raum im 17. Jahrhundert: Johannes Magirus (1615–1697), Köln/Weimar/Berlin 2018.

Schlegelmilch S. (2018) Die Konstruktion des Patienten/der Patientin: Blickkonzepte in Filmdokumenten des klinischen Alltags, in: Wilfried Köpke/Peter Stettner (Hg.): Non-fiktionale Filmdokumente in Wissenschaft und Medienpraxis, Köln, 60–79.

Stolberg M. (2018) Learning Anatomy in Late Sixteenth-Century Padua. In: History of Science 30, 381-402.

Stolberg M. (2018) Post-Mortems, Anatomical Dissections and Humoural Pathology in the Sixteenth and Early Seventeenth Centuries. In: S. de Renzi, M. Bresadola, M. Conforti (Hg.), Pathology in Practice. Diseases and Dissections in Early Modern Europe, London/New York, 79-95.

Stolberg M, Walter T. (2018) Martin Luthers viele Krankheiten. Ein unbekanntes Konsil von Matthäus Ratzenberger und die Problematik der retrospektiven Diagnose. In: Archiv für Reformationsgeschichte 109:126-151.

Department of Anaesthesiology and Critical Care

CONTACT DETAILS

Professor Dr. med. Dr. h.c. Norbert Roewer
(Head of the Department)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-30001
Fax: 0931/201-30019
E-mail: AN_Direktion@ukw.de
www.ukw.de/anaesthesie

Professor Dr. rer. nat. Carola Förster
Phone: 0931/201-30065

Professor Dr. med. Peter Kranke
Phone: 0931/201-30050

Professor Dr. med. Thomas Wurmb
Phone: 0931/201-30411

Mission and Structure

The Department of Anaesthesiology annually performs anaesthesia for approximately 31.000 surgical procedures in the Departments of the University Hospital and in the Department of Orthopaedic Surgery (König-Ludwig-Haus). In the Center for Interdisciplinary Pain, 1.500 postoperative patients are treated annually by the Acute Pain Service and 800 patients with chronic malignant and non-malignant pain by the Outpatient Pain service. In the Outpatient Pain Clinic 300 patients with chronic pain are treated annually by a structured interdisciplinary multimodal pain therapy program.
The department has an interdisciplinary Intensive Care Unit with 12 beds for critically ill patients after major surgery or those being treated in our Level I trauma center. Each intensive care bed is fully equipped with state-of-the-art bedside monitoring and data management systems as well as devices for the support in cases of organ failures. Patients with severe lung injury in the south of Germany can be locally equipped with artificial lung support (ECMO) and transferred to our ICU for further treatment. Over 50 patients are treated annually by ECMO for lung and/or circulatory support.
The department further consists of a section for Emergency and Disaster Relief Medicine (Chair: Prof. Dr. Thomas Wurmb) which is responsible for clinical education as well as research. Doctors of the department staff the Prehospital Emergency Service (NEF) and the Mobile Intensive Care Unit (ITW/VEF) for the interhospital transfer of critically ill patients. The section is responsible for the CPR-Training program of the entire University Hospital.
The department further provides a modern simulation center for anaesthesia and emergency cases. An artificial patient equipped with computer technology provides the resource for a realistic training of routine anaesthetic procedures as well as the management of rare emergency events.
The section "Experimental Anesthesiology" (chair: Prof. Dr. rer. nat. C. Förster) forms the foundation of a collaborative basic science research of clinicians and scientists using state of the art molecular research techniques.
In addition to patient care and education of students and residents the department runs a laboratory for the diagnosis of malignant hyperthermia. Malignant hyperthermia is a rare hereditary disorder that can be triggered by anaesthesia and is life-threatening. The outpatient clinic takes care of about 1500 patients from middle and southern Germany. Individual counseling is offered for susceptible patients as well as for attending physicians.

Major Research Interests

Drug delivery
(N. Roewer, J. Broscheit)

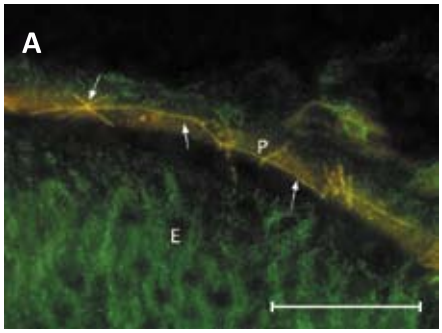
Drug delivery can be optimized by nanocarriers. Nanocarrier-based delivery systems (i) enhance drug delivery to the site of action, (ii) to prevent degradation during transport through the body, and (iii) to improve solubility (e.g. in blood) in order to achieve therapeutic drug plasma levels. Such carrier systems were designed for biogenic, especially plant derived drugs that could not be used for therapeutic purposes due to their chemical properties. The devolopment of drug delivery systems aims to ensure drug release in defined regions of the body at specified time points.

Pain research
(H. Rittner, A. Brack)

To improve the therapy of inflammatory and neuropathic pain we study on the one hand mechanisms of barrier breakdown of the blood-nerve barrier, the blood-dorsal root ganglion barrier and the blood-spinal cord barrier. We are exploring therapeutic strategies for barrier sealing like guidance factors and non-coding RNAs. In a second research focus, we are working on oxidized lipids using molecular, mass spectrometric and in vivo imaging methods. Novel strategies like specific antioxidants selectively target these mediators and thereby decrease pain. In translational projects (e.g. ncRNAPain), we work with clinicians and basic scientists to address chronic post-traumatic or postsurgical pain such as the complex regional pain syndrome (CRPS). Via clinical and molecular phenotyping, we want to identify biomarkers for the development and resolution of neuropathic pain and thus improve the treatment of these sometimes-rare diseases in an interdisciplinary way.

Clinical Trials & Systematic Reviews in perioperative Medicine
(P. Kranke)

Evidence Based Medicine aims to provide current best evidence based on the results of clinical trials and systematic reviews for clinical decision-making. The facilitation of an evidence based thinking and behaviour in the perioperative medicine is the aim of this



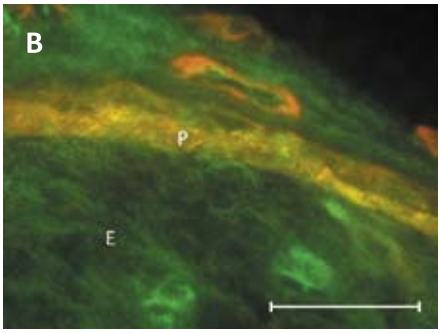


Fig.: Destruciton of the nerve barrier during neuropathy: the sciatic nerve (longitudinal section) is stained for two tight junction proteins (green: ZO-1, red: claudin-1). (A) Sciatic nerve of a healthy control rat: both tight junction molecules are detectable by confocal immunolhistochemical staining in the perineurium (P) of a healthy nerve at the site of cell-cell-contacts (arrow).The cell-cell contacts form the nerve barrier to the endoneurium (E). (B) Fewer tight junction are expressed in the sciatic nerve two weeks after nerve ligature (CCI). These tight junction molecules to not effectively contribute to the barrier function at the site of cell-cell-contacts.

group. For this purpose the clinical trial unit, apart from conducting clinical trials in perioperative medicine (Phase II-IV, including registration trials), performs systematic reviews in the field of anaesthesia, pain therapy, palliative medicine, intensive care medicine and affiliated disciplines and is engaged in the development of Cochrane Reviews. Clinical implementation of this evidence is facilitated by means of developing clinical guidelines. The clinical focus is on topics in perioperative medicine with special emphasis on the prevention of postoperative nausea and vomiting, and obstetric anaesthesia.

Blood-Brain Barrier
(C. Förster)

The blood-brain barrier (BBB) is formed by the endothelial cells of brain capillaries. In-vitro BBB models based on immortalized or primary endothelial cells are a useful tool to study the regulatory mechanisms of the BBB and to develop novel therapeutic strategies. Our research focuses on simulating various brain pathologies using cell culture, e.g. stroke by glucose/oxygen deprivation or brain injury by using a cell-stretch device. Regulatory molecules such as microRNA, hormones, diet additives, serum-, cell-derived factors and their role in the BBB-integrity are being evaluated. Candidate therapeutic agents from in vitro studies are being tested in vivo in mouse disease models. Furthermore, communication between brain endothelial cells and other cell types of the central nervous system as well as developmental issues of the BBB are being studied.

Acute respiratory distress syndrome
(M. Kredel)

The acute respiratory distress syndrome (ARDS) is still associated with a mortality rate of 40-60%. Beside the specific therapy of the underlying disease mechanical ventilation is crucial to ensure oxygenation and decarboxylation. However, mechanical ventilation induces further damage of the lungs. Therefore, lung protective ventilation strategies are used allowing lung healing and recovery. Using experimentally induced ARDS the influence of different ventilation modes and profiles on lung function and inflammation are investigated. In addition, clinical studies evaluating ultraprotective ventilation in ARDS-patients are performed. A special focus of our research is the use of extracorporeal membrane oxygenation (ECMO) in severe ARDS failing conventional ventilation.

Emergency and Disaster Relief Medicine
(T. Wurmb)

The research of Emergency and Disaster Relief Medicine focusses on the development of strategies for the management of mass casualties and mass killing incidents. Other important research projects are the impact of automated external defibrillators on cardiopulmonary resuscitation (CPR), the development of cognitive aids to facilitate emergency management, the simulation and training of CPR and the development of algorithms and standard operating procedures to provide optimal treatment for multiple trauma patients.

Simulation in anaesthesia and emergency medicine
(O. Happel)

The focus of our projects of simulation based research, some in cooperation with the Institute Human-Computer-Media of the Julius-Maximilians-Universität Würzburg, lies on developing and evaluating modern technology to assist acute care teams in their safety-critical work environment. Additional research projects are investigating and modelling situation awareness and the distribution of visual attention of teams in acute care.

Malignant hyperthermia
(F. Schuster)

The diagnosis of malignant hyperthermia is based on the diagnostic criteria of the European MH Group. It involves an in vitro contracture test, histological examinations and genetic analysis. The research focuses on the development of a minimal-invasive test to the diagnosis of malignant hyperthermia susceptibility and on interactions of clinically applied drugs on skeletal muscle metabolism.

SELECTED PUBLICATIONS

Burek M, ..., Förster CY. (2019) Hypoxia-induced microRNA 212/132 alter blood-brain barrier integrity through inhibition of tight junction-associated proteins in human and mouse brain mircovascular endothelial cells. Transl Stroke Res doi 10.1007/s12975-018-0683-2.

Grundgeiger T, ..., Happel O. (2017) An investigation into the effects of real vs. simulated cases and level of experience on the distribution of visual attention during induction of general anaesthesia. Anaesthesia 72:624-632.

Johannsen S, ..., Schuster F. (2018) Ultrasound elastography for rapid, real-time detection of localized muscular reaction in malignant hyperthermia susceptible pigs. Anesthesiology 129:989-999.

Mohammadi M, ..., Rittner HL. (2018) Antinociception by the anti-oxidized phospholipid antibody E06. Br J Pharmacol 175:2940-2955.

Weibel S, ..., Kranke P. (2018) Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev 6:CD009642.

Department of General, Visceral, Transplantation, Vascular and Pediatric Surgery (Surgery I)

CONTACT DETAILS

Professor Dr. med. Christoph-Thomas Germer (Head of the Department)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-31000
Fax: 0931/201-31009
E-mail: Germer_C@ukw.de
www.zom-wuerzburg.de

Professor Dr. med. Ingo Klein
Phone: 0931/201-31053

Professor Dr. med. Thomas Meyer
Phone: 0931/201-31071

Professor Dr. med. Nicolas Schlegel (since 4/2019)
Phone: 0931/201-31715

Mission and Structure

The Department of General, Visceral, Transplantation, Vascular and Pediatric Surgery offers excellent services for the whole gamut of general and visceral surgery, liver transplantation and many other specialties of surgery. The department has 132 beds, including a surgical Intensive Care Unit, an Intermediate Care Unit and three special units for vascular, paediatric, and transplantation and hepatobiliary surgery. Some six thousand surgical procedures are performed here annually.
The department of Surgery I is a major part of the German Cancer Society (DKG)-certified Comprehensive Cancer Center Mainfranken, supported by German Cancer Aid (Deutsche Krebshilfe e.V.). The Competence Center for Peritoneal Carcinosis forms another important part of Surgery I.
Colorectal carcinomas are treated in the certified center for Intestinal Medicine with innovative concepts and surgical expertise to restore or retain continence. Surgery I also has its own endoscopy unit. The complex field of coloproctology is another major focus of therapy.
The certified Pancreas Center provides hepatobiliary surgery and pancreas surgery for treating complex liver, bile duct and pancreas diseases. Liver transplants are routinely performed to treat liver failure and liver tumours in the Transplantation Center, Surgery I. In addition, the department is a member of the integrative Liver Center that provides interdisciplinary treatment of acute and chronic liver diseases based on the latest research findings.
The Thyroid Center Wuerzburg has strong expertise in the surgical treatment of endocrine diseases and is a certified reference center for endocrine surgery.
The Center for Obesity Medicine offers different surgical solutions for long-term weight loss for patients with morbid obesity.
The Pediatric Surgery Unit provides top surgical treatment for a wide range of diseases and conditions. This includes the surgical care of premature births, treatment of birth defects, basic pediatric urology, and pediatric traumatology. The children's surgical ward provides child-friendly pre- and postoperative care.
In the vascular surgery unit, abdominal aortic aneurysms are treated with aorta-iliac bifurcation prostheses. Endovascular surgery is available for aorta and iliac vascular diseases. Our surgeons are well experienced in femur crural artery bypass surgery and carotid artery surgery. A hybrid operating room provides high quality interventional care.

Major Research Interests

The department works together with many national and international groups as well as within the university hospital itself as part of a thriving research network. This has helped to successfully secure third party funding (DFG, BMBF), numerous patents, prizes, awards, and scholarships. Further information is available on our website (www.zom-wuerzburg.de).

Clinical Trials

(J. Lock, Th. Meyer, A. Wiegering, N. Schlegel)

The department is one of 14 regional centers in the surgical study network "Chir-Net" and plays an active part in planning and conducting clinical studies with surgical aims and objectives. Several multi-center prospective clinical trials (visceral surgery, oncology, pediatric surgery, laprascopic incisional hernia care) and different online registers (incisional hernia, inguinal hernia, open abdomen) are in progress with the support of the Chair of Artificial Intelligence and Applied Computer Science (Prof. Dr. F. Puppe) and the Institute for Clinical Epidemiology and Biometry (Prof. Dr. P. Heuschmann).

Sepsis

(N. Schlegel, N. Burkard, S. Flemming)

The pathophysiology of the microcirculation and microvascular endothelium barrier is being investigated in acute inflammation and in sepsis. In a DFG-funded project a potential marker for early diagnosis of sepsis and loss of microvascular barrier function is validated. Cellular mechanisms and the translational aspects underlying loss of endothelial barrier function in inflammation are investigated in detail.

Inflammation and chronic inflammatory bowel diseases

(N. Schlegel, S. Flemming, N. Burkard)

One focus of the department is the treatment of patients suffering from inflammatory bowel diseases. The research on this topic addresses the mechanisms underlying loss of intestinal epithelial barrier function in inflammatory bowel diseases and the contribution of the enteric nervous system to these changes. This project is funded by the DFG priority programm 1782. A main focus of the project is to understand the role of desmoso-

mal adhesion in the intestinal epithelial barrier in patients with Crohn's disease and ulcerative colitis. To address these question there are several collaborations with research in the USA and in Munich.

Oncology
(A. Wiegering, C. Otto)

Therapy-relevant intercellular signalling pathways in tumours in the gastrointestinal tract are currently under investigation. New strategies to reduce MYC expression and/or inhibit MYC function in colon cancer are also being explored in close cooperation with the Chair for Physiological Chemistry II (Prof. Dr. M. Eilers). Another main point of interest is the interaction between cancer cells and immune cells. Surgery I is a member of the Faculty of Medicine's National Biomaterial Bank and Database.

Metabolic Disorders
(F. Seyfried, C. Jurowich, C. Otto)

Metabolic/bariatric surgery is currently the most effective therapy for treating obesity. The physiological changes brought on by the operation are complex and not yet fully understood. Current studies: the changing bile flow and its influence on improving glycemic control and intestinal barrier function. Another main interest is examining neuroendocrine mechanisms of appetite regulation. The DFG is currently funding a research network of national and international cooperations.

Transplantation-Immunology, Hepatic Ischemia/Reperfusion Injuries
(I. Klein, M. Camara, J. Baur, C. Otto)

Injuries through ischemia/reperfusion and the immune system are clinically relevant problems following organ transplantation. The strategies for reducing ischemia and reperfusion injuries focus on conditioning the donor organ. Another main point of interest is finding more selective immune suppressants. An IZKF funded project is examining the transcription factor NFATc in cooperation with Molecular Pathology (Prof. Dr. E. Serfling, Dr. A. Avots).

Teaching

All aspects of modern surgery are covered in lectures and seminars, as well as practice-oriented bedside training. This commitment and the quality of our teaching have been honoured by the Bavarian State Ministry for Education, Science and the Arts with a prize for outstanding education. Student training takes place in both the teaching hospital and the Interdisciplinary Training and Simulation Center (INTUS). Here students can practice operations and interventions under realist conditions. The eLearning website provides information on important topics of general and visceral surgery. Training courses in coloproctology, thyroid and microsurgery, as well as laparoscopic operating procedures, are offered on a regular basis. The department has the authorization to provide advanced training and education in general and visceral surgery, special visceral surgery, vascular surgery, surgical intensive care medicine, pediatric surgery, and proctology.

SELECTED PUBLICATIONS

Baur J, Otto C, Steger U, Klein-Hessling S, Muhammad K, Pusch T, Murti K, Wismer R, Germer CT, Klein I, Müller N, Serfling E, Avots A. (2018) The Transcription Factor NFATc1 Supports the Rejection of Heterotopic Heart Allografts. Front Immunol. 9:1338.

Flemming S, Burkard N, Meir M, Schick MA, Germer CT, Schlegel N. (2018) Sphingosine-1-Phosphate Receptor-1 Agonist Sew2871 Causes Severe Cardiac Side Effects and Does Not Improve Microvascular Barrier Breakdown in Sepsis. Shock 49:71-81.

Hankir MK, Seyfried F, Hintschich CA, Diep TA, Kleberg K, Kranz M, Deuther-Conrad W, Tellez LA, Rullmann M, Patt M, Teichert J, Hesse S, Sabri O, Brust P, Hansen HS, de Araujo IE, Krügel U, Fenske WK. (2017) Gastric Bypass Surgery Recruits a Gut PPAR-α-Striatal D1R Pathway to Reduce Fat Appetite in Obese Rats. Cell Metab 25:335-344.

Lock JF, Westphal T, Rubin T, Malinowski M, Schulz A, Jara M, Bednarsch J, Stockmann M. (2017) Test Improves Diagnosis of Chemotherapy-Associated Liver Injury Before Resection of Colorectal Liver Metastases. Ann Surg Oncol 24:2447-55.

Wiegering A, Matthes N, Mühling B, Koospal M, Quenzer A, Peter S, Germer CT, Linnebacher M, Otto C. (2017) RITA (reactivating p53 and inducing tumor apoptosis) enhances the response of RITA-sensitive colorectal cancer cells to chemotherapeutic agents 5-fluorouracil and oxaliplatin. Neoplasia 19:301-309.

Department of Trauma, Hand, Plastic and Reconstructive Surgery

CONTACT DETAILS

Professor Dr. med. Rainer Meffert
(Head of the Department)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-37000
Fax: 0931/201-37009
E-mail: meffert_r@ukw.de
www.ukw.de/chirurgie-ii

Professor Dr. rer. nat. Torsten Blunk
Phone: 0931/201-37115

Professor Dr. med. Rafael Jakubietz
Phone: 0931/201-31175

Mission and Structure

In the Department of Trauma, Hand, Plastic and Reconstructive Surgery, 28 medical doctors are employed. For the treatment of patients, 60 beds are available on our wards. Additional beds are available in the Intensive Care Unit and the Intermediate Care Unit.
Within the ZOM, there is a close collaboration between the Department of General Surgery, the Department of Anaesthesiology, and the Institute of Radiology with regard to the interdisciplinary treatment of patients. Polytraumatized patients are first examined in the two newly built shock rooms with spiral CT. Other functional facilities are also of the highest standard, including the certified central sterilization unit, the operating theatres, the intensive care units, and the physiotherapy facilities. Furthermore, angiography, CT and MRI are available.
The different focuses of the Department of Trauma, Hand, Plastic and Reconstructive Surgery are represented in different consultation hours. With our department being the transregional trauma center, a trauma network was certified, which comprises 16 hospitals within the region.

Major Research Interests

The current clinical studies include prospective-randomized as well as retrospective studies. Major areas are spine traumatology and complex injuries of the knee joint, the cubital joint, the foot and the hand, and flap surgery.

Bone Fracture Healing and Muscle Regeneration
(R. Meffert)

In a unique rabbit model, the influence of proangiogenic factors on muscle and bone regeneration after musculoskeletal trauma is studied. Promising results were achieved with factors such as $VEGF_{165}$ and CYR61 resulting in distinct improvement of both muscle and bone regeneration. In further studies, a mouse model to investigate the restoration of muscle force is being established.

Biomechanics in Traumatology
(S. Hölscher-Doht, M. Jordan, R. Meffert)

Different fracture models (tibial plateau, pelvis, calcaneus a.o.) were established for biomechanical studies of locking plates and bone substitutes. Furthermore, different suture techniques for tendon repair are evaluated. In a DFG-funded project, a fracture model in synthetic bones for tibial head depression fractures is used with which different stabilization techniques are analyzed biomechanically. Conclusions from the results can be drawn with regard to clinical practice and the best operative technique, respectively. On the one hand, different osteosyntheses, screws, and plates in combination with screws, are compared with each other. On the other hand, established bone substitutes (calcium phosphate cements) are analyzed concerning their handling for filling a bone defect and their bonding with the spongiosa, which has a relevant influence on the stability under loading. Furthermore, in a calcaneus fracture model (IZKF funding) different implant configurations are tested (open vs. minimally invasive).

Gait Analysis
(H. Jansen, R. Meffert)

The gait lab comprises a pedobarographic system with which gait cycle and dynamic foot pressure can be analyzed (“catwalk”, 1.2 x 8.0 m). In real-time, the complete gait cycle is recorded and the foot pressure distribution is measured. The foot is divided into 10 single segments. Thus, key parameters such as peak pressure, contact duration, or pressure-time integral can be analyzed very precisely. The pedobarographic results can effectively contribute to the diagnosis of foot and gait pathologies as well as to follow-up examinations after foot and ankle surgery.

Tissue Engineering of Adipose Tissue
(P. Bauer-Kreisel, T. Blunk)

Tissue engineering of adipose tissue represents a major research area. The primary goal is the development of adipose tissue constructs for reconstructive and plastic surgery. Key aspects are the development of vascularization strategies and the maintenance of volume stability of adipose tissue constructs. For example, for the first time, we demonstrated that the stromal-vascular fraction (SVF) from adipose tissue can be successfully employed for adipose engineering. In an IZKF-funded project, the secretory function of adipose-derived stem cells (ASC) is investigated in an ischemic environment simulating conditions at the implantation site (collaboration with ENT clinic, PD Dr. Katrin Radeloff). Moreover, 2D and 3D adipose tissue models for basic research are established in which the crosstalk of different cell

types (e.g., stem cells and endothelial cells) and the role of cell-cell- and cell-extracellular matrix interaction in adipogenesis are investigated. Here, gap junctional intercellular communication in ASC was demonstrated to play an important role in adipogenesis.

Cartilage Regeneration
(T. Blunk)

Another focus of our research is the regeneration of cartilage tissue. In in vitro studies on cell-based therapies, chondrocytes, progenitor cells isolated from cartilage, and bone marrow-derived stem cells are employed and the effects of growth factors and morphogens (TGF-β1, GDF-5, IGF-I a.o.) are investigated, especially regarding the extracellular matrix in the developing cartilaginous tissue. Furthermore, biomimetic materials for cartilage regeneration are evaluated, e.g., providing the possibility of covalently binding chondrogenic peptides and growth factors. A specific emphasis is put on cartilage integration in the defect which is investigated in fundamental studies biomechanically as well as in cell culture (e.g., EU consortium HydroZONES). Novel biomimetic materials for cartilage development and for the improvement of cartilage integration are developed and evaluated in collaboration with the Department of Functional Materials in Medicine and Dentistry, Prof. Jürgen Groll.

Biofabrication
(T. Blunk)

Biofabrication, especially 3D bioprinting of cells and hydrogel materials, represents a still young research area aiming at the development of hierarchical tissue structures which can potentially be utilized in tissue regeneration and to establish novel tissue models. Within the Collaborative Research Center "From the Fundamentals of Biofabrication to Functional Tissue Models" (SFB/TRR 225), the research group develops and evaluates new hydrogel materials as bioinks for 3D bioprinting (collaboration with the Department of Functional Materials in Medicine and Dentistry, Prof. Jürgen Groll, Dr. Jörg Tessmar). An emphasis is put on the effects of the bioprinting process and different bioinks on the differentiation of mesenchymal stem cells and ECM development in the printed constructs. Another focus of our group in the area of biofabrication are self-assembling multicellular spheroids and their potential for tissue regeneration and as tissue models.

Teaching

Teaching is divided into education of students as well as into education of our doctors on daily rounds and discussions and in specific seminars. For students, there are two main lectures per week. At the end of the term, there are review courses in which the students are given the possibility to repeat the content of the semester with the help of patient-related cases.
Within the department, there are two grand rounds daily in which indications are discussed. For students, we offer a large variety of hospitations. Besides the local students, we continuously have foreign students visiting. The extensive curriculum offered to the students also integrates clinical investigation courses, training periods with "bedside teaching", weekly block training periods as well as different consultation hours. In order to improve practical examination techniques, specific courses, e.g., for the examination of the joints and the spine, are offered in the Skills Lab.
Every three months we organize an interdisciplinary polytrauma conference which is well accepted. At each conference, a specific topic is featured and therapy principles and recommendations are presented. Furthermore, the participants can present their own subject-related cases to be discussed.

SELECTED PUBLICATIONS

Böck T, Schill V, Krähnke M, Steinert AF, Tessmar J, Blunk T, Groll J. (2018) TGF-β1-modified hyaluronic acid / poly(glycidol) hydrogels for chondrogenic differentiation of human mesenchymal stromal cells. Macromol Biosci 18:e1700390.

Gilbert F, Meffert RH, Schmalzl J, Weng AM, Köstler H, Eden L. (2018) Grade of retraction and tendon thickness correlates with MR-spectroscopically measured amount of fatty degeneration in full thickness supraspinatus tears. BMC Musculoskelet Disord 19:197.

Jansen H, Jordan M, Frey S, Hölscher-Doht S, Meffert R, Heintel T. (2018) Active controlled motion in early rehabilitation improves outcome after ankle fractures: a randomized controlled trial. Clin Rehabil 32:312-318.

Stichler S, Böck T, Paxton NC, Bertlein S, Levato R, Schill V, Smolan W, Malda J, Tessmar J, Blunk T, Groll J. (2017) Double printing of hyaluronic acid / poly(glycidol) hybrid hydrogels with poly(ε-caprolactone) for MSC chondrogenesis. Biofabrication 9:044108.

Wiesner M, Berberich O, Hoefner C, Blunk T, Bauer-Kreisel P. (2018) Gap junctional intercellular communication in adipose-derived stromal/stem cells is cell density-dependent and positively impacts adipogenic differentiation. J Cell Physiol 233:3315-3329.

Department of Thoracic and Cardiovascular Surgery

CONTACT DETAILS

Professor Dr. med. Rainer G. Leyh
(Head of the Department)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931 201-33001
Fax: 0931 201-33009
E-mail: info_htc@ukw.de
www.ukw.de/herz-thorax-chirurgie

Mission and Structure

The department of Thoracic and Cardiovascular Surgery is a 66-bed department with 3.5 operating theaters and its own 12 bed intensive care and 8-bed intermediate care unit. At present 28 physicians are employed.
Approximately 2100 procedures are performed annually covering the entire field of adult heart and thoracic surgery. 1230 procedures are open heart surgeries with extracorporeal circulation.
In 2008 an assist device program was established and the heart transplant program relaunched. Specialized outpatient clinics provide care for heart transplant and VAD patients and for patients requiring aortic surgery. In addition there is an outpatient clinic for thoracic diseases.

Within a radius of 100 kms we are the sole institution which offers the full range of adult heart surgery including heart transplantation and simultaneous management of any kind of thoracic surgery including tracheal surgery.
Main areas of interest are total arterial revascularization, reconstructive valve surgery including DAVID-, YACOUB-procedures. In 2009 a transapical/transfermoral minimally-invasive aortic valve replacement program was launched. This is a joint project with the Department of Cardiology. In selected patients we also offer the ROSS procedure.

Approx. 500 thoracic cases are performed per year. Main areas of interest are minimally-invasive procedures like video-assisted lobectomies and hyperthermic intrathoracic chemotherapy for mesothelioma or malignant thymoma.
In addition we cover the entire field of arrhythmia surgery. Apart from pacemaker, ICD and biventricular device implantations we routinely perform Mini-MAZE procedures for the surgical treatment of atrial fibrillation and system extractions by means of Laser technology.

Major Research Interests

Cardiac surgery:

Minimally-invasive aortic valve replacement

By means of MR and CT-scanning we aim to compare minimally-invasive aortic valve replacement with ballon-expanding valves with conventional aortic valves implanted through a partial sternotomy (Dr. Hamouda, Prof. Leyh).

ECMO therapy: The research group (Mr. Radakovic, Prof. Aleksic) focusses on clinical topics regarding the use of va-ECMO therapy in post-cardiotomy patients. This patient subset is known to have the worst prognosis of all ECMO groups. Therefore, clinical issues like ideal cannulation site, benefits of ante- versus retrograde perfusion and management of complications are of utmost importance.

Analysis of cardiac muscle physiology
(C. Bening)

Apart from the well-established skinned fiber technique, we have started using intact human cardiac fibers with intact sarcolemma. These intact fibers are stimulated electrically and the following parameters, describing the contractile behavior of the fibers, are recorded: the half maximal relaxation and contraction time, time to peak and width of the resulting amplitude. By preserving the intact sarcolemma of the fibers, membrane-dependent processes like effect of medications can be analyzed and the in-vivo physiology can better be assessed. The possibility to combine both experimental approaches in correlation with clinical parameters of the patients enables a broad patient-individual analysis of cardiac contractility. Accordingly, we analyzed parameters predicting the occurrence of postoperative atrial fibrillation and the relationship of cardiac contractility in diabetic patients.
By establishing the ELISA technique in our lab, we can now examine several biomarkers, associated with endothelial dysfunction, inflammation and fibrosis. In correlation with these biomarkers we currently examine right heart function and the possible predictive value of these biomarkers.
In the meaentime, we have established a cooperation with the research group “mitochondrial respiration and function” of Prof. Maack (DZHI) and are currently able to analyze the mitochondrial function of our patients parallel to the contraction analysis of the patients’ atrial tissue. Considering the pathophysiological changes of atrial tissue in atrial fibrillation we aimed to examine mitochondrial respiration and function in these patients.

Prevention and therapy of deep sternal wound infections (DSWI)
(C. Schimmer)

Prof. Schimmer has been appointed guideline-coordinator by the German society

for Thoracic, Cardiac and Vascular Surgery (DGTHG) for the S3 guideline "Management of post-sternotomy mediastinitis after cardiac surgical procedures". The draft for this guideline to be published in accordance with the Working group of scnientific medical societies (AWMF) is under final review. In addition, Prof. Schimmer focusses on clinical studies in the ICU setting and has achieved a significant reduction of perioperative empiric antibiotic therapy.

Thoracic surgery

Prof. Dr. H. Aebert is head of the section of thoracic surgery since the end of 2016. His areas of interest include extended resections with the heart-lung-machine, hyperthermic intrathoracic chemotherapy and uniportal VAT surgery. Paralleling completion of the thoracic team several clinical research projects are under way

Teaching

All topics of cardiothoracic surgery relevant to the medical student are covered by a lecture series and regular „bed-side"-teaching plus grand rounds. Since 2007 2-3 medical students spend two weeks in the department as part of a mandatory surgical rotation. Final year medical students spend a 16 week rotation in our department. Students and residents are offered regular wet lab training in the department's own wet lab, where all surgical technqiues relevant for cardiothoracic surgery can be practiced on pig hearts and aortas.
A new weekly cardiology/cardiac surgery conference is a mainstay for the education of our residents.

SELECTED PUBLICATIONS

Bening C, Alhussini K, Mazalu EA, Yaqub J, Hamouda K, Radakovic D, Schimmer C, Hirnle G, Leyh R. (2018) Impact of diabetes mellitus on the contractile properties of the left and right atrial myofilaments. Eur J Cardiothorac Surg 54:826-831.

Bening C, Sikand A, Conzelmann LO, Stumpf N, Vahl CF. (2017) Reduced right atrial contractile force in patients with left ventricular diastolic dysfunction: A study in human atrial fibers-contractile force and diastolic dysfunction. Asian J Surg 40:23-28.

Herrmann S, Fries B, Salinger T, Liu D, Hu K, Gensler D, Strotmann J, Christa M, Beer M, Gattenlöhner S, Störk S, Voelker W, Bening C, Lorenz K, Leyh R, Frantz S, Ertl G, Weidemann F, Nordbeck P. (2018) Myocardial Fibrosis Predicts 10-Year Survival in Patients Undergoing Aortic Valve Replacement. Circ Cardiovasc Imaging 11: e007131.

Radakovic D, Reboredo J, Helm M, Weigel T, Schürlein S, Kupczyk E, Leyh RG, Walles H, Hansmann J. (2017) A multilayered electrospun graft as vascular access for hemodialysis. PLoS One 12:e0185916.

Schade I, Radakovic D, Hoffmann J, Sommer SP, Stefenelli U, Schimmer C, Leyh RG, Aleksic I. (2017) Secondary sclerosing cholangitis in cardiac surgical patients: A complication with a dismal prognosis. J Thorac Cardiovasc Surg 154:906-912.

Department of Urology and Paediatric Urology

CONTACT DETAILS

Professor Dr. med. Hubert Kübler
(Head of the Department)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-32001
Fax: 0931/201-32013
E-mail: urologie@mail-wuerzburg.de
www.ukw.de/urologie

Mission and Structure

The Department of Urology and Paediatric Urology is a tertiary referral center with two wards (48 beds), intensive care unit (8 beds) with haemodialysis facility, a busy outpatient clinic with uroradiology section, point-of-care lab and a research laboratory with an emphasis on molecular urooncology. Three state-of-the-art operating theatres allow the surgical treatment of approximately 2.500 adults and 350 children and adolescents with 2.700 open, laparoscopic and endoscopic procedures and more than 2.800 endourologic interventions per year. The equipment comprises a multi-function unit for extracorporeal shockwave lithotripsy, a computer-assisted (video-) urodynamic set-up, lasers of the most recent generation, a Da Vinci Xi surgical roboter with dual console, MRI/TRUS-fusion prostate biopsy system and several ultrasound units with colour-coded duplex sonography and transrectal probes.

The surgical spectrum encompasses the entire speciality of urology with special expertise in urooncology (cystoprostatectomy/ anterior exenteration (nerve sparing techniques) and orthotopic bladder substitution and continent cutaneous urinary diversion; radical retropubic and robot-assisted (DaVinci) prostatectomy (nerve-sparing techniques); DaVinci and open nephron-sparing surgery of renal cell cancer; surgical and medical treatment of testicular cancer; polychemotherapy; paediatric urology (correction of complex congenital malformations), reconstructive urology (all types of urinary diversion and conversion, reconstruction of the whole urinary tract, ureteral replacement, urethral reconstruction, complex fistula repair) including implantation of artificial urinary sphincters and penile prosthesis, urogynaecology.

Major Research Interests

Molecular mechanisms of microRNAs in high risk prostate cancer
(B. Kneitz, C. Kalogirou, M. Krebs)

The aim of our studies is the analysis of the role of miRNAs for the development and progression of prostate cancer. Tumor tissue from a European multicenter database is used for the analysis. Using microarrays and qRT-PCR miRNA analysis we detected specific miRNA signatures for prostate cancer. By bioinformatics and statistical analysis specific miRNAs were identified, which are linked to the development and progression of cancer. To study the molecular mechanisms of such miRNAs we are currently analysing the function of specific miRNAs *in vitro and in vivo*.

piRNAs as tumor suppressor gens in prostate cancer
(B. Kneitz, S. Kneitz, M. Schartl *(*Physiological Chemistry I))

Due to their differential expression in several tumor entities PIWI interacting small non-coding RNAs (piRNAs) attract more and more attention. Because of their role initially described in stem cells, the cancer stem cell theory is discussed in this context and a potential use of piRNA signatures for 'stemcellness'. Furthermore, evidence for an androgen dependent expression of piRNAs in prostate cancer cell lines (PCa) has been found. Based on these findings we want to study a potential tumor suppressive function of piRNAs. To study the hypothesis that the piRNA profile can be modified by androgen signaling, we want to find piRNAs regulated by the androgen signaling cascade. To examine a potential diagnostic and prognostic relevance of piRNAs associated with PCa, tissue samples of a high risk PCa patient cohort will be used. Based on the results of these studies, the importance of piRNAs as a novel tumor suppressors can be delineated and piRNAs as new biomarkers for diagnostics and prognostics can be characterized. Further, the possibility of transferring these results into clinics can be evaluated.

Experimental evaluation of altered cholesterol metabolism as a potential therapeutic target in prostate cancer
(C. Kalogirou, B. Kneitz, A. Schulze* (*Physiological Chemistry II)

Altered cholesterol biosynthesis is a central feature of many solid cancers since it confers significantly to membrane buildup and therefore unlimited growth. For hormone-depedent cancers such as prostate cancer (Pca), cholesterol metabolism is of further importance since it provides the starting metabolite of steroid hormone (in this case: testosterone) synthesis, which is the most important driver of PCa growth. Therefore, in our group, we characterize cholesterol metabolism in various cellular models of PCa using modern technology (i.a. metabolite-labeled mass spectrometry and CRISPR/Cas9 genome editing) to eventually exploit it for putative therapeutic approaches.

Prognostically relevant microRNA signatures in urological malignancies and their relevance for the immune responsiveness of tumour cells
(M. Krebs, B. Kneitz, B.Schilling* (*Department of Dermatology))

Project funding within the Else Kröner Integrative Clinician Scientist College for Translational Immunology, University Hospital Würzburg (MK) – Based on previous studies of our group regarding the role of microRNAs (miRs) in high-risk Prostate Cancer and Renal Cell Carcinoma, we aim to examine the influence of miRs on cellular interferon and TRAIL signals – thereby further examining a potential link and a modulation of response towards Immune Checkpoint therapy.

Identification and description of tumorsuppressor- und onco- microRNAs in renal cell carcinoma with venous invasion.
(B. Kneitz, D. Vergho, C. Kalogirou)

The aim of our studies is to analyse the role of miRNAs for the development and progression of renal cell cancer, especially the subgroup which develops venous invasion and inferior vena cava thrombi. Using microarrays and qRT-PCR miRNA analysis we detected specific miRNA signatures for both cancer entities. By bioinformatics and statistical analysis specific miRNAs were identified, which are linked to the development and progression of renal cell carcinoma. To study the molecular mechanisms of such miRNAs we are currently investigating the function of specific miRNAs in vitro and in patient samples (serum and tissue). The aim of our translational research is the optimization of diagnosis and treatment of renal cell carcinomas with and without venous invasion.

Metformin as a tumour-suppressor in urologic malignancies
(C. Kalogirou, B. Kneitz, M. Krebs)

For the biguanide Metformin (MF), besides its antidiabetic function, tumour-suppressive actions have been described in various solid cancers. To evaluate the molecular effect of MF – which is not completely understood to date – in prostate carcinomas and renal cell carcinomas, we currently explore the molecular effects of the drug in various cell lines. We could show that MF effects were at least partially mediated by specific microRNA expression patterns and their subsequent molecular pathways. The main aim of our research is the further illumination of molecular tumour-suppressive effects in prostate carcinomas, renal cell carcinomas and urothelial carcinomas.

Identification and description of tumorsuppressor- und onco-microRNAs using liquid biopsies of patient with progressive non-muscle-invasive urothelial carinomas (NMIBCs)
(M. Weinke, C. Kalogirou, B. Kneitz, A. Kocot)

The probability of progression of non-muscle-invasive urothelial carcinomas (NMIBC) into muscle-invasive urothelial carcinomas (MIBC) to date cannot be foreseen by "classic" clinical parameters like histological grading. Therefore we analyse microRNA patterns in NMIBC tissue and serum which show a rapid progression into MIBCs and compare them to NMIBC tissue which do not show a progression at all. Additionally, in vitro experimentation in cell lines are accomplished. Our scientific efforts aim to the establishment and validation of microRNA patterns, which are able to predict NMIBC progression efficiently.

Evaluation of treatment response assessment in metastatic prostate cancer patients using PSMA ligands ^{68}Ga-PSMA-I&T and ^{68}Ga-HBED-CC-PSMA
(A.K. Seitz, C. Kalogirou, M. Krebs, C. Lapa*, J. Brumberg* (*Department of Nuclear Medicine, UKW))

Conventional imaging has several limitations in response assessment in metastatic prostate cancer patients undergoing systemic therapy. In particular, discrimination of *treatment effects from true cancer* progression is challenging. In contrast, ^{68}Ga-PSMA PET detects changes in metabolism or receptor expression providing potential use for early therapy response prediction. Aim of this study is to establish an objective, accurate, and standardized system for tumor response assessment using ^{68}Ga-PSMA PET in metastatic prostate cancer patients.

Teaching

Traditional teaching formats (lecture with clinical case presentation and live transmission of surgical procedures from the operating theatre; clerkships/electives) are offered along with integrated and interdisciplinary approaches. Participation is offered in skills lab, e-learning-programmes, interdisciplinary oncology (seminar and lecture), integrated seminars in tumour biology, interdisciplinary paediatric pathophysiology and courses in prevention, epidemiology and biostatistics. Hospitation in the operating theatre and outpatient clinic is possible throughout the entire academic year.

SELECTED PUBLICATIONS

Kalogirou C, Breshnev S, Krebs M, Koneval L, Sokolakis I, Kübler H, Riedmiller H, Kocot A. (2018) Cognitive Status and Functional Dexterity as Outcome Predictors Following Urinary Diversion: A Combined Retrospective and Prospective Observational Study. Urol Int. 2018 Nov 21:1-9. doi: 10.1159/000494565. [Epub ahead of print].

Kalogirou C, Mulfinger P, Sokolakis I, Krebs M, Kübler H, Riedmiller H, Vergho D. (2017) Preoperative C-Reactive Protein Values as a Potential Component in Outcome Prediction Models of Metastasized Renal Cell Carcinoma Patients Receiving Cytoreductive Nephrectomy. Urol Int 99:297-307.

Kocot A, Kalogirou C, Vergho D, Riedmiller H. (2017) Long-term results of ileal ureteric replacement: a 25-year single-centre experience. BJU Int 120:273-279.

Seitz AK, Rauscher I, Haller B, Krönke M, Luther S, Heck MM, Horn T, Gschwend JE, Schwaiger M, Eiber M, Maurer T. (2018) Preliminary results on response assessment using 68Ga-HBED-CC-PSMA PET/CT in patients with metastatic prostate cancer undergoing docetaxel chemotherapy. Eur J Nucl Med Mol Imaging 45:602-612.

Tosco L, Laenen A, Briganti A, Gontero P, Karnes RJ, Albersen M, Bastian PJ, Chlosta P, Claessens F, Chun FK, Everaerts W, Gratzke C, Graefen M, Kneitz B, Marchioro G, Salas RS, Tombal B, Van den Broeck T, Moris L, Battaglia A, van der Poel H, Walz J, Bossi A, De Meerleer G, Haustermans K, Van Poppel H, Spahn M, Joniau S. (2017) The survival impact of neoadjuvant hormonal therapy before radical prostatectomy for treatment of high-risk prostate cancer. Prostate Cancer Prostatic Dis 20:407-412.

Department of Internal Medicine I

CONTACT DETAILS

Professor Dr. med. Stefan Frantz
(Head of the Department)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-39001
Fax: 0931/201-639001
E-mail: M1_Direktion@ukw.de
www.ukw.de/medizinische-klinik-i

Professor Dr. med. Martin Fassnacht
Phone: 0931/201-39200

Professor Dr. med. Stefanie Hahner
Phone: 0931/201-39937

Professor Dr. med. Stefan Störk
Phone: 0931/201-46363

Professor Dr. med. Christoph Wanner
Phone: 0931/201-3903

Professor Dr. med. Gülmisal Güder
(since 2/2017)
Phone: 0931/201-39989

Mission and Structure

The Department of Internal Medicine I (DIM I) includes six specialities in research, teaching, and patient care: Endocrinology, Internal Emergency- and Intensive Care, Cardiology/Angiology, Nephrology, and Pneumology.

Endocrinology is in charge of a ward specialized in endocrinology/diabetology as well as sophisticated outpatient clinics (for general endocrinology, diabetes and metabolism/obesity, and endocrine tumours) caring for more than 6000 outpatients annually. Since 2003, the Department has become the international reference center for adrenal carcinoma and treats more than 150 patients per year. The interdisciplinary team of the integrated obesity center cares for more than 400 patients annually.

Cardiology performs more than 3300 invasive procedures per year including percutaneous coronary interventions, catheter based implantations of closure devices in patients with atrial septal defects and persistently open foramen ovale, high frequency and cryo ablations of arrhythmias. In cooperation with the Department of Cardiac Surgery, minimally invasive stent-based aortic valves and Mitraclips are implanted. About 200 pacemakers and 200 ICD/CRT are implanted per year. A cardiac transplantation program is established. Since 2009, a modern cardiac research MRT is available.

The DIM includes a state of the art **intensive care** ward with 24 beds, an emergency ward / chest pain unit with 12 beds and the emergency room. The intensive care ward coordinates the Infarct Network Mainfranken - founded in 2007 - which manages 600 patients with acute coronary syndrome per year.

In **Nephrology** (kidney disease and high blood pressure) the wide range of services and treatments expands to new therapies for rare diseases. Specialized clinics care for patients with severe hypertension, vasculitis, polycystic kidney disease, the Fabry Disease, and kidney transplantation in cooperation with the transplantation center of the UKW. The focus of inpatients lies on the treatment of acute renal failure, preparation of living donation and the straight after-care of newly transplanted kidneys. More than 120 patients with Fabry Disease were treated as inpatients and more than 6000 treatments of haemodialysis, peritoneal dialysis, plasmapheresis, lipid apheresis, and immunoadsorptions were performed.

Pneumonology cares for inpatients and outpatients with bronchial carcinoma, complex organ sarcoidosis, severe COPD, pulmonary hypertension and interstitial lunge diseases. More than 4.000 outpatient contacts are in specialized clinics for rare diseases like interstitial lung disease, sarcoidosis, pulmonary hypertension, and alpha-1-antitrypsin-deficiency.

Major Research Interests

Research in DIM I is characterized by interdisciplinary projects and coordination or participation in research consortia including the Comprehensive Heart Failure Center (CHFC), the Cardiovascular Center, the Interdisciplinary Center for Clinical Research, the Comprehensive Cancer Center, the Center for Infectious Research, and the Interdisciplinary Training and Simulation Center (INTUS).

Endocrinology

(M. Fassnacht, S. Hahner, M. Kroiss)

A major research focus are translational and clinical studies in adrenocortical carcinoma. The Endocrinology co-funded the European Network for the Study of Adrenocortical Tumours (ENSAT). In cooperation with the Interdisciplinary Biobank a data- and tissue bank was integrated into the ENSAT network. Furthermore, two phase III therapeutic trials and a phase I study for adrenocortical carcinoma were coordinated.
A second focus, initiated by Endocrinology together with the Department of Nuclear Medicine, aims at developing and implementing new radioactive tracers for imaging and treatment in adrenocortical carcinoma. This new method is currently evaluated in a multicentre trial (FAMIAN) supported by the German Research Foundation (DFG) and the European Union. The adrenal research integrates further into the multicentre collaborative research network Transregio-SFB 205.
Due to participation in the interdisciplinary obesity center Würzburg the treatment of massive obesity is another important focus of our daily work and several clinical and preclinical studies are in full swing. Furthermore, clinical and pre-clinical studies on thyroid carcinoma are currently conducted.
Moreover, the DFG and the Deutsche Krebshilfe provide funding for basic research projects on adrenocortical adenoma and ACTH-producing pituitary adenoma.
In cooperation with the Clinical Laboratory Unit we run a new core facility for mass spectrometric analysis for routine and research applications including pharmacological stu-

dies, metabolomics, and steroid hormone analysis.

Cardiology/Angiology
(S. Frantz, W. Bauer, A. Frey, G. Güder, B. Haring, U. Hofmann, P. Nordbeck, S. Störk)

The cardiovascular research integrates in several research collaborative research centers. In 2010 the Comprehensive Heart Failure Center (CHFC) was founded. CHFC is an Integrated Research and Treatment Center supported by the German Ministry of Education and Research. More than 120 scientists conduct interdisciplinary basic, translational, and clinical research and provide innovative patient care in the field of heart failure. It coordinates the German Competence Network Heart Failure and has a close connection to an associated Interdisciplinary Biomaterial- and Databank (IBDW).

Basic science: Immunocardiology

There are two groups (Hofmann, Ramos) focusing on the role of immunity for the development and progression of myocardial disease. The research focuses on the role of adaptive immunity and lymphocytes and their interplay with macrophages and is funded by the German Research Foundation (DFG) and the European Union (ERA-NET-CVD program).
Ramos's team takes part in an european consortium to monitor T-cell repertoires in myocardial infarction patients. This project is cooperation amongst immunologists at the University of Sorbonne, cardiologists in Graz and the DIM I, and is funded by the European Research Area Network - Cardiovascular (ERA-NET-CVD). Together the groups wish to test whether analyses based on T-cell receptor sequencing could offer suitable prognostic tools to timely identify patients undergoing poor myocardial repair.
The prevalence of cardiovascular diseases (CVD) increases dramatically with age. Emerging evidences show that both the heart, and the immune system undergo dramatic changes with aging, and there is an unmet need to understand how those alterations ultimately affect the outcomes of cardiovascular diseases in elderly subjects. This gap is currently being addressed in Würzburg with support from DFG.
Furthermore, the group of Dr. Nordbeck studies inflammation in a model of Fabry Cardiomyopathy.
Another focus of research is modelling of cardiac transport processes (AG Bauer). On the cellular level, e.g. molecular transport through channels and pores, or transport of signalling molecules (cAMP), the main driving mechanism is diffusion. Up to now, it is not known how different substances cooperate or compete for transport or how the subcellular microstructure affects differential diffusion. We aim to understand these processes by generic modeling to understand channel/pore transport of differential cell regulation.

Translational research

Antigen-specificity is a hallmark of adaptive immune responses. Therefore, the immunocardiology teams have sought to map which cardiac antigens are important in eliciting T- and B-cell responses after myocardial infarction. The diagnostic CAMI-Study (Cardiac Antigens in Myocardial Infarction) phenotypes the T-cell receptor repertoire in post myocardial infarction patients.
Furthermore, in the group of Prof. Bauer there is a strong research focus on imaging: Readout of the cellular inflammatory response is 19F MRI. Molecular markers of inflammation are obtained from nuclear techniques. Both biomarkers of inflammatory response are correlated during healing with (micro)-structural/-functional changes, e.g. diffuse and patchy fibrosis, as well as with global and local mechanical function. The aim is, to gain inflammatory based parameters, which stratify the risk to develop heart failure. Another focus lays on imaging of local vessel wall mechanics and blood-vessel wall interaction and their relation to the development of atherosclerosis. High-end MRI techniques are developed as a readout for the mechanical function and interaction. They are applied to small animal models of atherosclerosis (e.g. APO E-/- mice). Our hypothesis is that functional / mechanical alterations precede the cellular and morphological alterations during the development of atherosclerosis. In addition to small animal models the functional and cellular/morphological processes in the development of atherosclerosis are also studied in tissue engineered vessel models of increasing complexity.
Myocardial sodium accumulation and its role for the development of heart failure is studied by 23 Na and conventional 1H MRI in small animal models. This project demands the development of sophisticated MRI methods which tackle the different sodium fractions in tissue, i.e. bound and free fraction with respect to the intra- and extracellular compartment. Animal models are mice in which a primary hyperaldosteronism is mimicked as well as a model of a secondary hyperaldosteronism after myocardial infarction. Our hypothesis is that an increased sodium amount affects (beside intracellular Ca handling and its consequences) also the composition of the extracellular matrix, and by this the mechanical function (diastolic dysfunction). Both processes are compared and studied with respect on their effect on the development of heart failure.

SELECTED PUBLICATIONS

Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, Maggioni AP, Lewis BS, Störk S, Ryden L, Fox KAA, Bhatt DL, Hart RG, Yusuf S; COMPASS Investigators. (2018) Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 391:219-229.

Bauer WR. (2017) Mechanism of cooperation and competition of two-species transport in narrow nanochannels. Phys Rev E 96:062109.

Fenske W, Refardt J, Chifu I, Schnyder I, Winzeler B, Drummond J, Ribeiro-Oliveira A Jr, Drescher T, Bilz S, Vogt DR, Malzahn U, Kroiss M, Christ E, Henzen C, Fischli S, Tönjes A, Mueller B, Schopohl J, Flitsch J, Brabant G, Fassnacht M, Christ-Crain M. (2018) A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus. N Engl J Med 379:428-439.

Frey A, Sell R, Homola GA, Malsch C, Kraft P, Gunreben I, Morbach C, Alkonyi B, Schmid E, Colonna I, Hofer E, Müllges W, Ertl G, Heuschmann P, Solymosi L, Schmidt R, Störk S, Stoll G. (2018) Cognitive Deficits and Related Brain Lesions in Patients With Chronic Heart Failure. JACC Heart Fail 6:583-592.

Heinze B, Fuss CT, Mulatero P, Beuschlein F, Reincke M, Mustafa M, Schirbel A, Deutschbein T, Williams TA, Rhayem Y, Quinkler M, Rayes N, Monticone S, Wild V, Gomez-Sanchez CE, Reis AC, Petersenn S, Wester HJ, Kropf S, Fassnacht M, Lang K, Herrmann K, Buck AK, Bluemel C, Hahner S. (2018) Targeting CXCR4 (CXC Chemokine Receptor Type 4) for Molecular Imaging of Aldosterone-Producing Adenoma. Hypertension 71:317-325.

Ramos GC, van den Berg A, Nunes-Silva V, Weirather J, Peters L, Burkard M, Friedrich M, Pinnecker J, Abeßer M, Heinze KG, Schuh K, Beyersdorf N, Kerkau T, Demengeot J, Frantz S, Hofmann U. (2017) Myocardial aging as a T-cell-mediated phenomenon. Proc Natl Acad Sci U S A 114: E2420-E2429.

Wanner C, Heerspink HJL, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, Hantel S, Woerle HJ, Broedl UC, von Eynatten M, Groop PH. (2018) Empagliflozin and kidney function decline in patients with type 2 diabetes: a slope analysis from the EMPA-REG OUTCOME Trial. J Am Soc Nephrol 29:2755-2769.

Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, Woerle HJ, Broedl UC, von Eynatten M, Zinman B. (2018) Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation 137:119-129.

Clinical research

Together with the department of Nuclear Medicine these techniques are applied in patients with inflammatory heart disease and after myocardial infarction. Our aim is to understand how inflammation affects healing on a short, intermediate and long time scale. This knowledge will be the base for potential anti-inflammatory therapies. On the one hand, new NUC techniques are validated with established MRI techniques. On the other hand, new MRI techniques are developed (e.g. fast fibrosis imaging). Analogously NUC and MR-imaging techniques are developed, validated and applied for imaging of amyloidosis. Here the aim is to develop a monitoring tool for appropriate therapy of amyloidosis.
In another clinical study we aim to analyse whether cMRI as a first line diagnostic tool makes cardiac catheterization, which actually is the first line recommended diagnostic instrument, in many cases superfluous.
Though implantation of conditional safe rhythm devices is becoming more and more the clinical standard, the cardiac MR-imaging of these patients is still challenging. Ironically these patients often would benefit at best from the diagnosis of cardiac MRI, however artifacts by the device and electrode make this challenging, especially at 3T. This conflict is addressed in this project. New imaging sequences are to be developed (special wide band pulses, changing offset) but also appropriate imaging protocols are a medical need. Both will considerably improve the imaging quality of cardiovascular structure, and hence, the patient's benefit.

Integrated Research and Patient Care at the Comprehensive Heart Failure Center (CHFC)
(S. Störk)

The DIM I is a pivotal supporter of the CHFC, which excels in the optimized structured interaction of clinical research and clinical care (please also refer to chapter on CHFC). The outpatient clinics of the DIM I build the centerpiece of this approach. Strong interactions were formed with various clinical departments, in particular endocrinology, pulmonology, nephrology, DIM II, heart and lung surgery. The general cardiological outpatient clinics, but also dedicated clinics for terminal heart failure, genetic heart disease (B. Gerull), morbid obesity, amyloidosis, treatment-resistant hypertension, are located on the premises of the CHFC. All outpatients are phenotyped and documented according to harmonized diagnostic algorithms, are screened for potential study eligibility, and then included into various projects after written informed consent has been obtained by trained dedicated staff. The portfolio of clinical studies encompasses drug trials (national and international level), studies investigating complex interventions, diagnostic studies, cohort studies observing the natural course of a disease, and early clinical trials. Currently running projects (IITs) address groups of patients with acutely decompensated heart failure (Acute Heart Failure Registry), heart failure and cognitive dysfunction (COGNITION-MATTERS.HF Follow-up Study), with morbid obesity (WAS trial), heart failure of any cause and severity (G-CHF study), high vascular risk (COMPASS trial), suspected or established systemic amyloidosis (AMYKOS registry). Further, the outpatient clinics serve the purpose of clinical-epidemiological education of young clinician scientists (cooperation with Inst. of Clinical Epidemiology & Biometry, P.U. Heuschmann) and echocardiography technicians (EchoCoreLab Facility, C. Morbach).

Nephrology
(C. Drechsler, V. Krane, D. Kraus, R. C. Wanner)

The clinical topic is the identification of predictors for heart failure and sudden cardiac death in type 2 diabetics with chronic kidney disease. Large multicentre randomized trials and cohort studies with biobanking are coordinated and evaluated (EMPA-REG-Outcome, CARMELINA, REVEAL, 4D and SHARP Follow-up). The MiREnDA study and the CARVIDA study are funded by the BMBF and address specific cardiovascular questions in patients on hemodialysis and patients with moderate chronic kidney disease. International co-operations with the University of Oxford and the George Institute of Global Health are maintained. Mainly immunomodulatory treatments are investigated in the studies of the transplantation unit. Würzburg hosts the chair for the worldwide Fabry registry and the co-leadership of the European guideline committee. In our experiments we study the pathomechanism of damaging and relaxation processes in acute ischemic stroke and the pathophysiology of transferases in obesity and diabetes. Specifically, the Kraus lab studies the role of a novel enzyme, nicotinamide-N-methyltransferase (NNMT) in the maintenance of energy homeostasis in adipose tissue. The research groups are funded by the DFG, BMBF, CHFC, IZKF, and the industry.

Pneumonology
(T. Pelzer)

Pneumology is deeply involved in the Würzburg center for sarcoidosis which also represents a department of the center of rare diseases. Together with our partners, e.g. CHFC, we are currently initiating a registry study on organ sarcoidosis. Oncological studies are carried out in cooperation with the comprehensive cancer center with novel therapies for bronchial carcinoma (e.g. MYSTIC). Furthermore, the pneumonology unit participates in studies of idiopathic lung fibrosis (PASSPORT, PANORAMA) or pulmonary hypertension (IMPRES). In basic science the pathogenesis and treatment of chronic thromboembolic pulmonary hypertension (CTEPH) is investigated.

Internal Intensive Care and Emergency Medicine
(D. Weismann)

The Intensive Care Unit participates in multicentric clinical trials investigating the treatment of critical ill patients with community acquired pneumonia and in a multicentric trial comparing drug-monitoring in critical ill patients requiring antibiotic treatment. Own projects comprise studies on hemodynamics in cardiogenic and septic shock, the treatment of symptomatic hyponatremia, antibiotic treatment of aspiration pneumonia and a study on thrombocyte function in critical ill patients.

Teaching

About 650 undergraduate clinical students participate in courses of the Internal Medicine each semester including the main lecture, practical training of physical examination, bedside teaching, 2 weeks elective, and internship. With about 3,000 hours of teaching per semester, the Internal Medicine is number one in teaching responsibilities in the medical curriculum. In 2013, new teaching modules for Clinical Sciences were implemented in cooperation with the Institute of Clinical Epidemiology and Biometry (Heuschmann) and the Comprehensive Heart Failure Center (Störk) including a Master and a PhD course Clinical Sciences at the Graduate School of Life Sciences. For further education and training of students and young medical and non-medical staff, the hospital offers lectures and courses in its Interdisciplinary Training- and Simulation Center (INTUS, W. Voelker).

CONTACT DETAILS

Professor Dr. med. Hermann Einsele
(Head of the Department)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-40001
Fax: 0931/201-640001
E-mail: Einsele_H@ukw.de
www.ukw.de/medizinische-klinik-ii

Professor Dr. med. Ralf Bargou
(Chair of Translational Oncology)
Phone: 0931/201-40014

Professor Dr. med. Alexander Meining
(since 4/2019, Chair of Gastroenterology)
Phone: 0931/201-40450

Professor Dr. Dr. med. Andreas Beilhack
Phone: 0931/201-44040

Professor Dr. med. Herbert Csef
Phone: 0931/201-40060

Professor Dr. med. Andreas Geier
Phone: 0931/201-40021

Professor Dr. med. Franziska Jundt
Phone: 0931/201-40983

Professor Dr. med. Stefan Knop
Phone: 0931/201-40941

Professor Dr. med. Volker Kunzmann
Phone: 0931/201-40003

Professor Dr. med. Michael Scheurlen
Phone: 0931/201-40201

Professor Dr. med. Max Topp
Phone: 0931/201-40915

Professor Dr. med. Andrew Ullmann
(currently: member of the
Deutscher Bundestag)
Phone: 0931/201-40115

General Information and Structure

The Department of Internal Medicine II (DIM II) includes six divisions in research, teaching, and patient care: Hematology and Medical Oncology, Gastroenterology, Rheumatology/Clinical Immunology, Hepatology, Infectious Diseases and Psychosomatics. All departments are integrated into the Center for Internal Medicine (Zentrum Innere Medizin, ZIM) and provide state-of-the-art infrastructure and logistics for patient care, teaching, clinical and translational research.

The **Division of Hematology (Prof. Dr. S. Knop, Prof. Dr. M. Topp)** offers the largest clinical and research program for patients with multiple myeloma in Germany and a highly innovative clinical program for patients with lymphomas and acute leukemia including novel immunotherapeutic strategies (bispecific antibodies, CAR-T cells). In special wards with HEPA filtered rooms autologous stem cell transplantation and the treatment of patients with leukemia, lymphoma and myeloma are performed. The Department of Medicine II runs the largest Early Clinical Trial Unit in Germany (Phase I unit) for first-in-man applications and innovative phase I/II trials, esp. with novel immune therapeutic strategies (CAR T cells, TCR-transduced T cells, bi-specific antibodies, etc.).

A completely new **Stem Cell Transplantation Unit (PD Dr. G. Grigoleit, S. Kraus)** runs the second largest stem cell transplantation program in Germany (280 stem cell transplantations/year). This highly innovative program includes transplantation from haploidentical donors, cord blood transplantation and adoptive immunotherapy to improve infection and tumor control post-transplant.

The **Division of Medical Oncology (Prof. Dr. V. Kunzmann)** runs a special ward but also a large interdisciplinary oncological outpatient clinic in which more than 12.000 patients with a broad spectrum of oncological disorders are treated. A specific focus of the division of Medical Oncology in association with the divisions of gastroenterology and hepatology is the care of patients with gastrointestinal tumors esp. gastric, pancreatic hepatocellular and cholangiocarcinoma, but also has a focus on the treatment of patients with sarcoma.

The **Division of Gastroenterology (Prof. Dr. M. Scheurlen)** is in charge of a specialized ward and the gastrointestinal outpatients clinic. More than 5000 endoscopic procedures are performed per year (specific focus on chronic inflammatory bowel disorders, tumors of the gastrointestinal tract (hereditary neoplastic disorders, neuroendocrine tumors (ENETS Center of Excellence Würzburg), ,a certified PNET center and gastric and pancreatic carcinoma). Since 2007 a “Darmzentrum” is established including an unit for pancreatic carcinoma.

The **Division of Hepatology (Prof. Dr. A. Geier)** has been established to strengthen the treatment of liver disorders including a

SELECTED PUBLICATIONS

Deterding K, Spinner CD, Schott E, Welzel TM, Gerken G, Klinker H, Spengler U, Wiegand J, Zur Wiesch JS, Pathil A, Cornberg M, Umgelter A, Zöllner C, Zeuzem S, Papkalla A, Weber K, Hardtke S, von der Leyen H, Koch A, von Witzendorff D, Manns P, Wedemeyer H; HepNet Acute HCV IV Study Group.(2017) Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis 17:215-222.

Gogishvili T, Danhof S, Prommersberger S, Rydzek J, Schreder M, Brede C, Einsele H, Hudecek M. (2017) SLAMF7-CAR T cells eliminate myeloma and confer selective fratricide of SLAMF7+ normal lymphocytes. Blood 130:2838-2847.

Hefner J, Berberich S, Lanvers E, Sanning M, Steimer AK, Kunzmann V. (2018) Patient-doctor relationship and adherence to capecitabine in outpatients of a German comprehensive cancer center. Patient Prefer Adherence 12:1875-1887.

Jabbour E, Düll J, Yilmaz M, Khoury JD, Ravandi F, Jain N, Einsele H, Garcia-Manero G, Konopleva M, Short NJ, Thompson PA, Wierda W, Daver N, Cortes J, O'brien S, Kantarjian H, Topp MS. (2018) Outcome of patients with relapsed/refractory acute lymphoblastic leukemia after blinatumomab failure: No change in the level of CD19 expression. Am J Hematol 93:371-374.

Jetani H, Garcia-Cadenas I, Nerreter T, Thomas S, Rydzek J, Meijide JB, Bonig H, Herr W, Sierra J, Einsele H, Hudecek M. (2018) CAR T-cells targeting FLT3 have potent activity against FLT3-ITD+ AML and act synergistically with the FLT3-inhibitor crenolanib. Leukemia 32:1168-1179.

Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, Wei A, Dombret H, Foà R, Bassan R, Arslan Ö, Sanz MA, Bergeron J, Demirkan F, Lech-Maranda E, Rambaldi A, Thomas X, Horst HA, Brüggemann M, Klapper W, Wood BL, Fleishman A, Nagorsen D, Holland C, Zimmerman Z, Topp MS. (2017) Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 376:836-847.

Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, Haider S, Ullmann AJ, Katayama Y, Brown J, Mullane KM, Boeckh M, Blumberg EA, Einsele H, Snydman DR, Kanda Y, DiNubile MJ, Teal VL, Wan H, Murata Y, Kartsonis NA, Leavitt RY, Badshah C. (2017) Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med 377:2433-2444.

Neuenhahn M, Albrecht J, Odendahl M, Schlott F, Dössinger G, Schiemann M, Lakshmipathi S, Martin K, Bunjes D, Harsdorf S, Weissinger EM, Menzel H, Verbeek M, Uharek L, Kröger N, Wagner E, Kobbe G, Schroeder T, Schmitt M, Held G, Herr W, Germeroth L, Bonig H, Tonn T, Einsele H, Busch DH, Grigoleit GU. (2017) Transfer of minimally manipulated CMV-specific T cells from stem cell or third-party donors to treat CMV infection after allo-HSCT. Leukemia 31:2161-2171.

liver transplant program (22 transplants in 2018 - specialized inpatient and outpatient facilities). The clinical and research focuses are metabolic liver disorders such as Non-alcoholic fatty liver disease (NAFLD), viral hepatitis B and C as well as malignant tumors of the liver. Many clinical studies to develop new drugs for NAFLD or liver cancer are conducted as national lead center. For non-alcoholic fatty liver disease a national clinical research network (NAFLD CSG) is coordinated by our center. A functional liver testing unit has been established. Würzburg is serving as a national lead center within the IMI2 EU consortium LITMUS for NAFLD biomarker research.

In the **Division of Clinical Immunology/ Rheumatology (Prof. Dr. H.-P. Tony, Dr. M. Schmalzing)**, patients with severe forms of rheumatoid arthritis, spondyloarthritis, connective tissue diseases, primary vasculitis, and primary immunodeficiencies are cared for. In the specific ward of the division and its outpatient clinics, more than 3.000 patients per year are seen. Specific expertise of the division are the diagnosis and treatment of autoimmune disorders including novel therapeutic interventions in phase II-III studies. The division is one of few in Germany, which can offer autologous stem cell transplantation after immunoablative conditioning for patients with aggressive forms of autoimmune diseases. Due to the systemic character of most diseases the division relies on interdisciplinary patient care to a particularly high extent.

A **Division of Infectiology (Prof. Dr. H. Klinker, Prof. Dr. A. Ullmann)** was certified in 2005 as one of the first centers in Germany by the Deutsche Gesellschaft für Infektiologie as a center of infectiology. Patients with infectious disorders are cared for in the special ward for infectious disorders but also in a large outpatient clinic (4.000 patients per year). Re-certifications were successfully completed in 2012 and 2017. The clinical focuses of the division are severe organ infections, complex systemic infections, HIV-infections, chronic virus hepatitis, and opportunistic infections in immunocompromised, esp hematological patients. Innovative therapeutic strategies are used, especially in phase II- and III-studies. The group is very active in consulting and participates in the clinic-wide antibiotic stewardship program. The work in the scientific laboratory is focused on pharmacokinetics and drug monitoring.

In the **Division of Psychosomatics** (**Prof. Dr. H. Csef)** runs a specific outpatient clinic for oncological patients and for patients with psychosomatic disorders. In an outpatient department, which is run in close collaboration with the department of psychiatry, daycare of patients with psychosomatic disorders is offered. Specific research activities comprise the supportive care of patients undergoing stem cell transplantation.

Interdisciplinary projects

The co-chair of the TR/CRC124 FungiNet and the TR/CRC 221 (H.Einsele). H. Einsele is also the speaker of the EU-funded network FP7 T-Control, the EU Horizon 2020 Program (CARAMBA, EURE-CART (Einsele, Hudecek). A. Beilhack coordinates the physician-scientist training program of the Else-Kröner-Forschungskolleg for interdisciplinary translational immunology that has been generously funded for a second training period by the Else Kröner-Fresenius-Stiftung. Furthermore, A. Beilhack has been awarded with an Interdisciplinary Center for Clinical Research (IZKF) Research Group, which fosters the research between basic and translational research across disciplines within Würzburg University and internationally. The IZKF research group advances and utilizes preclinical models of inflammation, cancer and infectious diseases to develop novel immunotherapeutic strategies and diagnostics.

Research in Hematology/Oncology
Hämatologisch/Internistisch-Onkologische Forschungsschwerpunkte
(H. Einsele, R. Bargou, T. Bumm, S. Danhof, U. Grigoleit, M. Hudecek, F. Jundt, M. Kortüm, S. Knop, V. Kunzmann, L. Rasche, G. Stuhler, M. Topp)

Early clinical trials in the field of gastrointestinal tumors with their specific focus on stomach carcinoma, pancreas carcinoma and peritoneal carcinosis have been performed (V. Kunzmann) supported by grants from the BMBF, EU and the Deutsche Krebshilfe. Research groups address the genetics, pathophysiology and therapeutic approaches in multiple myeloma in *in vitro* and *in vivo* models and other lymphoid malignancies. The Deutsche Studiengruppe Multiples Myelom is chaired by H. Einsele and S. Knop since 14 years. In addition a therapeutic treatment unit Multiple Myeloma has been funded by the Sander-Stiftung. A. Beilhack investigates novel strategies to exploit multiple myeloma–immune interactions within the national DFG SKELMET consortium (FOR1586) on the biology of bone metastases. Another research focus is allogeneic stem cell transplantation: new technologies of haploidentical stem cell transplantation, cord blood transplantation, adoptive immunotherapy are evaluated in international studies chaired by Wuerzburg PIs These research programs are funded by the EU (FP7 T-Control, coordinator H. Einsele), BMBF (PACT, coordinator U. Grigoleit), the EU-Horizon 2020 programs CARAMBA and EURE-CART (M. Hudecek, H. Einsele) and Sander Foundation (H. Einsele, A. Beilhack). A third research focus is the development of immunotherapeutic strategies based on novel antibody constructs (bi-specific, trispecific antibodies, fusion proteins and gene modified redirected T cells (A. Beilhack, T. Bumm, G. Stuhler, L. M. Topp, and H. Wajant). The Max Eder Research Group 'CAR T-cell engineering' lead by Dr. Michael Hudecek is working on the currently 'hottest topic' in hematology – tumor-reactive T cells that are equipped with synthetic chimeric antigen receptors (CARs) (Dr. Thomas Nerreter). Development of CAR-modified T cells targeting multiple myeloma in the Hudecek lab is supported by the Myeloma Crowd Research Initiative. Dr. Michael Hudecek and Dr. Julia Wegner received the M4 Award of the State of Bavaria for the most innovative research projects in personalized medicine and immunotherapy and focus on the development and commercialization of next-generation CAR T cells also recently supported by a grant from the Deutsche Krebshilfe in the Translational Oncology Program. The groups of A. Beilhack and H. Wajant develop novel drugs that target the tumor microenvironment, e.g. by blocking regulatory T cells to reactivate the immune system for combating tumors. This work has also been recognized with an M4 Award of the State of Bavaria for the most innovative research projects in personalized medicine and immunotherapy.

A completely new **Stem Cell Transplantation Unit (PD Dr. G. U. Grigoleit, Dr. S. Kraus)** runs the second largest stem cell transplantation program in Germany (280 stem cell transplantations/year). This highly innovative program includes transplantation from haploidentical donors, cord blood transplantation and adoptive immunotherapy to improve infection and tumor control post-transplant.

Research in Gastroenterology
(M. Scheurlen, T. Kudlich, S. Reimer, A. Weich)

Basic research: With the support of the IZKF and BMBF a tumour bank with focus on stomach cancer and colorectal carcinoma was established and treatment concepts in gastric cancer and pancreatic carcinoma are developed with new innovative combinations of tyrosine kinase inhibitors and new cytotoxic agents. As a part of the DFG research con-

sortium FOR 2314 Würzburg-Tübingen novel strategies in cancer therapy are pursued, particularly for pancreatic cancer (A. Beilhack). Further basic research fields are pathogenesis and new therapeutic strategies in neuroendocrine tumours (beta-catenin-WNT-pathway) as well as intestinal barrier function.
Clinical research projects: New diagnostic and therapeutic options in the field of neuroendocrine tumours (Theranostics, Freehand-SPECT) in cooperation with the Department of Nuclear Medicine. Ultrasound in inflammatory bowel disease (within multi-center studies). Influence of injection solution on resection status in endoscopic polypectomy.

Research in Hepatology
(A. Geier, H. Hermanns, D. Jahn, O. Götze, M. Rau, J. Weiss)

Clinical research projects in Hepatology address the pathophysiology and treatment of chronic liver disorders with special emphasis on metabolic liver disorders, viral hepatitis as well as liver cancer including prospective cohort studies with biobanking for non-alcoholic fatty liver disease (NAFLD) and liver cancer (HCC, CCC). The NAFLD cohort is integrated into the national NAFLD CSG research network (coordinating center) and the pan-European LITMUS consortium (national lead). New research focus is the enterohepatic functional diagnostic platform with longitudinal studies investigating the predictive value of 13C breath testing (methionin, methacetin) in chronic liver disease and liver cancer. An international translational research project on liver cancer research (*TRANSFER 2* study) has been incorporated into the German Alliance for Liver Cancer Research (GALC). Additional basic and translational research projects address the role of the microbiome, enterohepatic signalling and pro-inflammatory cytokines in the pathophysiology of human fatty liver disease and therapeutic anti-cytokine strategies in murine models. Funding is received from the European Union (IMI2 call), the German Science Foundation (DFG), the Interdisciplinary Center for Clinical Research (IZKF) and the Else-Kröner-Fresenius Foundation (EKFS). A phase II therapeutic intervention IIT in NAFLD (*PINPOINT* study) is currently set up with financial support from pharma industry.

Research in Immunology/Rheumatology
(H.-P. Tony, M. Schmalzing)

The research focus of the division of clinical immunology/rheumatology in basic but also translational research includes modulation of the B cell-repertoire in autoimmune disorders. Specific topics are the modulation of the memory B cell-compartment by novel cytokine targets. Additional topics are immune reconstitution in patients with immunological disorders following more intensive forms of immune suppression such as autologous stem cell transplantation, the development of biomarkers for monitoring of treatment of autoimmune disorders and the pathological immunological regulation in systemic sclerosis. In the context of the Center for primary immunodeficiencies and autoinflammation, patient care is evaluated together with the pediatric department.

Research in Infectiology
(A. Ullmann, H. Klinker, W. Heinz, S. Wiebecke, J. Löffler, H. Einsele)

New treatment strategies in HIV-infection are evaluated in early and phase III trials (clinical study center in the international HIV-study network INSIGHT of the Institute of Health/USA). Initiated with the DFG-funded international Research Training Group (IRTG) 1522: HIV –Aids and associated infectious diseases therapeutic drug monitoring for antiretroviral agents is performed in clinical multicenter studies. In the antiviral treatment strategies of chronic Hepatitis B and C the division of infectiology is internationally recognized (numerous phase II- and III-studies, the pharmacokinetics and drug monitoring of innovative antiviral agents). An additional research focus is infections in the immunocompromised patients with therapeutic drug monitoring of antifungal agents and CMV-therapeutics (Letermovir, Ganciclovir). The group of J. Löffler and A. Ullmann develops new diagnostic strategies, risk stratification, biomarker determinations and new therapeutic approaches for patients with invasive fungal infections. The research is funded by the BMBF, Wilhelm Sander-Stiftung, BayImmuNet, EU FP7 T-Control, and the SFB/Transregio124. The DFG research training group 2157 (A. Beilhack; Speaker: T. Rudel) employs innovative 3D tissue models for studying microbial infections by human pathogens.

Teaching

The „Medizinische Klinik und Poliklinik II“ offers numerous courses for medical students and for postgraduate professional education. Prof. Dr. H. Einsele is certified trainer for the whole field of Internal Medicine. In addition, authorized training and education is available for the following specialties (2 years each): Prof. Dr. H. Einsele (Hematology/Oncology), Prof. Dr. M. Scheurlen (Gastroenterology), Prof. Dr. H.-P. Tony (Rheumatology) and Prof. Dr. H. Klinker (Infectious Diseases). The hospital organizes numerous advanced training courses and scientific meetings for both physicians and patients. A web-based teaching concept teaching concept is funded by the Virtuelle Hochschule Bayern (VHB). This joined project with the University Hospital Regensburg with 499 users in 2017 and > 15.000 processed cases is extremely accepted.

SELECTED PUBLICATIONS

O'Connor J, Vjecha MJ, Phillips AN, Angus B, Cooper D, Grinsztejn B, Lopardo G, Das S, Wood R, Wilkin A, Klinker H, Kantipong P, Klingman KL, Jilich D, Herieka E, Denning E, Abubakar I, Gordin F, Lundgren JD; INSIGHT START study group. (2017) Effect of immediate initiation of antiretroviral therapy on risk of severe bacterial infections in HIV-positive people with CD4 cell counts of more than 500 cells per µL: secondary outcome results from a randomised controlled trial. Lancet HIV 4: e105-e112.

Rau M, Rehman A, Dittrich M, Groen AK, Hermanns HM, Seyfried F, Beyersdorf N, Dandekar T, Rosenstiel P, Geier A. (2018) Fecal SCFAs and SCFA-producing bacteria in gut microbiome of human NAFLD as a putative link to systemic T-cell activation and advanced disease. United European Gastroenterol J 6:1496-1507.

Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Jäger U, Jaglowski S, Andreadis C, Westin JR, Fleury I, Bachanova V, Foley SR, Ho PJ, Mielke S, Magenau JM, Holte H, Pantano S, Pacaud LB, Awasthi R, Chu J, Anak Ö, Salles G, Maziarz RT; JULIET Investigators. (2019) Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 380:45-56.

Schwaneck EC, Renner R, Junker L, Einsele H, Gadeholt O, Geissinger E, Kleinert S, Gernert M, Tony HP, Schmalzing M. (2018) Prevalence and Characteristics of Persistent Clonal T Cell Large Granular Lymphocyte Expansions in Rheumatoid Arthritis: A Comprehensive Analysis of 529 Patients. Arthritis Rheumatol 70:1914-1922.

Shitara K, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandalà M, Ryu MH, Fornaro L, Olesiński T, Caglevic C, Chung HC, Muro K, Goekkurt E, Mansoor W, McDermott RS, Shacham-Shmueli E, Chen X, Mayo C, Kang SP, Ohtsu A, Fuchs CS; KEYNOTE-061 investigators. (2018) Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 392:123-133

*Strnad P, Buch S, Hamesch K, Fischer J, Rosendahl J, ..., Geier A, ..., Hampe J, Berg T, Trautwein C. (2018) Heterozygous carriage of the alpha1-antitrypsin Pi*Z variant increases the risk to develop liver cirrhosis. Gut pii: gutjnl-2018-316228. doi: 10.1136/gutjnl-2018-316228. [Epub ahead of print].*

Division of Molecular Internal Medicine

CONTACT DETAILS

Professor Dr. rer. nat. Harald Wajant (Head)

Auvera Haus
Grombühlstr. 12
97080 Würzburg
Phone: 0931/201-71000
Fax: 0931/201-71070
E-mail: harald.wajant@mail.uni-wuerzburg.de
www.ukw.de/medizinische-klinik-ii/abteilung-molekulare-innere-medizin/team/detail/name/wajant-harald

Mission and Structure

The scientific focus of the division of Molecular Internal Medicine lies i) on basic biomedical research and applied clinical investigations in molecular immunology and oncology and ii) on the preclinical development of therapeutic antibodies and fusion proteins of the tumor necrosis factor (TNF) superfamily (TNFSF). Allocation of personnel includes a scientific research position and part time secretary. Further, a transitory scientific position (Rotationsstelle) is available for clinicians of the Department of Internal Medicine II to temporarily pursue full time research that fits into the framework of the division. This initial option for scientific research is aimed to enable scientifically interested clinicians to acquire preliminary results offering a chance to achieve independent external funding. The various research projects of the division of Molecular Internal Medicine are currently funded by:

- the German Research Foundation
- the Mildred Scheel Foundation for Cancer Research
- the German José Carreras Leukaemia foundation
- the Bavarian Ministry of Economic Affairs (m4-award)

Major Research Interests

The main research topic of the division is the TNFSF and the receptors of the TNF receptor superfamily (TNFRSF). Ligands and receptors of the TNF family are of pivotal importance in immunoregulation, but are also of relevance in development and the control of tissue homeostasis. The division is organized in three research groups engaged in the investigation of clinically relevant aspects of signal transduction by receptors of the TNFRSF and in the development of therapeutic useful recombinant TNFSF ligand variants and anti-TNFRSF receptor antibodies.

Research Group: Therapeutic Fusion Proteins and Antibodies

Many ligands of the TNFSF stimulate the immune system or trigger apoptosis. The potential therapeutic application of these properties, however, is limited due to the serious side effects that are usually associated with systemic activation of receptors of the TNFRSF. The research group thus develops fusion proteins of TNFSF ligands that selectively activate TNFRSF receptors locally in the tumor areal. In one approach, the fact is exploited that a subset of TNFRSF receptors (e.g. 4-1BB, CD27, CD95, OX40, TNFR2, TRAILR1/2) is naturally activated by membrane-bound ligands of the TNFSF, but not by soluble, still receptor binding-competent variants derived from these molecules. However, if such inactive soluble TNFSF ligands are artificially anchored on the cell surface, they acquire the same TNFRSF receptor-stimulating activities as their natural occurring membrane-bound counterparts. Now, the activating effect of cell surface-immobilization can be reached by fusing the soluble TNFSF ligand variant genetically to a targeting domain (e.g. an antibody fragment) recognizing a cell surface-associated molecular structure. Utilization of targeting domains which interact with tumor specific structures facilitates then the anticipated favorable local activation of TNFRSF receptors without causing systemic side effects. It is also possible to overcome the poor responsiveness of TNFRSF receptors to binding of soluble

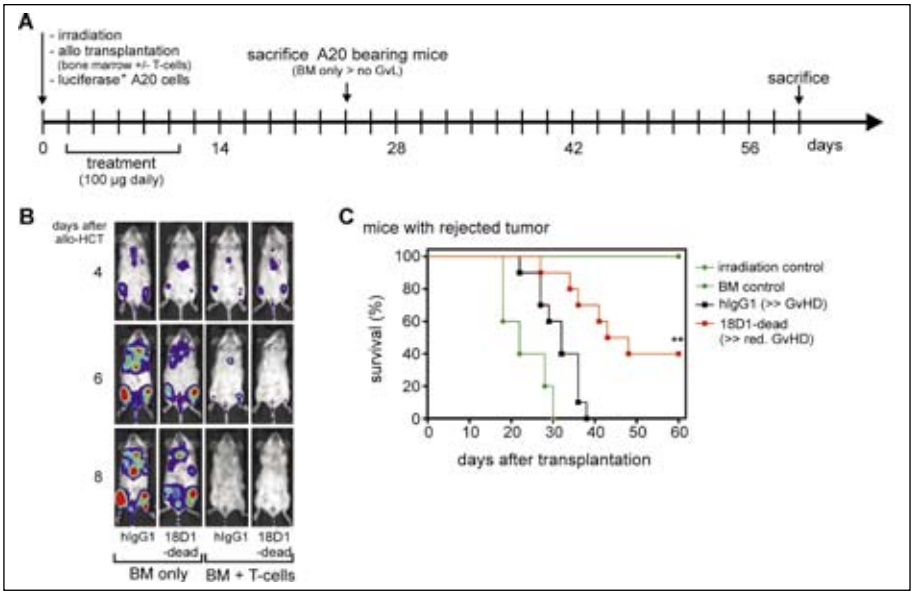


Fig. 1: The blocking, ADCC-defective Fn14-specific antibody variant 18D1 inhibits graft versus host disease (GvHD) without interference with the graft versus leukemia (GvL)-effect. (A) Mice were lethally irradiated and reconstituted with allogeneic bone marrow cells with (GvHD and GvL) or without (control; no GvHD and GvL) allogeneic T cells and luciferase expressing A20 leukemic cells. Subsequently mice were treated for a week with 18D1-dead or a control antibody (hIgG1) and the development of the tumor cell load and GvHD were monitored. (B) In vivo-bioluminescence imaging showed that treatment with 18D1-dead neither affects A20 tumor cell growth (columns 1 and 2) nor the T cell-dependent GvL-activity (columns 3 and 4). (C) GvHD induction due to the cotransplanted allogenic T cells, however, was significantly reduced by treatment with 18D1-dead (compare black and red squares).

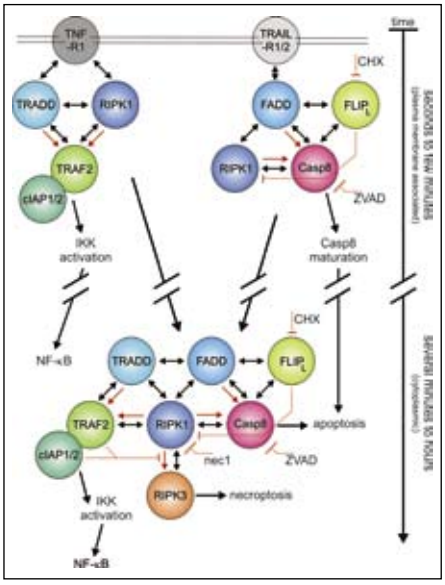


Fig. 2: Redundant and receptor-specific activities of the signaling proteins TRADD, RIPK1, FADD, Caspase-8 and TRAF2 in the signal transduction of death receptors. Double-headed arrows refer to protein-protein interactions. Red headed arrows indicate activating/stimulating events. Red dotted blocked lines refer to inhibitory events/effects. For details see text. RIPK3 is a key factor for necroptosis and cIAP1/2 are TRAF2-associated factors.

TNFSF ligands by secondary oligomerization of the ligand molecules. Against this background this group also develops and evaluates various scaffolds for multimerization of TNFSF ligands and agonistic TNFRSF receptor-specific antibody fragments. Primary aim is here the development of potent TNFR2- and CD40 specific agonists for activation of regulatory T-cells and dendritic cells. Sustained and/or overshooting activation of receptors of the TNFRSF are of crucial relevance in a variety of diseases reaching from rheumatoid arthritis to cancer. The research group "Therapeutic Fusion Proteins and Antibodies" develops therefore also novel antibodies and antibody formats that allow efficient inhibition of TNFRSF receptors (e.g. Fn14) in vivo (Fig. 1).

Research Group: Death Receptors
(D. Siegmund)

Death receptors, a subgroup of the TNFRSF that includes CD95, TRAILR1 and TRAILR2, were initially studied because of their strong apoptosis inducing activity which relies on the ability of these receptors to trigger activation of the protease caspase-8. Over the last years, we and others could show, however, that death receptors can also trigger an alternative form of cell death, called necroptosis, and furthermore activate pro-inflammatory signaling pathways. The latter is especially apparent in cells that are resistant towards death receptor-induced apoptosis and necroptosis. Inflammation can enhance metastasis and angiogenesis of tumor cells. In accordance with this fact, the group of Dr. Siegmund showed in vitro and in vivo that initial anti-tumoral effects of death receptors are turned into mechanisms of tumor promotion in apoptosis resistant tumor cells. General research efforts of this group are thus aimed to characterize precise conditions, where stimulation of death receptors leads to enhanced metastasis and aggressive tumor growth. Worth mentioning, TNF receptor-1 (TNFR1) another death receptor of the TNFRSF primarily acts as a proinflammatory receptor and triggers cell death only under special sensitized conditions despite using the same singling proteins as CD95 and the TRAIL death receptors. The research group of Dr. Siegmund found that the qualitatively complementary activities of TNFR1 versus CD95 and the TRAIL death receptors are due to the hierarchical reciprocal use of the common inflammatory and cytotoxic signalling molecules (Fig. 2). TNFR1 recruits initially the gene inductive signalling proteins TRADD, RIPK1 and TRAF2 and stimulates the apoptotic proteins FADD and caspase-8 secondarily in the cytoplasm. In contrast, CD95 and the TRAIL death receptors recruit and activate first FADD and caspase-8 and stimulate secondarily a cytoplasmic complex containing TRAF2, TRADD and RIPK1. Under circumstances where gene induction and apoptosis are inhibited, all death receptors triggers necroptosis, a special form of cell death, via RIPK1-mediated activation of RIPK3 in the cytoplasm (Fig. 2). Currently the group of Dr. Siegmund investigates how the balance between apoptotic, necroptotic and proinflammatory signaling by death receptors is controlled at the molecular level by TRAF2- and RIPK1-associated regulatory proteins.

Research Group: Co-operation of TNFR1 and TNFR2

TNF, the name giving cytokine of the entire TNF superfamily, occurs naturally in two forms, as a transmembrane protein and as a soluble factor derived thereof by proteolytic processing. The two forms of TNF differ in their capacities to activate the two TNF receptors TNFR1 and TNFR2. Both TNF receptors can induce in a cell type-specific manner the production of their own ligand TNF and show counteracting, but also synergistic effects dependent on the cell type. The precise cellular effects of TNF are therefore dependent on TNF-receptor expression, cell type, extracellular conditions and, importantly, on the form of TNF that was used for receptor stimulation. Moreover, the crosstalk mechanisms used by TNFR2 to control the quality and activity of TNFR1 signaling can also be triggered by TNFR2-related TNF receptors, e.g. Fn14. As a consequence, such TNFR2-related receptors can modulate the activity of the TNFR1-TNFR2 system and adjust so TNF responsiveness. The major concerns of this group are the investigation of the regulatory principles that cause the exceptional complexity of TNF signaling and evaluation of the relevance of the TNFR1 TNFR2 crosstalk mechanisms for TNF biology and tumor metastasis.

Teaching

Courses, colloquia, seminars and lectures related to the research topics of the division are offered for students of Biology and Medicine.

SELECTED PUBLICATIONS

Anany MA, Kreckel J, Füllsack S, Rosenthal A, Otto C, Siegmund D, Wajant H. (2018) Soluble TNF-like weak inducer of apoptosis (TWEAK) enhances poly(I:C)-induced RIPK1-mediated necroptosis. Cell Death Dis 9:1084.

Cuchet-Lourenço D, Eletto D, Wu C, Plagnol V, Papapietro O, Curtis J, Ceron-Gutierrez L, Bacon CM, Hackett S, Alsaleem B, Maes M, Gaspar M, Alisaac A, Goss E, Alldrissi E, Siegmund D, Wajant H, Kumararatne D, AlZahrani MS, Arkwright-PD, Abinun M, Doffinger R, Nejentsev S. (2018) Biallelic RIPK1 mutations in humans cause severe immunodeficiency, arthritis, and intestinal inflammation. Science 361:810-813.

Kums J, Nelke J, Rüth B, Schäfer V, Siegmund D, Wajant H. (2017) Quantitative analysis of cell surface antigen-antibody interaction using Gaussia princeps luciferase antibody fusion proteins. MAbs 9:506-520.

Siegmund D, Ehrenschwender M, Wajant H. (2018) TNFR2 unlocks a RIPK1 kinase activity-dependent mode of proinflammatory TNFR1 signaling. Cell Death Dis 9:921.

Siegmund D, Lang I, Wajant H. (2017) Cell death-independent activities of the death receptors CD95, TRAILR1, and TRAILR2. FEBS J 284:1131-1159.

Institute of Transfusion Medicine and Haemotherapy

CONTACT DETAILS

Professor Dr. med. Markus Böck
(Head of the Institute)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-31300
Fax: 0931/201-31376
E-mail: boeck_m@ukw.de
www.ukw.de/transfusionsmedizin

Mission and Structure

The Institute of Transfusion Medicine and Haemotherapy is localized at three positions within the hospital area. It provides

- a laboratory for blood group serology
- a laboratory for HLA-typing
- a GMP-laboratory for modification and cryopreservation of stem cell concentrates
- a blood bank for supplying the university hospital with blood components
- a blood donation department (incl. autologous and allogeneic stem cells)
- a department for therapeutical apheresis, photopheresis and immuoadsorption
- a register for stem cell donors
- a research laboratory

Clinical Activities

The Institute of Transfusion Medicine and Haemotherapy supplies the university hospital of Wuerzburg with all required blood products, e.g. red cell concentrates, platelet concentrates and fresh frozen plasma. Additionally, it is competent for the production of autologous and allogenic stem cell concentrates for adult patients of the hospital. Beside immuno-haematological laboratory analyses (e.g. blood group serology, red blood cell cross match, antibody screening, antibody differentiation) the Institute of Transfusion Medicine and Haemotherapy provides HLA-testing for the patients of the hospital with serological and DNA-based methods. It organizes a stem cell donor registry for the national and international donor mediation. In addition, the Institute of Transfusion Medicine and Haemotherapy is specialized in the enforcement of photophereses and therapeutical aphereses (e.g. plasmapheresis, immunoadsorption, cell-apheresis). Furthermore, quality assurance in haemotherapy for the university hospital is one of the central functions of the institute.

Major Research Interests

Molecular mechanisms of „platelet storage lesion“ and optimization of storage conditions of platelet concentrates

Scientific efforts of the institute are focused on alterations of signal transduction cascades in platelets associated with different physical and biochemical storage conditions. The aim is to elucidate mechanisms leading to “platelet storage lesion” on a molecular level. The understanding of these processes is an essential requirement to find appropriate strategies for the optimization of storage conditions, to improve clinical efficacy and to avoid adverse transfusion-related events.

Two projects exploring the proteasome-dependent regulation of the toll-like receptor system in platelets are supported by DFG grants (project leaders: Dr. Jürgen Koessler, Dr. A. Kobsar).

Influence of therapeutic and preparative aphereses on physiological and pharmacological conditions in human blood

Apheresis procedures are known to be very effective regarding intended effects (e.g. reduction of antibody levels) and have very low complication rates. During apheresis treatments, however, changes of blood characteristics may occur potentially resulting in clinical adverse events. It is, therefore, of special interest to analyze effects on drug levels and on protein, electrolyte or hormone regulation caused by different apheresis procedures. The major interest is the exploration of effects on coagulation and platelet function, e.g. after contact of blood with artificial surfaces.

Teaching

- Main lecture “transfusion medicine”
- Lecture “Blood group serology and transfusion therapy”
- Lecture “Immunohaematology”
- Lecture “Therapeutical and preparative apheresis”
- Lecture “Transfusion in critical situations
- Lecture “Production of blood components”
- Lecture “Stem cell transplantation: from the donor to the transplant”
- Lecture “The HLA-system”
- Practical training “Transfusion medicine and immunohaematology”
- Practical training “Blood group serology”
- Lecture “Transfusion of platelets: biochemical and physiological basics”

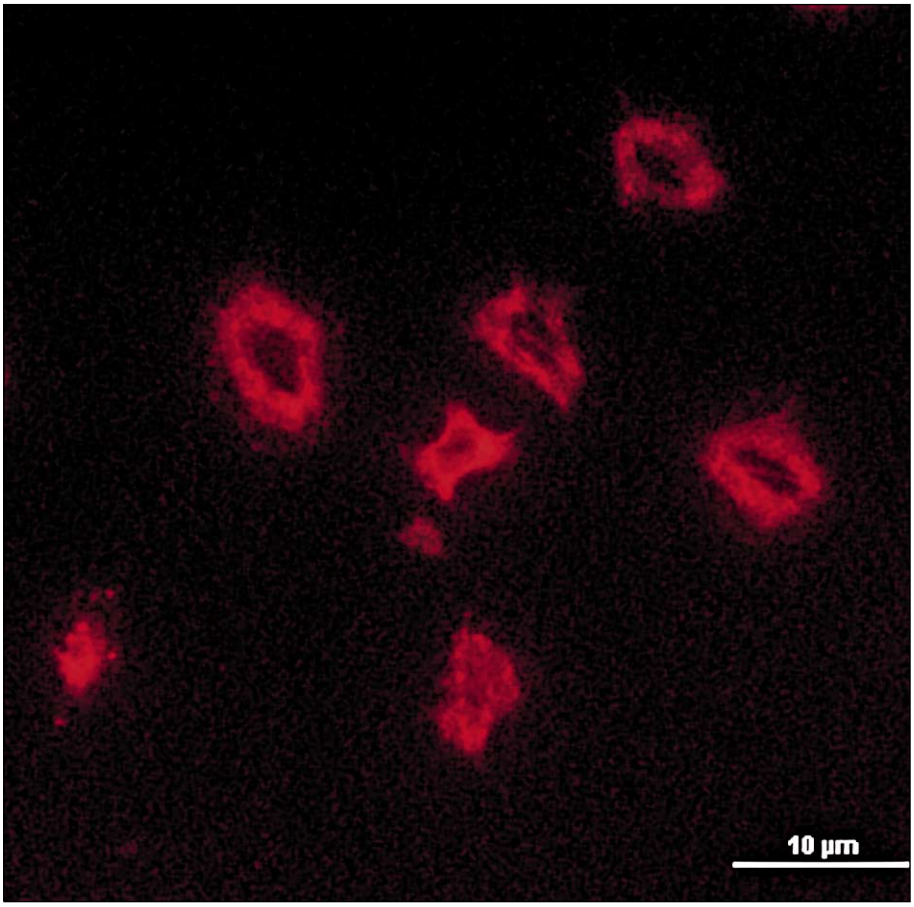


Fig.: Activated platelets (fluorescence microscopy).

SELECTED PUBLICATIONS

Koessler J, Trulley VN, Bosch A, Weber K, Koessler A, Boeck M, Kobsar A. (2018) The role of agonist-induced activation and inhibition for the regulation of purinergic receptor expression in human platelets. Thomb Res 168:40-46.

Koessler J, Schwarz M, Weber K, Etzel J, Koessler A, Boeck M, Kobsar A. (2017) The role of adenosine diphosphate mediated platelet responsiveness for the stability of platelet integrity in citrated whole blood under ex vivo conditions. PLoS One 12:e0188193.

Kössler J, Etzel J, Weber K, Böck M, Kobsar A. (2016) Evaluation of dose-dependent effects of the proteasome Inhibitor bortezomib in human platelets. Eur J of Pharmacol 791:99-104.

Kössler J, Hermann S, Weber K, Koessler A, Kuhn S, Boeck M, Kobsar A. (2016) Role of purinergic receptor expression and function for reduced responsiveness to adenosine diphosphate in washed human platelets. PLoS One 11:e0147370.

Koessler J, Weber K, Koessler A, Yilmaz P, Boeck M, Kobsar A. (2015) Expression and function of purinergic receptors in platelets from apheresis-derived platelet concentrates. Blood Transfus 14:545-551.

Department of Diagnostic and Interventional Radiology

CONTACT DETAILS

Professor Dr. med. Thorsten Bley
(Head of the Department)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-34001
Fax: 0931/201-634001
E-mail: Bley_T@ukw.de
www.ukw.de/radiologie

Professor Dr. med. Ralph Kickuth
Phone: 0931/201-34057

Professor Dr. rer. nat. Herbert Köstler
Phone: 0931/201-34211

Mission and Structure

The Department of Diagnostic and Interventional Radiology provides the complete spectrum of modern radiological services at the University Hospital of Würzburg including pediatric radiology. 45 physicians and ten scientists as well as 49 technicians work together to ensure state-of-the-art diagnostics and interventional radiology.
Five MRI systems (3 x 1,5T, 2 x 3T) and three Spiral-CT scanners are available for emergency patients 24 hours per day and serve to examine over 30.300 patients annually. Sonography is performed on roughly 10.300 patients per year with five machines. To rule out breast cancer 3.100 female patients are examined with mammography, ultrasound and MRI. A further focus is the minimally invasive treatment of stenosies of the vascular and biliary system with balloon catheters or metal stents.
Pedatric radiology offers the full imaging spectrum ranging from premature infants to teenagers. A strong focus is set on radiation protection, ultrasound and magnetic resonance imaging. Main topics of the section are pediatric uroradiology, oncology, diagnostics of skeletal age und pediatric malformations.
The section of Experimental Radiology is focused on developing new techniques for MR-spectroscopy and MR-imaging in close-knit interdisciplinary partnership with special emphasis on functional cardiovascular and thoracic examinations.
The Department of Diagnostic and Interventional Radiology offers postgraduate training in Radiology including the subspecialty of Pediatric Radiology.

Major Topics of Research

Cardiovascular Imaging

(Th. Bley, H. Köstler, T. Wech, T. Gassenmaier, B. Petritsch, A. Weng, A. Kosmala)

The assessment of functional and metabolic parameters and tissue characterization are the foci of cardiac high field MR imaging. In cooperation with the DZHI and under funding of the BMBF, the interactions between myocardial edema, myocardial perfusion defects and myocardial necrosis are investigated in patients with myocardial infarction. Artificial intelligence algorithms are evaluated regarding their possibilities concerning the analysis of cardiac MR scans. Furthermore, sodium content of skeletal muscle and myocardium is quantified in patients suffering from hyperaldosteronism using high-field sodium MR imaging.

Another research project aims to improve the MR diagnosis of giant cell arteritis (DFG grant). A comprehensive characterization of inflammatory changes of the arterial vessel lumina and the vessel wall of the head, neck, chest, and abdomen will be developed using new MRI methods.

Novel MR Methods

(H. Köstler, T. Wech, A. Slawig, S. Veldhoen, A. Weng)

New methods are being developed to accelerate MRI of the human heart and lungs with funding by the DFG. Quantification of fat content, fast mapping of relaxation parameters and artefact reduction in fast imaging are additional topics. For these projects, we apply techniques using non-Cartesian data acquisition and reconstructions with prior knowledge.

MRI of the lungs

(S. Veldhoen, A. Kunz, C. Kestler, C. Wirth, A. Weng, H. Köstler, Th. Bley)

To date, the use of radiation and/or intravenous contrast agents is necessary to obtain site-resolved information on lung perfusion and ventilation. The SENCEFUL sequence (Selfgated Non-Contrast-Enhanced Functional Lung imaging) provides this information as part of a magnetic resonance imaging protocol in free breathing and without the use of contrast agents. This technique is being evaluated in clinical use within a research project funded by the DFG.

Dual Energy CT / Cardiac CT Imaging

(B. Petritsch, A. Kosmala, T. Gassenmaier, A. Weng, H. Köstler, Th. Bley)

In cooperation with the Department of Internal Medicine II, the potential of dual energy

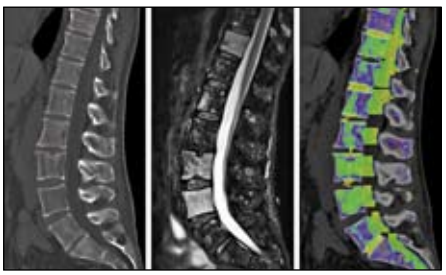


Fig. 1: Normal appearance of the spine in standard CT (a). MRI reveals multiple focal Myelom manifestations (b; bright) which are also detected in the Dual-Energy CT (c; green).

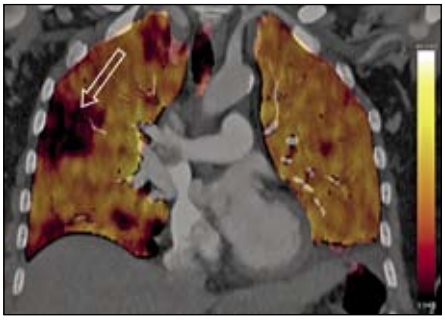


Fig. 2: Coronal view of Dual-Energy Iodine map demonstrating a peripheral perfusion defect (arrow) in a patient with segmental pulmonary embolism.

CT to improve the detection of Myelom lesions, especially in the meaning of different infiltration patterns (Fig. 1). Moreover Dual energy computed tomography (CT) is used for assessment of bone marrow edema in occult fractures.
The variation of the coronary calcium score (Agatston score) as a function of tube-voltage and tube current on a 3rd generation dual-source CT is evaluated in a phantom (QRM-phantom) and ex-vivo (explanted human hearts) study. In addition, the impact of new iterative reconstruction algorithms is investigated. Moreover different cardiac CT-protocols are evaluated regarding image quality and radiation dose.
In a cohort with patients suffering from (suspected) pulmonary embolism, the possibilities of DECT regarding the detection of perfusion deficits (Fig. 2) and potential savings in radiation dose are evaluated.

Interventional Radiology
(R. Kickuth, A. Augustin, F. Fluck, N. Rickert)

Actually, there is a close cooperation with the Medical Department II (section hepatology) concerning the evaluation of the impact of transarterial chemoembolization (TACE) on dynamic liver function by means of 13C-methacetin breath test in patients with hepatocellular carcinoma. With regard to this topic, it is not clear if there is a difference between conventional TACE (cTACE) and TACE with grug-eluting beads (DEB-TACE). Within this interdisciplinary project, the evaluation of dynamic liver function is also regarded to be transferred to other therapeutic procedures like selective internal radiotherapy or chemosaturation percutaneous hepatic perfusion in the treatment of primary or secondary liver tumors.

Pediatric Radiology
(Th. Bley, H. Köstler, S. Veldhoen, A. Weng, C. Benoit)

Whole-body MR procedures, including diffusion weighted imaging in inflammatory and oncological diseases are developed in interdisciplinary projects. Ultrasound-based tissue elastography is analyzed for thyroid and liver diseases. Other interdisciplinary projects include long-term studies of contrast agent safety in ultrasound and morphological changes in hypophosphatasia under enzyme replacement therapy.

MR mammography of pathologies of the female breast
(S. Sauer, T. Pabst, A. Weng)

Aiming to improve specificity of MR-mammography, high temporal resolution 3T-MRI techniques for visualization and quantification of contrast agent enhancement and fat saturation imaging methods of the breast are performed.

Magnetic Particle Imaging (MPI)
(S. Herz, P. Vogel, S. Veldhoen, R. Kickuth, Th. Bley)

MPI is a new, fast and sensitive tomographic imaging modality to visualize the spatial distribution of superparamagnetic iron-oxide nanoparticles. It has the potential to overcome limitations of established cross-sectional imaging modalities and might play a crucial role in moving towards radiation-free real-time cardiovascular imaging technology. Our research focuses on experimental MPI-guided angioplasty techniques and the development of MPI-suitable endovascular instruments and stents in cooperation with the Department of Experimental Physics V of the University of Würzburg.

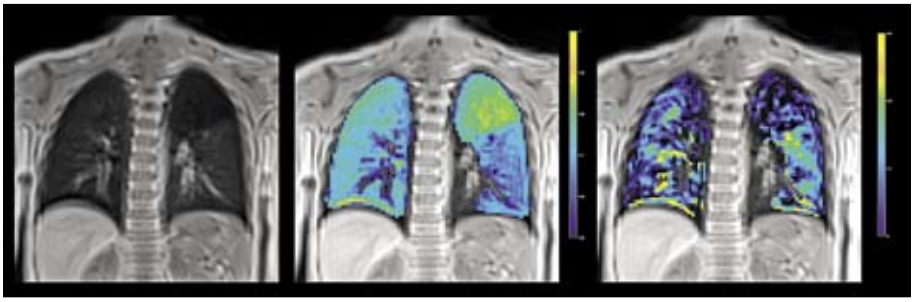


Fig. 3: MR image of the lungs of a patient with congenital lobar emphysema in the left upper lobe (left), determination of the gas ratio (middle) and ventilation (right). The elevated gas ratio and the reduced ventilation in the upper part of the left lung can be clearly seen.

Teaching

The Department of Diagnostic and Interventional Radiology conducts lectures on radiology for medical students, as well as interdisciplinary courses for scientists and schooling for radiological technicions at the local Berufsfachschule. Regular sessions for continued medical education for physicians are organized.
In close cooperation with the institute of medical education and research in medical education scientific projects are scheduled concerning the restructuring of the seminar “interventional Radiology”. In general, those projects are targeted on the continuous improvement of medical education by offering “hands-on-projects”

SELECTED PUBLICATIONS

Herz S, Vogel P, Kampf T, Rückert MA, Veldhoen S, Behr VC, Bley TA. (2018) Magnetic Particle Imaging for Quantification of Vascular Stenoses: A Phantom Study. IEEE Trans Med Imaging 37:61-67.

Kosmala A, Weng AM, Heidemeier A, Krauss B, Knop S, Bley TA, Petritsch B. (2018) Multiple Myeloma and Dual-Energy CT: Diagnostic Accuracy of Virtual Noncalcium Technique for Detection of Bone Marrow Infiltration of the Spine and Pelvis. Radiology 286:205-213.

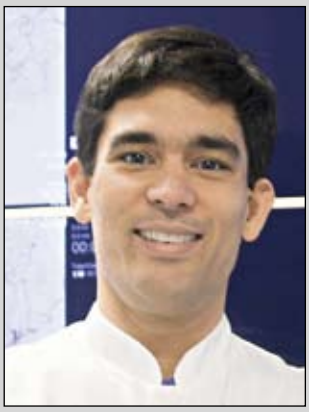
Petritsch B, Kosmala A, Weng AM, Krauss B, Heidemeier A, Wagner R, Heintel TM, Gassenmaier T, Bley TA. (2017) Vertebral Compression Fractures: Third-Generation Dual-Energy CT for Detection of Bone Marrow Edema at Visual and Quantitative Analyses. Radiology 284:161-168.

Slawig A, Wech T, Ratz V, Tran-Gia J, Neubauer H, Bley T, Köstler H. (2017) Multifrequency reconstruction for frequency-modulated bSSFP. Magn Reson Med 78:2226-2235.

Veldhoen S, Weng AM, Knapp J, Kunz AS, Stäb D, Wirth C, Segerer F, Hebestreit H, Malzahn U, Köstler H, Bley TA. (2017) Self-gated Non-Contrast-enhanced Functional Lung MR Imaging for Quantitative Ventilation Assessment in Patients with Cystic Fibrosis. Radiology 283:242-251.

Department of Diagnostic and Interventional Neuroradiology

CONTACT DETAILS



Professor Dr. med. Mirko Pham
(Head of the Department)

Josef-Schneider-Str. 11
97080 Würzburg
Phone: 0931/201-34790
Fax: 0931/201-34803
E-mail: a-neuroradiologie@ukw.de
www.ukw.de/neuroradiologie

Mission and Structure

With the appointment of Prof. Dr. M. Pham in 10/2016 the Chair of Neuroradiology was founded. The discipline of Neuroradiology provides endovascular procedures for the diagnosis and therapy of neurovascular disorders including vascular disorders of the brain, the head-neck region and the spine including the spinal cord. The clinical effectiveness of neuroradiological endovascular procedures has become particularly strong in the treatment of acute ischemic stroke and in the minimally-invasive treatment of cerebral aneurysms. Mechanical embolectomy/thrombectomy in acute ischemic stroke due to large-vessel-occlusion is typically performed via transfemoral access and is one of the strongest available treatments for acute circulatory-vascular disorders. The interventional stroke service of the Department of Neuroradiology is organized within TRANSIT, the regional network of stroke care. The spectrum of endovascular procedures regularly comprises also other acute and elective interventions targeting the vessels of the supraaortal region (vascular stenosis, vascular malformations as for example AV-Fistulas, dural AV-Fistulas, cerebral arteriovenous malformations). The diagnostic procedures typically performed by the neuroradiological service are characterized by a growing organ- and disease specific technological-radiological degree of development.
The experimental and clinical-scientific focus of the Department of Neuroradiology at UK Würzburg Campus on the one hand is associated with the continuous and dynamic technological innovations in the field of magnetic-resonance-imaging and computed-tomography. On the other hand, own research is dedicated to topics such as high-resolution imaging methods for diseases of the Peripheral Nervous System (see Figure, funding within the SFB 1158 in close collaboration with Profs. N. Üceyler and C. Sommer of the Dept. of Neurology). Translational research focuses on clinical stroke and its experimental models. We have developed key endovascular methods for the observation of cellular and molecular processes during the hyperacute stage of ischemic brain injury (funding within the transregio SFB 240, Speaker Prof. Dr. B. Nieswandt, project collaboration with Prof. Dr. G. Stoll and Dr. M. Schuhmann of the Department of Neurology. Other interdisciplinary scientific topics include the close collaboration with the partner disciplines in the Kopfklinik-environment (particularly Neurology, Neurosurgery, ENT, Ophthalmology and Radiation Therapy) in the fields of functional MR-Imaging, imaging of neurodegenerative and neurovascular disorders. The close collaboration particularly with the Section of Pediatric Neurosurgery and Pediatric Neurooncology defines another clinical-scientific and diagnostic focus of the Department.

Staff:
3 Senior-/Consultant Neuroradiologists
13 Physicians with fellow-status
16 Radiology-Technicians
4.5 Physician-Scientists
4 student research assistants
2 MR physicists.

Equipment:
3 MRI, 1 Multislice CT
1 MRI operated jointly in the Pediatric Clinic with the Department of Radiology (Prof. Bely)
2 Fluoroscopy/Angiography-Units for Neuroendovascular Interventions
2 CR Units for conventional X-ray studies

Major Research Interests

Neuroimaging
(G. Homola, T. Kampf)

As part of the Comprehensive Heart Failure Center (CHFC) Würzburg we focus on research and treatment of heart failure. Structural and functional consequences of chronic heart failure in the brain are investigated in animal models and long-term studies. The project area F2/HB.4 is a joint venture with the neurology and cardiology. Research includes innovative imaging methods without applying contrast agents (ASL), as well as diffusion and perfusion protocols. Voxel-based statistics and volumetric analysis of individual brain regions are also performed. In cooperation with the Research Center for Magnetic Resonance Bavaria (MRB) we explore quantification of MR relaxation times for improved diagnosis of neurodegenerative disorders like Multiple sclerosis (MS, cf. Fig.). Third-party funded by the German Research Foundation (Deutschen Forschungsgemeinschaft, DFG).

Neurooncology
(A. Stock, B. Bison)

The neuroradiological reference site for HIT-Studies is located in the Department of Neuroradiology and serves all German multicentric, pediatric neurooncological studies. Classification of different stages of the disease is the basis for treatment recommendations. Reference staging is an inclusion cri-

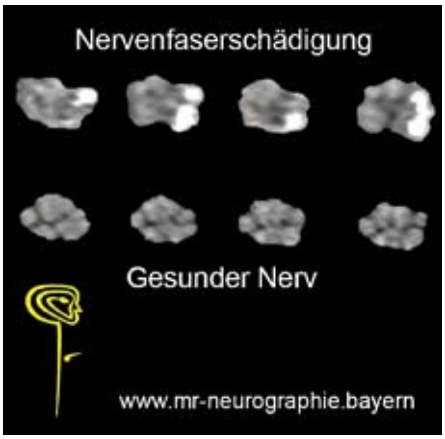


Fig.: One of the research topics to which the Department of Neuroradiology is dedicated deals with high-resolution nerve imaging. On this representative image fine details of nerve-fiber-bundle lesions are visualized which so far have remained elusive by any other diagnostic method including clinical-neurophysiological testing.

terion for most of the pediatric brain tumor studies. New methods and treatment concepts are permanently discussed, explored and designed with the national and international reference centers, ensuring standardized guidelines for the imaging of children with brain tumors. Third-party funded by the German Child Cancer Foundation (Deutsche Kinderkrebsstiftung).

Pediatric Neuroradiology
(A. Stock, B. Bison)

Close collaboration with the Division of Pediatric Neurosurgery in imaging, diagnosis and treatment of CNS neoplasms, spinal and vascular malformations.

Experimental MR Imaging
(G. Homola, T. Kampf)

Exploration of new in vivo imaging methods of vascular diseases in close cooperation with the Department of Neurology. Special coils, optimized MR sequences und contrast agents with altered molecular structure are applied. Furthermore, the impact of metabolic disorders on the CNS is examined by multimodality imaging techniques. Plasticity of the auditory system related to vestibular schwannoma is analyzed by diffusion tractography and diffusion tensor imaging (DTI) in collaboration with the Department of Neurosurgery. The latter funded by the Interdisciplinary Center of Clinical Research Würzburg (IZKF).

Functional and Diffusion-MR-Imaging, MR-Spectroscopy
(G. Homola)

Joint research projects with the Department of Neurosurgery, the Department of Neurology and the Clinic for Psychiatry as well as the Department of Neuroradiology of the University of Heidelberg and the Radiology Bamberg. Exploration of the link between structure and function in the human brain on the basis of cognitive facial age processing by probabilistic tractography of diffusion data and by calculating spatial cross-correlations. We relate fMRI activation probabilities and structural connectivities in presurgical language mapping to assist intraoperative neuronavigation with the view to preserve functionally vital cortical areas and fiber tracts from surgical damage. Characterization and quantification of neuronal resting-state networks by fMRI. Improving in vivo magnetic resonance spectroscopy (MRS) and quantified perfusion techniques in malignant brain tumors. In close collaboration with the Department of Psychiatry, Psychosomatics and Psychotherapy as well as the Department of Child and Adolescent Psychiatry we explore the neurobiology of the attention network in anxiety and anxiety disorders. The latter funded by the Interdisciplinary Center of Clinical Research Würzburg (IZKF).

Interventional Neuroradiology – Vessel-occlusive Therapies
(A. Kollikowski, D. Engel, M. Pham)

Endovascular treatment of vascular malformations and highly-vascularized tumors in international and national studies. Optimization of embolization materials and -techniques. Research on effective therapeutic approaches on large cerebral aneurysms.

Interventional Neuroradiology – Vessel-recanalizing Therapies
(A. Kollikowski, D. Engel, M. Pham)

Improvement of the effectiveness of vessel recanalization. Examination of pharmacological and mechanical recanalization.Interventional treatment of acute strokes with new stent-based methods. Diagnostics and interventional treatment of vasospasms after subarachnoidal hemorrhages.

Teaching

The Department of Neuroradiology offers students of the University of Würzburg a wide range of lectures and courses within the radiological and neuroradiological teaching. The head of the department is authorized to full neuroradiological training (3 years). The department is actively engaged in the education of Bachelor, Master and PhD students.

SELECTED PUBLICATIONS

Bäumer P, Kele H, Xia A, Weiler M, Schwarz D, Bendszus M, Pham M. (2016) Posterior interosseous neuropathy: Supinator syndrome vs fascicular radial neuropathy. Neurology 87:1884-1891.

Godel T, Pham M, Heiland S, Bendszus M, Bäumer P. (2016) Human dorsal-root-ganglion perfusion measured in-vivo by MRI. Neuroimage 141:81-87.

Hoffmann A, Pfeil J, Alfonso J, Kurz FT, Sahm F, Heiland S, Monyer H, Bendszus M, Mueller AK, Helluy X, Pham M. (2016) Experimental Cerebral Malaria Spreads along the Rostral Migratory Stream. PLoS Pathog 12:e1005470.

Kampf T, Sturm VJF, Basse-Lüsebrink TC, Fischer A, ..., Pham M, Stoll G, Jakob PM. (2019) Improved compressed sensing reconstruction for 19F magnetic resonance imaging. MAGMA doi: 10.1007/s10334-018-0729-1. [Epub ahead of print].

Kollikowski AM, Amaya F, Stoll G, Müllges W, Schuhmann MK, Pham M. (2018) Impact of landmark endovascular stroke trials on logistical performance measures: a before-and-after evaluation of real-world data from a regional stroke system of care. J Neurointerv Surg pii: neurintsurg-2018-014286. [Epub ahead of print].

Department of Nuclear Medicine

CONTACT DETAILS

Professor Dr. med. Andreas K. Buck
(Head of the Department)

Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-35001
Fax: 0931/201-635000
E-mail: buck_a@ukw.de
www.ukw.de/nuklearmedizin

Professor Dr. med. Takahiro Higuchi
Phone: 0931/201-35455

Professor Dr. rer. nat. Michael Lassmann
Phone: 0931/201-35410

Professor Dr. rer. nat. Samuel Samnick
Phone: 0931/201-35080

Mission and Structure

The Department of Nuclear Medicine employs unsealed radioactive tracers for research purposes, education, diagnosis and therapy of a multitude of diseases. Using 2 PET/CT systems, 3 gamma cameras, 2 SPECT/CT, 3 ultrasound devices, 1 bone densitometer and 1 whole body counter, approximately 16,000 examinations are performed annually. In addition, more than 750 in-patients and 200 out-patients are treated with radioactive isotopes.
The Division of Experimental Nuclear Medicine and Radiochemistry operates a cyclotron to produce the PET-radioisotopes ^{18}F, ^{11}C, ^{15}O, ^{13}N and ^{124}I in fully equipped and GMP-certified radiochemical/radiopharmaceutical laboratories. Full nuclear medicine specialist training is available.

Major Research Interests

Radiochemistry / Radiopharmacy
(AG Samnick / Schirbel)

Translational research is supported by providing innovative imaging biomarkers for molecular imaging with PET/CT and SPECT/CT as well as radionuclide based therapies. On a daily basis, up to 20 different tracers are provided. Besides clinical applications, the following interdisciplinary research projects could be initiated or supported: SFB/TRR 205 „Adrenal research“ (DFG), „FDG-PET and Iodo-Metomidate Imaging for Adrenocortical Tumors (FAMIAN)“ (DFG), „Forschungsverbund Tumordiagnostik für Individualisierte Therapie“ (BFS), IFB „Prevention of heart failure and its complications“ (BMBF), „Therapy unit multiple myeloma“ (Wilhelm Sander-Stiftung), „Clinical Evaluation of ^{124}I-PET/CT in thyroid cancer“ (Krebshilfe), „Imaging Dyskinesia in People with Parkinson's Disease” (Michael J. Fox Foundation), and „Imaging of molecular biomarkers for clinical heterogeneity and disease progression in Parkinson´s disease” (IZKF).

Cardiology / pre-clinical imaging
(AG Higuchi / Werner)

A high number of imaging biomarkers are utilized in translational research projects based on µPET and µSPECT. A variety of research projects have been initiated in the past 3 years, addressing cardiac innervation, perfusion and metabolic processes such as cardiac regulation of the angiotensin II type 1 receptor. A further key aspect includes the development of novel F18-labelled PET-radiotracers and their characterization using cell uptake assays, ex-vivo analysis and in-vitro imaging. Regulation of the cardiac glucose turnover in type 2-diabetes, studies on the cardiac remodeling after myocardial infarction and imaging of hypertrophic cardiomyopathy in an autoimmune rat model are further projects addressed. The working group of Prof. Higuchi is supported by DFG, BMBF and the European Union.

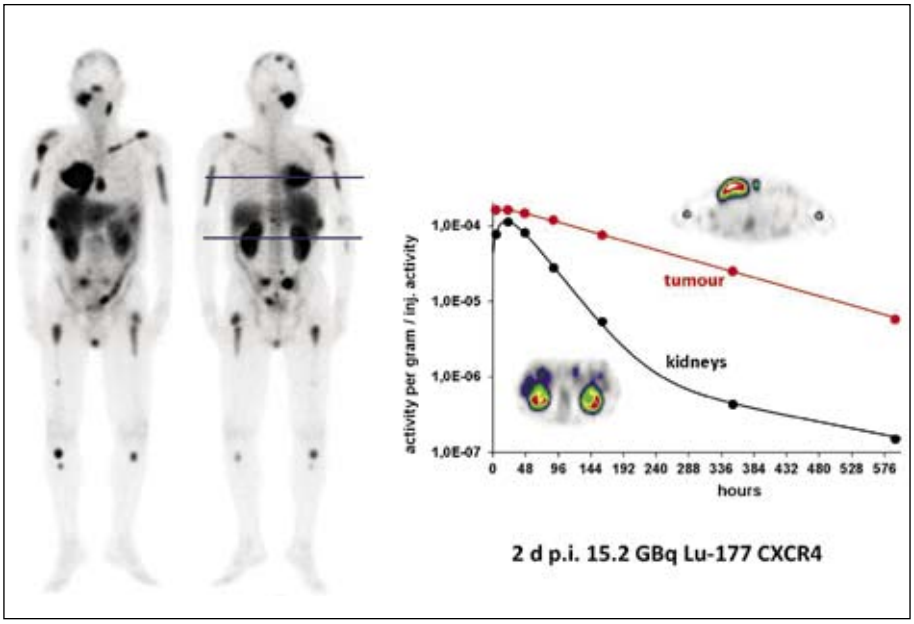


Fig.: Planning of a radioligand based therapy (RLT) in advanced multiple myeloma. Dosimetry shows preferential and long-term retention of 177Lu-CPCR4-2 in bone tumors, facilitating effective tumor cell kill and bone marrow eradication prior to stem cell transplantation.

Medical Physics / Radiation Safety / Biodosimetry
(AG Lassmann)

On-going research projects include radiation protection, internal dosimetry, the combination of biodosimetry with physical dosimetry as well as improvement of methods for dosimetry after radionuclide therapies. Participation in the European project "MRT Dosimetry" enables further improvement of quantitative imaging and absorbed dose calculations. Aim of this project is the standardization of dosimetry in nuclear medicine. The DFG-sponsored project "Comparison of physical and biologic DNA dosimetry after treatment with radionuclides", initiated in 2012, was finished successfully by the end of 2018. This research project is a collaboration project with the Bundeswehr Institute of Radiobiology. In this project, the induction and repair of DNA double strand breaks in human lymphocytes is assessed. In 2017, the EU funded project MEDIRAD has been initiated. Aim of this project is the assessment of patient specific absorbed doses in organs and tissues after radioiodine therapy, based on quantitative imaging.

Clinical Oncology
(AG Buck / Lapa)

For clinical research, imaging biomarkers of glucose metabolism (^{18}F-FDG), lipid metabolism (^{11}C-choline) and protein biosynthesis / amino acid transport (^{18}F-FET, ^{11}C-MET) are available. In addition to established radiotracers, new peptide based ligands have been introduced to clinical practice. With the PET tracers ^{68}Ga-PSMA and ^{68}Ga-CXCR4-2, in-vivo imaging of the prostate specific membrane antigen (PSMA) or the chemokine receptor 4 (CXCR4) can be performed. ^{68}Ga-FAPI is used for the visualization of fibroblast activating protein expression. In addition, peptide based radioligands have been used for radionuclide based therapies. In Würzburg, the 1st CXCR4-directed RLT in multiple myeloma has been performed using ^{177}Lu-Pentixather as the theranostic compound. In addition, treatment of advanced prostate cancer using ^{177}Lu-PSMA has been established.

Preclinical Cancer Imaging
(AG Stolzenburg)

The group is interested in identifying and characterizing key processes of tumor biology including heterogeneity of cancer. In a translational approach, highly promising biomarkers for molecular imaging are used in preclinical models to study a potential role in cancer imaging, response assessment and as prognostic marker. The aim is to select the most appropriate therapeutic regimen based on molecular imaging. A further focus lies on the establishment of novel theranostic concepts. For this purpose, membrane proteins on the cellular surface are utilized for targeted radionuclide therapies.

Neurology / Psychiatry
(AG Isaias, Samnick, Brumberg)

Functional imaging of the brain using innovative radiotracers such as ^{123}I-5IA, ^{11}C-Methylreboxetin and ^{18}F-Fallypride is performed in close collaboration with the Department of Neurology. Prof. Isaias is the leader of the research group "Imaging of Molecular Biomarkers for Clinical Heterogeneity and Disease Progression in Parkinson's Disease", which is funded by the IZKF (F-255). Aim of this project is the assessment of the clinical-pathological connection in Parkinson's Disease based on novel, multiparametric imaging (PET, SPECT). In addition, further imaging modalities such as MRI and high-density EEG are considered.

Thyroid / Endocrinology
(AG Biko, Schirbel, Buck)

Thyroid cancer represents the major interest of clinical research. In collaboration with the CCC Mainfranken, a regional tumor registry has been established. The Department of Nuclear Medicine supports ongoing phase-III studies for thyroid cancer (e.g. E7080). In patients with cancer of the adrenal gland, the radiotracer ^{123}I-Iodmetomidate is now increasingly used. This tracer accumulates in the tumor tissue based on specific expression of 11ß-hydroxylase. Research projects performed together with members of the Department of Endocrinology (e.g. FAMIAN) have been funded by the DFG since 2013.

WHO REMPAN-Center
(AG Reiners, Schneider, Buck)

In 2017, the WHO Collaboration Center REMPAN (Radiation Emergency Medical Preparedness Assistance Network) has been newly accredited by the WHO. Major focus is the further development and organization of medical care in case of radiation emergencies. In addition, the WHO is supported in case of radiation emergencies. In this context, the REMPAN Center has actively contributed to a novel guideline of the International Agency for Research on Cancer regarding long-term strategies for thyroid monitoring after nuclear accidents.

Teaching

Teaching of students is coordinated together with the Institute for Diagnostic and Interventional Radiology and the Department of Radiation Oncology. In addition, the Department of Nuclear Medicine participates in interdisciplinary lectures (i.e., "Interdisciplinary Oncology", "Communication in Oncology"). Lectures at a local technical school are performed, as well as dedicated programs for assistant medical doctors. Since 2016, Nuclear Medicine is actively involved in the degree program ´Translational Neurosciences`.

SELECTED PUBLICATIONS

Lapa C, Hänscheid H, Kircher M, Schirbel A, Wunderlich G, Werner RA, Samnick S, Kotzerke J, Einsele H, Buck AK, Wester HJ, Grigoleit GU. (2019) Feasibility of CXCR4-Directed Radioligand Therapy in Advanced Diffuse Large B-Cell Lymphoma. J Nucl Med 60:60-64.

Reich MM, Brumberg J, Pozzi NG, Marotta G, Roothans J, Åström M, Musacchio T, Lopiano L, Lanotte M, Lehrke R, Buck AK, Volkmann J, Isaias IU. (2016) Progressive gait ataxia following deep brain stimulation for essential tremor: adverse effect or lack of efficacy? Brain 139:2948-2956.

Samnick S, Al-Momani E, Schmid JS, Mottok A, Buck AK, Lapa C. (2018) Initial Clinical Investigation of [18F]Tetrafluoroborate PET/CT in Comparison to [124I]Iodine PET/CT for Imaging Thyroid Cancer. Clin Nucl Med 43:162-167.

Tran-Gia J, Lassmann M. (2019) Characterization of Noise and Resolution for Quantitative 177Lu SPECT/CT with xSPECT Quant. J Nucl Med 60:50-59.

Werner RA, Wakabayashi H, Bauer J, Schütz C, Zechmeister C, Hayakawa N, Javadi MS, Lapa C, Jahns R, Ergün S, Jahns V, Higuchi T. (2019) Longitudinal 18F-FDG PET imaging in a rat model of autoimmune myocarditis. Eur Heart J Cardiovasc Imaging 20:467-474.

Department of Radiation Oncology

CONTACT DETAILS

Professor Dr. med. Michael Flentje
(Head of the Department)

Josef-Schneider-Str. 11
97080 Würzburg
Phone: 0931/201-28891
Fax: 0931/201-28396
E-mail: flentje_m@ukw.de
www.strahlentherapie.ukw.de

Professor Dr. med. Birgitt van Oorschot
Phone: 0931/201-28857

General Information

The Dept. of Radiation Oncology (staff: 18 physicians, 13 medical physicists, 19 radiographers, 16 nurses) uses 4 linear accelerators (including IGRT by means of cone beam CT) and an afterloading unit for remote controlled inserts of radioactive sources. Patients are treated in a policlinic department, in a ward with 20 beds and in a day care unit with 12 treatment places. The division of palliative care of the university hospital with additional 10 beds is linked to our department (4 physicians, 14 nurses 1 psycho-oncologist). Spiral-CT, ultra sound, as well as examinations with MR-tomography in co-operation with the Institute of diagnostic radiology and PET-CT scans at the nuclear medicine department provide the anatomical and physical data base for computerised treatment planning. Radiation planning, dose calculations and the calibration and quality assurance of the treatment units are carried out by the section of medical physics. About 2200 patients are treated annually. By means of the day care unit it is possible to avoid hospitalisation even in more intensive parts of the treatment, e.g. during concurrent chemotherapy. In addition to the typical spectrum of radiation therapy, intra- and extracranial radio surgery, total body irradiation before stem cell transplantation, contact irradiation for tumours of the eye and interstitial brachytherapy of tumours in the head and neck, prostate, mamma and of the extremities are provided.

Major Research Interests

Development of highly conformal treatment techniques

The optimisation of the temporal and spatial dose distribution, aiming to concentrate the impact at the tumour tissue and concurrently sparing nearby organs at risk is the general objective of our research.
Further developments of stereotactic treatments in the region of the body, of inverse planning techniques, the integration of temporal and spatial uncertainties and of functional imaging are undertaken.

Medical Physics
(O. Sauer)

The medical physics group supports the development of new concepts for radiation oncology and guarantees for their safe application. Treatment planning, i.e. optimization and calculation of dose distributions and quality assurance of the irradiation facilities, as well as of individual treatment plans belongs to the core responsibilities. Additionally, further developing personalized medicine, image guidance is of increasing importance. Research concerns image guided radiotherapy (IGRT), optimisation and adaptation of intensity modulated radiation therapy (IMRT) and dosimetry of ionising radiation. Topics are: - computation of tomographic images with the patient in treatment position, - tracking of moving targets, - adaptation of intensity modulated radiotherapy and of fast application methods like volumetric arc therapy (VMAT), - development of non-coplanar techniques for the body region, - virtual isocenter, dose measurement and dose calculation under non-equilibrium conditions, especially for small fields and online dosimetry (Fig.2).

Radiation Biology
(T. Djuzenova)

Our radiobiological laboratory (2 scientists, 2 technicians, 1 grant position) is appropriately

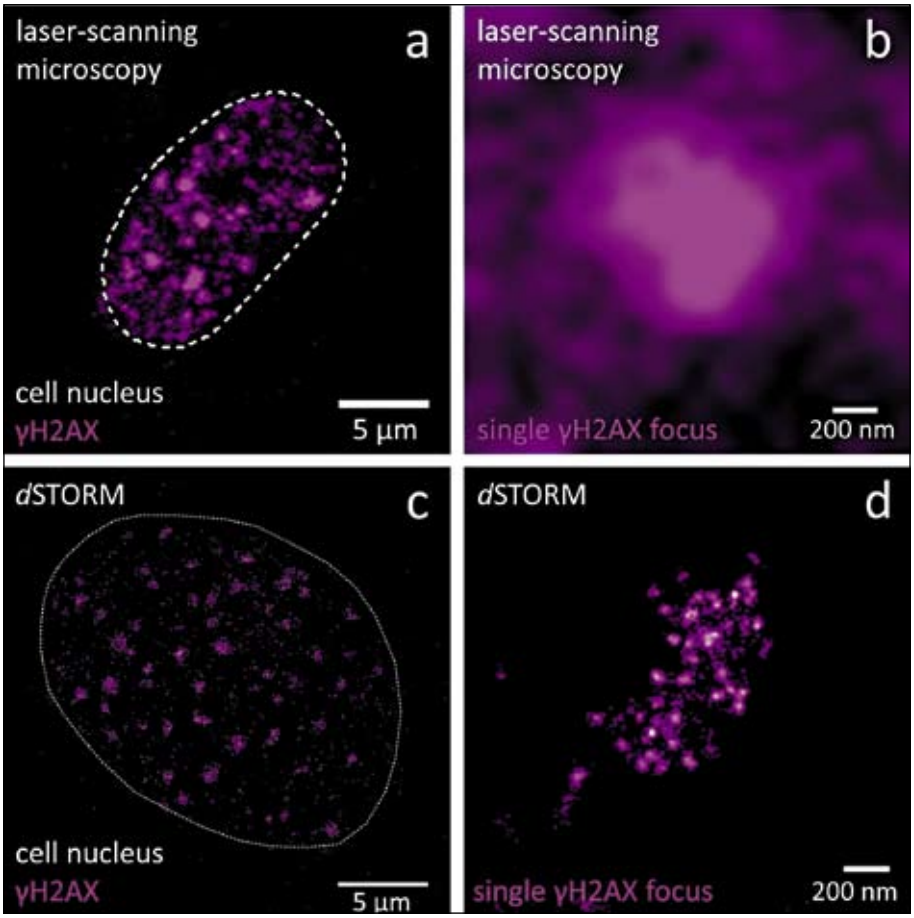


Fig. 1. Representative fluorescence images of glioblastoma cell line DK-MG (a, b – confocal LSM with the resolution of ~200 nm, c and d – superresolution dSTORM with the resolution of ~20 nm). Cells were irradiated with 2 Gy, fixed 30 min post-irradiation and immonostained for the DNA DBS marker – histone H2AX (Sisario, Memmel et al., 2018).

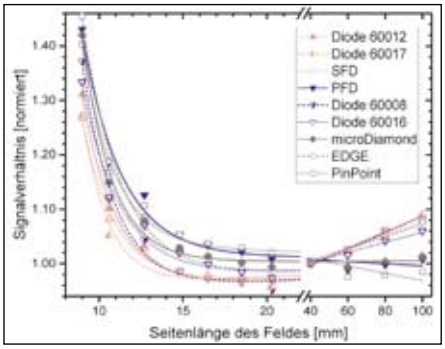


Fig. 2: Response of different detectors to scattered radiation only in relation to the response of EBT3-film. The detectors were positioned centrally in 10 cm depth in water, where the primary radiation was blocked with a steel rod.

equipped to carry out basic research on the biological effects of ionizing radiation (IR) in human tumor cells. During the last 2 years we extended our earlier experiments to analyze the structure and the repair mechanisms of DNA double-strand breaks (DSBs). Induction of DNA DSBs by IR leads to formation of micrometer sized DNA-repair foci of the histone ãH2AX, a marker of DSBs (Fig. 1a, b), whose organization on the nanometer-scale remains unknown because of the diffraction limit (~200 nm) of conventional microscopy (Fig. 1b). Therefore we applied the diffraction-unlimited, direct stochastic optical reconstruction microscopy (dSTORM) with a lateral resolution of ~20 nm to gain an insight into the nanostructure of DNA repair foci (Fig. 1c). We found (Sisario, Memmel et al., 2018) that a single ãH2AX focus consists of distinct circular subunits ("nanofoci") with a diameter of ~45 nm (Fig. 1d).

In addition, within the scope of a grant from the Deutsche Krebshilfe we studied the migration of different glioblastoma multiforme cell lines. We found striking differences not only in the migration pattern among the cell lines studied but also in their migratory response to the dual PI3K and mTOR inhibitor PI-103 (Memmel et al., 2017). Thus, we found that PI-103 inhibited migration of DK-MG (p53 wt, PTEN wt) but not of SNB19 (p53 mut, PTEN mut) cells probably due to an aberrant reactivation of the PI3K pathway in SNB19 cells treated with PI-103.

Palliative Care
(B. van Oorschot)

In addition to individual projects on the palliative care unit for the identification of patients with delir, regarding palliative sedation and advanced care planning, palliative care need assessment with subsequent targeted and needs-oriented interventions is a major research focus. A electronically screening based on the nursing anamnesis and the self-assessment sheet in radiation oncology is currently being validated, accompanied by 2 prospective randomized intervention studies (empowerment study, fatigue intervention). Another study deals with the identification of frail older radiotherapy patients (frailty project).

Clinical trials and quality assurance

The department is engaged in conception and realisation of radiation therapy in national and international therapy studies for head and neck tumours and lung cancer. Two randomized multi-center studies on laryngeal / hypopharyngeal cancers (Delos-2 trial) and on combined radio-chemotherapy in locally advanced lung cancer (GILT-CRT trial) have been successfully completed and published in 2016 and 2018. Our department is involved in international consortia on dose escalating high-precision radiotherapy (ELEKTA Spine group, SBRT working group of the DEGRO) and in brachytherapy within the GEC-ESTRO breast working group. The department provides a dedicated study center, which is equipped with a medical doctor and a study nurse. Having this infrastructure, we have been able to increase our trial activities and to publish the data from large phase II/III trials in prostate, breast and rectal cancer in leading oncology journals.

The chairman of the department is heading the "Ärztliche Stelle § 83 StrlSCHV" of the Bavarian State Medical Chamber and is member of the Radiation Protection Commission at the federal ministry of environment.
An additional activity is palliative radiation oncology. Currently studies concerning adequate access to specialized palliative care and quality of life during end of life care are conducted.

Teaching

Apart from the obligatory courses on radiology the working groups give classes and hold seminars for residents, medical physicists and biologists. PhD, MD, master and bachelor thesis are supervised.

SELECTED PUBLICATIONS

Dietz A, Wichmann G, Kuhnt T, Pfreundner L, Hagen R, ... Flentje M, Keilholz U. (2018) Induction chemotherapy (IC) followed by radiotherapy (RT) versus cetuximab plus IC and RT in advanced laryngeal/hypopharyngeal cancer resectable only by total laryngectomy-final results of the larynx organ preservation trial DeLOS-II. Ann Oncol 29:2105-2114.

Memmel S, Sisario D, Zöller C, Fiedler V, Katzer A, Heiden R, Becker N, Eing L, Ferreira FLR, Zimmermann H, Sauer M, Flentje M, Sukhorukov VL, Djuzenova CS. (2017) Migration pattern, actin cytoskeleton organization and response to PI3K-, mTOR-, and Hsp90-inhibition of glioblastoma cells with different invasive capacities. Oncotarget 8:45298-45310.

Schäfer R, Strnad V, Polgár C, ... Polat B; Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). (2018) Quality-of-life results for accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breast-conserving surgery (GEC-ESTRO): 5-year results of a randomised, phase 3 trial. Lancet Oncol 19:834-844.

Sisario D, Memmel S, Doose S, Neubauer J, Zimmermann H, Flentje M, Djuzenova CS, Sauer M, Sukhorukov VL. (2018) Nanostructure of DNA repair foci revealed by superresolution microscopy. FASEB J 32:6469-6477.

Wegener S., Sauer OA. (2018) Energy response corrections for profile measurements using a combination of different detector types. Med Phys 45:898-907.

Department of Obstetrics and Gynecology

CONTACT DETAILS

Professor Dr. med. Achim Wöckel
(Head of the Department)

Josef-Schneider-Str. 4
97080 Würzburg
Phone: 0931/201-25251
Fax: 0931/201-25258
E-mail: woeckel_a@ukw.de
www.ukw.de/frauenklinik

Professor Dr. med. Daniel Herr
Phone: 0931/201-25253

Professor Dr. med. Christiane Wulff
Phone: 0931/201 25253

Professor Dr. rer. nat. Jörg Wischhusen
Phone: 0931/201 25291

Mission and Structure

The Woman's Hospital (bed capacity of 85, 35 doctors, 74 nurses, 27 midwives, 7 assistant medical technicians) has two obstetrical and three gynecological wards, 5 labours and delivery rooms and a Level I Perinatal Center with 8 neonatal intensive-care beds, three operating rooms of most modern standards, an operating room for caesarean sections, an intermediate-care unit, outpatient clinics for gynecology and obstetrics, gynecological oncology, breast cancer, dysplasias of the cervix, child and adolescence gynecology, urogynecology, endocrinology and reproductive medicine, prenatal diagnostics. There are laboratories cytology and reproductive medicine with andrology. Programs include a midwifery school. In the women's clinic are also department of the Clinic for Radiation Therapy (external radiation; brachytherapy) and the Institute of Radiology (mammography, vacuum biopsy) and the Department of Anaesthesiology (pain ambulance).

Per annum, approximately 2,500 operations, 1,900 deliveries, 5,900 DRG cases, 25,000 outpatient therapies (of which 1,800 were chemotherapies) have been performed. Centers of the clinic are: The interdisciplinary treatment of gynecological cancers, including breast (certified breast center), the center for hereditary breast and ovarian cancer, the treatment of urinary incontinence and pelvic floor dysfunction, care of risk pregnancies and infertility treatment including in vitro fertilisation.

Major Research Interests

Research Group "Oncological Care Research"
(A. Wöckel, T. Stüber, J. Diessner, R. Stein, C. Bartmann)
The research group „Oncological Care Research" deals with projects of the BRENDA Study group. These are large cohort studies, in which the survival data of patients with primary breast carcinomas are analyzed. The aim of these ongoing observational studies is to determine the influence of a guideline-compliant treatment of breast cancer on relevant endpoints such as recurrence-free survival and overall survival. Furthermore, current treatment recommendations can be checked or validated under everyday conditions in this collective and in defined subgroups. Therefore, this analysis complements the results from prospective clinical treatment trials. In addition, based on prospective study models, we try to identify factors that may lead to a modification of the therapy in the health care reality. These include in particular the impact of somatic and mental comorbidities, age, and toxicities of systemic therapies. A future focus will be the development and validation of patient-relevant outcome parameters in patients with metastatic disease.

Research Group: "Physiology and Pathophysiology of Angiogenesis, Migration, Infiltration and Cell Adhesion in the Female Reproductive Tract"
(C. Wulff, S. Löb, S Herbert, A. Fick)
Although endometriosis is a benign disease, it behaves comparable to ovarian cancer regarding spread into the abdominal cavity. In both cases, cells implant at the peritoneum by cell adhesion, migration, proliferation and angiogenesis. The research group examines the molecular regulation of these processes, especially by studying potential target regulators such as VEGF, Renin-Angiotensin and their receptors or the so called magic roundabouts Robo/Slit, different cell adhesion proteins or hormones. The aim of the scientific program is to identify key regulators of the above processes in both endometriosis and ovarian cancer, and to discover similarities or differences in both diseases. We are about to establish a 3D peritoneal model, in which signalling pathways will be studied.

Research Group: "Reproductive Immunology and Tumor Metabolism"
(C. Bartmann, M. Kapp, U. Kämmerer)
In the area of reproductive immunology, we investigate the role of maternal immune cells in the protection of a healthy pregnancy. The current focuses the characterization of keycells of the immune response, known as „myeloid derived suppressor cells"(MDSC). Those were identified and characterized in the maternal endometrium for the first time by our group. In the focus of tumor metabolism, we carry outstudies on the effect of specific metabolites, the so-called"ketone bodies", in tumor cells of breast and ovarian cancer, on immune cells and important treatment-related intracellular signaling pathways. Within this focus, the scientific supervision of the"KOLIBRI" study (NCT02092753), which analyzed metabolism-modifying diets in breast cancer patients was carried out.

Research Group: "Targeting of preexisting and induced Breast Cancer Stem Cells with new HER2 specific Drugs."
(J. Diessner, J. Wischhusen)
The antibody trastuzumab (Herceptin) has substantially improved overall survival for patients with aggressive HER2-positive breast cancer. However, many patients face relapse. This may be related to an insufficient targeting of the CD44high CD24low breast cancer stem cell subset, which is not only highly resistant to chemotherapy and radiotherapy but also a poor target for trastuzumab due to low HER2 surface expression.
Hence, we explored whether the new antibody-drug conjugate T-DM1, which consists of the potent chemotherapeutic DM1 coupled to trastuzumab, could improve the targeting of these tumor-initiating or metastasis-initiating cells. Our study reveals an unanticipated targeting of stem cell like breast cancer cells by T-DM1. In particular, this gives hope for the suppression of recurrences, which was actually proven in the KATHERINE study (ClinicalTrials.gov number, NCT01772472, NEJM2018).

Research Group "Reprogramming of Breast Cancer Stem Cells in Breast and Ovarian Cancer"
(R. G. Stein, P. Hauck, E. Horn, J. Diessner, J. Wischhusen)
Cancer stem cells (CSCs) are a subpopulation of cancer cells characterized by their potential to self-renew and rebuild heterogeneous tumor tissue. They were described in many solid and hematological tumors. Our group previously discovered and further characterized a mode of CSC reprogramming in interaction with functionally impaired immune cells. From 4/2015 to 4/2018 this pro-

ject was funded by the IZKF. Initial findings were discovered during Dr. Stein's Else-Kröner-Fresenius-Scholarship in cooperation with the Reijo Pera Group at Stanford University (Palo Alto, CA). Pluripotency in embryonic stem cells or iPSCs is achieved by several factors that are not only used to reprogram iPSCs but are also overexpressed in CSCs. We seek to establish a standardized protocol for individual CSC reprogramming, enrichment and *in vitro* culture. This aims to further characterize individual CSCs and optimize anti-cancer therapy by *in vitro* testing.

Research Group "Microscopic and molecular Analysis for efficancy Improvement of the in-vitro-fertility laboratory"
(C. Staib, R. Pavlik, M. Schwab)
The IVF laboratory studies the morphokinetic development of human embryos and analyses the molecular basis of the complex interaction of spermatozoa with factors of the female reproductive system. Morphokinetic characteristics are essential for successful development of a given embryo. Using state-of-the-art techniques such as time-lapse-microscopy morphokinetic parameters of embryonal development are studied and correlated with the potential of implantation, with the aim to improve the therapeutic outcome. We further analysed the potential of miRNAs secreted from pre-implantation embryos into the embryonic culture media as biomarkers to predict successful pregnancy. During fundamental research the interaction of microorganisms with human spermatozoa is studied, using various molecular methods. The mucosal surfaces of the lower part of the female reproductive tract are highly populated by a complex microbial flora, in addition, microbes can also be transmitted by the male ejaculate. In order to provide novel insights in the complex mechanisms of host-microbe-interaction in this specific niche, selected factors of the extracellular matrix are tested for their potential impact on spermatozoa and the human pathogenic yeast Candida albicans.

Research Group "The anti-tumor Function of ROR1-CAR modified T Cells against triple-negative Breast Cancer is enhanced by shielding from immunosuppressive TGF-ß"
(T. Stüber, J. Wischhusen, M. Hudecek, H. Einsele)
Adoptive immunotherapy with genetically engineered autologous T-cells expressing a tumor-reactive chimeric antigen receptor (CAR) is an innovative experimental therapeutic option for advanced malignancies. CARs are synthetic receptors, which bind to correspondingsurface molecules and thus induce T-cell activation. Object of research is the prevention or reduction of immunosuppressive factors by the tumor microenvironment (TGF-ß) on the functionality of ROR1CART-cells in triple-negative breast cancer. Support from the IZKF of the University of Würzburg and the society „Help fighting cancer e.V."

Section for Experimental Tumor Immunology
(J. Wischhusen, M. Haake, V. Bruttel, P Romer Roche, N. Vashist, F.Ahsan, F. Wedekink, V. Thiemann, K. Thein, T. Schäfer, S. Ebert, M. Wustrow, S. Häusler, J. Diessner, B. Fischer, K. Eichler, H. Wecklein, E. Horn, P. Hauck)
One focus of our research interest is the immunological characterization of tumor-initiating cells. In this context, we were able to show that (a) tumor-initiating cells selectively escape the cytotoxic effects of a HER2-specific tumor-/immunotherapy and (b) partially differentiated tumor cells de-differentiate under immunological selection pressure into „tumor stem cells" and thus escape from the immune response.Furthermore, immune evasion mechanisms of advanced tumors were examined, in which soluble factors of the tumor microenvironment (a) suppress effector functions of innate and adaptive immunity and (b) induce and sustain stem cell-like properties of tumor-initiating cells. Therapeutic targets are derived from the understanding of the mechanisms and analysed preclinically. The translational implementation of the strategies is particularly pursued in the project „Antagonization of GDF-15 in solid tumors", for which a broad portfolio of patents has been built up. This project was funded by the BMBF until 05/2016 as part of GO-Bio program. After an interim financing granted by the IZKF, a venture capital-funded spin-off was formed in 08/2016. The start of a first interventional study is currently planned for March/April 2020. In cooperation with the Department of Microbiology, possible links between an infection with Chlamydia trachomatis and ovarian cancer were investigated, resulting in a publication in the journal Cell Reports.Finally, in clinical trials, the diagnostic utility of tumor-dependent induced miRNA patterns will be investigated in blood lymphocytes.
The group is supported by the Bavarian Ministry of Economic Affairs, the IZKF, the Else-Kröner-Fresenius-Foundation, the TaNeDS program of Daiichi Sankyo and others.

Targeted inhibition of autoimmune reactions by AutoImmunity Modifying Biologicals (AIM Biologicals)
(V. Bruttel, F.Ahsan, H. Wecklein, S.M. Jayaram, J. Wischhusen)
During pregnancy, embryonal (in particular paternal) antigens must be protected from the maternal immune system. During this period of enhanced immune tolerance, autoimmune diseases also become asymptomatic while protective immune reactions against e.g. pathogens still build up. This implies selective antigen-specific tolerance induction. A new mechanism explaining this phenomenon was found by Dr. Bruttel while performing his PhD thesis in Prof. Wischhusen´s group. Based on in vitro models, this was developed into the platform technology AIM Biologicals. Funded by an m4 Award this platform shall now be adapted and extensively tested for treatment of Autoimmune Diseases.

Teaching

The curricular teaching in Obstetrics and Gynecology consist of a main lecture, seminars, bedside teaching (9th semester) and a practical training / Internship (10th semester). Additionally a „Skills Lab" focus on practical aspects of the subject. With gynecological models and case studies, students learn to deal with clinical situations and to handle diagnostic equipment. The training is complemented by a number of interdisciplinary subjects like ethics, preventive medicine, emergency medicine, infectious diseases, tumor biology and oncology. For doctors in private practice, we organize regular interdisciplinary conferences as part of the perinatal center.

SELECTED PUBLICATIONS

Abu-Halima M, Häusler S, Backes C, Fehlmann T, Staib C, Nestel S, Nazarenko I, Meese E, Keller A. (2017) Micro-ribonucleic acids and extracellular vesicles repertoire in the spent culture media is altered in women undergoing In Vitro Fertilization. Sci Rep 7:13525.

Stüber TN, Stangl S, Jackisch C, Janni W, Brucker SY, Hartkopf A, Gerber B, Budach W, Lux MP, Wöckel A. (2018) Implementation of a Systematic Literature Search Strategy in a National Breast Cancer Guideline: The Relevance of Systemic Therapy in Lymph Node Recurrent Disease. Oncol Res Treat 41:554-559.

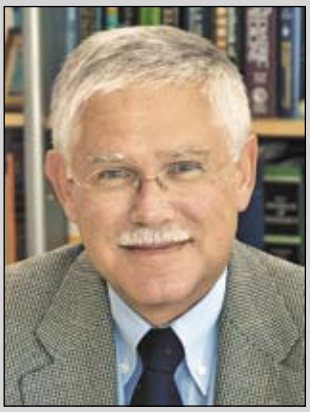
Wöckel A, Albert US, Janni W, Scharl A, Kreienberg R, Stüber T. (2018) The Screening, Diagnosis, Treatment, and Follow-Up of Breast Cancer. Dtsch Arztebl Int 115:p.316-323.

Stein RG, Ebert S, Schlahsa L, Scholz CJ, ..., Rosenwald A, Diessner JE, Wöckel A, Wischhusen J. (2019) Cognate Non-Lytic Interactions between CD8+ T cells and Breast Cancer Cells Induce Cancer Stem Cell-like Properties. Cancer 79:1507-1519.

Yang Z, Xu S, Li X, ... Wischhusen J, et al. Fibroblast-centered spheroids are actively engaged in early peritoneal metastasis of ovarian cancer. J Exp Med (accepted).

Department of Pediatrics

CONTACT DETAILS



Professor Dr. med. Christian P. Speer FRCP (Edin.)
(Head of the Department)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/201-27830
Fax: 0931/201-27833
E-mail: speer_c@ukw.de
www.ukw.de/kinderklinik

Professor Dr. med. Matthias Eyrich
Phone: 0931/201-27620

Professor Dr. med. Helge Hebestreit
Phone: 0931/201-27889

Professor Dr. med. Johannes Liese, MSc
Phone: 0931/201-27731

Professor Dr. med. Martina Prelog, MSc
Phone: 0931/201-27708

Professor Dr. med. Paul-Gerhard Schlegel
Phone: 0931/201-27888

Mission and Structure

The Children's Hospital of the University of Würzburg (staff: 67 MD's, 152 nurses, 47 technicians / administrative staff) comprises of 115 beds including a pediatric-neonatal intensive care unit and a neonatal intensive care unit in the perinatal center (obstetrics and gynecology). The Children's Hospital is divided into the following functional sections: neonatology, pediatric intensive care, oncology / hematology / stem cell therapy, cardiology, pulmonology / cystic fibrosis / sports medicine, gastroenterology, nephrology, endocrinology, diabetes, neuropediatrics / social pediatrics, immunology / infectiology, rheumatology, and others. Every year approximately 6500 patient in the inpatient and 25000 patients in the outpatient setting are being treated.

Major Research Interests

Neonatology

Preterm infants, in particular very immature ones, are at high risk of severe infections and major short- and long-term morbidities, such as chronic lung disease (bronchopulmonary dysplasia, BPD) and brain injury. Although the pathogenesis of each entity is multifactorial, inflammation has been acknowledged as a contributing mechanism. An inflammatory state is presumed to be either initiated prenatally by chorioamnionitis or induced and sustained by pro-inflammatory postnatal conditions, such as neonatal infection, mechanical ventilation and oxygen toxicity. Underlying mechanisms largely remain to be elucidated.
Previous studies provide evidence that *Ureaplasma* species, considered as commensals of the adult urogenital tract, may be true pathogens especially in very immature preterm infants and may cause considerable lung and CNS inflammation. Using primary human monocytes and human brain microvascular endothelial cells, we investigate potential pro-inflammatory, anti-inflammatory and immunomodulatory capacities of *Ureaplasma parvum* and *U. urealyticum in vitro*. A prospective clinical study evaluates the impact of perinatal colonization and infection with *Ureaplasma spp.* on neonatal outcome in preterm infants < 30 weeks of gestation.
Additional approaches focus on characterization of airway remodeling in acute and chronic lung disease of premature infants and newborns. Using various in vitro models, we analyze the impact of coffeine, commonly used to treat apnea in preterm infants, and assess its possible contribution to immunmodulation, mitigating inflammatory responses, and airway remodeling.

Pediatric Oncology, Hematology and Stem cell transplantation

Immunotherapy is at the center of our research aimed for rapid clinical translation by our GMP-facility. Haploidentical stem cell transplantation has been proven safe and effective using TCRαß/CD19-depletion of the graft. Add-back of sorted memory T-cells may further improve immunological recovery. As part of an international consortium (MAGIC) we prospectively validate biomarkers for the early diagnosis of Graft-versus-Host-disease. Other studies focus on factors such as HLA-DP mismatch in pediatric transplantation.
Using dendritic cells, glioma patients are currently vaccinated therapeutically as part of a phase I/II clinical study. Within an EU-TRANSCAN consortium, we develop and validate vaccination strategies with peptides derived from the tumor ligandome. A xenograft model for group 3 medulloblastoma is used to identify novel treatment options for this tumor type. Novel immunotherapeutics (checkpoint-inhibitors, bispecific antibodies) are used within clinical studies.
Inborn thrombocytopathies are being molecularly characterized as part of an interdisciplinary project. An international registry data base and biobank is being built. We also focus on membrane- and enzyme-defects in erythrocytes and participate in a phase-III clinical study on pyruvate-kinase-deficiency.

Pediatric Infectious Diseases

The burden of pediatric infectious diseases and the effects of vaccination programs on their epidemiology in children and adolescents is evaluated in prospective and retrospective studies. Viral and bacterial pathogens are identified, using various molecular-biological methods. Furthermore, we investigate disease severity in new influenza and RSV-variants. In a nation-wide study, the role of serotype-replacement of pneumococci in pleural empyema is evaluated. Another focus are biomarkers (such as CXCL13) for the diagnosis of neuroborreliosis in children.

Clinical Immunology

Primary immunodeficiencies (PIDs) are clinically characterized by a high rate of infections and a dysbalanced immunregulation. We analyse the genetic background of yet less-well defined B-cell associated PIDs. Fur-

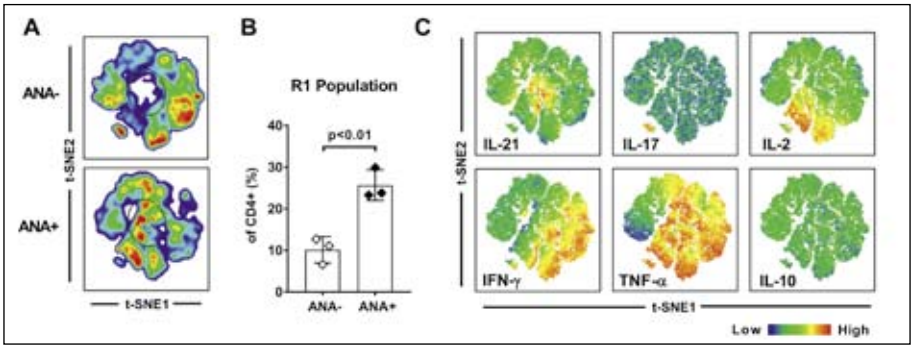


Fig.: Identification of specific CD4+ T-helper population from the synovial fluid of ANA+ JIA-patients using t-SNE analyis of high-dimensional flow cytometry (source: Morbach).

thermore we ask, why immunotolerance is disturbed and auto-antibodies are produced in these patients. We use such PIDs as "model diseases" to better understand disease-specific mechanisms, but also to gain insight into how our immune system functions.

Pediatric rheumatology

ANA positive, juvenile idiopathic arthritis (JIA) is a potentially homogenous subgroup characterized by early disease onset and uveitis. We could show that pathophysiologically, a distinct T-helper population adds to dysregulated B-cell activation (Fig. 1). High-throughput sequencing of the TCR repertoire and cloning of B-cell receptors allows the evaluation of reactivity towards anti-nuclear auto-antigens.

Pathophysiology of T-cell mediated autoimmune diseases

An imbalance between inflammatory T cells and regulatory T cells is characteristic for T-cell mediated autoimmune disorders. The activation of inflammatory T cells can be modulated by in vitro polarization by various cytokines, by epigenetic modifications and interaction with mesenchymal stem cells, as well as by modulation of migration factors. Using these approaches novel therapeutic targets may be identified for the treatment of autoimmune disorders. Further projects aim to investigate the role of immunosuppressive/immunomodulatory therapy on effector mechanisms against latent virus infections and on the humoral and cellular immune response to vaccine antigens to improve vaccination schedules for immunocompromised patients.

Osteology

Hypophosphatasia is a rare bone disease characterized by reduced tissue nonspecific alkaline phosphatase. Bone mineralisation, renal function and possibly CNS function are impaired. Our interdisciplinary team (Children's Hospital/Orthopedic Center for musculoskeletal Research) provides patient care for the largest patient cohort throughout Europe. Research projects range from pathophysiology to preclinical treatment approaches. Further projects focus on health related quality of life and physical assessment in patients with pediatric HPP and participation in an international HPP registry.

Pediatric Pulmonology / Cystic Fibrosis / Sports Medicine

Regular physical activity and exercise have become a major component in the care for people with cystic fibrosis (CF). We focus on how people with CF might be motivated to engage in regular physical exercises and which effects such an intervention might have on the outcome. Methods to monitor physical activity and pulmonary function were standardized to allow international studies for chronic lung diseases. In a multicentre study, coordinated by the Würzburg team, we evaluated the effects of increased physical activity on CF morbidity. Other research areas include collaborative projects on functional, MRT-based imaging of lung disease and individualized tissue models.

Teaching

The Children's Hospital of the University of Würzburg offers several courses for medical students. Prof. Dr. C. P. Speer is authorized to fully train MDs in pediatrics, as well as in neonatology and pediatric intensive care. The heads of the sections for pediatric hematology and oncology, neuropediatrics, and pediatric pulmonology are qualified to train MDs in their respective subspecialties. The Children's Hospital organizes regularly clinical rounds and educational seminars for pediatricians on a regional and national level. In addition, every year scientific meetings and symposia are organized in Würzburg, e.g. every 3rd year the international symposium "Recent Advances in Neonatal Medicine" with participants from more than 60 nations. Outside of the United States of America this symposium represents the largest scientific forum for neonatology.

SELECTED PUBLICATIONS

Glaser K, Silwedel C, Fehrholz M, Waaga-Gasser AM, Henrich B, Claus H, Speer CP. (2017) Ureaplasma species differentially modulate pro- and anti-inflammatory cytokine responses in newborn and adult human monocytes pushing the state toward pro-inflammation. Front Cell Infect Microbiol 7:484.

Hebestreit H, Hulzebos EH, Schneiderman JE, Karila C, Boas SR, Kriemler S, Dwyer T, Sahlberg M, Urquhart DS, Lands LC, Ratjen F, Takken T, Varanistkaya L, Rücker V, Hebestreit A, Usemann J, Radtke T. (2018) Prognostic value of CPET in CF study group. Cardiopulmonary exercise testing provides additional prognostic information in cystic fibrosis. Am J Respir Crit Care Med doi:10.1164/rccm.201806-1110OC [Epub ahead of print].

Liese JG, Schoen C, van der Linden M, Lehmann L, Goettler D, Keller S, Maier A, Segerer F, Rose MA, Streng A. (2018) Changes in the incidence and bacterial aetiology of paediatric parapneumonic pleural effusions/empyema in Germany, 2010-2017: a nationwide surveillance study. Clin Microbiol Infect pii: S1198-743X(18)30725-0. doi: 10.1016/j.cmi.2018.10.020 [Epub ahead of print].

Löhr M, Freitag B, Technau A, Krauss J, Monoranu CM, Rachor J, Lutz MB, Hagemann C, Kessler AF, Linsenmann T, Wölfl M, Ernestus RI, Engelhardt S, Gelbrich G, Schlegel PG, Eyrich M. (2018) High-grade glioma associated immunosuppression does not prevent immune responses induced by therapeutic vaccines in combination with T(reg) depletion. Cancer Immunol Immunother 67:1545-1558.

Major-Monfried H, Renteria AS, Pawarode A), Reddy P, Ayuk F, Holler E, Efebera YA, Hogan WJ, Wölfl M, Qayed M, Hexner EO, Wudhikarn K, Ordemann R, Young R, Shah J, Hartwell MJ, Chaudhry MS, Aziz M, Etra A, Yanik GA, Kröger N, Weber D, Chen YB, Nakamura R, Rösler W, Kitko CL, Harris AC, Pulsipher M, Reshef R, Kowalyk S, Morales G, Torres I, Özbek U, Ferrara JLM, Levine JE. (2018) MAGIC biomarkers predict long-term outcomes for steroid-resistant acute GVHD. Blood 131:2846-2855.

Department of Dermatology, Venereology and Allergology

CONTACT DETAILS

Professor Dr. med. Matthias Goebeler
(Head of the Department)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/201-26351
Fax: 0931/201-26700
E-mail: Goebeler_M1@ukw.de
www.ukw.de/hautklinik

Professor Dr. med. Henning Hamm
Phone: 0931/201-26738

Professor Dr. med. Bastian Schilling
(since 2/2017)
Phone: 0931/201-26779

Professor Dr. rer. nat. Marc Schmidt
Phone: 0931/201-26396

Mission and Structure

The Department of Dermatology, Venereology and Allergology offers the entire spectrum of conservative dermatology, allergology, dermatologic surgery and dermato-oncology in patient care, research and teaching. Residents can obtain a full specialization in dermatology and venereology; additional board certifications include allergology, dermatohistopathology and proctology. Since 2009 the department is certified according to DIN EN ISO 9001:2008 and all diagnostic laboratories are accredited by the DAkkS. In 2010, a certified Skin Cancer Center was established, which is an integral part of the *Comprehensive Cancer Center Mainfranken*. In 2013, the Interdisciplinary Center for Allergic Diseases *(Allergiezentrum Mainfranken)* was founded. Apart from the department head, 3 professors of dermatology or molecular dermatology and 5 associate professors have been working in research and education during the period under report. Twelve attendings, 4 further specialists in dermatology and 18 residents are practising at the department. In research projects, basic life scientists are employed on regular positions and third-party funds. The department comprises the following divisions:

- Outpatient clinic
- Consultations for specific skin diseases (e.g. pediatric dermatology, psoriasis, hidradenitis suppurativa/ acne inversa, autoimmune bullous diseases, lupus erythematosus and vasculitis, sarcoidosis, hair diseases, proctology)
- Inpatient clinic for conservative dermatology and dermato-surgery
- Skin Cancer Center with inpatient clinic for dermato-oncology
- Interdisciplinary therapy unit for dermato-oncology
- Day clinic (leg ulcers/wounds, general dermatology, dermato-oncology)
- Allergy Center Mainfranken with outpatient clinic for allergology
- Outpatient clinic for phototherapy and photodynamic therapy
- Division of dermatohistopathology and autoimmune diagnostics
- Laboratory for dermatologic infectiology (mycology, serology)
- Research laboratories with focus on dermato-oncology, immunology and inflammation

Focuses of Clinical Interest

- Dermatooncology (B. Schilling, A. Gesierich, M. Wobser)
- Allergology (A. Trautmann, A. Kerstan, J. Stoevesandt)

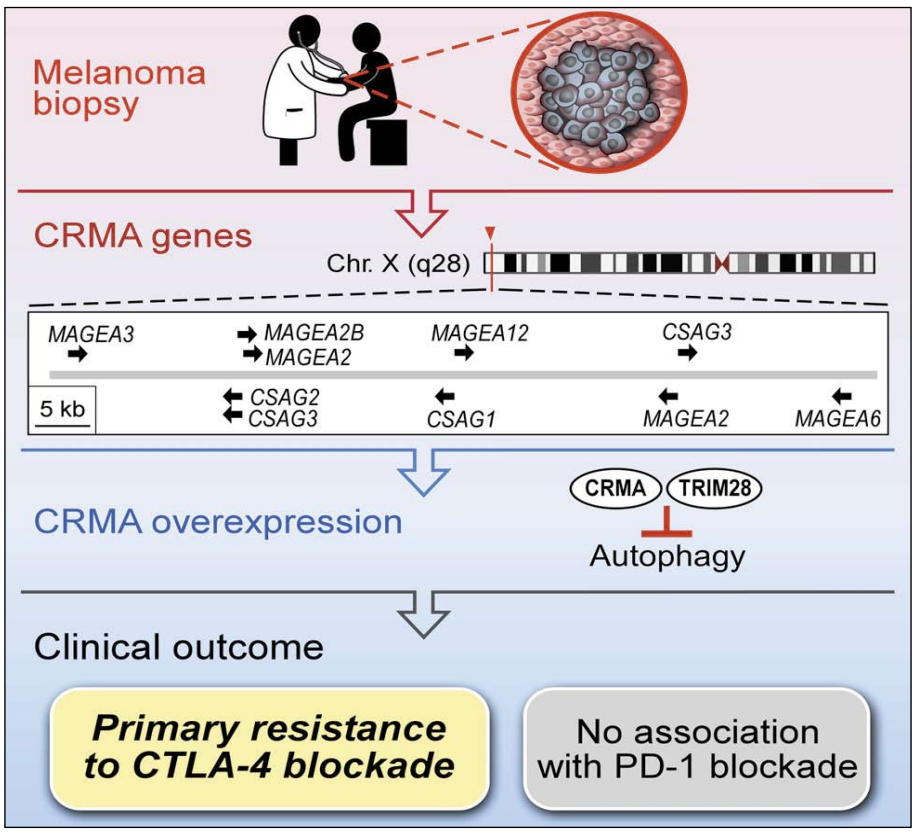


Fig. 1: Blockade of the immune checkpoint CTLA-4 provides long-term benefit to a subset of patients with metastatic melanoma. In this study, we have identified a cluster of genes on the X-chromosome located within a narrow 75 kilobases region that predicts resistance to CTLA-4 blockade. This association was not found in patients receiving PD-1 blockade. Outcome prediction and specificity of this gene signature was validated in an independent patient cohort. The genes within this cluster all encode cancer germline antigens of the MAGE family. Mechanistically, overexpression of MAGE antigens suppresses autophagy, a process critical for optimal anti-cancer immunity. In line with this, expression of the key autophagosome component LC3B and other activators of autophagy are negatively associated with MAGE protein levels in human melanomas, including samples from patients with resistance to CTLA-4 blockade. Taken together, these findings implicate autophagy suppression as a mechanism of resistance to CTLA-4 but not PD-1 blockade in advanced melanoma, suggesting autophagy induction as a potential therapeutic strategy (Reprinted from Shukla SA et al., Cell 173: 624-633 (2018); with permission from the publisher (Elsevier)).

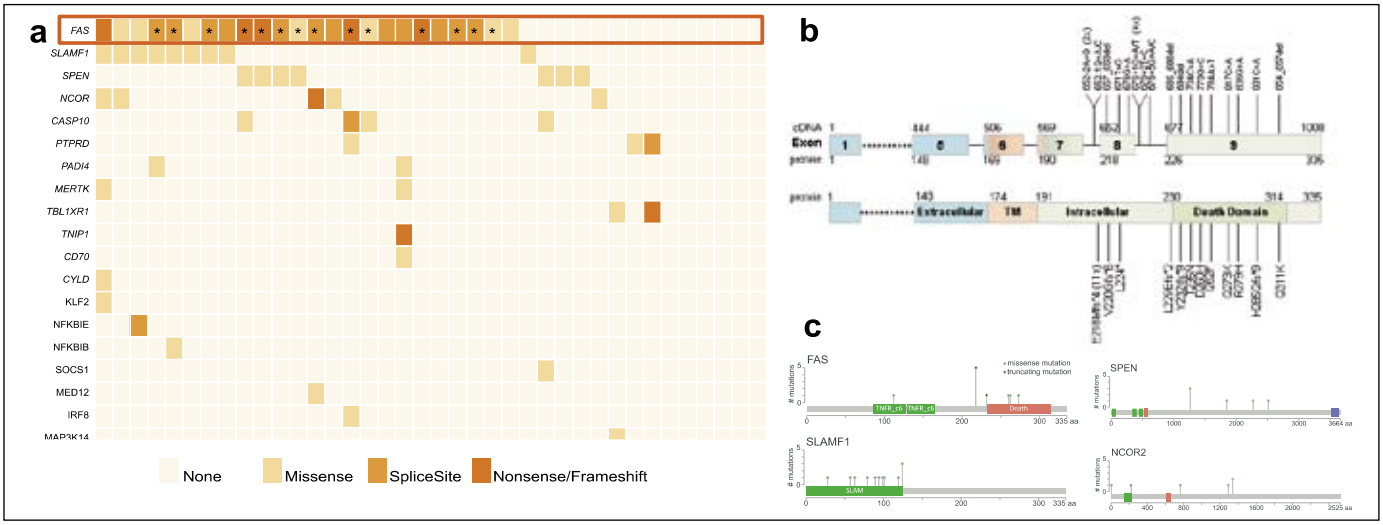


Fig. 2: The molecular mechanisms underlying primary cutaneous marginal zone lymphoma are widely unknown. By next-generation sequencing (a) we identified inactivating, dominant-negative mutations within the FAS gene, which encodes for an apoptosis-promoting receptor of the TNF receptor family. The prevailing type of mutations was splice-site mutations. All of the mutations affected the functionally relevant death domain (DD) of the FAS receptor (b). These data suggest that consecutive impaired cell death plays a central role for the pathogenesis of cutaneous marginal zone lymphoma. Albeit with lower frequency we identified additional recurrent mutations in genes such as SLAMF1, SPEN and NCOR2 (c). For a detailed description of our findings please refer to Maurus K et al., J Invest Dermatol. 138:1573-1581 (2018).

- Autoimmune and inflammatory skin diseases (M. Goebeler, S. Benoit, J. Stoevesandt, A. Kerstan)
- Hair diseases (H. Hamm, A. Kerstan)
- Dermatologic surgery (D. Presser, I. Stolze, A. Gesierich)
- Proctology (A. Gesierich, D. Presser)
- Paediatric dermatology (H. Hamm, S. Benoit, M. Wobser)
- Dermatologic infectiology (A. Kolb-Mäurer)
- Dermatohistopathology (H. Kneitz, A. Kerstan, M. Wobser)

Major Research Interests

Tumour biology and tumour immunology

Many patients are referred to the Dermatology department because of skin cancers. A main field of research therefore addresses aspects of the biology of cutaneous tumours. Focuses during the period under report were:

- signal transduction in Merkel cell carcinoma
- viral carcinogenesis
- tumour senescence
- MAP kinase pathways in melanoma
- tumour suppressor proteins in skin cancer
- melanoma immunology
- melanoma genetics and mutation analysis
- cell migration and neoangiogenesis
- pathogenesis of primary cutaneous B- and T-cell lymphoma
- phenotypic and molecular characterization of rare cutaneous lymphoma subtypes (peripheral T-cell lymphoma, NOS)

Immunology and inflammation

- pathogenesis of allergic contact dermatitis
- interaction between T-lymphocytes and keratinocytes in dermatitis
- immunotherapy with wasp venom as model for therapeutic immune modulation in humans
- mechanisms of signal transduction in the context of innate immunity
- role of B and T lymphocytes in chronic inflammatory skin diseases

Genodermatoses

- clinical and genetic characterization of genodermatoses

Teaching

The entire spectrum of dermatology, venereology, allergology and dermatooncology is taught to medical and dental students in tutorials, practical courses and lectures. The department is also involved in the interdisciplinary education of medical students and in the biomedicine degree program. Main topics of bachelor, master and doctoral theses derive from the research projects listed above.

SELECTED PUBLICATIONS

Adam C, Wohlfarth J, Haußmann M, Sennefelder H, Rodin A, Maler M, Martin SF, Goebeler M, Schmidt M. (2017) Allergy-Inducing Chromium Compounds Trigger Potent Innate Immune Stimulation Via ROS-Dependent Inflammasome Activation. J Invest Dermatol 137:367-376.

Dogliotti G, Kullmann L, Dhumale P, Thiele C, Panichkina O, Mendl G, Houben R, Haferkamp S, Puschel AW, Krahn MP. (2017) Membrane-binding and activation of LKB1 by phosphatidic acid is essential for development and tumour suppression. Nat Commun 8:15747.

Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, ..., Gesierich A, ..., Wang HJ, Elashoff DA, Elashoff RM. (2017) Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. New Engl J Med 376:2211-2222.

Maurus K, Appenzeller S, Roth S, Kuper J, Rost S, Meierjohann S, Arampatzi P, Goebeler M, Rosenwald A, Geissinger E, Wobser M. (2018) Panel Sequencing Shows Recurrent Genetic FAS Alterations in Primary Cutaneous Marginal Zone Lymphoma. J Invest Dermatol 138:1573-1581.

Shukla SA, Bachireddy P, Schilling B, Galonska C, Zhan Q, Lee PC,1 Gusenleitner, Keskin DB, Babadi M, Mohammad A, Gnirke A, Clement K, Van Allen EM, Miao D, Snyder A, Merghoub T, Wolchok JD, Garraway LA, Meissner A, Weber JS, Hacohen N, Neuberg D, Potts PR, Murphy GF, Lian CG, Schadendorf D, Hodi FS, Wu CJ. (2018) Cancer-germline antigens discriminate clinical outcome to CTLA4 blockade. Cell 173:624-633.

Department of Oto-Rhino-Laryngology, Plastic, Aesthetic and Reconstructive Head and Neck Surgery

CONTACT DETAILS

Professor Dr. med. Dr. h.c. Rudolf Hagen
(Head of the Department)

Josef-Schneider-Str. 11
97080 Würzburg
Phone: 0931/201-21701
Fax: 0931/201-21248
E-mail: Hagen_R@ukw.de
www.ukw.de/hno-klinik

Professor Dr. rer. nat. Dr. rer. med.
Andreas Bahmer
Phone: 0931/201-21779

Professor Dr. med. Norbert Kleinsasser
Phone: 0931/201-21322

Mission and Structure

The Clinic of Otorhinolaryngology, Plastic, Aesthetic and Reconstructive Head and Neck Surgery (28 physicians, 5 scientists, 7 research fellows) has 92 regular beds including 4 intensive care units. Besides the complete basic care in the field of ORL there exist the following clinical specialities: device based and surgical supply of all kind of hearing disabilities by special diagnostics, conventional middle ear surgery, new active middle ear implants, implantable hearing aids as well as cochlear implantation (international reference center), interdisciplinary skull base surgery (tumours, traumas), diagnostics and therapy of head and neck tumours with main focus on organ and function preserving and microsurgical techniques and plastic-reconstructive surgery (laryngeal reconstruction, autotransplantation of submandibular gland), national reference center for surgical treatment of pediatric sarcomas of the head and neck, phoniatrics (including phonosurgery), pedaudiology, allergology, sleep medicine (devices based and surgical treatment), neurootology, plastic and aesthetic interventions of the head and neck. Support of foreign ORL clinics in all continents by visitant professorships and practical education of foreign ENT doctors. National and international surgical courses with 3D-Video-Live-Transmission of surgical interventions.

Main Research Interests

Theoretical and clinical-experimental neurophysiology
(A. Bahmer, S. Pieper, F. Keller, D. Herrmann)

Development of new concepts for stimulation of the auditory system

Middle ear implants
(R. Hagen, K. Rak, S. Kaulitz)

Development of new middle ear implants including implantable active middle ear amplifiers in cooperation with medical technology industry

Biophysics of middle ear
(A. Bahmer, S. Kaulitz, R. Hagen, R. Keim, M. Cebulla)

Investigations of middle ear structures as a dynamic-mechanical system in sound transmission processes using LASER vibrometry; EDP supported documentation and evaluation of surgical and audiological outcome in patients with tympanoplasty and implantation of electronic hearing devices. Intraoperative monitoring of transfer function of active middle ear implants.

Inner ear biology
(K. Rak, J. Völker, in cooperation with the Institute of Neurobiology, M. Sendtner, S. Jablonka)

Evidence and functional properties of neuronal stem cells in the rat cochlear nucleus. Dynamic changes of the neurogenic potential in the rat cochlear nucleus during postnatal development. Effects of defined gene mutations (TBCE gene) on inner ear structure in the pmn/pmn mouse. Interactions of neuronal structures with semiconductor materials.

Therapeutic use of stem cells in the damaged cochlea
(P. Schendzielorz)

Improvement of survival of ganglion cells following experimental deafening by local stem cell application in the cochlea of the guinea pig. Development of a stem cell coating on inner ear electrodes for optimization of functional linkage in cochlear implants.

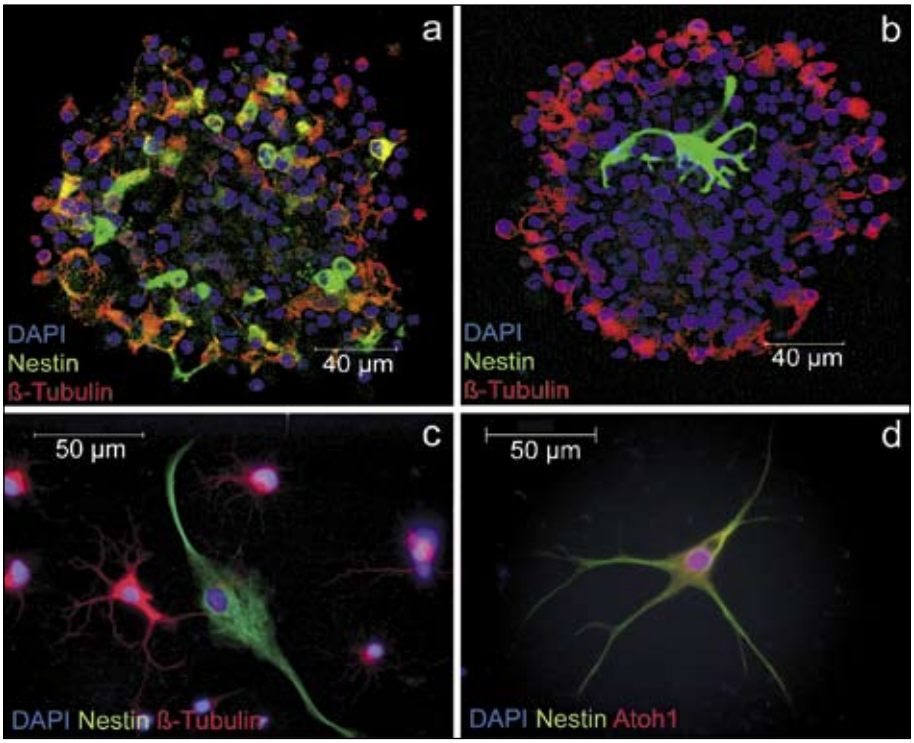


Fig. 1: Stem cells cultured from the nucleus cochlearis of the rat.

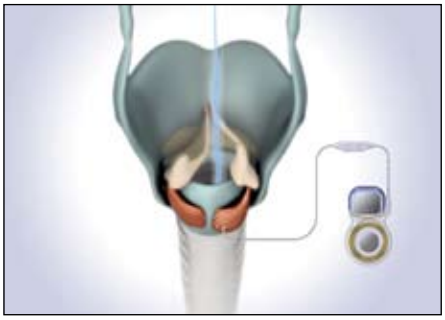


Fig. 2: Schematic drawing of the new Medel laryngeal pacemaker.

Pedaudiological tests, newborn hearing screening, hearing development, genetics of hearing disorders
(W. Shehata-Dieler, D. Ehrmann-Müller, D. Back, R. Keim, M. Cebulla, H. Kühn in cooperation with the Center for Prelingual Speech Development, K. Wermke and the Institute for Human Genetics, T. Haaf, J. Schröder)

Development of new objective testing procedures for frequency specific screening in newborns. Analysis of prespeech sounds in babies to objectify early speech development in pedaudiology. Documentation program for hearing development, genetic evaluation of hearing disorders.

Cochlear- and brain- stem-implants
(K. Rak, W. Shehata-Dieler, A. Bahmer, A. Kurz in cooperation with the Department for Neurosurgery, C. Matthies, and the University of Innsbruck, Austria)

Investigations to improve speech intelligibility following cochlear implantation, development of new surgical techniques and innovative implant models, physiology and pathophysiology of the auditory pathway following uni- and bilateral electrostimulation considering functional anatomical correlations while stimulating different parts of the auditory pathway. Development of new monitoring and telemetry systems

Experimental audiology
(M. Cebulla, U. Geiger)

Further development of diagnostic tools for objective frequency specific measurements of the absolute threshold of hearing. Standardisation of different methods of acoumetry. Investigations in the fine structure of responses to click-stimuli in comparison to transit time corrected stimulation. Objectification of binaural hearing in persons with normal and impaired hearing.

Tumour biology and functional rehabilitation following tumour surgery
(S. Hackenberg, R. Hagen, T. Gehrke, M. Schmidt, M. Scheich, A. Scherzad, S. Hackenberg, N. Kleinsasser)

Molecular biological investigations in head and neck carcinomas (HNC), induced expression of a deletional mutant of Pseudomonas exotoxin A in cell lines of HNC, development of a new control plasmid by subcloning (pGeneA-EGFP), investigations in chemotaxis and angiogenesis of tumour cells, effects of herbal anti-tumoural extracts on paclitaxel sensitive and – resistant HNC cell lines, development of new surgical reconstructive techniques of larynx and trachea.

Ecological toxicology of the upper aerodigestive tract (UADT)
(A. Scherzad, S. Hackenberg, P. Ickrath, N. Kleinsasser)

Investigations on the toxicological effects of ecological toxins in tumour initiation testing human tissue cultures of the UADT, characterisation of genotoxical effects of tobacco smoke and environmental toxins (nitrogen dioxide) on mini organ cultures of UADT.

Functional electrostimulation of the larynx
(R. Hagen, F. Kraus, A. Kurz in cooperation with the University Departments of Oto-Rhino-Laryngology in Jena, Germany and in Innsbruck, Austria)

Development of a laryngeal pacemaker for treatment of vocal cord paralysis.

Use of nanomaterials in tumor therapy
(S. Hackenberg, A. Scherzed in cooperation with the Institute for Tissue Engineering and Regenerative Medicine and Institute for Functional Materials, J. Groll, Department of Dermatology, R. Houben, Fraunhofer Institute for silicate research, C. Gellermann)

Establishment of an interdisziplinary research group “use of nanomaterials in oncology“.

Cooperation with the Center of Rare Diseases
(S. Hackenberg in cooperation with the pediatric department, H. Hebestreit)

Project for the development of a 3D-in-vitro-test-system for primary ciliary diskinesia.

Raman-spectroscopy
(S. Hackenberg, T. Meier in cooperation with the Institute of Pathology, E. Hartmann and the Fraunhofer-Translation-Center for Regenerative Therapies TLZ-RT, M. Steinke)

IZKF-supported project for integration of Raman-spectroscopy into diagnostics of tumors of salivary glands.

Personalized tumor therapy
(S. Hackenberg, M. Scheich in cooperation with the CCC, R. Bargou, C. Sayehli, the Institute of Pathology, A. Rosenwald and the Dept. of Maxillofacial Surgery, A. Kübler and coworkers)

Development of new concepts for a personalized tumor therapy.

Teaching

Coworkers with postdoctoral lecture qualification take part in the medical main lecture and in the clinical courses for medical students. Initiation and coaching of experimental and clinical medical dissertations. Annual German and English speaking surgical courses for microsurgery of the ear, skull base surgery, phonosurgery, reconstructive laryngeal surgery, endonasal surgery with live-3D-transmission and practical exercises for consultants. The foreign twin clinics are served by course instructors (DAAD) in all the participating countries, 4 training fellowships for practical education.

SELECTED PUBLICATIONS

Bahmer A, Gupta DS. (2018) Role of Oscillations in Auditory Temporal Processing: A General Model for Temporal Processing of Sensory Information in the Brain? Front Neurosci 12:793.

Cebulla M, Geiger U, Hagen R, Radeloff A. (2017) Device optimised chirp stimulus for ABR measurements with an active middle ear implant. Int J Audiol 56:607-611.

Rak K, Schraven SP, Schendzielorz P, Kurz A, Shehata-Dieler W, Hagen R, Radeloff A. (2017) Stable Longitudinal Performance of Adult Cochlear Implant Users for More Than 10 Years. Otol Neurotol 38:315-319.

Schendzielorz P, Vollmer M, Rak K, Wiegner A, Nada N, Radeloff K, Hagen R, Radeloff A. (2017) Adipose-derived stromal cells enhance auditory neuron survival in an animal model of sensory hearing loss. Cytotherapy 19:1197-1207.

Völker J, Kohm F, Jürgens L, Scherzad A, Schendzielorz P, Schraven SP, Mlynski R, Radeloff A, Hagen R, Rak K. (2018) Patterned semiconductor structures modulate neuronal outgrowth: Implication for the development of a neurobionic interface. J Biomed Mater Res A 106:65-72.

Department of Ophthalmology

CONTACT DETAILS

Professor Dr. med. Jost Hillenkamp (Head of Department)

Josef-Schneider-Str. 11
97080 Würzburg
Phone: 0931/201-20601
Fax: 0931/201-20245
E-mail: k-augen@augenklinik.uni-wuerzburg.de
www.ukw.de/augenklinik

Professor Dr. med. Martin Nentwich
Phone: 0931/201-20612

Professor Dr. med. Nils A. Loewen (since 4/2019)
Phone: 0931/201-20602

Professor Dr. med. André Rosentreter (until 6/2018)

Mission and Structure

A staff of 34 physicians and about 90 nurses, technicians and scientists care for approximately 22.000 outpatients and about 5.500 inpatients annually. In 2018, more than 8000 surgical procedures and approximately 2000 laser treatments were performed.
The University Eye Hospital provides comprehensive care in all subspecialties of ophthalmology. The ophthalmic ward hosts 66 beds and surgery is performed in 4 operation theaters.
In the field of vitreo-retinal diseases, the University Eye Hospital is a supraregional center for adults as well as for children and offers up-to-date specialized care both in medial retina and in vitreo-retinal surgery. It is a renowned center for surgical care of severe ocular trauma.
The Glaucoma Unit is equipped with all modern diagnostic devices and offers all types of glaucoma surgery for patients with medically insufficiently controlled intraocular pressure. Specialized teams of ophthalmologists take care of patients with conjunctival, corneal, eyelid and orbital problems. The Unit for Pediatric Ophthalmology, Strabismus and Neuro-ophthalmology offers up-to-date diagnostic and surgical care of all visual problems in childhood, all forms of strabismus and neuro-ophthalmologic diseases. All forms of ophthalmic imaging and electrophysiological testing are offered in the Diagnostic Unit.
Many surgical procedures can be offered on an inpatient as well as on an outpatient basis depending on the patients' general medical condition and individual ophthalmological findings.

Major Research Interests

Clinical Research
Anterior Segment

The team of ophthalmologists caring for anterior segment diseases of the eye and the Glaucoma Unit evaluate treatments for disorders of the ocular surface, modern types of keratoplasty, long-term results of corneal cross-linking in keratoconus and other keratektasias as well as measures to reduce scarring after glaucoma surgery. In addition, the University Eye Hospital has a major role in the development of novel methods for monitoring intraocular pressure.
New imaging techniques such as imaging of the peripapillary nerve fiber layer using spectral-domain OCT augmented morphological follow-up examinations of glaucoma patients.

Retina and Imaging of the Posterior Segment
Quantified Fundus Autofluorescence (qAF) - a new Tool for the Diagnosis and Follow-up of Retinal Changes

Imaging of autofluorescence of the posterior segment of the eye (FAF) gives information on the status of the retina and adjacent structures of the eye. FAF helps to differentiate between pathologic and healthy structures within the retinal pigment epithelium. FAF imaging is non-invasive and routinely performed at the University Eye Hospital. Quantified fundus autofluorescence (qAF) is a further development of this technique and allows for the first time comparison of one patient´s examinations over time and between different patients. Quantified fundus autofluorescence has been used at the University Eye Hospital during the past few years. During this time qAF standard parameters have been obtained and special software has been developed for analysis (AG PD Dr T. Ach).

Basic Research
Anterior Segment

In-situ regeneration of amitotic ocular tissues, especially of corneal endothelium and retinal pigment epithelium, by means of gene-transfer of transcription factors (Dr. Dr. D. Kampik in cooperation with the UCL Institute of Ophthalmology, London).
The cooperation with the Chair for Tissue Engineering and Regenerative Medicine of the University Hospital Würzburg includes two topics:
First, the development of a 3-dimensional artificial cornea-tissue model as a replacement for animal experiments and for preclinical testing of drugs. Second, the development of a cornea-bioreactor for optimizing *ex vivo* culture of donor-cornea (Dr. Dr. D. Kampik).

Posterior Segment
Characteristics of intracellular granules of the retinal pigment epithelium – Investigations using high-resolution Spectral Microscopy

Cells of the retinal pigment epithelium (RPE) intracellularly accumulate different autofluorescent granules. Of these especially lipofuscin and melanin are of clinical relevance. Lipofuscin has been associated with the development of AMD (age-related macular degeneration), however, this association has recently been questioned in the light of new histological studies. Melanin/melanosomes on the other hand are regarded to have a protective effect on the retinal pigment epithelium.

Fig. 1: Title page of the journal "Gene Therapy" with a picture from the publication "In situ regeneration of retinal pigment epithelium by gene transfer of E2F2" by Kampik D. et al. (Picture: Dr. Dr. D. Kampik).

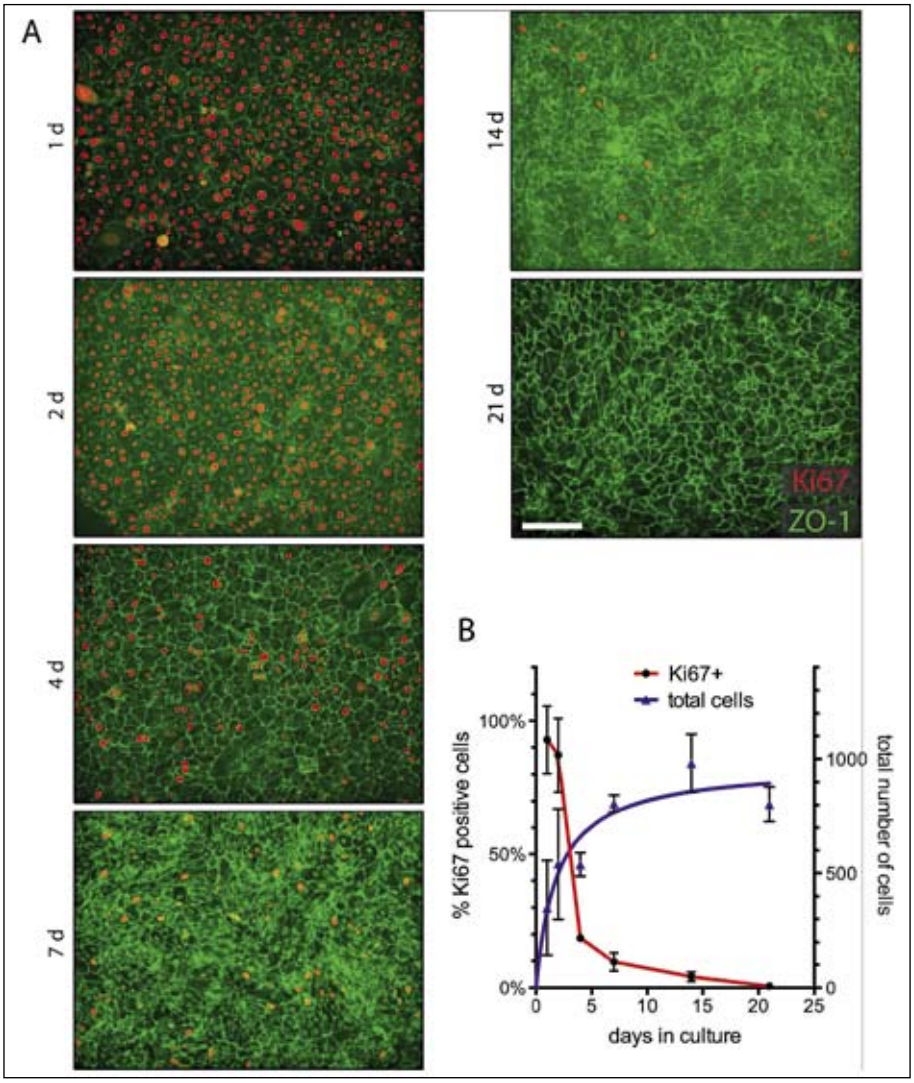


Fig. 2: Formation of contact inhibition in vitro: Correlation of the tight junction-marker ZO-1, cell-density and cell-proliferation (Ki67) of one RPE-cell line over time (Picture: Dr. Dr. D. Kampik).

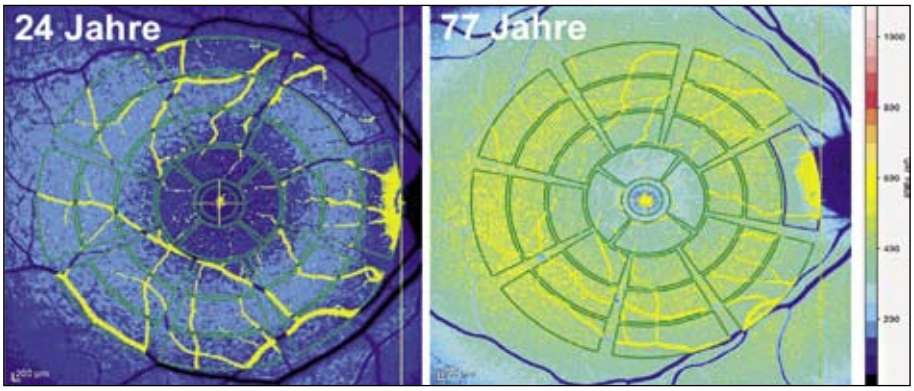


Fig. 3: Quantified fundus autofluorescence (qAF) enables for the first time the comparison of posterior-segment autofluorescent-images and clearly demonstrates the physiological rise in autofluorescence with increasing age (Picture PD Dr. T. Ach).

A project supported by the NIH (AG PD Dr T. Ach; 2017-2021) studies the exact intracellular localization and the autofluorescent characteristics of these granules using high-resolution spectral microscopy. Differences in the lipofuscin/melanosome content of single RPE-cells depend on the location within the retina and age. Whether different diseases of the macula such as AMD cause changes in the content/spectrum of the granule is being studied on human donor-tissue.

Teaching

Lectures, practical training and special interest seminars are offered to undergraduate medical students. The University Eye Hospital also teaches practical skills such as fundoscopy and microsurgical techniques to medical students. The residency program comprises daily morning rounds with case presentations and CME-seminars. A series of three extensive seminars per year is dedicated to update colleagues in private practice on the most recent developments in the field of ophthalmology. In addition, lecturers from the University Eye Hospital teach at regional, national and international ophthalmology conferences.

SELECTED PUBLICATIONS

Curcio CA, Zanzottera EC, Ach T, Balaratnasingam C, Freund KB. (2017) Activated Retinal Pigment Epithelium, an Optical Coherence Tomography Biomarker for Progression in Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci 58: BIO211-BIO226.

Kampik D, Basche M, Luhmann UFO, Nishiguchi KM, Williams JAE, Greenwood J, Moss SE, Han H, Azam S, Duran Y, Robbie SJ, Bainbridge JWB, Larkin DF, Smith AJ, Ali RR. (2017) In situ regeneration of retinal pigment epithelium by gene transfer of E2F2: a potential strategy for treatment of macular degenerations. Gene Ther 24:810-818.

Matlach J, Wagner M, Malzahn U, Schmidtmann I, Steigerwald F, Musacchio T, Volkmann J, Grehn F, Göbel W, Klebe S. (2018) Retinal changes in Parkinson's disease and glaucoma. Parkinsonism Relat Disord 56:41-46.

Nentwich MM, Klauß V, Guthoff R. (2017) German ophthalmology in developing countries : Partnerships with eye clinics in developing countries - an initiative of the German Ophthalmological Society. Ophthalmologe 114:794-803.

Treumer F, Wienand S, Purtskhvanidze K, Roider J, Hillenkamp J. (2017) The role of pigment epithelial detachment in AMD with submacular hemorrhage treated with vitrectomy and subretinal co-application of rtPA and anti-VEGF. Graefes Arch Clin Exp Ophthalmol 255:1115-1123.

Department of Neurosurgery

CONTACT DETAILS

Professor Dr. med. Ralf-Ingo Ernestus
(Head of the Department)

Josef-Schneider-Str. 11
97080 Würzburg
Phone: 0931/201-24800
Fax: 0931/201-24635
E-mail: klinik@nch.uni-wuerzburg.de
www.ukw.de/neurochirurgie

Professor Dr. med. Cordula Matthies
Phone: 0931/201-24805

Professor Dr. Anna-Leena Sirén
Phone: 0931/201-24579

Clinical Focus and Structure

The Department of Neurosurgery employs 29 medical doctors, 3 scientists, 96 nurses and 8 technicians. The clinical wards are comprised of a total of 70 beds with single, double and triple patient rooms and an intensive care unit of 19 beds providing treatment for patients with cranial and spinal trauma, vascular malformations and spontaneous haemorrhage, with brain or spinal cord surgery as well as early neurological rehabilitation within a subunit for intermediate care. The operating unit consists of 5 operating theatres including one OR for outpatients and emergencies. Over the last 2 years (2017-2018), 3,668 patients were treated surgically and 14,792 patients in the outpatient department. The out-patient clinic offers consultation for all neurosurgical diagnoses in specialized clinics such as brain tumours, degenerative spine and disc disease, pain syndromes, peripheral nerve lesions, pituitary tumours and dysfunction, neurovascular disease, skull base tumours (jointly with Department of ORL) and movement disorders (jointly with Department of Neurology).
Infants and children with inborn malformations of the nervous system and of the skull and spine as well as children with neoplasia and trauma are taken care of by the Division of Paediatric Neurosurgery.
The whole range of neurosurgery is performed at latest technique and supported by modern technological devices such as neuronavigation, neuroendoscopy, intraoperative ultrasound and micro-dopplersonography as well as continuous neuroanesthesiological and neurophysiological monitoring. Special interdisciplinary treatment protocols have been established for patients with vascular malformations (in close cooperation with the Department of Neuroradiology), furthermore for patients with brain tumours together with radiotherapists and neurooncologists as well as for skull base lesions, namely vestibular schwannomas and meningiomas with ORL surgeons. Spine surgery for complex neoplastic and neurovascular lesions as well as for degenerative disease is performed at high incidence and for certain indications together with orthopedic and trauma surgery. Regular quality control conferences guarantee an ongoing high standard in routine and in most sophisticated operations.
The Division of Experimental Neurosurgery performs studies on neurotrauma, neurodegeneration and –regeneration, neurovascular pathophysiology and neurooncology and holds established collaborations with other basic science and clinical departments.

Main Research Foci

Neurooncology
R.-I. Ernestus, C. Hagemann, M. Löhr, A. F. Keßler, T. Linsenmann, M. Breun, S. Rückriegel, C. Matthies)

The Deparment treats a large patient population with primary brain tumours. All treatment have been certified by the Comprehensive Cancer Center Mainfranken (CCCMF). Tumour samples are obtained at surgery for primary cell cultures and are frozen in liquid nitrogen. They form the basis for the research of specific molecular characteristics in the Tumour Biology Research Laboratory. Several experimental animal models, cell lines and functional assays have been established for investigation of tumour immunology, tumour cell invasion and cell cycle regulation. Tumour biology and mutation analysis in benign pathologies such as schwannomas and meningiomas, are investigated in national and international cooperations. Cell de-differentiation, adhesion molecules, tumour invasion and promotors of apoptosis are targets of investigation in benign tumour cell cultures, and these readouts are compared for different clinical courses despite identical histology. Large regular outpatient clinics for patients with skull base tumours, sporadic and genetically based vestibular schwannomas and meningiomas (neurofibromatosis types 1 and 2) are the basis for these laboratory investigations and for clinical studies focusing on long-time functional outcome and quality-of-life. Culture models are developed to study tumour growth and invasion and for testing of pharmacological agents and antibody-based approaches for future individualized adjuvant therapies.

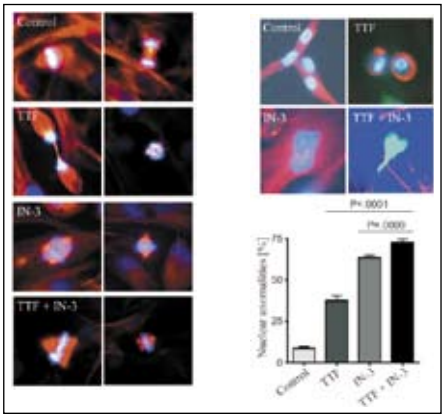


Fig.: Kessler, AF et al, 2018, Cell Death & Discovery.

Functional Microsurgery & Neurostimulation
(C. Matthies, M. Breun, P. Fricke, R. Nickl, V. Sturm)

Functional microsurgery refers to a microsurgical technique guided by information from continuous neurophysiological monitoring to treat pathologies at the skull base, brainstem, medulla and specific functional brain areas along with functional integrity of neural structures. Prospective clinical studies are being run on improving current techniques of monitoring and adapting them to the microsurgical process. A prospective study on motor evoked potentials of the cranial nerves has shown an increase in monitoring safety and improved prognosis of functional outcome in tumour surgery. A further study on continuous monitoring on the ICU after surgery has detected functional changes in this early period and has prompted new intensive medication protocols, among those the application of rheologically active substances.
Neurostimulation therapy has been established for retrocochlear deafness and a center for "new diagnostic and treatment modalities" (NUB) has been set up for the application of auditory brainstem implants in cooperation with the Department of ORL. The current study shows – different to previous international reports – that also in patients with large tumours or with previous implant trials – very satisfactory results can be obtained. The technique applied here by the interdisciplinary team and the modern stimulation processors provide useful auditory perception in the majority of patients and increasing rates of speech discrimination. This option applies for tumour patients as well as for others with post-infectious deafness or with inborn malformations.
In cooperation with the Departments of Neurology, Neuroradiology and Psychiatry, patients with movement disorders (Parkinson's disease, tremor, dystonia) are treated by high frequency stimulation therapy. Refined electrode placement is guaranteed by precise pre-operative imaging and target planning as well as intra-operative micro-recording and micro-stimulation tests in the thalamus, pallidum or subthalamic nucleus. Besides these established indications for deep brain stimulation, further patients are carefully selected, investigated and treated by stimulation in previous ischemic brain lesions and life threatening dystonic storms, and neurodegenerative disorders (Parkinson- and Alzheimer) associated dementia. A developing topic is the combination of neuroprotective and regenerative factors.

Neurovascular Disease
(E. Kunze, N. Lilla, C. Stetter, J. Weiland, T. Westermaier)

Main focus lies on the cell-biological mechanisms of early brain injury and cerebral vasospasm after subarachnoid haemorrhage with an aim towards developing new therapies and monitoring cerebral oxygenation and brain metabolism. Vascular dynamics are controlled by invasive monitoring, transcranial Doppler sonography and perfusion imaging during surgery and neurosurgical intensive care as well as in the experimental setting in animal models. These approaches are combined with electrophysiological techniques in order to counteract cerebral vasospasm. Further studies deal with the comparison of interventional and surgical aneurysm treatment and with dural arterio-venous fistulas. Funding: Else-Kröner Foundation, IZKF Würzburg.

Translational Neurotrauma Research
(R.-I. Ernestus, C. Held, E. Kunze, A.-L. Sirén, C. Stetter, T. Westermaier)

Main focus of research is on the mechanisms of neuroprotection and -regeneration after brain injury and on translation of this knowledge into new therapeutic approaches for human brain disease using cell culture, transgenic animals and experimental models of brain traumaAs one of the inaugurating members of the interdisciplinary "Concussion-Center-Würzburg" we study the long-term consequences of sport-associated mild traumatic injuries with the aim to develop better diagnostic and therapeutic approaches. On-going preclinical work focuses on thromboinflammatory processes and their role in chronic posttraumatic pathology and functional deficits. Another important goal is to characterize the changes in synaptic structural plasticity and their impact on functional deterioration after brain injury. In Cooperation with Neurophysiology and Biocenter we elucidate regeneration and synaptic plasticity after trauma at the level of individual synapses by using transgenic and experimental brain injury models and super resolution light- and electron microscopy. Funding: DFG, , BMBF-EU, IZKF Würzburg.

Craniofacial Malformations
(T. Schweitzer, J. Krauß)

An interdisciplinary team of pediatric neurosurgeons, neuropediatricians, neuroradiologists, maxillo-facial surgeons and specialists from seven further disciplines treats children with craniofacial malformations, especially craniosynostosis, and cares long-term for over 800 children all over the country. Investigations focus on underlying causes of the disease, refinement of phenotypic classification, molecular genetic diagnostics, secondary diseases and improvement of surgical techniques. Longitudinal studies investigate problems of morphometrics and development of infants with craniosynostosis and positional deformations.

Teaching

Weekly lectures and associated bedside teaching are offered to medical students of all clinical years. Third and fourth years students undergo a joint introduction to neuro-intensive medicine, neurological-neurosurgical history taking and examination in a cooperative teaching programme by the Departments of Neurology and Neurosurgery. Throughout the year, medical students of the last clinical year may perform their period of choice or an elective period and are fully integrated into the clinical programme and supervised by neurosurgeons and consultants. Doctoral and diploma students from medicine and related sciences as well as for post-doctoral fellows are working in projects at the Section of Experimental Neurosurgery, the Laboratory of Tumorbiology and the Neurophysiology Laboratory.

SELECTED PUBLICATIONS

Breun M, Schwerdtfeger A, Martellotta DD, Kessler AF, Perez JM, Monoranu CM, Ernestus RI, Matthies C, Löhr M, Hagemann C. (2018) CXCR4: A new player in vestibular schwannoma pathogenesis. Oncotarget 9:9940-9950.

Hopp S, Nolte MW, Stetter C, Kleinschnitz C, Sirén AL, Albert-Weissenberger C. (2017) Alleviation of secondary brain injury, posttraumatic inflammation, and brain edema formation by inhibition of factor XIIa. J Neuroinflamm 14:39.

Lilla N, Rinne C, Weiland J, Linsenmann T, Ernestus RI, Westermaier T. (2018) Early Administration of Hypertonic-Hyperoncotic Hydroxyethyl Starch (HyperHES) Improves Cerebral Blood Flow and Outcome After Experimental Subarachnoid Hemorrhage in Rats. World Neurosurg 116:e57-e65.

Linz C, Collmann H, Kübler A, Böhm H, Schweitzer T. (2017) Patient-specific biodegradable implant in pediatric craniofacial surgery. J Craniomaxillofac Surg 45:1111.

Schüpbach WMM, Chabardes S, Matthies C, Pollo C, Steigerwald F, Timmermann L, Visser Vandewalle V, Volkmann J, Schuurman PR. (2017) Directional leads for deep brain stimulation: Opportunities and challenges. Mov Disord 32:1371-1375.

Department of Neurology

CONTACT DETAILS

Professor Dr. med. Jens Volkmann
(Head of the Department)

Josef-Schneider-Str. 11
97080 Würzburg
Phone: 0931/201-23751
Fax: 0931/201-23946
E-mail: nl_direktion@ukw.de
www.ukw.de/neurologie

Professor Dr. Dr. med. Ioannis U. Isaias
Phone: 093120123605

Professor Dr. med. Karl Georg Häusler
(since 7/2018)
Phone: 0931/201-23755

Professor Dr. rer. nat. Rudolf Martini
Phone: 0931/201-23268

Professor Dr. med. Claudia Sommer
Phone: 0931/201-23763

Professor Dr. med. Guido Stoll
Phone: 0931/201-23769

Professor Dr. med. Nurcan Üçeyler
(since 7/2018)
Phone: 0931/201-23542

Mission and Structure

The in- and outpatient services of the Department of Neurology cover the entire spectrum of neurological disorders. The inpatient service has 86 beds including an 8 bed Stroke Unit, a 10 bed Neurological Intensive Care Unit (ICU) and a neurological-neurosurgical emergency room. In 2018 we treated 3.400 inpatients including 574 cases on the ICU. On our emergency service we took care of almost 5.000 patients per year of whom 3.870 had neurological problems. About two thirds of our patients are emergency admissions. The outpatient department provides for over 11.000 out-patient visits and in-house consultations.

The special expertise of the Neurological Department includes Parkinson´s disease and other movement disorders with treatment by deep brain stimulation, neuro-immunological diseases (multiple sclerosis, autoimmune neuromuscular disorders), degenerative neuromuscular disorders including an integrated nerve/muscle pathology service, cerebrovascular disorders, epilepsy, pain and neurointensive care. The Department has integrated a Division for Developmental Neurobiology including electron microscopy (Prof. R. Martini), a clinical laboratory for neurochemical and cerebrospinal fluid analysis, as well as a IZKF-funded junior research group „Imaging for molecular biomarkers for clinical heterogeneity and disease progression in Parkinson´s disease“ (Prof. Isaias) in cooperation with the Department of Nuclear Medicine. The Department of Neurology in addition runs an interdisciplinary neuro-gerontopsychiatric outpatient clinic (“day care clinic”) in collaboration with the Department of Psychiatry which takes care of up to 18 mobile patients with neuropsychiatric disorders on a daytime basis. The neurological focus lies on the multimodal treatment of patients with advanced Parkinsonian disorders.

The Department has 56 full time medical and academic members, 72 nursing staff members, 26 technicians and 17 staff members in administration and special services. Additional 14 academic positions are supported by extramural grants. The Department of Neurology contributed to the cardiovascular Sonderforschungsbereich (Cooperative Project Center Grant) 688 and the newly funded SFB/TR 240 “Platelets”, joint projects within the FP7 and Horizon 2020 Programme of the European Community, and the Chronic Heart Failure Center Würzburg funded by the Federal Ministry of Education and Research

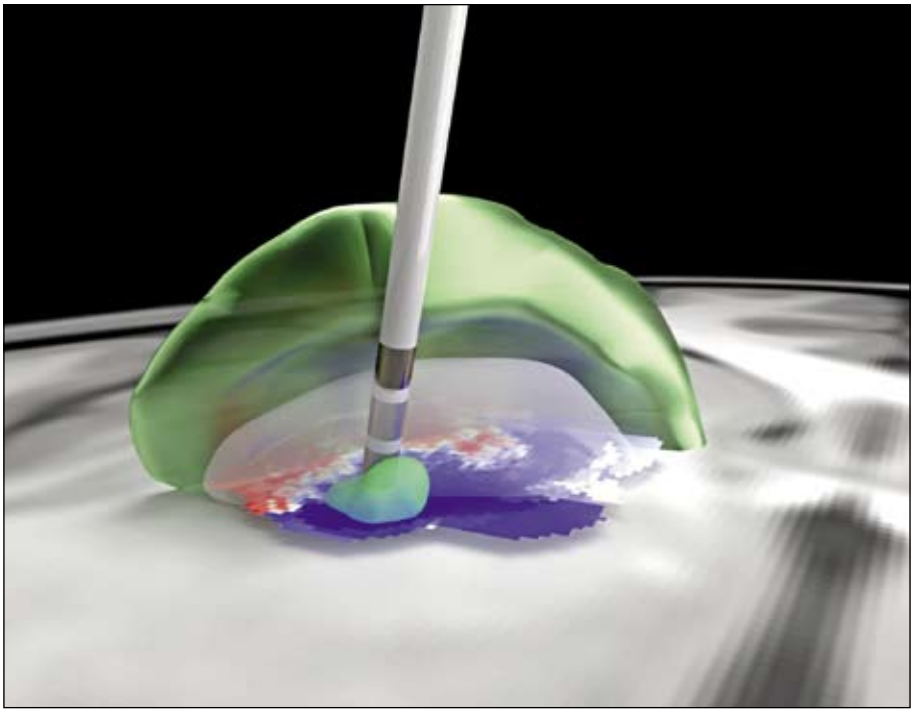


Fig.: Three-dimensional anatomical model of the globus pallidus with cartography of the clinical effect of deep brain stimulation in patients with dystonia. Colour-coded probabilities of clinical improvement after stimulation (red-blue chart) of the volumes depicted within the globus pallidus internus (grey) und externus (light green) based on the analysis of 87 patients with generalized or segmental dystonia. Voxel with the highest probability of a good treatment effect („sweet spot“) in all patients (green). Adapted from Reich et al., Brain, 2019, in press.

(BMBF). Würzburg is coordinating center of the German Network for Translational Research and Treatment of Dystonic Disorders (DYSTRACT) funded by the BMBF within the network of rare disorders. A W2- professorship for Translational Somatosensorics to Prof. Nurcan Üçeyler has been funded since July 2018 by the DFG within the Heisenberg programme.

Major Research Interests

Parkinson´s Disease and Neurodegenerative Disorders
(J. Volkmann, F. Steigerwald, C.W. Ip, I.U. Isaias, K. Doppler, C. Sommer in cooperation with C. Matthies, Department of Neurosurgery, and A. Buck, Nuclear Medicine)

Deep brain stimulation: Clinical and experimental neurophysiological investigations on underlying mechanisms (Musacchio et al., 2017); acute and chronic ("brainradio") recordings in movement disorders; development of improved stimulation procedures. Kinematic laboratory: Evaluation of treatment effects in movement disorders, pathophysiology of gait disturbances; pathogenesis of dystonia in rodent models; skin biopsies as an early histological marker for Parkinson´s disease; molecular imaging (PET, SPECT) of movement disorders; genetics of rare movement disorders. Functional and structural analysis of brain networks by MRI to predict treatment effects of deep brain stimulation.

Stroke and Neuroimmunology
(G. Stoll, M. Schuhmann, W. Müllges, S. Doerck, K.G. Häusler since 7/2018)

Assessment of molecular mechanisms of thrombus formation in experimental cerebral ischemia and the contribution of innate immunity to stroke development ("thrombo-inflammation") within the SFB 688 and TR/SFB 240; development of novel anti-platelet strategies and anticoagulants not affecting hemostasis (cooperation with Prof. B. Nieswandt; Rudolf Virchow Center); molecular mechanisms underlying breakdown of the blood brain barrier; clinical studies on cognitive decline and interactions between heart and brain function during heart failure and stroke (Chronic Heart Failure Center, Würzburg) (Frey et al., 2018); supraregional stroke telemedicine network TRANSIT-Stroke incl. research on stroke epidemiology (collaboration Prof. Heuschmann, IKE-B); interdisciplinary neurovascular board; cerebrovascular outpatient clinic; international treatment trials.

Neuromorphology, Pain Research and Antibody-Associated Neurological Diseases
(C. Sommer, N. Üçeyler)

Pathophysiology of neuropathic and generalized chronic pain with focus on neuro-immune interactions and their molecular regulation (Joint projects TOBeATPAIN, PRUSEARCH, DoloRes); skin biopsies as a diagnostic tool in neurology (neuropathies, M. Parkinson); pathophysiology of neuropathies and small fibre pathology among others in M. Fabry and fibromyalgia (Üçeyler et al., 2018); Heisenberg-professorship Translational Somatosensorics (N.Ü.); pathophysiology of antibody-associated disorders of the CNS and PNS (cooperation Prof. Villmann); international trials on treatment of pain and neuropathies.

Experimental Developmental Neurobiology
(R. Martini, J. Groh, D. Klein)

Research is focussed on pathogenic mechanisms underlying aging, genetically-mediated demyelination and neurodegeneration in the central and peripheral nervous system using mouse mutants with spontaneous and genetically engineered defects in myelinating glial cells and other neural cells. Particular emphasis lies on the role of the immune system as "disease amplifier" (Yuan et al., 2018). Consequently, immunomodulation emerges as a novel treatment strategy targeting common effector pathways in aging and disease progression in mouse models of multiple sclerosis, leukodystrophies and storage diseases as well as in hereditary neuropathies. Analysis of pathological alterations by confocal and electron microscopy. Particular focus is on analytical techniques related to clinical translation, such as electronic gait analysis (CatWalk), optical coherence tomography and experimental assessment of visual acuity in mice.

Clinical Neurophysiology and Neuromuscular Disease Center; Motor Neuron Disorders
(D. Zeller, C. Sommer, C.W. Ip)

Neurophysiological examinations in patients with neuromuscular and CNS disorders (> 15,000 single measurements per year); coordination of the Interdisciplinary Neuromuscular Center, participation in the Musculo-Sceletal Center of the University of Würzburg and the Amyloidosis Center Northern Bavaria; mechanisms underlying functional compensation in multiple sclerosis and movement disorders, and body self awareness; collaboration within the German Network for Motoneuron Disorders, studies on ALS therapy (Ludolph et al., 2018) and on SMA therapy with Nusinersen; molecular assessment of disease-modifiers in sporadic and familial ALS (in collaboration with Prof. Sendtner, Institute of Clinical Neurobiology).

Teaching

In the lectures, seminars and curricular courses of general neurology the basics in clinical neurology are taught accompanied by bedside teaching in small groups of students. The Department of Neurology moreover provides special seminars covering differential diagnosis of neurological disorders, neuromuscular diseases and nerve/muscle pathology and participates in numerous interdisciplinary seminars (Anatomy, Physiology, Clinical Chemistry, Biomedicine, Oncology Center, Pain-Curriculum, Psychology, Neurobiology and all classes of the Würzburg International Graduate School of Life Sciences). Teaching languages are German and English.

SELECTED PUBLICATIONS

Frey A, Sell R, Homola GA, Malsch C, Kraft P, Gunreben I, Morbach C, Alkonyi B, Schmid E, Colonna I, Hofer E, Müllges W, Ertl G, Heuschmann P, Solymosi L, Schmidt R, Störk S, Stoll G. (2018) Cognitive deficits and related brain lesions in patients with chronic heart failure. JACC Heart Fail 6:583-592.

Ludolph AC, Schuster J, Dorst J, Dupuis L, Dreyhaupt J, Weishaupt JH, Kassubek J, Weiland U, Petri S, Meyer T, Grosskreutz J, Schrank B, Boentert M, Emmer A, Hermann A, Zeller D, Prudlo J, Winkler AS, Grehl T, Heneka MT, Wollebaek Johannesen S, Goricke B. (2018) Safety and efficacy of rasagiline as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomised, double-blind, parallel-group, placebo-controlled, phase 2 trial. Lancet Neurol 17:681-688.

Musacchio T, Rebenstorff M, Fluri F, Brotchie JM, Volkmann J, Koprich JB, Ip CW. (2017) Subthalamic nucleus deep brain stimulation is neuroprotective in the A53T alpha-synuclein Parkinson's disease rat model. Ann Neurol 81:825-836.

Üçeyler N, Vollert J, Broll B, Riediger N, Langjahr M, Saffer N, Schubert AL, Siedler G, Sommer C. (2018) Sensory profiles and skin innervation of patients with painful and painless neuropathies. Pain 159:1867-1876.

Yuan X, Klein D, Kerscher S, West BL, Weis J, Katona I, Martini R. (2018) Macrophage depletion ameliorates peripheral neuropathy in aging mice. J Neurosci 38:4610-4620.

Department of Psychiatry, Psychosomatics and Psychotherapy

CONTACT DETAILS

Professor Dr. med. Jürgen Deckert
(Head of the Department)

Margarete-Höppel-Platz 1
97080 Würzburg
Phone: 0931/201-77010
Fax: 0931/201-77020
E-mail: PS_Sekr@ukw.de
www.ukw.de/psychiatrie

Professor Dr. med. Klaus-Peter Lesch
(Chair of Molecular Psychiatry)
Phone: 0931/201-77610

Professor Dr. rer. nat. Ulrike Lüken
(until 12/2017)

Professor Dr. rer. nat. Grit Hein
(since 10/2017)
Phone: 0931/201-77411

Professor Dr. med. Manuel Mattheisen
(since 11/2017)
Phone: 0931/201-76370

Professor Dr. med. Martin Krupinski
(Head of Division of Forensic Psychiatry)
Phone: 0931/201-77500

Mission and Structure

The department of Psychiatry, Psychosomatics and Psychotherapy (PPP) as part of the Center of Mental Health at the UKWürzburg (UKW) offers comprehensive out-patient, day-care and in-patient diagnostic and therapeutic services for all mental (psychiatric and psychosomatic) disorders. The therapeutic focus of the clinic is on affective disorders and psychoses of the schizophrenia spectrum, but also on dementias and substance abuse disorders, as well as anxiety disorders and adult attention deficit/hyperactivity disorder. Specialized out-patient services as part of the outpatient clinic - also on autism and chromosome 22q11.2 syndrome - as well as 55 day-care therapy slots for psychiatric, psychosomatic and neurogerontopsychiatric disorders complement the 145 in-patient therapy slots with two intensive care units and units specialized on affective disorders (bipolar depression and treatment-resistant depression), psychotic disorders, substance abuse therapy and psychotherapy. Specialized diagnostic and therapeutic options are provided by the laboratory of therapeutic drug monitoring and the laboratory of psychophysiology. Basic and animal model research is performed at the chair of molecular psychiatry. The integrated division of forensic psychiatry provides expert opinions on legal aspects of mental disorders.

Major Research Interests

The research activities of the clinic are characterized by their interdisciplinarity with research groups of psychiatrists, psychologists and biologists and their internationality which is reflected not only by its cooperations, but also by its researchers who come from the Netherlands, Estonia, Spain, Italy, Bosnia, Russia, Turkey, Chile, Columbia, Nigeria, Tanzania, Japan and China. Close ooperations at the level of the UKW exist in the context of the SFB TR 58, the GK 1253, the GSLS, the IZKF, the CSP Union-CVD, the DHZI and the ZESE, at the national level in the context of cooperations with institutes of the Max-Planck Society, the Helmholtz Society and participation in BMBF programs for Panic Disorder, Depression and Frontotemporal Lobe Dementia and as core laboratory of BfARM-networks on Therapeutic Drug Monitoring. At the international level, the PPP participates in cooperations with the NIMH and Kings College and takes part in international research collaborations such as the Enigma Anxiety Consortium, Psychiatric GWAS Consortia leading the anxiety and obsessive-compulsive disorder consortia as well as EU networks on anxiety disorders and affective disorders. Of special importance is the close cooperation with the department of child and adolescent psychiatry, psychosomatics and psychotherapy to allow for studies on developmental aspects and prevention of mental disorders.

The interdisciplinarity and internationality, but also the developmental and preventive aspects were recently formalized by the foundation of the Center of Mental Health with members of the University Hospital and the University of Würzburg as well as an international scientific advisory board (figure 1), the scientific focus by establishing a Comprehensive Anxiety Center with a national network of scientists and an A-Center on Anxiety Disorders with a regional network of hospitals and practitioners.

Methodological approaches on the basis of differentiated clinical and neuropsychological diagnostic procedures cover a broad range from psychopysiological and modern imaging approaches such as near infrared spectroscopy and functional magnetic resonance tomography (in cooperation with the department of neuroradiology, the research center Magnet-

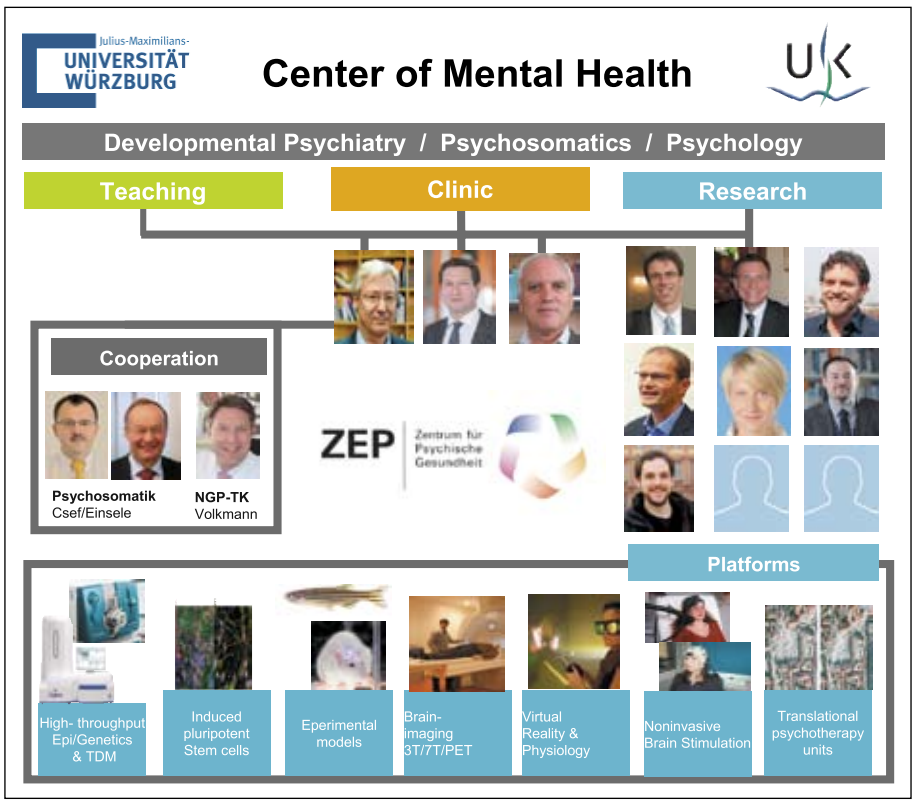


Fig. 1: Center of Mental Health of the University Hospital and University of Würzburg 12/2018.

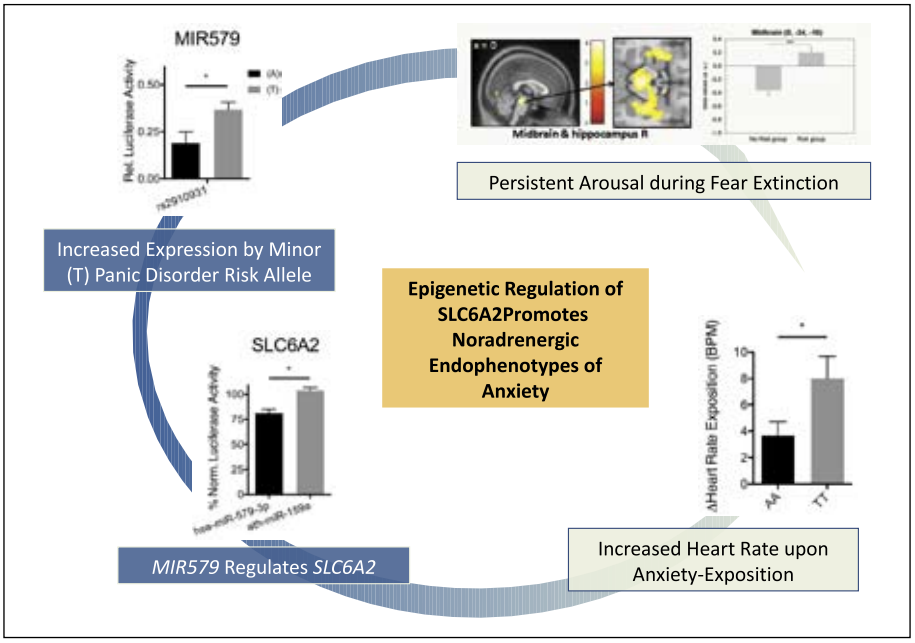


Fig. 2: Role of mikroRNA hsa-miR-573-39 for noradrenergic regulation of fear and anxiety (kindly provided by LG Hommers based on Hommers et al. 2018).

Resonanz-Bayern e.V. and the institute of psychology I) over modern methods of genomics and proteomics such as high throughput genotyping (core facility genetics in cooperation with the institute of clinical biochemistry and the institute of human genetics as well as the core unit systems medicine) and their combination in the context of imaging genomics up to cell culture and animal models, in particular knockout and transgenic mouse models (in cooperation with the Institute of Clinical Neurobiology, the ZEMM and the Biocenter).

For clinical studies according to GCP guidelines a specialized clinical studies group was established (J. Deckert, K. Domschke, M. Gawlik, U. Lüken, A. Menke, T. Polak, S. Unterecker, B. Warrings), which cooperates closely with the ZKS. The signature of the department is the close interaction between translational research laboratories of the PPP, such as the laboratories on Molecular Psychiatry, Psychiatric Neurobiology, Functional Genomics (K.-P. Lesch, A. Reif, K. Domschke), Functiona Neuroanatomy Research (A. Schmitt) and Psychophysiology & Functional Imaging (M.J. Herrmann, U. Lüken) with the clinical research groups of the department on one hand and core facilities of the UKW and external research facilities on the other hand. Research topics include clinical neuroscience aspects such as the therapy including psychotherapy and noninvasive stimulation therapies of mental disorders, translational aspects such as the pathogenesis of mental disorders including the functional characterization of the identified pathomechanisms by means of modern imaging techniques and animal models as well as basic neuroscience aspects such as emotional and cognitive processes, gene-environment-interactions, epigenetics such as methylation processes and regulatory mRNAs, neuronal plasticity, adult neurogenesis and induced pluripotent stem cells.

This research focus on anxiety and affective disorders represented by J.Deckert, K.P. Lesch and U.Lüken in the context of the SFB TR 58, the GK1253, the CSP Union-CVD and the DZHI was supported by the recruitment of G.Hein as W2-professor of Translational Neuroscience and M.Mattheisen as W2-professor as W2 professor of Psychiatric Genetics and Epigenetics as well as the association of established scientists such as Prof. D.vandenHove from Maastricht and Prof. S.Meier from Halifax in double affilations.

The main research topics thus are:

- Markers for early diagnosis and innovative preventive and therapeutic as well as personalized approaches in anxiety disorders, affective disorders, dementias, adult ADHD, and rare disorders (Herrmann et al. 2017).
- Identification of (epi)genetic factors in anxiety disorders, affective disorders, demenatias, adult ADHD and rare syndromes (Hommers et al. 2018, figure 2; Wray et al. 2018).
- Imaging of emotional and cognitive processes in adults, adolescents and children with a focus on social interactions and in close cooperation with the department of child and adolescent psychiatry, psychosomatics and psychotherapy (Lüken et al. 2017).
- Gene-environment-interactions, neuronal plasticity, adult neurogenesis and induced pluripotent stem cells in humans and in rodent models (Sun et al. 2018).

Teaching

An integrated lecture and course on psychiatry and psychosomatics are organized and held by the PPP in cooperation with the KJPPP and other departments and institutes. They are complemented by novel E-learning courses in the context of the VHB Bayern (M.Lauer). Special curricular seminars are provided for interns and students. In addition to the curricular lecture and course for medical students the PPP also provides curricular lectures and courses for students of biomedicine, biology, psychology and logopedics. Extracurricular seminars are offered to graduate students of medicine, experimental medicine, biology, psychology and law. J. Deckert is on the board of the postgraduate psychotherapy studies of the psychology institute and has contributed to the development of the Orpheus-AMSE-WMFE Guidelines for MDPD programs. To facilitate further internationalization in close cooperation with the institute of clinical neurobiology since 2015 an international Elite Master in Translational Neuroscience is offered in English.

SELECTED PUBLICATIONS

Herrmann MJ, Katzorke A, Busch Y, Gromer D, Polak T, Pauli P, Deckert J. (2017) Medial prefrontal cortex stimulation accelerates therapy response of exposure therapy in acrophobia. Brain Stimul 10:291-297.

Hommers LG, Richter J, Yang Y, ... Lohse MJ, Lueken U, Deckert J. (2018) A functional genetic variation of SLC6A2 repressor hsa-miR-579-3p upregulates sympathetic noradrenergic processes of fear and anxiety. Transl Psychiatry 8:226.

Lueken U, Kuhn M, Yang Y, ... Domschke K, Deckert J, Lonsdorf TB. (2017) Modulation of defensive reactivity by GLRB allelic variation: converging evidence from an intermediate phenotype approach. Transl Psychiatry 7:e1227.

Sun P, Ortega G, Tan Y, Hua Q, Riederer PF, Deckert J, Schmitt-Böhrer AG. (2018) Streptozotocin Impairs Proliferation and Differentiation of Adult Hippocampal Neural Stem Cells in Vitro-Correlation With Alterations in the Expression of Proteins Associated With the Insulin System. Front Aging Neurosci 10:145.

Wray NR, Ripke S, Mattheisen M, ..., Breen G, Børglum AD, Sullivan PF; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. (2018) Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet 50:668-681.

Division of Molecular Psychiatry

CONTACT DETAILS

Professor Dr. med. Klaus-Peter Lesch (Chair)

Margarete-Höppel-Platz 1
97080 Würzburg, Germany
Phone: 0931/201-77600
Fax: 0931/201-77620
E-mail: kplesch@mail.uni-wuerzburg.de
www.ukw.de/forschung-lehre/lehrstuhl-fuer-molekulare-psychiatrie

Mission and Structure

The Division of Molecular Psychiatry with the Research Unit on Disorders of Neurodevelopment and Cognition in conjunction with the Laboratory of Translational Neuroscience as part of the Center of Mental Health at the UK-Würzburg (UKW) is leading in its field with an outstanding track record in psychiatric neuroscience research at the boundary between molecular genetics, cellular neurobiology and behaviour. Interdisciplinary and translational research strategies are employed to elucidate the pathogenesis of neurodevelopmental and a wide spectrum of life-spanning psychiatric disorders, ranging from depression and anxiety, psychotic and neurodegenerative disorders, to attention-deficit/hyperactivity, autism spectrum and substance use disorders (Kiser et al. 2015). Finally, mechanisms of pharmacologic and psychotherapeutic treatments are studied.

To elucidate mechanisms of pathologically altered synaptic plasticity (synaptopathy), intraneuronal signaling (neuronal dysregulation) and interneuronal communication (system dysfunction) as well as their impact on the pathophysiology of psychiatric disease, the work uncompromisingly integrates pertinent research strategies. The long-term aim is to identify convergent pathways which could selectively be targeted by novel treatments (precision medicine). It accommodates core competences with unique methodological portfolios complementary to participating national and international collaborators.

Broad experience in the design, generation and phenotyping of genetically modified mice and zebrafish allows the identification of factors that act as determinants of vulnerability to a spectrum of disorders. Each approach to pathophysiological mechanisms is using cutting edge and innovative methodology: Animal models are phenotyped at a behavioral level using a validated set of paradigms and at molecular, cellular and systems levels using, morphological techniques optogenetic/ electrophysiologic recordings in brain slices as well as transcriptomic/ epigenetic profiling and morpho-functional ultrahigh-field MRI.

Moreover, there is an increasingly successful track record in the search for functionally relevant common and rare variation in risk genes for psychiatric disorders by conducting genome-wide association studies and whole-exome/ genome sequencing in large cohorts and multiplex families segregating various unique neurodevelopmental disorders and psychiatric syndromes. Finally, the areas of convergence between the fields of neuropsychology, psycho- and neurobiology as well as child, adolescent and adult psychiatry are strengthening the connections between the individual disciplines by establishing and maintaining research groups, who are investigating mutual topics. In that, a unique environment for the study of the molecular and neural foundations in the etiopathogenesis and long-term course of neuropsychiatric disease has been put into practice.

Major Research Interests

The overarching aim is to find pathways to "precision medicine" for psychiatry through understanding molecular and neuronal pathomechanisms of common disorders. The starting point for this is defined by the pertinent concept of neurodevelopmental and psychiatric disorders as synaptopathies. The strategy is that preclinical and clinically oriented research groups jointly work on molecular genetic and neurobiological essentials of brain function and specific molecular mechanisms of neuronal cell activity as well as on the structural-functional basis of psychiatric disorder-related complex behaviour. Predictors/ biomarkers and differential strategies for innovative therapy during the long-term course of illness are also developed. Specifically, the goal comprises 1) a translational axis for endophenotypic profiling of neurodevelopmental/ psychiatric disease in behavioural, (epi)genetic and neurophysiologic terms, and 2) a platform for the elucidation of pathogenetic brain mechanisms and thereby the development of personalised therapies for neurodevelopmental/ psychiatric disease and their comorbidities. In order to achieve this goal the following primary objectives are pursued:

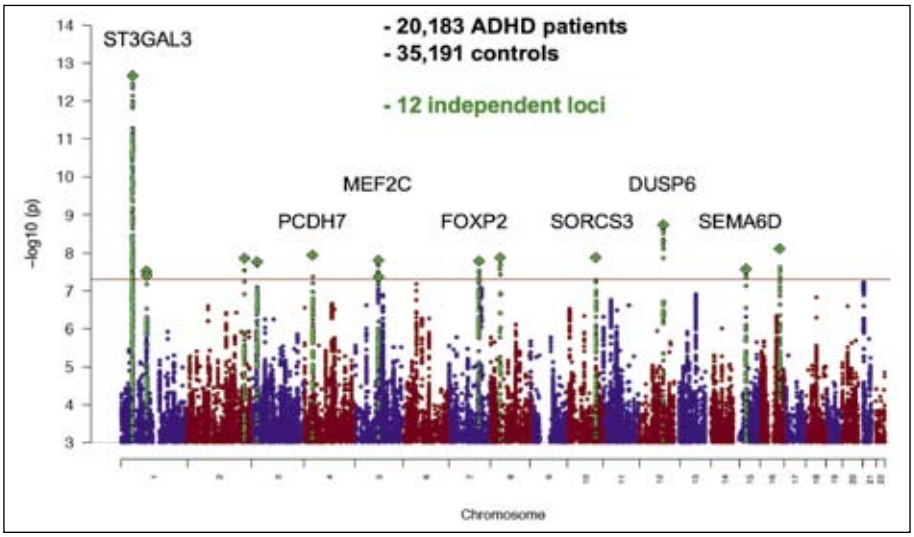


Fig. 1: Manhatten plot of genome-wide association (GWAS) meta-analysis of attention deficit/ hyperactivity disorder (ADHD). Variants surpassing genome-wide significance in 12 independent chromosomal loci reveal new information about the underlying neurobiology of ADHD (Demontis et al. 2019).

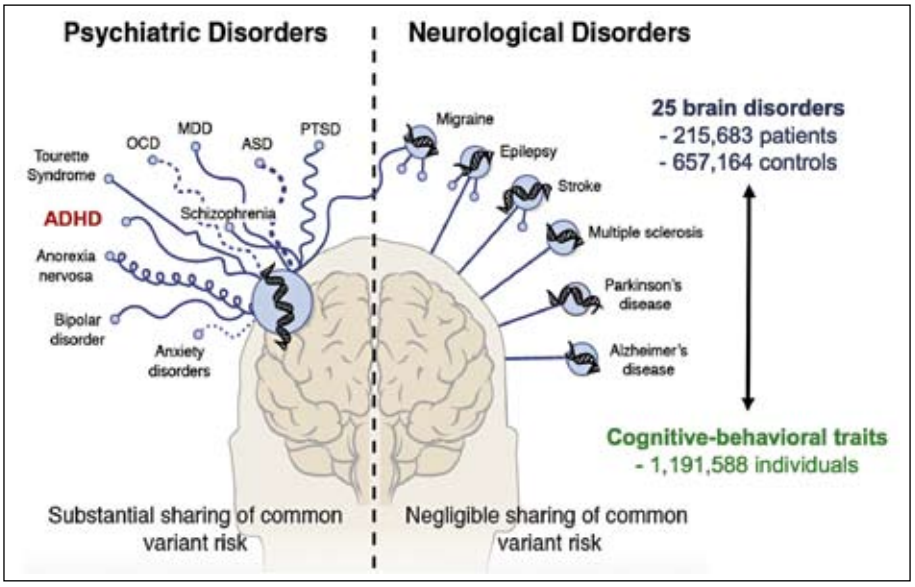


Fig. 2: Shared heritability in 25 disorders of the brain. Psychiatric disorders, including attention deficit/hyperactivity disorder (ADHD), share common variant risk, while neurological disorders appear more distinct from one another and from the psychiatric disorders. There is also significant sharing between disorders and various brain phenotypes, including cognitive measures (The Brainstorm Consortium 2018).

- Identification of common and rare variation in risk genes using genome-wide approaches (GWAS, CNV screening, whole-exome/genome sequencing), preferentially in large data sets of clinical cohorts (The Brainstorm Consortium 2018; Demontis et al. 2019) (Fig. 1 und 2) as well as in multiplex families with high density of ADHD, psychotic and bipolar disorder (Corominas et al. 2018).
- Validation of genetic findings and integrative genomic approaches through advances in the development of model systems of increasing complexity by combining (epi-)genetics approaches with bioinformatics, mutation-specific iPSC lines and animal models (targeted gene modification in mouse and zebrafish) to understand disease mechanisms.
- Integration of gene expression-neuroimaging-cognition data sets of well characterised cohorts and extended pedigrees to bridge the gap between genome-wide screenings and testable pathophysiological hypotheses and to push forward the understanding of the neurobiology leading from gene to cognitive dysfunction and disease.
- Investigation of epigenetic programming by early-life stressors in genetically modified mouse models subjected to maternal deprivation und andere Stressoren (GxE mouse models) that simulate neurobehavioural characteristics of psychiatric disorders (e.g. 5-Htt, Tph2, Cdh13 and Lphn3 knockout mouse models).
- Translation of novel epigenetically regulated psychiatric disease-related risk genes derived from GxE mouse models in human cohorts characterised for environmental adversity that exhibit disease-associated traits/behaviour and determine their utility as biomarkers.
- Investigation of the link between excitatory-inhibitory dysbalance and impaired synaptic plasticity. These mechanisms require meticulous dissection at several levels of complexity to pinpoint dysfunction related to disease mechanisms, using cellular (iPSCs), *in vivo* animal models and neural systems using neuroimaging.
- Exploration of alternative disease definition based on the discovery of molecular, cellular and system-related disease mechanisms for various neurodevelopmental/psychiatric disorders, that are currently primarily defined by symptoms, rather than by aetiology. Finally, work towards precision treatment has been initiated: use novel cognitive assessments to evaluate non-pharmacological treatment options, in addition to developing new compounds for pharmacological treatment optimisation and individualisation.

The basis for the pursuit of these objectives is the interdisciplinary composition of the group and its integration into a wide spectrum of local, national and international collaborations (e.g. DFG Transregio 58, ERA-NET Neuron/BMBF, Aggressotype, Eat2BeNICE, MiND, IMpACT).

Teaching

Integrated lectures and courses on molecular psychobiology and psychiatric neurosciences are offered. Extracurricular and special seminars are provided for interns, Bachelor, Master and Ph.D. students of medicine, biomedicine, psychology and biology.

SELECTED PUBLICATIONS

Bodden C, van den Hove D, Lesch KP, Sachser N. (2017) Impact of varying social experiences during life history on behaviour, gene expression, and vasopressin receptor gene methylation in mice. Sci Rep 7:8719.

Corominas J, Klein M, Zayats T, Rivero O, Ziegler G, Pauper M, Neveling K, Poelmans G, Jansch C, Svirin E, Geissler J, Weber H, Reif A, ..., Franke B, Lesch KP. (2018) Identification of ADHD risk genes in extended pedigrees by combining linkage analysis and whole-exome sequencing. Mol Psychiatry, Aug 16 [Epub ahead of print]

Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, Baldursson G, Belliveau R, ..., Langley K, Lesch KP, Middeldorp C, Reif A, ..., Faraone SV, Børglum AD, Neale BM. (2019) Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 51:63-75.

Jansch J, Günther K, Waider J, Ziegler G, Svirin E, Pühringer D, Kwok CK, Ullmann R, Maierhofer A, Flunkert J, Haaf T, Edenhofer F, Lesch KP. (2018) Generation of a human induced pluripotent stem cell (iPSC) line from a 51-year-old female with attention-deficit/hyperactivity disorder (ADHD) carrying a duplication of SLC2A3. Stem Cell Res 28:136-140.

The Brainstorm Consortium, Anttila V, Bulik-Sullivan B, Finucane HK, ..., Reif A, Lesch KP, Freitag C, Rivero O, ..., Edenberg HJ, Murray R. (2018) Analysis of shared heritability in common disorders of the brain. Science 360:1313-1314.

Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy

CONTACT DETAILS

Professor Dr. med. Marcel Romanos
(Head of the Department)

Margarete-Höppel-Platz 1
97080 Würzburg
Phone: 0931/201-78000
Fax: 0931/201-78040
E-mail: info@kjp.uni-wuerzburg.de
www.kjp.ukw.de

Mission and Structure

The Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy provides care for patients up to the age of 18 years who are affected by the whole spectrum of mental disorders. The department consists of 2 open in-patient units, each with 16 beds, an out-patient unit, a closed ward (14 beds), the „Klinik am Greinberg“ (responsible body Bezirk Unterfranken with 14 and 15 beds, respectively), and a day clinic (funding body Diakonia with 14 beds). In addition, there is a parent pavilion (funding body Verein Menschenskinder e.V.) and since 2014 the therapy house „Sternstunden“. The department cooperates with the Wichernschool and Graf-zu-Bentheim-school. A neurobiological laboratory and a laboratory for therapeutic drug monitoring have been set up for research as a joint institution with the Department of Psychiatry, Psychosomatics and Psychotherapy. Therapeutic measures comprise such therapies as behavioural and dialectic-behavioural therapy, cognitive therapy, systemic family therapy, occupational therapy, physiotherapy, speech therapy, music therapy, art therapy, and animal assisted therapy and many more. The staff consists of a total of 140 persons, of which 24 are medical physicians, 14 psychologists, 6 medical technicians, 13 therapeutic practitioners, 11 secretaries, and 75 nurses. In all sections of the department, the utilization is 100 % and about 2500 patients per year are treated in the out-patient unit.

Research Projects

Anxiety Disorders

(M. Romanos, J. Reinhard)

Within the SFB TRR 58 (Collaborative Research Center Anxiety) the department is part of the subproject Z02 in cooperation with the adult psychiatry (Prof. Deckert) and the Institute of Biological Psychology (Prof. Pauli). We were able to show that healthy children between 8 and 12 years display stronger generalization compared to healthy adults. Furthermore, generalization is correlated with dimensional anxious traits. Currently, we continue to study the cohort longitudinally and check to what extent a boosted fear generalization influences the predisposition or development of anxiety disorders. At this stage we have started to recruit clinical cohorts with pathological anxiety forms.

Autism Spectrum Disorders

(R. Taurines, T. Jans, J. Geissler, A. Leben)

In a DFG-funded clinical randomized multicentre study (A-FFIP) an intensive early intervention in children with autism aged 2-5 years is examined for its effectiveness in Würzburg as one of four locations in Germany. A proof of efficacy of this intervention will significantly improve the treatment options for this patient group. In a BMBF-funded randomized-controlled multicentre study (ASD-Net) we assess to what extent the effectiveness of a group training for adolescents with autism can be increased by the administration of the hormone oxytocin.

Attention-Deficit /Hyperactivity Disorder (ADHD)

(M. Romanos, J. Geissler, T. Jans)

With the DFG-funded Clinical Research Unit KFO 125 (2004-2012) and the BMBF-funded psychotherapy study ADHD-Net expertise in large studies on ADHD exists in Würzburg for many years. In the Framework of the national BMBF psychotherapy networks the ESCAlife consortium consists of four multicentre randomized clinical trials with significant participation of the KJPPP. In the consortium a total of 1200 patients with ADHD of different age groups are examined in a demanding stepped-care approach within a randomized-controlled design. The study will be completed in 2020. In a cross-sectional project (ESCAmark) guided by the KJPPP and the ZI Mannheim we collect blood and saliva for the identification of therapeutic relevant biomarkers.

Biomarkers

(J. Geissler, R. Taurines, C. Drepper, M. Romanos, M. Gerlach)

A biological marker is defined as a characteristic feature, which, after validation, serves to measure normal biological and pathogenic processes. It can also serve to measure the pharmacological responsiveness to therapeutic interventions. Using different methods (such as real-time PCR, proteomics, epigenetics, olfactory tests, transcranial sonography) potential measurement parameters are evaluated as biomarkers in order to achieve a significant improvement in the diagnosis and personalized treatment of psychiatric diseases.

Pharmacovigilance and Therapeutic Drug Monitoring

(K. Egberts, S. Fekete, S.-Y. Dang, T. Vloet, R. Taurines, M. Romanos, M. Gerlach)

As a national pharmacovigilance center under the leadership of the KJPPP, the multicentre project TDMVIGIL (funded by the BfArM) systematically records the prescription behaviour of off-label psychotropic drugs, evaluates the benefit-risk balance of drugs and adverse drug reactions and minimizes risks through the use of therapeutic drug monitoring (TDM). We included more than 700 patients treated with antipsychotics and antidepressants and 500 patients receiving stimulant medication in the registry study at more than 20 sites in Germany, Austria and Switzerland. The study will be completed in mid-2019. The KIDsafe network project, funded by the Innovation Fund, introduces a drug information system in various regions of Germany

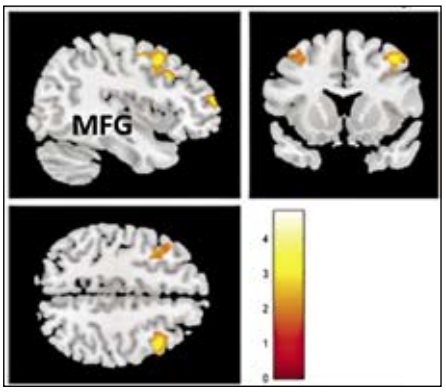


Fig. 1: Forty children and adolescents aged 10-14 years were studied using a fMRI generalization paradigm. Prefrontal activation as an expression of inhibiting top-down regulation (anxiety control) correlated positively with the age of the subjects (J. Reinhard, S. Neufang)

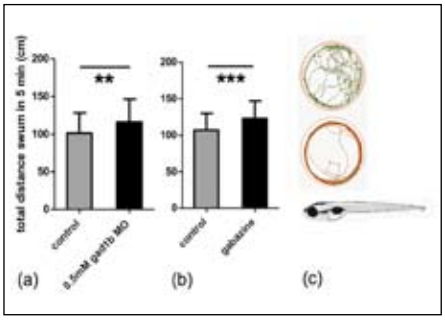


Fig. 2: Increased motor activity of zebrafish larvae as a model for hyperactive symptom dimensions in ADHD: (a) Mutant with transient knockdown of the ADHD candidate gene gad1b, which converts glutamate to GABA. (b) Wild type animals with pharmacological blockade of GABA receptors. (c) Plot of motor activity of zebrafish larvae measured with the ZebraBox. Top wild type, bottom mutant.

to reduce the rate of adverse effect-related hospitalization in paediatric hospitals. The KJPPP Würzburg is the only child and adolescent psychiatric consortium partner in the network and investigates in a subproject the applicability of the information system to the psychopharmacological treatment of children and adolescents.

Developmental Neuroimaging
(S. Neufang, A. Akrif)

The AG Developmental Neuroimaging focuses on the examination of brain organic maturation and the development of cognitive skills. For this purpose, functional imaging methods such as e.g. fMRI (task and resting state fMRI) and structural MRI (morphometric studies, DTI) are applied. The AG is active in various projects, e.g. within the framework of the SFB TRR 58, IZKF-funded projects and network studies funded by the BMBF. The AG will be realigned in 2019 by the appointment of a new W2 professorship for Experimental Neurosciences in Developmental Psychiatry.

Developmental Psychiatric Neurobiology
(C. Lillesaar, C. Drepper, M. Romanos)

The AG Developmental Psychiatric Neurobiology is dedicated to the development of biological models of neuropsychiatric diseases using the developmental animal model zebrafish. Due to the increasing identification of disease-associated gene variants in humans, the functional characterization of these variants in the model organism becomes essential for the understanding of the involved pathomechanism. The IZKF funded project (IZKF N-320) has developed zebrafish models that allows the functional study of genetic characteristics from larval-stage to adult. The group uses, among others, the CRISPR / CAS9 methodology, behavioural investigations and various laboratory analysis techniques to study CNS structural and neurochemical changes.

Centre Deletion Syndrome 22q11.2 (ZEDE 22q11)
(M. Romanos, M. Mattheisen, M. Fischer, J. Deckert)

The deletion syndrome 22q11.2 (DS22q11) is the most common human deletion and represents a high-risk syndrome for somatic and psychiatric disorders. For almost 15 years, the clinic has been cooperating with the national self-help association Kids-22q11 e.V. In the centre ZEDE 22q11, founded in 2018, an interdisciplinary care provision will be established. In various research projects mechanisms of psychiatric and somatic disease mechanisms are investigated.

Intellectual Disability
(M. Romanos, C. Ratz)

In cooperation with the chair of Special Education for Intellectual Disabilities (Prof. Ratz), we are conducting research into inpatient facilities within the scope of the REDUGIA project with the support of the Bavarian Ministry of Social Affairs with the aim of reducing freedom-removing measures in children and adolescents with intellectual disability and mental illness.

Teaching

In its role as interface study programme, our department is involved in the training of medical doctors, bio-medicine students, psychologists, educators, biologists, and medical and nursing professions. The interdisciplinary curricular lectures for physicians are carried out jointly by representatives of adult psychiatry, our department, medical psychology and the departments of medical clinics. For medical students, elective courses, a block course or semester internships are offered. Furthermore, there is an extensive curricular teaching export to psychology and special education. The department offers several seminars within the master's program "Translational Neuroscience"

SELECTED PUBLICATIONS

Anttila V, Bulik-Sullivan B, Finucane HK, Walter RK, Bras J, Duncan L, Escott-Price V, Falcone GJ, Gormley P, Malik R, Patsopoulos NA, Ripke S, Wei Z, Yu D, Lee PH, Turley P, Grenier-Boley B, Chouraki V, Kamatani Y, Berr C, Letenneur L, Romanos M et al. (2018) Analysis of shared heritability in common disorders of the brain. Science 360:1313.

Albantakis L, Egberts K, Burger R, Kulpok C, Mehler-Wex C, Taurines R, Unterecker S, Wewetzer C, Romanos M, Gerlach M. (2017) Relationship between daily dose, serum concentration and clinical response to quetiapine in children and adolescents with psychotic and mood disorders. Pharmacopsychiatry 50:248-255.

Banaschewski T, Becker K, Döpfner M, Holtmann M, Rösler M, Romanos M. (2017) Attention-Deficit/Hyperactivity Disorder. Dtsch Arztebl Int 114:149-159.

Domschke K, Akhrif A, Romanos M, Bajer C, Mainusch M, Winkelmann J, Zimmer C, Neufang S. (2017) Neuropeptide S receptor gene variation differentially modulates fronto-limbic effective connectivity in childhood and adolescence. Cereb Cortex 27:554-566.

Geißler J, Jans T, Banaschewski T, Becker K, Renner T, Brandeis D, Dopfner M, Dose C, Hautmann C, Holtmann M, Jenker C, Millenet S, Romanos M. (2018) Individualised short-therm therapy for adolescents impaired by attention- deficit/hyperactivitiy disorder despite previous routine care treatment (ESCAadol) – study protocol of a randomised controlled trial within the consortium ESCAlief. Trials 19:254.

Department of Medical Psychology, Psychotherapy, Medical Sociology, and Rehabilitation Research

CONTACT DETAILS

Professor Dr. med. Dr. phil. Hermann Faller
(Head until 3/2019)

Klinikstr. 3
97070 Würzburg
Phone: 0931/318-2713
Fax: 0931/318-27130
E-mail: psychotherapie@uni-wuerzburg.de
www.psychotherapie.uni-wuerzburg.de

Mission and Structure

The focus areas of the Department of Medical Psychology, Psychotherapy, Medical Sociology, and Rehabilitation Research include research, education, and patient care. The research topics comprise psychosocial factors of somatic diseases and processes involved in disease coping and rehabilitation. The department also offers a variety of medical education courses, including "Medical Psychology and Sociology" in the pre-clinical study section and "Psychotherapy and Psychosomatic Medicine" as well as "Rehabilitation" in the clinical section. In the area of patient care, a psychotherapeutic out-patient department and consultation-liaison services for the University Hospital are provided. Several close research co-operations exist with the University Hospital. The department is a member of the Center for Mental Health, the Comprehensive Heart Failure Center and the Comprehensive Cancer Center, with Prof. Faller serving as head of the Psychooncological Service.

Major Research Interests

Psycho-Cardiology

(H. Faller)

Our research, which is performed in cooperation with the Department of Internal Medicine I (Prof. Angermann, Prof. Störk, Prof. Ertl), explores the association of depression with mortality among patients with chronic heart failure. In particular, we evaluated screening tools for depression regarding their potential of identifying patients at increased risk of mortality and rehospitalisation, considering gender effects.

Psycho-Oncology

(H. Faller, M. Schuler, K. Meng)

In one of the largest studies worldwide, which comprised five centers, i.e. Hamburg, Freiburg, Heidelberg, Leipzig, and Würzburg, we determined the prevalence of psychological distress and mental disorders among cancer patients. In this study as well as other multicenter studies carried out in both acute care and rehabilitation, patients' needs for information, psychosocial support and other supportive offers were assessed. A current project performed in oncological rehabilitation aims to explore the reasons why distressed patients do not disclose their distress and supportive needs to their professional care providers.

Patient Education

(H. Faller, K. Meng, A. Reusch, H. Vogel)

Innovative educational concepts aimed at improving coping and self-management have been developed and evaluated for various chronic conditions, including chronic low back pain, coronary artery disease, chronic heart failure, breast cancer, fibromyalgia syndrome, and inflammatory bowel disease. These concepts were designed to improve patient-centeredness through the employment of new didactic methods. In other projects, a generic self-management program and the dissemination of innovative educational programs into routine health care were evaluated. We showed, for the first time, that improved self-management competencies predicted increased health-related quality of life. Currently, modular concepts (e.g. in rheumatology), education programs for different provider groups in medical rehabilitation (e.g., exercise therapists and diet therapists), and online-based aftercare programs are being developed.

Patient-reported Outcomes

(H. Faller, M. Schuler)

A research focus is on the development and psychometric evaluation of self-assessment instruments for health-related quality of life and other patient-reported outcomes, such as self-management skills. Using complex statistical approaches, such as structural equation modelling and network analysis, we evaluated the measuring properties of these instruments.

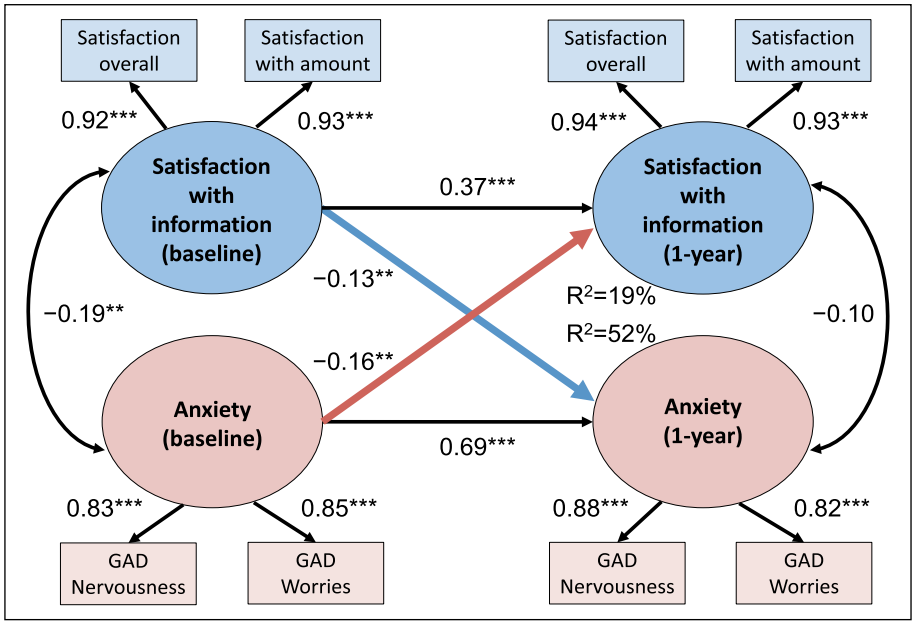


Fig. 1: Bidirectional prospective relationship between information satisfaction and anxiety over 1 year (standardized coefficients; R2=explained variance; Goodness-of-fit indicators: CFI=0.99, RMSEA=0.047, SRMR=0.015). Adapted from: Faller H, Strahl A, Richard M, Niehues C, Meng K (2017) The prospective relationship between satisfaction with information and symptoms of depression and anxiety in breast cancer: A structural equation modeling analysis. Psycho-Oncology 26:1741-1748).

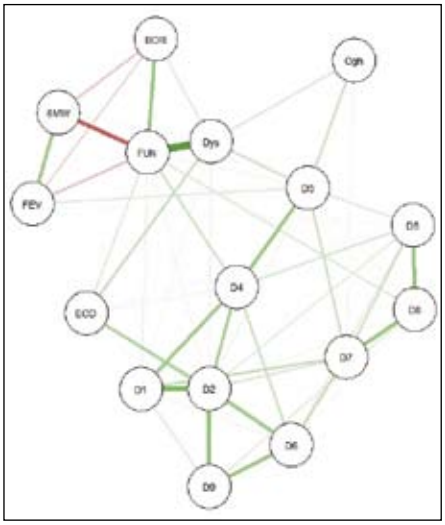


Fig. 2: Partial correlation network among aspects of dyspnea and symptoms of depression (green lines=positive partial correlations; red lines=negative partial correlations). Adapted from: Schuler M, Wittmann M, Faller H, Schultz K (2018) The interrelations among aspects of dyspnea and symptoms of depression in COPD patients – a network analysis. Journal of Affective Disorders 240:33-40).

Psychotherapy Research
(H. Vogel)

Within our outpatient service, an integrated ambulatory health care concept including regional health insurance companies and psychotherapists in private practice has been developed and is being continuously evaluated. Furthermore, we are evaluating the ambulatory psychotherapeutic services of the German Statutory Accident Insurance. In this setting, systems innovations, such as first-line counselling, screening and supervision, are being developed, implemented, and evaluated.

Occupational Rehabilitation
(M. Schuler, M. Lukasczik, H. Vogel)

In medical rehabilitation, patients with vocational impediments are provided special treatments addressing work (so-called work-related interventions). A current project showed that MBOR interventions as performed in routine rehabilitation increased return to work. Further projects deal with the development and evaluation of specific work-related interventions, the classification of work-related treatment programs and the dissemination of benchmark models into routine rehabilitation (www.medizinisch-berufliche-orientierung.de).

Effects of Medical Rehabilitation
(M. Schuler, H. Faller)

A randomized controlled trial using a waitlist control group showed, for the first time worldwide, that inpatient medical rehabilitation for asthma had statistically significant as well as clinically relevant effects on important outcomes, both in the short and medium term. In another project, we currently perform a meta-analysis using both aggregate and individual patient data to examine pre-post changes in main outcomes of medical rehabilitation for various disorders in Germany.

Quality Assurance and Quality Management
(H. Vogel, J. Ahnert, M. Lukasczik)

Quality management programs have been developed for various clinical institutions. These include quality management concepts for medical rehabilitation carried out by the German Statutory Accident Insurance and the development of treatment standards for medical rehabilitation carried out by the German Statutory Pension Insurance. In the context of the guideline program of the German Statutory Pension Insurance, the department is responsible for the field of medical rehabilitation for children and youth.

Social Medicine Assessment
(H. Vogel)

Funded by the German Statutory Pension Insurance, our department for several years has addressed the further development of the social medicine fundamentals of decisions made by the pension insurance concerning access to both rehabilitation and disability pensions. In a current project, research evidence is synthesized for use in developing assessment guidelines. We have structured the disability pension assessment, as a prerequisite for further quality development. Moreover, a concept for quality assurance of the social medicine assessment of the German Statutory Pension Insurance has been developed and evaluated. Finally, new didactic approaches in social medicine education have been tested and evaluated.

Prevention and Health Promotion
(H. Faller, A. Reusch, H. Vogel)

Our department has extended its research on prevention and health promotion. We performed a project on mental risk assessment in cooperation with the German Statutory Accident Insurance, developed and evaluated an educational program for prevention and reduction of smoking in nursing students and are educating teachers in motivational interviewing for tobacco prevention in their students. Currently, our focus is on programs targeting prevention and health promotion offered to students in the region.

Teaching

As part of the subject "Medical Psychology and Medical Sociology", the following classes are provided: Lectures, Courses, and Integrated Seminars/Seminars with Clinical Aspects. An optional seminar "Research Methods and Evaluation (Evidence-Based Medicine)" is also offered. Moreover, the Department coordinates the Lecture "Rehabilitation", offers the Seminar "Rehabilitation Research", and co-teaches the integrated lecture and integrated practical courses "Psychiatry, Psychosomatics, and Psychotherapy". The integration of simulation patients into various parts of the medical curriculum is coordinated. In several research projects, innovative educational methods, such as the use of simulation patients in both medical education and psychotherapy training, are being evaluated.

SELECTED PUBLICATIONS

Faller H, Weis J, Koch U, Brähler E, Härter M, Keller M, Schulz H, Wegscheider K, Boehncke A, Hund B, Reuter K, Richard M, Sehner S, Wittchen HU, Mehnert A. (2017) Utilization of professional psychological care in a large German sample of cancer patients. Psychooncology 26:537–543.

Meng K, Reusch A, Musekamp G, Seekatz B, Zietz B, Steimann G, Altstidl R, Haug G, Worringen U, Faller H. (2018) Self-management education for rehabilitation inpatients: A cluster-randomized controlled trial. Patient Educ Couns 101:1630-1638.

Musekamp G, Schuler M, Seekatz B, Bengel J, Faller H, Meng K. (2017) Does improvement in self-management skills predict improvement in quality of life and depressive symptoms? A prospective study in patients with heart failure up to one year after self-management education. BMC Cardiovasc Disord 17:51.

Piepenburg SM, Faller H, Störk S, Ertl G, Angermann CA. (2019) Symptom patterns and clinical outcomes in women versus men with systolic heart failure and depression. Clin Res Cardiol 108:244-253.

Schuler M, Strohmayer M, Mühlig S, Schwaighofer M, Wittmann M, Faller H, Schultz K. (2018) Assessment of depression before and after inpatient rehabilitation in COPD patients: Psychometric properties of the Patient Health Questionnaire (PHQ-9/PHQ-2). J Affect Disord 232:268-275.

Institute of Experimental Biomedicine, Chair of Experimental Biomedicine I

CONTACT DETAILS

Professor Dr. rer. nat. Bernhard Nieswandt (Head of the Institute)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-80405
Fax: 0931/201-61652
E-mail: bernhard.nieswandt@virchow.uni-wuerzburg.de
www.ukw.de/forschung-lehre/institut-fuer-experimentelle-biomedizin/experimentelle-biomedizin-lehrstuhl-i
www.platelets.eu

Professor Dr. rer. nat. Michael Bösl
Phone: 0931/201-44078

Professor Dr. rer. nat. Harald Schulze
Phone: 0931/201-1881622

Mission and Structure

The Chair of Experimental Biomedicine I was established in 2008 as part of the Rudolf Virchow Center for Experimental Biomedicine (RVZ) and is co-funded by the University Hospital Würzburg where it is integrated in the Institute of Experimental Biomedicine. The chair focuses on basic research in the field of cardiovascular diseases and is actively engaged in the education of Bachelor and Master students of Biomedicine. Until the end of 2017, large parts of the research projects were integrated into the Collaborative Research Center 688 (SFB 688) at the University of Würzburg and are since July 2018 associated with the newly founded Collaborative Research Center TransRegio 240 "Platelets" (CRC/TR 240) between Würzburg and Tübingen.

Major Research Interests

Our scientific work focuses on the molecular pathways underlying platelet and immune cell activation in physiological and pathological processes as well as the mechanisms of thrombopoiesis in the bone marrow.
Platelets are anuclear organelle-rich cell fragments derived from bone marrow megakaryocytes that safeguard vascular integrity. Damage of the endothelial layer of blood vessels results in rapid adhesion and activation of platelets at the site of injury, followed by coagulant activity and subsequent formation of fibrin-rich thrombi that seal the wound. These processes are crucial to prevent excessive blood loss (hemostasis), however, in diseased vessels they can lead to complete occlusion and thus to ischemic infarction of vital organs. Our main scientific interest lies in the elucidation of the function of platelet surface receptors and their intracellular signaling pathways in hemostasis as well as thrombotic and inflammatory events. By the use of genetically modified mouse lines that display defined defects in platelet receptors or signaling pathways we aim to investigate the molecular mechanisms that regulate platelet biogenesis, platelet adhesion, activation and interaction with other cells types of the immune system. These experiments serve as a basis for the development of novel therapeutic strategies to treat vascular diseases which are subsequently tested using *in vivo* models of ischemic and inflammatory conditions.

Twinfilin 2a regulates platelet reactivity and turnover in mice

Regulated reorganization of the actin cytoskeleton is a prerequisite for proper platelet production and function. Consequently, defects in proteins controlling actin dynamics have been associated with platelet disorders in humans and mice. Twinfilin 2a (Twf2a) is a small actin-binding protein that inhibits actin filament rearrangements. Even though Twf2a has pronounced effects on actin dynamics *in vitro*, only little was known about its function *in vivo*. We could show that constitutive Twf2a-deficient ($Twf2a^{-/-}$) mice exhibited mild macrothrombocytopenia (reduced platelet count with increased platelet size) due to a markedly accelerated platelet clearance in the spleen, resulting in a pronouncedly decreased life span of circulating platelets *in vivo*. $Twf2a^{-/-}$ platelets showed enhanced activation of integrin GPIIbIIIa, which is essential for the aggregation process, as well as granule release in response to all tested platelet agonists, increased ad-

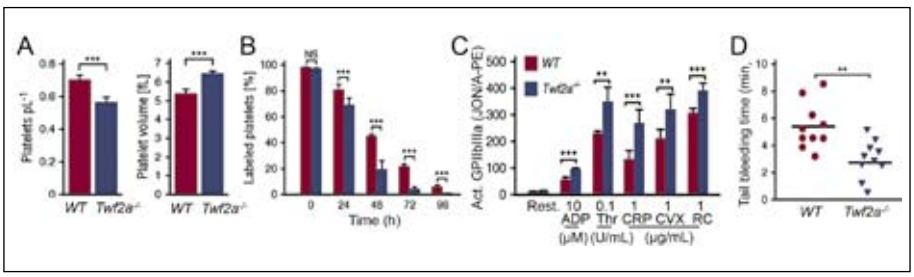


*Fig. 1: Twinfilin 2a regulates platelet turnover and reactivity in mice. (A) Platelet count (left) and size (right) in $Twf2a^{-/-}$ and wildtype (WT) mice were determined with an automated blood cell analyzer. (B) Platelet lifespan was assessed by flow cytometric measurement of the fluorescence-positive platelet population at the indicated time points after injection of a fluorophore-conjugated platelet-specific (GPIX) antibody derivative. (C) Increased integrin GPIIbIIIa activation (JON/A-PE) in $Twf2a^{-/-}$ platelets as determined by flow cytometry. Thr: thrombin, CRP: collagen-related peptide, CVX: convulxin, RC: rhodocytin. (D) Shortened tail bleeding times indicating accelerated hemostatic plug formation in $Twf2a^{-/-}$ mice. Each symbol represents 1 individual. Horizontal lines represent mean. ***P<0.001, **P<0.01.*

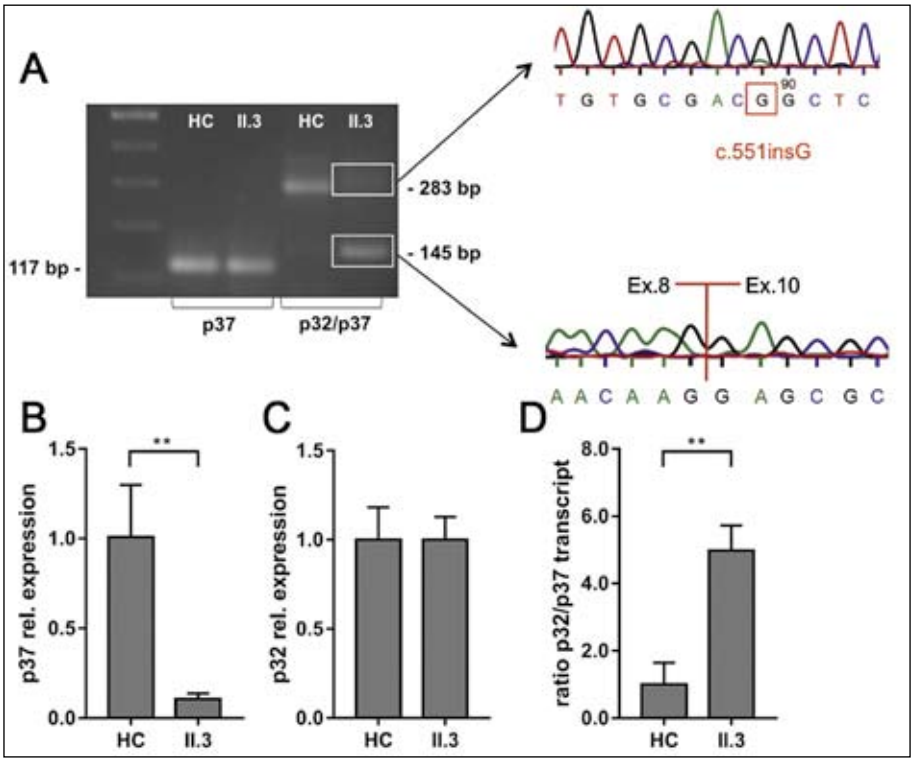


*Fig. 2: The splice-specific mutation leads to loss of GFI1B-p37 in platelets. (A) Agarose-gel showing the GFI1B-p37 transcript (117 bp; left) and a diverse band pattern for one healthy control (HC) and index-patient II.3 after p32/p37 amplification of both GFI1B transcript variants. p37 (283 bp) and p32 (145 bp) bands from the patient were gel-purified, and PCR products were sequenced. Relative expression of (B) GFI1B-p37 and (C) GFI1B-p32 as well as (D) the ratio of p32/p37 transcripts, each comparing 3 healthy controls (HC) to index patient II.3, were analyzed using qPCR. **P<0.01.*

hesion and aggregate formation on a thrombogenic collagen surface under flow, and accelerated spreading on fibrinogen *in vitro*. *In vivo*, Twf2a deficiency resulted in shortened tail bleeding times and shorter occlusion times in experimental models of arterial thrombus formation. The hyperreactivity of Twf2a$^{-/-}$ platelets could be attributed to enhanced actin dynamics, characterized by an increased activity of the actin turnover-regulating proteins n-cofilin and profilin 1. In summary, our results reveal the first *in vivo* functions of mammalian Twf2a and demonstrate that Twf2a-controlled actin rearrangements regulate platelet reactivity and half-life in mice (Stritt *et al.*, Blood 2017).

Recessive grey platelet-like syndrome with unaffected erythropoiesis in the absence of the splice isoform GFI1B-p37.

Genetic mutations or variants in genes that affect platelet biogenesis or function can lead to bleeding. Despite improved diagnostic tools to identify the genetic cause of defective platelet function, for about half of those patients, no clear diagnosis can be given. We developed and implemented a high throughput sequencing approach which allows us to test a panel of up to 60 genes with a known role in platelet production or function. In a Chechen family from Eastern Georgia, whose affected members presented with a severe, life-threatening bleeding diathesis, we identified a novel, homozygous single nucleotide insertion in the zinc finger-based transcription factor *GFI1B*. The frameshift (p.Ser185Leufs*3) is expected to result in the formation of a premature stop codon. The homozygous variant co-segregated with the phenotype, while several unaffected family members were heterozygous, suggesting an autosomal-recessive trait for this gene. Unexpectedly, the shorter splice variant p32 was normally expressed in affected patients, implying that the remaining zinc fingers motifs are sufficient to maintain normal red blood cell production. These findings help to dissect the role of the distinct zinc finger domains in Gfi1-b for their function in platelet biogenesis and function (Schulze *et al.*, Haematologica 2017).

Teaching

The Chair of Experimental Biomedicine is engaged in the education of students in the Bachelor and Master Program in Biomedicine, where we offer lectures, seminars and practical lab courses. All doctoral students are members of the section "Biomedicine" of the "Graduate School of Life Sciences" at the University of Würzburg. The chair regularly participates in the organization of symposia and conferences for medical and natural scientists.

SELECTED PUBLICATIONS

Gupta S, Cherpokova D, Spindler M, Morowski M, Bender M, Nieswandt B. (2018) GPVI signaling is compromised in newly formed platelets after acute thrombocytopenia in mice. Blood 131:1106-1110.

Schulze H, Schlagenhauf A, Manukjan G, Beham-Schmid C, Andres O, Klopocki E, König EM, Haidl H, Panzer S, Althaus K, Muntean WE, Schwinger W, Urban C, Greinacher A, Bakchoul T, Seidel MG. (2017) Recessive grey platelet-like syndrome withunaffected erythropoiesis in the absence of the splice isoform GFI1B-p37. Haematologica 102:e375-e378.

Spindler M, van Eeuwijk JMM, Schurr Y, Nurden P, Nieswandt B, Stegner D, Reinhold A, Bender M. (2018) ADAP deficiency impairs megakaryocyte polarization with ectopic proplatelet release and causes microthrombocytopenia. Blood 132:635-646.

Stegner D, van Eeuwijk JMM, Angay O, Gorelashvili MG, Semeniak D, Pinnecker J, Schmithausen P, Meyer I, Friedrich M, Dütting S, Brede C, Beilhack A, Schulze H, Nieswandt B, Heinze KG. (2017) Thrombopoiesis is spatially regulated by the bone marrow vasculature. Nat Commun 8:127.

Stritt S, Beck S, Becker IC, Vögtle T, Hakala M, Heinze KG, Du X, Bender M, Braun A, Lappalainen P, Nieswandt B. (2017) Twinfilin 2a regulates platelet reactivity and turnover in mice. Blood 130:1746-1756.

Institute of Experimental Biomedicine, Chair of Experimental Biomedicine II

CONTACT DETAILS

Professor Dr. med. Alma Zernecke-Madsen (Head of the Institute)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/201-48331
Fax: 0931/201-648341
E-mail: institut@klin-biochem.uni-wuerzburg.de
www.ukw.de/forschung-lehre/institut-fuer-experimentelle-biomedizin/experimentelle-biomedizin-lehrstuhl-ii

Professor Dr. rer. nat. Michael Zimmer
Phone: 0931/201-48334

Mission and Structure

The Chair of Experimental Biomedicine II at the Institute of Experimental Biomedicine was established in 2014 (previously Chair and Institute of Clinical Biochemistry and Pathobiochemistry). The chair primarily focuses on basic research in the field of cardiovascular diseases and is actively engaged in teaching curricula of different faculties and in postgraduate education. Since 2018, the Chair together with the Interdisciplinary Center of Clinical Research supports a Junior Research Group at the Comprehensive Heart Failure Center led by Clement Cochain, PhD, which further strengthens research in the field of cardiac repair mechanisms. The Humboldt-fellow Maja Bundalo in addition joined the Chair mid-2018 and further supports the research activities in the field of vascular inflammation.

Major Research Interests

Cardiovascular Diseases

Our scientific work focuses on cardiovascular diseases. Atherosclerosis (also known as arteriosclerotic vascular disease) with its clinical manifestations of myocardial infarction, stroke and peripheral artery disease, is imminently becoming the leading cause of death worldwide. Prevention and therapeutic possibilities currently are limited and mainly aim at reducing known risk factors. Likewise, the recovery and preservation of cardiac function following myocardial infarction remain important clinical challenges.

Atherosclerosis is characterized by the continued thickening of the vessel wall, which can lead to the occlusion of blood vessels. Inflammation has emerged as a crucial force driving the initiation and progression of atherosclerotic lesion formation and controlling cardiac repair mechanisms after myocardial infarction and during the myocardial remodelling process. Leukocytes are recruited and accumulate in atherosclerotic lesions and the injured myocardium. Mononuclear cells found in the lesions are predominantly comprised of monocytes/macrophages; but also other immune cells, namely T cells and dendritic cells can be found in the diseased vessel wall and heart. We are investigating the generation and differentiation of immune cells and their recruitment to the inflamed tissue. In particular, the systemic interplay of these mechanisms is of interest. In addition, we investigate the mechanisms and role of different effector molecules such as cytokines, growth factors and RNA molecules by which immune cells control vascular and myocardial diseases.

For instance, we could recently show that the coagulation factor XII plays a critical role in atherosclerosis by directly activating macrophages to secrete pro-inflammatory cytokines. Deficiency in factor XII in atherosclerosis-prone apolipoprotein E-deficient (*Apoe* $^{-/-}$) mice reduced inflammation and atherosclerotic lesion formation in the aortic sinus and aorta (Fig. 1).

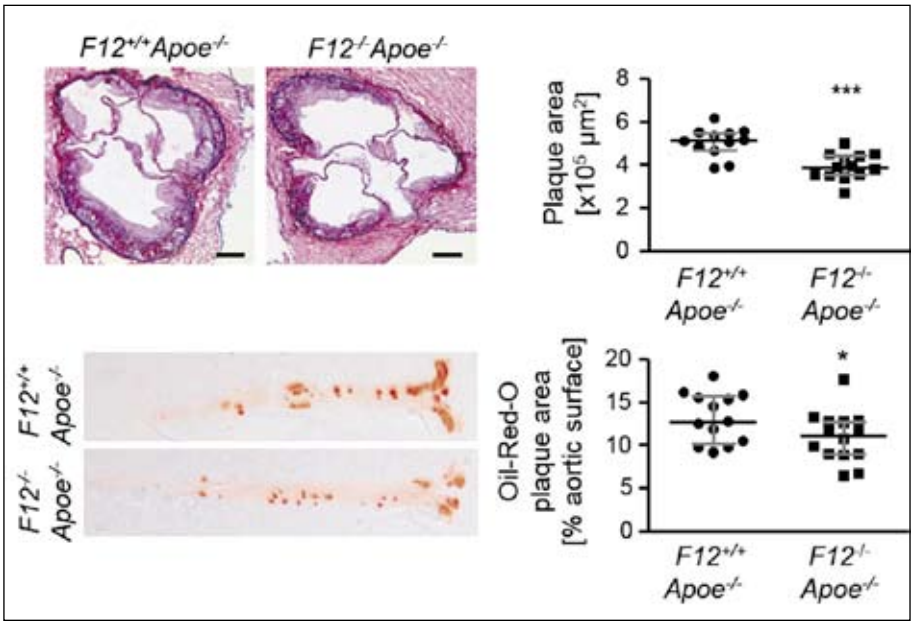


Fig. 1: Atherosclerotic lesion formation was analyzed in atherosclerosis-prone F12 $^{+/+}$*ApoE* $^{-/-}$ *and F12* $^{-/-}$*ApoE* $^{-/-}$ *mice fed a high fat diet for 12 weeks. Quantification of plaque area in Aldehyde-Fuchsin stained aortic root sections (representative sections are shown, scale bars, 200 µm, (top) and in Oil-Red-O stained aortas (representative aortas are shown).*

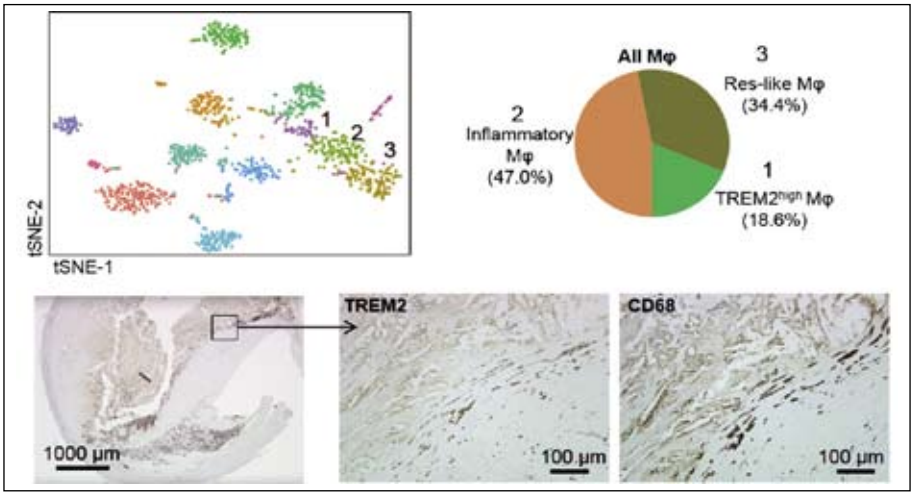


Fig. 2: t-SNE representation of aligned gene expression data in single cells extracted from control and atherosclerotic aortas of atherosclerotic Ldlr $^{-/-}$ mice showing partition into 13 distinct clusters, including macrophage populations 1-3 (top left). Proportions of Inflammatory, Res-like and TREM2hi macrophages (Mϕ) among all macrophages in leukocytes extracted from the aortas of atherosclerosis-prone Ldlr $^{-/-}$ mice after 11 weeks of high fat diet feeding (top right). Immunostaining of the macrophage marker CD68 and of TREM2 in human carotid endarterectomy specimens (bottom).

In addition, we have recently for the first time applied the technology of single-cell RNA sequencing as an unbiased profiling strategy to interrogate and classify aortic immune cells and macrophage heterogeneity at the single-cell level in healthy and atherosclerotic murine aortas from low density lipoprotein receptor-deficient (*Ldlr* $^{-/-}$) mice and could identify three distinct macrophage populations. By their unique gene expression profiles, these macrophages could play specialized roles in atherosclerotic lesion formation. Importantly, among macrophages we could identify a previously unrecognized Trem2hi macrophage population. Notably, the presence of Trem2-expressing macrophages could also be shown in human carotid atherosclerotic lesions (Fig. 2). The exact function of the different macrophage and immune cell populations is currently being addressed.
Elucidating the pathways and a better understanding of the mechanisms underlying cardiovascular diseases is perquisite for the development of novel therapeutic approaches.

In addition, our Chair addresses pathophysiological, genetic and diagnostic aspects in the field of cancer research with a particular focus on the protein LASP-1 in different tumour entities.

Genetics of cardiac diseases
(M. Zimmer)

The group is interested in the genetics of cardiac diseases and cardiomyopathies. Currently, a new disease gene causing dilated cardiomyopathy identified by positional cloning is being studied. Other research areas focus on laminopathies which result from haploinsufficiency of the lamin A/C gene, diagnostics for mutations of DCM genes, and high-throughput SNP-typing using MALDI-TOF/Sequenom technology.

Teaching

The Institute provides teaching in the areas clinical biochemistry, pathobiochemistry, and laboratory medicine. It offers lectures, seminars and practical courses, as well as active participation in research projects as part of bachelor or master theses for undergraduate and graduate students of medicine, biology, pharmacy, and chemistry, including the MD-/PhD-program and the International Graduate School of Life Sciences (GSLS).

SELECTED PUBLICATIONS

Cochain C, Vafadarnejad E, Arampatzi P, Pelisek J, Winkels H, Ley K, Wolf D, Saliba AE, Zernecke A. (2018) Single-Cell RNA-Seq Reveals the Transcriptional Landscape and Heterogeneity of Aortic Macrophages in Murine Atherosclerosis. Circ Res 122:1661-1674.

Glinzer A, Ma X, Prakash J, Kimm MA, Lohöfer F, Kosanke K, Pelisek J, Thon MP, Vorlova S, Heinze KG, Eckstein HH, Gee MW, Ntziachristos V, Zernecke A, Wildgruber M. (2017) Targeting Elastase for Molecular Imaging of Early Atherosclerotic Lesions. Arterioscler Thromb Vasc Biol 37:525-533.

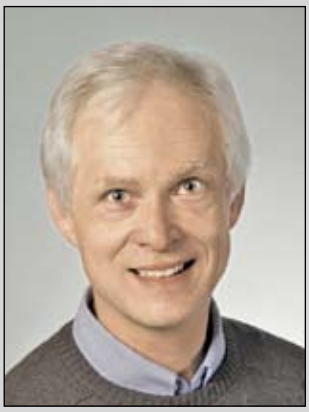
Wildgruber M, Aschenbrenner T, Wendorff H, Czubba M, Glinzer A, Haller B, Schiemann M, Zimmermann A, Berger H, Eckstein HH, Meier R, Wohlgemuth WA, Libby P, Zernecke A. (2016) The „Intermediate" CD14++CD16+ monocyte subset increases in severe peripheral artery disease in humans. Sci Rep 6:39483.

Winkels H, Ehinger E, Vassallo M, Buscher K, Dinh HQ, Kobiyama K, Hamers AAJ, Cochain C, Vafadarnejad E, Saliba AE, Zernecke A, Pramod AB, Ghosh AK, Anto Michel N, Hoppe N, Hilgendorf I, Zirlik A, Hedrick CC, Ley K, Wolf D. (2018) Atlas of the Immune Cell Repertoire in Mouse Atherosclerosis Defined by Single-Cell RNA-Sequencing and Mass Cytometry. Circ Res 122:1675-1688.

Vorlova S, Koch M, Manthey HD, Cochain C, Busch M, Chaudhari SM, Stegner D, Yepes M, Lorenz K, Nolte MW, Nieswandt B, Zernecke A. (2017) Coagulation factor XII induces pro-inflammatory cytokine responses in macrophages and promotes atherosclerosis in mice. Thromb Haemost 117:176-187.

Institute of Clinical Neurobiology, Chair of Clinical Neurobiology – Chair of Systems Neurobiology

CONTACT DETAILS



Professor Dr. med. Michael Sendtner
(Head of Institute, Chair of Clinical Neurobiology)

Professor Dr. rer. nat. Philip Tovote
(Co-Director, Chair of Systems Neurobiology)

Versbacher Str. 5
97078 Würzburg
Phone: 0931/201-44000 (Sendtner)
Fax: 0931/201-44009
E-mail: Sendtner_M@ukw.de
Phone: 0931/201-44052 (Tovote)
Fax: 0931/201-44009
E-mail: Tovote_P@ukw.de
www.ukw.de/forschung-lehre/neurobiologie/institut-fuer-klinische-neurobiologie

Professor Dr. rer. nat. Carmen Villmann
Phone: 0931/201-44035

Mission and Structure

The Institute of Clinical Neurobiology was founded in 2000 as an independent research institute at the University Hospital. Scientific work of the Institute focuses on the cellular and molecular mechanisms of neurodegenerative disorders. The Institute is also involved in sustaining the special unit for motoneuron diseases at the Department of Neurology, in order to allow and ensure the transfer of scientific achievements into clinical applications. With the appointment of Prof. Tovote in 2017, the focus was expanded to systems neurobiology to address research questions in the areas of neural networks for motor control and anxiety that are central focus of clinical and basic research within the Departments for Neurology and Psychiatry. Since 2010, the Institute of Clinical Neurobiology is situated in building E4.

Major Research Interests

Central research focus are pathomechanisms of neurodegenerative motoneuron disorders, such as amyotrophic laterals sclerosis and spinal muscular atrophy, research on neuronal networks for complex brain functions such as anxiety and motor control, and the structure-function relationship in neuropsychiatric disorders caused by mutations in ion channels.

The molecular neurobiology research group guided by Prof. Sendtner works on pathomechanisms of neurodegenerative disorders, in particular motoneuron diseases. Central focus are signaling pathways and cellular mechanisms for neuronal survival, axonal maintenance and plasticity of synapses and axonal connections. For these research lines, new cell culture and mouse models of motoneuron diseases are established. Another focus are the role of neurotrophic factors, in particular Brain-derived neurotrophic factor (BDNF and Ciliary neurotrophic Factor (CNTF) and how these proteins modulate plasticity mechanisms at presymptomatic stages of motoneuron diseases and other neuropsychiatric disorders.

Another research focus is the analysis of the pathophysiology of spinal muscular atrophy, the most common form of motoneuron disease in children. This disease is characterized by axonal defects and defects of neurotransmission at neuromuscular synapses. These defects are due to disturbed transport of mRNAs and also of non-coding RNAs (ncRNAs) in axonal projections of motoneurons. On the basis of these experiments, new therapeutic strategies for this disease can now be developed.

The "Defense Circuits Lab" (DCL) of the Tovote group is interested in the neural networks that underlie fear and anxiety states. Our main aim is to characterize brainstem regions which control, via descending projections, both anxiety behaviors and the function of other body organs important for anxiety reactions, such as the heart. Another focus of our research is on the mechanisms of integrating ascending cardiac information from the periphery into the fear networks of the central nervous system. We conduct systems neuroscience research and combine a variety of observational (e.g., viral neuroanatomical tracings, miniscope calcium imaging) and pertubational (e.g., optogenetics) experimental approaches in freely moving mice.
We work together thematically and personally with the psychiatric clinics (PPP and KJPPP) and collaborate with the Psychological Institute of the University of Würzburg. With the German Center for Heart Failure (DZHI) Würzburg we develop cardiac optogenetics and in cooperation with the neurological clinic in Würzburg we investigate motor networks and their dysregulation in Parkinson's disease, which is often associated with anxiety disorders.

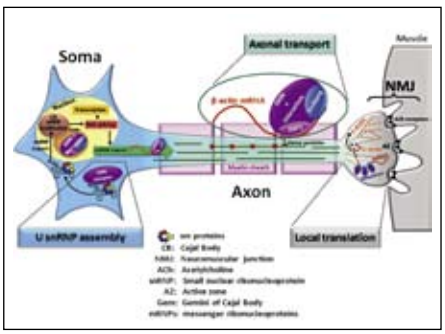


Fig. 1: Schematic representation of SMN protein functions in different subcellular compartments of motoneurons. In the cell body of motoneurons, SMN participates in snRNP assembly. While snRNPs are transported to the nucleus for further processing, SMN and its interaction partner hnRNPR, a β-actin binding protein, reside in the Gemini of Cajal Bodies (Gems). SMN also plays a role in mRNP formation, and together with hnRNPR modulates the transport of mRNPs along the axon. In the presynaptic compartment, SMN is involved in the regulation of local translation, in particular of actin isoforms to maintain the balance between globular and filamentous actin. (Reproduced from Jablonka and Sendtner, Gene Therapy 2017, 1-8)

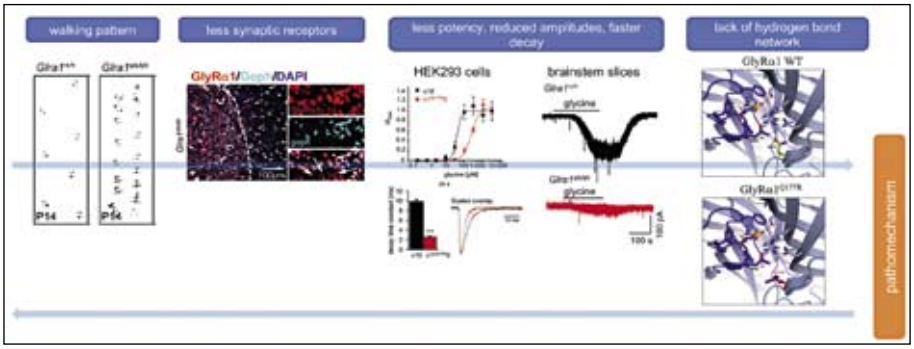


Fig. 2: Identification of the pathomechanism of a novel startle mutation. A changed walking pattern is typical for a neuromotor disorder. At the cellular level, reduced synaptic localization of GlyRalpha1 was demonstrated. Furthermore, reduced current amplitudes, reduced glycine potency, and faster decay time constants were observed. In line with the recently identified cryo-EM structure of the glycine receptor, the underlying mutation was dedicated to a novel gating region of the receptor and the disruption of the hydrogen bond network in close proximity to the agonist binding site. These data expand the current view at the molecular basis of startle disease. (modified from Schaefer et al., J. Neurosci. 2017 and Janzen et al., Front Mol Neurosci 10: 322, 2017)

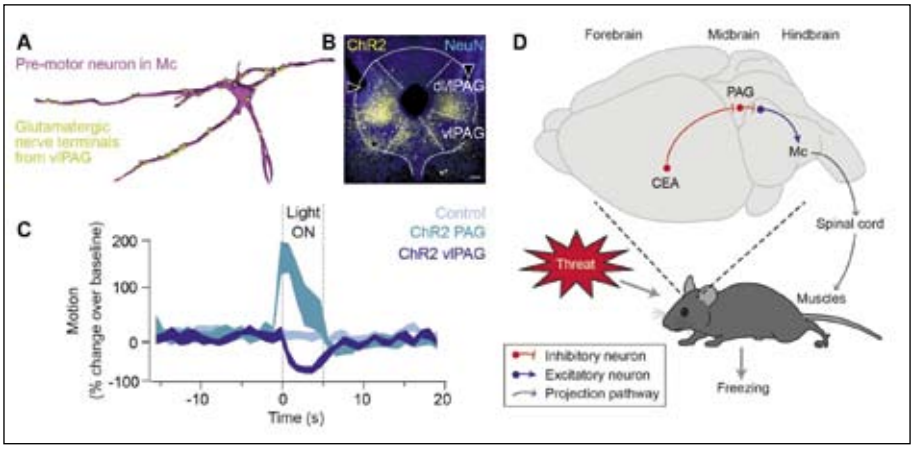


Fig. 3: Dissection of neural circuits for defensive behavior. A) Reconstruction of a premotor neuron of the magnocellular nucleus of the medulla (Mc), which was traced back from the forelimb using virally-mediated neuroanatomical tracing. These cells get excitatory input from the midbrain and mediate freezing during anxiety states . B) Viral expression of optical actuators in the midbrain, through which a light-induced flight reaction can be evoked. C) Freezing and flight evoked by optogenetic stimulation of excitatory midbrain neurons. D) Schematic of the freezing pathway. (modified from Tovote et al., Nature 2016)

The group of Prof. Carmen Villmann investigates the molecular pathomechanisms of neuromotor disorders. Those disorders are associated with dysfunction of glycinergic inhibition. Mutants in genes encoding glycine receptor subunits as well as autoantibodies directed against glycine receptors are discussed to underlie the neurological disorders hyperekplexia (startle disease, stiff baby syndrome) and Stiff-Person-Syndrome. Established mouse models harboring mutations in glycine receptor subunits such as spastic, spasmodic, oscillator, and shaky are useful tools to characterize the diseases at the molecular and cellular level. In collaboration with the Center of Psychiatric Health we identified a connection between DNA polymorphisms in the GLRB gene and anxiety and panic disorders. Since 2017, the group is developing 3D cell culture models of primary neurons based on various bioinks within the SFB-TRR225.

Central technologies, besides modern cell culture methods for primary motoneurons, viral vector production and the generation and analysis of mouse models, are modern microscopic techniques, including confocal microscopy, 2-photon microscopy and life imaging, as well as optogenetics and behavioural analyses in order to study dynamics and defects in structure and function in neurons and neuronal circuits.

Teaching

The Institute of Clinical Neurobiology is involved in the training of students in the International Master Program for *Translational Neuroscience* which has been established in 2015 at the Faculty for Medicine. This course is supported by the Bavarian Government as an Elite Teaching program. Furthermore, students of Medicine and Biology (Bachelor and MSc Courses) are trained in Clinical Neurobiology. Further courses are offered for students within the training program of *Experimental Medicine* for MD students. Another focus is the training of students enrolled in programs for Biomedicine and Biochemistry and the training of PhD students for the Neuroscience class of the Graduate School Life Science at the University of Würzburg.

SELECTED PUBLICATIONS

Briese M, Saal-Bauernschubert L, Changhe J, Moradi M, Ghanawi H, Uhl M, Appenzeller S, Backofen R, Sendtner M. (2018) hnRNP R and its main interactor, the noncoding RNA 7SK, coregulate the axonal transcriptome of motoneurons. Proc Natl Acad Sci USA 115:E2859-E2868.

Fadok JP, Krabbe S, Courtin J, Markovic M, Xu C, Massi L, Bott P, Bylund, K, Müller C, Tovote P, Luthi A. (2017) A competitive inhibitory circuit for selection of active and passive fear responses. Nature 542:96-100.

Fadok JP, Markovic M, Tovote P, Lüthi A. (2018) New perspectives on central amygdala function. Curr Opin Neurobiol 49:141-147.

Lüningschrör P, Binotti B, Dombert B, Heimann P, Perez-Lara A, Slotta C, Thau-Habermann N, Rüth von Collenberg C, Karl F, Damme M, Horowitz A, Maystadt I, Füchtbauer A, Füchtbauer EM, Jablonka S, Blum R, Üçeyler N, Petri S, Kaltschmidt B, Jahn R, Kaltschmidt C, Sendtner M. (2017) Plekhg5-regulated autophagy of synaptic vesicles reveals a pathogenic mechanism in motoneuron disease. Nat Commun 8:678.

Schaefer N, Berger A, van Brederode H, Zheng F, Zhang Y, Leacock S, Littau L, Jablonka S, Malhotra S, Topf M, Winter F, Davydova D, Lynch JW, Paige CJ, Alzheimer C, Harvey RJ, Villmann C. (2017) Disruption of a structurally important extracellular element at the glycine receptor leads to decreased synaptic integration and signaling resulting in severe startle disease. J Neurosci 37:7948-7961.

Chair of Tissue Engineering and Regenerative Medicine (TERM)

CONTACT DETAILS

Professor Dr. rer. nat. Jürgen Groll
(acting Head since 11/2018)

Professor Dr. human. biol. Heike Walles
(Chair until 10/2018)

Röntgenring 11
97070 Würzburg
Phone: 0931/201-73610 (Office FMZ)
Phone: 0931/31-80183 (Office TERM)
Fax: 0931/31-81068
E-mail: Juergen.Groll@fmz.uni-wuerzburg.de
www.ukw.de/forschung-lehre/lehrstuhlfuer-tissue-engineering-und-regenerative-medizin-term

General Information and Structure

The department TERM focuses on the production of 3-dimensional tissue equivalents, which either can be used as a test system in both basic and applied research, but also - assuming GMP guidelines - in patients as tissue replacement or transplanted as “drug delivery” system. With these models it is possible to study interactions of cells and materials, tissues and agents or tissues and microorganisms. In order to provide the widest possible range of models, a high degree of research interdisciplinarity is required. Only in this way is it possible to produce tissue of high quality using suitable (stem)-cells, individually functionalized materials, media of defined composition and bioreactors optimized for the mechanics of the tissue to be formed. National and international collaborations have been made possible by the previously realized tissue models and the associated potential in scientific use, the results of which are documented by renowned publications and awards and serve as the basis for the successful acquisition of various projects that sustainably support the strategic orientation of the department.

Research Interests

Junior Research Group ETFACE
(J. Hansmann, T. Schmitz, M. Jannasch - Entwicklung nahtloser Gewebe-Technik-Schnittstellen)

The junior research group ETFace is part of the BMBF program NanoMatFutur and deals specifically with cell-material interactions. The scientific focus here is placed on materials that are used for electrodes for tissue stimulation (pacemakers). More than half of the energy of a pacemaker battery is lost due to leakage currents at the pacemaker-tissue interface. The project aims to develop nanostructured electrodes designed to provide a seamless connection between tissue and electrode.

Bioreactores
(J. Hansmann, S. Schürlein, T. Schwarz)

Bioreactor systems developed at the TERM for e.g. blood vessels, intestinal or lung tissues enable to mimic the native physiological environments fort the partiuclar tissue equivalents. For further development the scalability of the systems will be realized through modular platform technologies. In addition, the systems are also being developed for implant production under GMP conditions. Another focus relies on automatization. Using state-of-the-art robotic technologies processes of 3D tissue culture formation and various biological tests can be reflected.

Modified growth factors
(J. Nickel, C. Siverino)

The quality of tissues is highly dependent on the stimuli that permanently affect them. In addition to the action of mechanical sti-

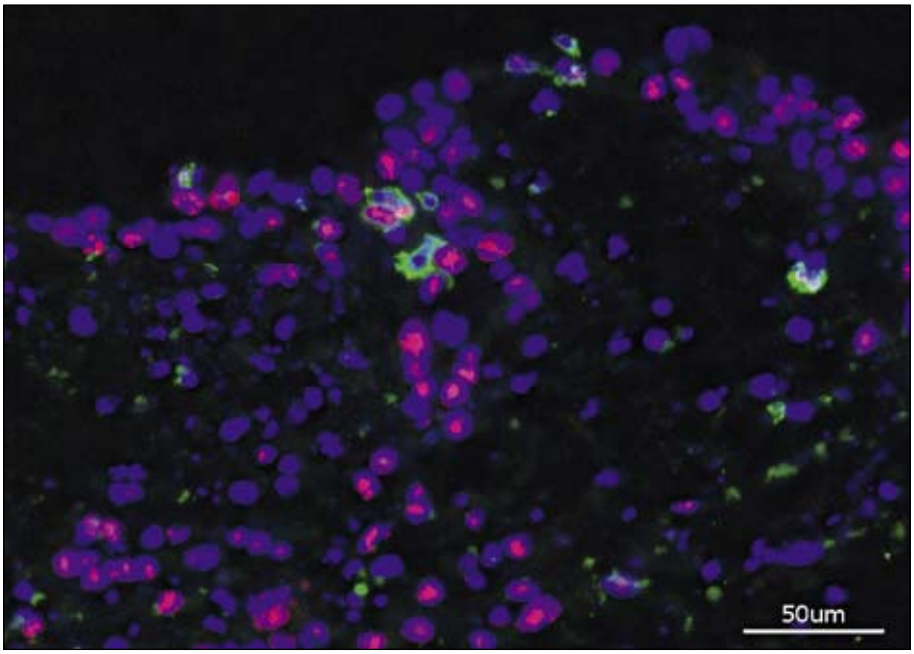


Fig. 1: CAR T-Cells (green: CD45) in a 3D lung tumor model.

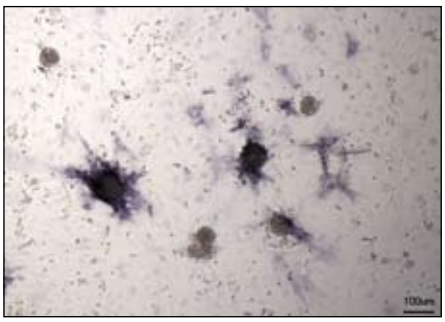


Fig. 2: BMP2 functionalized beads induce osteogenic differentiation of C2C12 cells upon direct contact.

muli, which can be generated in tissue engineering by suitable bioreactors, (bio) -chemical transferable signals are also essential for the tissue´s native functionality. A major problem for the application of locally acting proteins in vivo is that they are removed by diffusion processes from the site of action. Therefore, unphysiological high protein doses usually have to be implanted, which in turn leads to undesirable side effects. Within the framework of an EU-funded project (BioInspire), variants of a bone growth inducing protein (BMP-2) could be developed, which can be covalently coupled to scaffold structures using so-called "click" chemistry. Initial animal experiments have already proven the functionality of these protein variants, so that in the future safe, side-effect-poor medical devices can be produced.

Human tissue models

(A. Appelt-Menzel, D. Zdzieblo - iPS technology for setting up test systems; F. Ehlicke, J. Nickel - tissue models for musculoskeletal Issues; G. Dandekar and S. Nietzer - tumor tissue models; M. Steinke, A. Rossi, M. Metzger S. Kress and M. Schweinlin - human barrier models; M. Steinke, M. Metzger, C. Lotz - models for infection studies)

Barrier models

The 3D tissue models used at our department serve primarily as barrier models and allow the analysis of e.g. barrier integrity damaging substances. Thus, corneal models were established, which provide insights into the drivers of eye irritation and received great international attention as a substitute for animal experiments. An IPS-cell-based blood-brain barrier model immediately scored two awards, including the prestigious Lush Prize. However, the models used also allow detailed molecular genetic analyzes such as e.g. the bioinformatic breakdown of the EGFR signaling pathway in a lung cancer model. Further developments aimed at investigating the mechanisms of cryopreservation in order to improve the storage of tissues and transplants. Since 2017, the project "3D-RoboMuk" (Robot-based production of personalized organoid test systems for the *in vitro* testing of CFTR mutation-specific cystic fibrosis active substances) in collaboration with Opto GmbH and Prof. H. Hebestreit (FM) is funded by the STMWI Bavaria. In this project, patient-specific drugs are tested using gut and respiratory organoid cultures, employing flexible, interactive robotic technologies to produce these cultures.

Infection/desease models

The 3D tissue models developed at TERM address a wide range of questions on pathomechanisms of infectious and cancer diseases and colaborate with other departments of the university hospital, the university of Würzburg and external universities. A very interesting project deals with the infection mechanisms of sleeping sickness caused by trypanosomes. In collaboration with Prof. M. Engstler (University of Würzburg) trypanosome infections caused by Tse-Tse flies were reproduced on the basis of 3D skin models. As part of the GRK 2157, the DFG has been funding the project "3D tissue models for the investigation of microbial infections by human pathogens" (M. Steinke) since 2016. In close cooperation with Prof. R. Gross (Department of Microbiology, University of Würzburg) and Prof. Dr. med. P. Sebo (Czech Academy of Sciences, Prague) interactions of Bordetella pertussis´ adenylate cyclase toxin (ACT) with primary human respiratory epithelial cells under 2D and 3D culture conditions. In the field of tumor assay systems, an IZKF-funded project (G. Dandekar, B-354) was launched in 2017 to investigate the efficacy of CAR T cells in solid tumor tissue models. In a BMBF project (Alternative Methods to Animal Experiments), the efficacy of targeted drugs in lung tumor tissue models is investigated and compared with traditional animal models.

Autologous implants

(P. Bittorf, M. Haddad-Weber, O. Pullig)

For the production of implants, (autologous) cell-matrix products based on the BioVaSc© technology, CellPouch™ or collagen membranes are developed. The working group cooperates closely with various clinical facilities of UKW to use autologous donor material for the development of therapeutically effective medical products. Our regulatory expertise allows competent translation of preclinical research into clinical application.
The EU project HemAcure successfully isolates and genetically corrects specific subtypes of endothelial cells from hemophilia A patients to produce the missing coagulation factor VIII. Important safety aspects for this cell therapeutic approach are being explored both *in vitro* and *in vivo*. Focal points are the investigation of the biodistribution of the genetically corrected cells in the mouse model as well as the examination of the cells with regard to their virus safety and microbiological safety.

Teaching

The lecturers of the TERM are actively involved in the design and holding of lectures, seminars and internships. A manifold of courses for students of various faculties (medicine (study program Biomedicine), biology, and chemistry (study course „functional materials") are offered.

SELECTED PUBLICATIONS

Appelt-Menzel A, Cubukova A, Gunther K, Edenhofer F, Piontek J, Krause G, Stuber T, Walles H, Neuhaus W, Metzger M. (2017) Establishment of a Human Blood-Brain Barrier Co-culture Model Mimicking the Neurovascular Unit Using Induced Pluri- and Multipotent Stem Cells. Stem Cell Reports 8:894-906.

Kress S, Baur J, Otto C, Burkard N, Braspenning J, Walles H, Nickel J, Metzger M. (2018) Evaluation of a Miniaturized Biologically Vascularized Scaffold in vitro and in vivo. Sci Rep 8:4719.

Lotz C, Kiesewetter L, Schmid FF, Hansmann J, Walles H, Groeber-Becker F. (2018) Replacing the Draize eye test: Impedance spectroscopy as a 3R method to discriminate between all GHS categories for eye irritation. Sci Rep 8:15049.

Schmid FF, Groeber-Becker F, Schwab S, Thude S, Walles H, Hansmann J. (2018) A standardized method based on pigmented epidermal models evaluates sensitivity against UV-irradiation. ALTEX 35:390-396.

Tabisz B, Schmitz W, Schmitz M, Luehmann T, Heusler E, Rybak JC, Meinel L, Fiebig JE, Mueller TD, Nickel J. (2017) Site-Directed Immobilization of BMP-2: Two Approaches for the Production of Innovative Osteoinductive Scaffolds. Biomacromolecules 18:695-708.

Department of Orthopaedics

CONTACT DETAILS

Professor Dr. med. Maximilian Rudert
(Head of the Department)

König-Ludwig-Haus
Brettreichstr. 11
97074 Würzburg
Phone: 0931/803-1101
Fax: 0931/803-1109
E-mail: ortho.klh@mail.uni-wuerzburg.de
www.med.uni-wuerzburg.de/orthopaedie

Professor Dr. med. Franz Jakob
Phone: 0931/803-1580

Professor Dr. med. Boris Holzapfel, PhD
Phone: 0931/803-3122

Mission and Structure

The Orthopaedic Hospital Koenig-Ludwig-Haus is a level one hospital specialized in the treatment of musculoskeletal diseases and injuries. The hospital is operated by the District of Lower Franconia (Unterfranken). Integrated are the Chair of Orthopaedics and the Outpatient Department for Orthopedics of the University Hospital, as well as the Orthopaedic Center for Musculoskeletal Research. The Chairman of the Department, one full Professor for Osteology, one full Professor for Translational Orthopaedic Surgery, 6 Associated Professors, 9 Consultant Surgeons, and 15 Residents are taking care of the patients and are responsible for teaching. The hospital has 123 beds and each year more than 4.175 surgical procedures are performed in 5 operating theatres. The University Outpatient Department provides care for about 20.000 patients a year. Integral part of the Outpatient Department is a team of physicians specialized in the treatment of metabolic bone diseases treating approximately 2000 patients per year. The Koenig-Ludwig-Haus also runs its own x-ray and physiotherapy department.

The Orthopaedic Center for Musculoskeletal Research is an interactive platform between basic science, translational research and one of its major aims is the implementation of innovative therapeutic strategies into the clinic. The major research topics are mesenchymal stem cell biology and the development of cell-based therapeutic strategies for the regeneration of mesenchymal tissues, such as bone, cartilage, tendons and ligaments. Furthermore, an intensive interaction with the oncology departments of the clinic has been established in recent years, this research focuses on bone metastasis, especially bone disease in multiple myeloma.
The Center supports the chair in the field of Orthopedic Surgery concerning research and teaching. The Head of the Center, Prof. Dr. Franz Jakob, is also the chairman of the Interdisciplinary Musculoskeletal Center Wuerzburg MCW, which plays an important role in the development of a growing research landscape in the field of regenerative medicine at the University of Wuerzburg.

Specialities in the treatment of orthopedic patients are

- Arthroplasty of the Hip, Knee, Shoulder, Elbow and Tumor Prostheses
- Shoulder and ElbowSurgery
- Sports Medicine
- Ankleand Foot Surgery
- Pediatric Orthopedic Surgery
- Spine Surgery
- Tumor Surgery
- Orthopedic Rheumatology
- Arthroscopyof the Knee, Shoulder, Elbow and Ankle
- Osteology (metabolic and degenerative diseases with a special focus in osteoporosis, malignant bone disease and bone metastasis)
- Rare dieseases with a special expertise for hypophosphatasia, phosphate wasting syndromes in oncogenic osteomalacia and Paget´s Disease (in close cooperation with the Center for Rare Diseases)

Orthopaedic consulting is offered for several other hospitals and centers for disabled persons.

Major Research Interests

The OrthopaedicCenter for Musculoskeletal Research is located within a 600 sq. m labo-

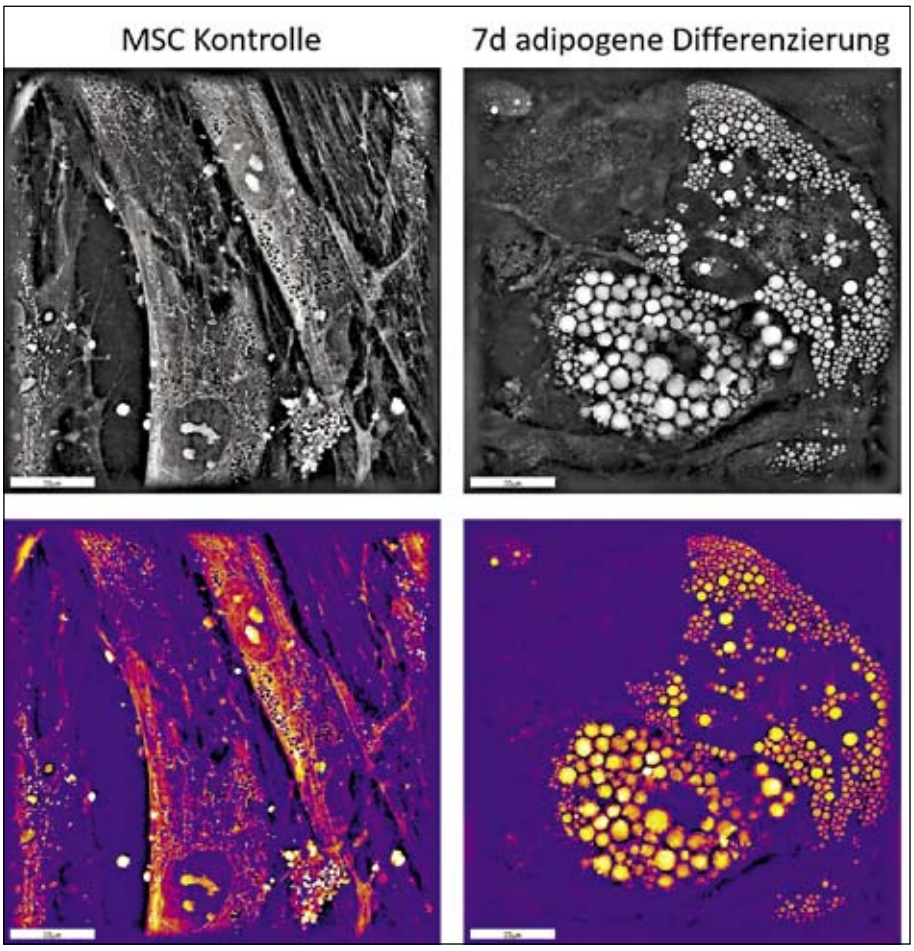


Fig. 1: Holotomographic microscopy of adipose differentiation of mescenchymal stem cells (https://nanolive.ch/).

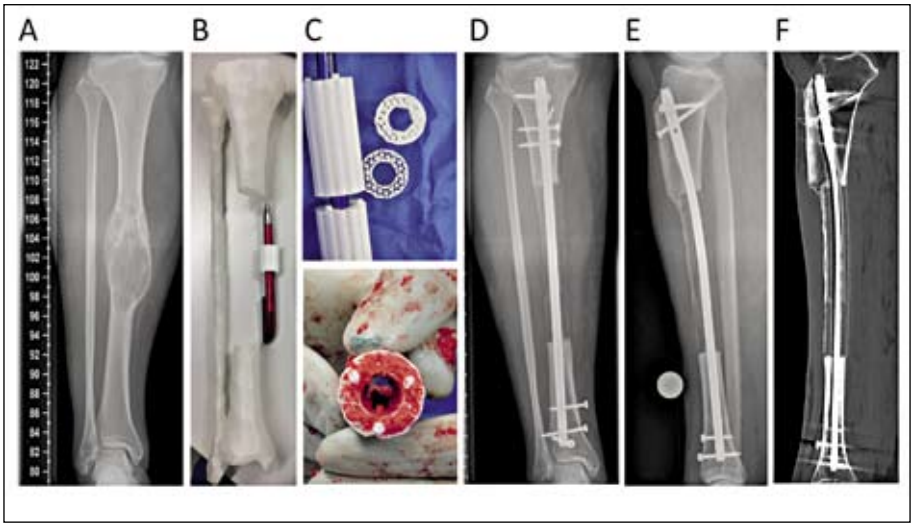


Fig. 2: Regeneration of a critical-sized bone defect after tumour resection of the tibia using a patient-specific, polymer Scaffold. A) a.p. view of the tibia tumour. B) 3D printed model of the tibia and the expected defect after modelling of the resection. C) 3D printed, bioresorbable and highly-porous scaffolds are tailored in a patient-specific way to perfectly fit the resection defect and the osteosynthetic material. Prior to implantation, the scaffolds are loaded with autologous bone graft. D) + E) a.p. and lateral view of the tibia after reconstruction showing increasing mineralization of the defect. F) Computed tomography 6 months after reconstruction demonstrating a continuous ventral osseous bridging of the defect.

ratory (S1, S2, radioactivity) with one location at Brettreichstrasse 11 and another at Roentgenring 11 and a third one at Friedrich-Bergius-Ring 15 in the "Gruenderzentrum" of Wuerzburg University. The Center is supported by the District of Unterfranken. It is funded by the German Research Society (DFG Research Units FOR 1586, several single projects), the German Ministry of Research BMBF (Network DIMEOs, the German/French Consortium OBELICS), the European Union (EU-Consortia VASCUBONE and HydroZONES), the Interdisciplinary Center for Clinical Research IZKF of the University of Wuerzburg, the Arthrose Hilfe e. V. and the Research Fund of the State of Bavaria (Research Consortium on Sarcopenia and Osteoporosis – Consequences of impaired Regeneration in the Elderly FORMOsA), as well as several industry collaborations. In 2015 funding has been granted through the European Fond for Regional Development EFRE (http://www.efre-bayern.de/) for the construction of a Center for Locomotion Research. The number of positions funded is 19 (as ofDecember2015). In 2018 Prof. Boris Holzapfel was appointed full Professor for Translational Orthopaedic Surgery with the aim of closing the translation gap between basic research and clinical practise. Furthermore, the clinic provides a clinical study Unit (Head Dr. L. Seefried) which runs Phase II/III-IV clinical studies and is operated in close connection with the scientific projects and the Fraunhofer Translation Center, as well as the basic science projects.

Key Issues in Research

- Biology of Mesenchymal Stem Cells (F. Jakob, R. Ebert, B. Mentrup, S. Müller-Deubert, L. Seefried, C. Hofmann (guest scientist Pediatric Hospital)
- Epigenetics und chromatin in mesenchymal stem cells (F. Jakob, R. Ebert, B. Mentrup)
- Tumor Orthopedics and bone metastases (DFG FOR 1586, Sanderstiftung Treatment Unit Multiple Myeloma) (M. Rudert, F. Jakob, N. Schütze, R. Ebert, M. Lüdemann, L. Seefried, J. Dotterweich, B. Holzapfel)
- Molecular Orthopedics and Cell Biology (N. Schütze, T. Schilling, S. Hondke, M. Simann, B. Hafen, S. LeBlanc)
- Tissue Engineering, Regenerative Medicine, Translation in Cell Therapy (B.Holzapfel, M. Rudert)
- Gene Therapy and Regenerative Medicine in Musculoskeletal Diseases (M. Weissenberger, B. Holzapfel, B. Geyer)
- Simulation Technologies in Teaching and Eduction (S. Reppenhagen, M. Rudert)
- Biomechanics and Mechanobiology (F. Jakob, L. Seefried, S. Müller-Deubert, R. Ebert)
- Tissue Engineering of the Meniscus (M. Rudert, M. Weissenberger)
- Nanofiber Technology and Electrospinning (F. Jakob. R. Ebert)
- Tumor Surgery and 3D Surgical Reconstruction (M. Rudert, B. Holzapfel)
- Special Techniques in Shoulder Joint Reconstruction (P. Plumhoff, L. Seefried)
- Autologous Chondrocyte Transplantation (S. Reppenhagen, T. Barthel)
- Application of mesenchymal stem cells for the therapy of Femoral Head Necrosis and Osteoarthritis (M. Rudert)
- Endoprosthesis of Hip and Knee (M. Rudert, J. Arnholdt, B. Holzapfel, M. Luedemann)
- Patient individual joint supply of knee, hip and pelvis (M. Rudert, J. Arnholdt, B. Holzapfel)
- Special Orthopaedic Pediatric Surgery, Spine and Foot Surgery (P. Raab, B. Thumes)
- Clinical Studies on Osteoporosis and Metbolic Bone Diseases (F. Jakob, L. Seefried, G. Baron, F. Genest)
- Rickets in Nigeria (P. Raab, R. Ebert, F. Jakob)

Teaching

- Course in clinical examination techniques for operative and conservative orthopedics
- Lectures in Basics of Orthopedics (also accompanying the practical course)
- Practical Course in Orthopedics (bedside teaching in small groups, demonstrations in physiotherapy, plaster techniques and orthopedic technical devices and corselets)
- Clinical ward Rounds, x-ray discussions, orthopedic colloquia
- Molecular Aspects of Bone Diseases – Genes and Cell Biology
- Molecular Methods for osteology in basic science
- Integrated Seminar on Blood and Bone
- TecFunTechnology of Functional Materials

SELECTED PUBLICATIONS

Boelch SP, Jakuscheit A, Doerries S, Fraissler L, Hoberg M, Arnholdt J, Rudert M. (2018) Periprosthetic infection is the major indication for TKA revision. BMC Musculoskelet Disord 19:395.

Dondossola E, Alexander S, Holzapfel BM, et al. (2018) Intravital microscopy of osteolytic progression and therapy response of cancer lesions in the bone. Sci Transl Med 10:pii:eaao5726.

Fernandez-Rebollo E, Eipel M, Seefried L, Hoffmann P, Strathmann K, Jakob F, Wagner W. (2018) Primary Osteoporosis Is Not Reflected by Disease-Specific DNA Methylation or Accelerated Epigenetic Age in Blood. J Bone Miner Res 33:356-361.

Martine LC, Holzapfel BM, et al. (2017) Engineering a humanized bone organ model in mice to study bone metastases. Nat Protoc 12:639-663.

Solimando AG, Brandl A, Mattenheimer K, Graf C, Ritz M, Ruckdeschel A, Stühmer T, Mokhtari Z, Rudelius M, Dotterweich J, Bittrich M, Desantis V, Ebert R, Trerotoli P, Frassanito MA, Rosenwald A, Vacca A, Einsele H, Jakob F, Beilhack A. (2018) JAM-A as a prognostic factor and new therapeutic target in multiple myeloma. Leukemia 32:736-743.

Institute of General Practice

CONTACT DETAILS

Professor Dr. med. Ildikó Gágyor (Director)

Professor Dr. med. Anne Simmenroth (Director)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/210-47802
Fax: 0931/201-6047802
E-mail: gagyor_i@ukw.de,
E-mail: simmenroth_a@ukw.de
www.allgemeinmedizin.uni-wuerzburg.de

Mission and Structure

The Chair in General Practice at the University Hospital in Würzburg (UKW) was established under the leadership of Prof. Dr. Anne Simmenroth and Prof. Dr. Ildikó Gágyor at the beginning of 2018. The so-called "Teaching Department of General Practice" that was already in existence has now become a fully-fledged university institute, equally dedicated to both research and teaching on all levels of education from undergraduate to vocational medical education.

Our interdisciplinary team is tasked with teaching in the subject of general practice as well as in a number of cross-disciplinary subjects, coordinating the placements and elective course in general practice during the Practical Year, research in primary healthcare together with healthcare providers in the region, as well as participation in national and international research collaborations, and finally the involvement in vocational training and further education of physicians as colleagues. A distinctive feature of our subject is the integration of general practices in the region as academic teaching practices in the teaching of students.

Research Foci

The Institute of General Practice is helping to strengthen primary healthcare research in Germany and to put the results of research into practice. In order to achieve this aim, the Institute is working closely with regional healthcare providers and above all with general practitioners.

Within the framework of research, the Institute is participating in regional, national, and international research alliances. A further focus lies on the field of teaching research.

KARDIO Study

The clinical pathways of people with chest pain differ from one another when compared both nationally and internationally, at state or regional level. The consortium-based project KARDIO was initiated in May 2017 headed by the Department of General Practice, Preventive, and Rehabilitative Medicine of the Philipps University in Marburg to evaluate the reasons for this. This study is a major joint project lasting three years and is funded by the Innovation Committee of the Joint Federal Committee. Further partners in the consortium comprise healthcare insurance companies (AOK – Federal Association (AOK-BV) and AOK Scientific Institute (WIdO), TK and Barmer), several university departments/institutes (Health Service Management – LMU Munich, Institute of Health Economy and Healthcare Research at UKE Hamburg, the Faculty of Applied Social and Health Sciences of the OTH in Regensburg, Ruhr-University Bochum, Institute of General Practice, Charité – University Medical Centre Berlin, Institute of General Practice, and Georg-August-University Göttingen, University Medical Centre Göttingen (UMG), Institute of General Practice) as well as the German Society of Cardiology – Heart and Circulation Research Association, the Stiftung Institut für Herzinfarktforschung (Foundation Institute for Research into Myocardial Infarction), the Medical Centre for Quality in Medicine, and the Association of the Scientific Medical Societies in Germany (AWMF). A total of four regions are under investigation with four universities primarily involved locally.

KARDIO investigates clinical pathways from primary healthcare encounter via specialist outpatient care to treatment as an inpatient, originating from the term "chest pain" via primary diagnostics, access to coronary angiography, and the changes to treatment instigated on confirmed diagnosis. An observation phase is planned at the outset: In each region, approximately 200 patients are to be recruited from the hospitals or primary healthcare facilities (GPs or specialist cardiology practices) with which the Institute is currently establishing cooperation. In the second phase, a local agreement and description of the interface beyond the realm of the healthcare sector is planned, which will then be evaluated.

REDARES Study

With a prevalence of 1.7 – 3.1%, uncomplicated urinary tract infections (UTI) are amongst the most common bacterial infections in outpatient healthcare and are generally treated with antibiotics. In the current healthcare environment, a large percentage of second-line antibiotics such as quinolones are being employed. Primary data on pathogen and resistance tests are to be collected from 3,500 urine samples of patients with UTI and the associated prescription data from throughout Germany, distributed among five regions in Bavaria, Baden-Württemberg, Lower Saxony, and Berlin. The results of the study should enable us to model the pathogen resistance data in uncomplicated UTI in future and be made available to physicians in outpatient healthcare.

The REDARES study is also investigating how the adherence to guidelines by physicians in primary healthcare when prescribing antibiotics to treat uncomplicated UTI may be improved by means of a multimodal intervention. The planned implementation of guideline recommendations, practicable information material for doctors and patients, as well as information on the regional status relating to pathogens and resistance in UTI may lead to a reduction in the number of prescriptions for second-line antibiotics in patients with uncomplicated UTI.

UTI-IPD

The effectiveness of treatment approaches to reduce the consumption of antibiotics in comparison with immediate antibiosis is to be investigated in a meta-analysis based on individual patient data (UTI-IPD). In addition, the prognostic factors and moderators of various courses of diseases will be identified. The individual patient data enable us to analyse the effects of treatment strategies to reduce antibiotics consumption in comparison with immediate antibiotic treatment as well as compare the differences between each individual strategy.

Doctoral Thesis Projects

A primary focus in education research in the field of general practice lies in the identification of factors influencing the effective conveyance of communicative competencies and the optimum methods of acquiring these. In this fashion for example, we are comparing a newly developed seminar on the subject of nicotine withdrawal with an e-learning module. In the course on medical history taking, we are examining the extent to which exercises in history taking with simulated patients affect the achievements in the objective structured clinical examination (OSCE). We are also assessing the creation of virtual patients by students with respect to knowledge gain and performance on examination and during placements/clerkships. Further projects concern healthcare research both by and in general practices.

Teaching and Academic Teaching Practices

Lectures and seminars aimed at students in their ninth semester of medical school and the two-week-long placement in an academic teaching practice during the tenth semester form the focus of academic teaching. The spectrum of general practice teaching in terms of content is focussed on fundamental characteristics of the subject, such as how to deal with chronic pain, patients with psychiatric and psychosomatic disorders and problems of addiction, cardiovascular preventive measures in the outpatient sector, as well as the treatment of geriatric patients at life's end including introduction to house visits, to name a few examples. The fundamental theory is consolidated during the placement/clerkship: all students are integrated into the daily routine of a general practice for two weeks, during which time they examine and interview patients gathering important experience in outpatient healthcare. The current network of around 70 academic teaching practices is spread over the district of Lower Franconia and the bordering regions of Middle and Upper Franconia as well as Baden-Württemberg.
In addition to the genuine teaching directly in the field of general practice, the Institute teaching staff are also involved in the cross-disciplinary fields of palliative medicine, prevention and health promotion, medicine of ageing and the elderly, as well as the course in practical clinical examination techniques. Rounding off the teaching is an elective in preclinical medical school titled "Introduction to the processes of thought and conduct for general practice," available to students as early on as their second semester of medical school and providing the opportunity to gain practical experience within the framework of seminars and work shadowing. A new elective to be introduced in the summer semester of 2019, titled "Physician and entrepreneur," will take business aspects in working life as a doctor into perspective – be it as owner or partial owner of a practice or physician in a clinic. The primary aim is to safeguard outpatient healthcare through new generations of doctors.

Vocational Training

The Institute offers both its medical colleagues from academic teaching practices as well as all those interested vocational training opportunities quarterly, during which a wide range of current topics are addressed. These meetings will be supplemented by the "Day of General Practice," which first took place in 2018 and will continue annually. The event is for vocational training free of external interests, by general practitioners for general practitioners and their teams.

SELECTED PUBLICATIONS

Afshar K, Fleischmann N, Schmiemann G, Bleidorn J, Hummer-Pradier E, Friede T, Wegscheider K, Moore M, Gágyor I. (2018) Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with uva-ursi (REGATTA) - a double-blind, randomized, controlled comparative effectiveness trial. BMC Complement Altern Med 18:203.

Furaijat G, Kleinert E, Simmenroth A, Müller F. (2019) Implementing a digital communication assistance tool to collect the medical history of refugee patients: DICTUM Friedland - an action-oriented mixed methods study protocol. BMC Health Serv Res 19:103.

Loudon K, Zwarenstein M, Sullivan FM, Donnan PT, Gágyor I, Hobbelen HJSM et al. (2017) The PRECIS-2 tool has good interrater reliability and modest discriminant validity. J Clin Epidemiol 88:113–121.

McIsaac WJ, Moineddin R, Gágyor I, Mazzulli T. (2017) External validation study of a clinical decision aid to reduce unnecessary antibiotic prescriptions in women with acute cystitis. BMC Fam Pract 18:89.

Simmenroth-Nayda A, Marx G, Lorkowski T, Himmel W. (2016) Working as simulated patient has effects on real patient life - Preliminary insights from a qualitative study. GMS J Med Educ 33: Doc42.

Institute of Medical Teaching and Medical Education Research

CONTACT DETAILS

Professor Dr. med. Sarah König, MME (Director)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/201-55220
Fax. 0931/201-55222
E-mail: koenig_sarah@ukw.de
www.medizinlehre-wuerzburg.de

Mission and Structure

The activities of the Institute of Medical Teaching and Medical Education Research comprise the development and scientific assessment of innovative teaching and examination concepts as well as new strategies of evaluation. In addition, the Institute has taken over the central tasks of curricular (competency-based teaching) and Faculty development (teacher training courses in medical didactics). Furthermore, an advisory service comprising didactics specialists experienced in higher education as well as statisticians has been integrated, providing counselling for numerous teaching projects in the Faculty with respect to efficient teaching methods and evidence-based medical education and education research. The aim of medical education research is to explore the effectiveness of academic interventions and the composition of quality-assured examinations.

Research Foci

Research into evaluation

(C. Rabe, J. Backhaus and S. König)

Research in the field of evaluation serves the scientific rating of teaching, projects, and curricular development. Moreover, the results of evaluation serve to assure quality, in order to identify strengths and room for improvement. The Institute has set research into evaluation as one of its priorities and has thus established a number of different projects in collaboration with clinics and institutes. Valid and reliable instruments of measure constitute a fundamental requirement.

One such project is the **evaluation of the Practical Year**, in which students rated the compulsory rotations in surgery and internal medicine on the basis of their personal perception of their learning outcome and the study climate they experienced for the first time ever. As a whole, the results mirrored the different degrees of satisfaction with the practically oriented training experienced. It was also the first time that students' personally perceived knowledge gain could be calculated and compared. In collaboration with the Surgery Department and with the assistance of a newly developed, standardized questionnaire during the placement in surgery, we collected data on the **learning climate in theatre**, which were subsequently assessed psychometrically. Scaling the results allowed us to correct ratings when comparing the participating clinics, as well as determine a more positive assessment of the medical supervisors by female students. We investigated the **strengths and weaknesses of peer teaching** in conjunction with the Department of Emergency Medicine. The results confirmed that learning practical skills is eased through the social and cognitive congruence between students and their peers.

In cooperation with the field of interventional radiology, it was important to identify the determinants of a **positive experience while learning during a clinical seminar with practical exercises**. With respect to **learning outcome**, it would appear that spatial ability has a moderating function. In order to determine the attitude and stance of first-semester students in the context of good scientific practice, we employed the **situational judgement test** in the required course (seminar) to survey the **individual perspective** and change in opinion resulting from a **group discussion**. Following an exchange with the small group, the students' opinions approached those of experts, whose opinions had not been made public up until that point.

Within the framework of a qualitative study, we are studying the individual **motives for specialist training** (selection of specialty and institution) by means of semi-structured interviews. The study focus lies on the factors influencing the choice of occupation and the demands of working life for the so-called "Generation Y."

Interventional studies

(J. Backhaus & S. König)

Interventional studies count as a special form of evaluation, which intends a planned action or change in order to observe or measure changes. **Comparison of a vodcast (video podcast) with a traditional lecture** revealed that students with a greater affinity to digital media had a reduced learning outcome with the lecture. In a further study, students were taught on a laparoscopy trainer. The group assigned to the studying technique **"deconstruction into key steps"** was able to commit the procedural skills to long-term memory more effectively than the group simply practicing for the same time span. Together with the Department of Microbiology and Virology, we collected data on **students' perception of a viva voce examination**, comparing data from two consecutive semesters with and without examiner training. Essential factors appeared to determine the perception of a good examination and may be influenced by training examiners specifically. The advantages and disadvantages of acquiring practical skills through training with **3D-teeth** in endodontology is currently under investigation in the Department of Conservative Dentistry and Periodontology. The teeth produced on a 3D-printer are comparable to the Plexiglas blocks, however offer a number of advantages with respect to standardized training.

Diagnostic competence

(J. Backhaus & S. König)

Competence diagnostics make cognitive abilities and skills measureable, whereby **item-response theory (IRT)** is most commonly applied. Thanks to IRT, we were able to take the difficulty of tasks and covariates into con-

Fig. 1: Interdisciplinary communication und teamwork in theatre: Workshop participants use Playmobil figures to represent teams in theatre either experienced or prototypical in nature, reflecting on the responsibilities, personal influence, and conflicts. Photo: Andrew Entwistle.

Fig. 2: "Cutting through barriers" is a teaching project aimed at students and trainees. Together, communication and teamwork are made possible to experience and analyzed. The implementation was financed by the Robert Bosch Foundation. Illustration source: Robert Bosch Foundation, Graphic Recording: Visual Facilitators, Katrin Faensen

sideration during the **evaluation of practical clinical examination results** (OSCE in basic medical skills in the fifth semester). Moreover, examiner effects could be corrected and factored in. The validity and reliability of the evaluation was thus improved.
Acquiring knowledge or skills is often calculated as the difference between **before and after (pre vs. post)**. Every lecturer or instructor is aware that competencies are more difficult to impart to advanced students than to novices. The absolute knowledge gain is reduced in the former. We have been working on a simple to implement formula in the Institute that calculates **knowledge gain independently of initial level of knowledge**.
Furthermore, a particular focus of the Institute lies on the **validation of complex simulation models**. A study in the context of undergraduate and postgraduate training examined realistic **silicone-based models** of the surgical treatment of **umbilical hernia** with respect to acquiring procedural skills. The models were considered as suitable for students without any restriction with a fast learning curve. When used by doctors in specialty training, the model was found to train the more complex steps of the procedure often underestimated at the outset.

Stereotypes in inter-professional cooperation and attitudes towards inter-professional education (IPE)

(S. Sippel)

The Robert Bosch Foundation is funding a novel teaching concept at the Institute, in which **medical students and trainees in healthcare professions are taught together as a team**. **Stereotypes** influence inter-professional cooperation in the healthcare sector and can have a negative effect upon it. Within the framework of a research project, the perceptions of both medical students and trainees towards their own and the other professional group was determined with the aid of quantitative and qualitative methods. Subsequently, fitting recommendations can be developed from the signs pointing to individual mechanisms of action to counteract the prejudice. Significant changes were evident following participation in an inter-professional workshop with an increase in positive appraisals of the foreign occupation and a differentiated view of one's own occupation.
In addition, we also recorded the attitudes towards **inter-professional education (IPE)**. Such are influenced by personal experience. With the aid of a questionnaire, we identified and quantified the attitudes. Differences in changes to each occupational field seem to imply that individual aspects (occupational role, leadership qualities, understanding of clinical issues) have different meanings to physicians and nurses.

Teaching

Teacher training (Certificate in Medical Didactics)

The Institute has implemented a training programme as a basic qualification in didactics (the foundation course comprises 60 hours of teaching) for teaching staff in medicine. The qualification programme is recognized throughout the whole of Bavaria and teaching staff from any profession in healthcare may attend (doctors, nurses, therapists, and students). One hundred fifty-five teachers participated during 2017 and 2018.
Participants are introduced to the general framework and underlying concepts of training in medicine. They define competence-based learning objectives and utilize fitting teaching methods and congruent forms of examination/assessment. They learn presentation skills and a repertoire of methods to be applied professionally in the courses they hold. Participants experience in practice how they may optimize their didactic skills. Moreover, they learn how to integrate their teaching in everyday working life into their daily routine at work in healthcare (outpatients' clinic, on ward) or in research. Furthermore, strategies are conveyed towards purposeful course evaluation and competence-based written examinations.

Communication skills as an important competency in medicine and dentistry

The Institute has developed a **training course in communications aimed at "obtaining informed consent prior to surgery"** in the surgery placement. The course was divided into two parts in terms of the *flipped classroom* concept: E-learning was used as preparation. Students learned the basics of obtaining informed consent, the legal aspects, the structure of the interview, as well as background information on three surgical procedures. During interviews to obtain informed consent from simulated patients and using assessment checklists, students received 360-degree feedback from peers, tutors, simulated patients, and medical experts.
A **training course in general communication in dentistry** has been in place since the summer semester of 2018, in which students practice the difficult task of communicating with patients during treatment. Following an introductory presentation on the background theory comprising dentist-patient relationships, communication models, the application of active listening, motivation, and how to deal with angry or frightened patients, all students apply their newly gained knowledge by practicing on simulated patients.

SELECTED PUBLICATIONS

Backhaus J, Huth K, König S, Homayounfar K, Entwistle A. (2019) Digital affinity in medical students influences learning outcome: a cluster analytical design comparing vodcast with traditional lecture. J Surg Educ 76:711-719.

Backhaus J, Jeske D, Poinstingl H, Koenig S. (2017) Assessing Efficiency of Prompts Based on Learner Characteristics. Computers 6:7.

König S, Stieger P, Sippel S, Kadmon M, Werwick K, Sterz J, Höfer S, Rüsseler M, Walcher F, Adili F. (2019) Professionalisation of didactics in daily clinical routine - the personal perception of clinical teaching staff with respect to didactic competence and the framework conditions of teaching. Zentralbl Chir doi: 10.1055/a-0824-7666. [Epub ahead of print].

König S, Hörnlein A. (2018): Examinations while studying medicine - more than simply grades. Wien Med Wochenschr 6 doi: 10.1007/s10354-018-0650-2.

Schleicher I, Leitner K, Juenger J, Moeltner A, Ruesseler M, Bender B, Sterz J, Schuettler K-F, Koenig S, Kreude JG. (2017) Examiner effect on the objective structured clinical exam – a study at five medical schools. BMC Med Educ 17:71.

Department for Functional Materials in Medicine and Dentistry

CONTACT DETAILS

Professor Dr. rer. nat. Jürgen Groll
(Head of the Departement)

Pleicherwall 2
97070 Würzburg
Phone: 0931/201-72610
Fax: 0931/201-73500
E-mail: office@fmz.uni-wuerzburg.de
www.fmz.uni-wuerzburg.de

Professor Dr. rer. nat. Paul Dalton
Phone: 0931/201-74081

Mission and Structure

The Department for Functional Materials in Medicine and Dentistry is located at the Dental Hospital and the overall aim is the development of innovative, biocompatible and bioactive materials for applications in biomedical basic research and clinics with a focus on regenerative materials and therapies. The department has an interdisciplinary team of biologists, chemists, pharmacists, material scientists, physicists and collaborates with clinicians to realize the departments´ mission statement "Higher life quality by innovative materials". The Department is divided into five competence platforms: hierarchical structures, biofabrication, bioactive inorganic scaffolds, nano-biotechnology and (micro-)biological testing. The research of the department was financially supported during the past two years by the German Research Foundation (DFG), the Federal Ministry for Education and Research (BMBF), the European Union (FP7 and ERC) and the VW foundation.

Main Research Foci

Hierarchical systems

Within the human body, cells are surrounded by extracellular matrix (ECM) which supports cell survival and strongly influences and controls their form and function. The ECM is predominantly hydrogels, and they maintain homeostasis of cells which support the cells as mechanically stable scaffold. Tissues are usually hierarchically structured and heterogeneous, providing areas with different biochemical composition and mechanical properties, which accordingly house different cell types in a very tissue specific structure. In many cases additional basal membranes act as thin barriers between tissues and accordingly have specific cell polarization, as can be seen in human skin for example.
One core activity of the department is the synthesis, processing and characterization of mainly polymer-based biodegradable materials, in order to generate structures, which ideally mimic the natural ECM and the hierarchy of the tissue of interest, both in its biochemical composition as well as in the three dimensional structure. For this approach, natural biopolymers are modified as well as new functional and biocompatible polymers are developed and synthesized. In order to create defined structures from these materials different technical procedures are applied, which include electrostatic spinning of polymer solutions as well as cryostructuring of hydrogels.

Biofabrication

During additive manufacturing (commonly known as 3D printing) the fabricated object is initially designed on a computer, where it is divided into several horizontal slices. Subsequently manufacturing of the object is performed without additional templates in a layer-by-layer fashion by adding appropriate materials using a suitable process technology. The simultaneous processing of cells and materials using such approaches for biomaterials research or regenerative medicine is called Biofabrication. Within this field, the research of the department is focused on the development of printable and cell compatible hydrogels and their application for the biofabrication of different tissues. Melt electrowriting (MEW) is a type of 3D printing, and is specialized within FMZ with a dedicated MEW 3D printing laboratory. MEW fabricates nano- and micrometer-sized diameter fibres from biodegradable medical polymers, for use as biomaterials, lattices for cell culture or as reinforcement structures for bioinks and hydrogels. An advantage of MEW is that the diameter of the fibre can be changed during a print, so that multi-modal, multi-phasic structures can be printed with s single nozzle during a print (Figure 1). This precision is achieved by combining electrostatic drawing

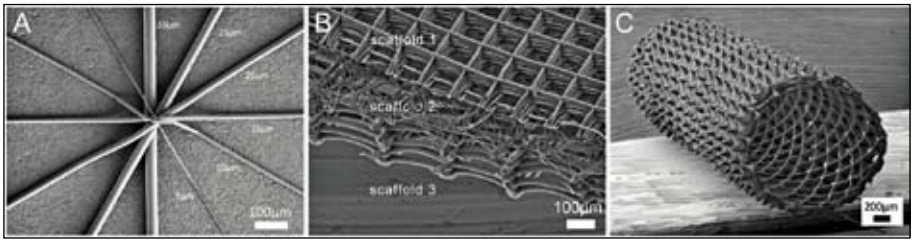


Fig. 1: (a) different diameter fibres of medical-grade polymers can be direct-written using MEW 3D printing allowing (b) multimodal and multiphasic scaffolds for biomedical applications while (c) tubes made are also able to be made that have unique mechanical properties. A & B reproduced from Hrynevich et al. (2018) and C from McColl et al. (2018) both with permission via Creative Commons Attribution 4.0 International License.

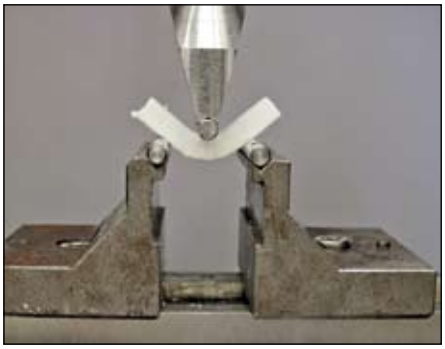


Fig. 2: Pseudo-ductile specimen of a dual-curing bone cement under bending.

of polymer melts together with automatized collection of the formed fibres.

Bioactive inorganic scaffolds

Ceramic support structures are mainly used in the field of bone replacement and serve as a guide for newly growing hard tissue. The preparation of such structures is primarily made of calcium phosphates, whereas a cement reaction is often used to solidify the structures. Such cement pastes can be used conventionally as an aqueous paste or after setting in the form of granules or preformed monoliths. The latter are also fabricated by additive manufacturing processes such as 3D powder printing. This has the advantage that patient-specific implants can be manufactured, which will fit accurately into a defect. Recent developments in the field of such biocements are focused on improving the mechanical properties, in particular reducing the brittle fracture behavior of the materials. Here, in addition to fiber reinforcement, especially dual-curing cement systems are suitable, in which an additional hydrogel phase is formed in the cement such that the implant subsequently obtains pseudo-ductile properties (Figure 2). An improvement in the biological properties of the materials is also achieved by incorporated drugs that are released slowly directly in the bone defect. In addition to the use of protein-based growth factors, the equipment of the ceramics with bioactive ions such as Sr^{2+} or Cu^{2+} is also being researched. As a new development, magnesium phosphates for bone replacement are currently in focus. Here, the better dissolution of such compounds in the physiological environment should cause faster bone healing.

Nano-biotechnology

Nanoparticles are large enough to incorporate biological active substances, but at the same time small enough to be internalized by cells via active transport mechanisms. This opens a wide potential for a controlled transport of delicate drugs through physiological barriers into the target tissue. Various nanoparticles and applications are investigated at the Department. A specific working area are colloid hydrogel particles known as nanogels. The latter combine the characteristics of hydrogels such as biocompatibility, high water content and adjustable chemical and mechanical properties with the characteristics of nanoparticles like high specific surface area and a dimension in the size of cell compartments. This makes nanogels highly attractive to encapsulate bioactive molecules and to protect them from degradation by providing a hydrophilic environment. The oxidative cross-linking of thiol-functionalized polymers yields in nanogels, which are stable in the acidic environment of the stomach, but will be mucoadhesive in the alkaline environment of the intestine, where they adhere to the intestine wall and release their drug load. For instance, this enabled the transport of peptides into intestinal cells after oral administration to regulate the resorption of glucose.

(Micro-)biological testing

The biological laboratory investigates the interaction of cells with biomaterials and functional materials developed in the department. Subjects are, among others, cell-surface interactions analysed dependent on surface properties in 2D and 3D culture systems and also the effect of pore size in scaffold materials like gels and fibres on cell differentiation pathways and immune response (Figure 3). For these experiments primary mesenchymal stem cells or monocytes and neutrophils are used. In addition, the interaction of cells with nanomaterials and co-culture systems are key aspects. Furthermore, an accredited and ZLG approved testing laboratory is associated to this competence field. Here cytocompatibility testing according to DIN EN ISO 10993-5 as well as biocompatibility testing according to DIN EN ISO 10993-6 is performed also for materials by order of external customers.

Teaching

The teaching activity contains lectures about biomaterials, biofabrication, polymers and material composites as well as medical application of X-rays on humans. The lectures are designed for dental students and graduate students of Biomedicine. Special attention is laid on the transfacultative and interdisciplinary bachelor- and master programme “Funktionswerkstoffe”. One outstanding academic program is offered in form of the EU-funded double-master course Biofabrication together with the University of Utrecht (NL) and the Queensland University of Technology (QUT, AUS).

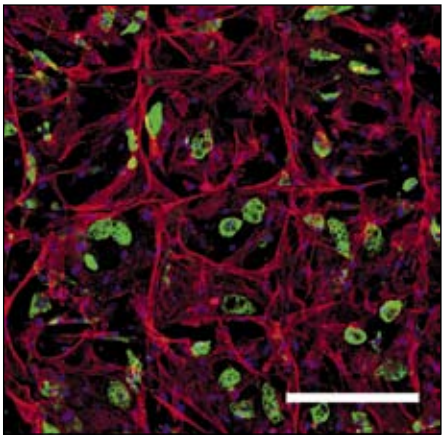


Fig. 3: Adipogenic differentiation of stem cells on MEW scaffolds. Scale bar 200 µm.

SELECTED PUBLICATIONS

Bertlein S, Brown G, Lim KS, Juengst T, Boeck T, Blunk T, Tessmar J, Hooper GJ, Woodfield T, Groll J. (2017) Thiol-ene Clickable Gelatin: a Platform Bioink for Multiple 3D Biofabrication Technologies. Adv Mater 29:1703404.

Feineis S, Lutz J, Heffele L, Endl E, Albrecht K, Groll J. (2018) Thioether-Polyglycidol as Multivalent and Multifunctional Coating System for Gold Nanoparticles. Adv Mater 30:1704972.

Hrynevich A Şen Elçi B, Haigh JN, McMaster R, Youssef A, Blum C, Blunk T, Hochleitner G, Groll J, Dalton PD. (2018) Dimension-based design of melt electrowritten scaffolds. Small 14:1800232.

Schamel M, Barralet JE, Gelinsky M, Groll J, Gbureck U. (2017) Intrinsic 3D Prestressing: A New Route for Increasing Strength and Improving Toughness of Hybrid Inorganic Biocements. Adv Mater 29:1701035.

Stuckensen K, Schwab A , Knauer M, Ehlicke F, Reboredo J, Gbureck U, Walles H, Groll J. (2018). Tissue mimicry in morphology and composition promotes hierarchical matrix remodelling of invading stem cells. Adv Mater 30:1706754.

Department of Orthodontics

CONTACT DETAILS

Professor Dr. med. dent.
Angelika Stellzig-Eisenhauer
(Head of the Department)

Pleicherwall 2
97070 Würzburg
Phone: 0931/201-73320
Fax: 00931/201-73300
E-mail: Stellzig_A@ukw.de
www.ukw.de/kieferorthopaedie

Professor Dr. rer. nat. Kathleen Wermke
Phone: 0931/201-73310

General Information

In the Department of Orthodontics under the directorship of Professor Stellzig-Eisenhauer, nine research assistants work in patient care, research and student teaching.
Patient care in the Department of Orthodontics covers the whole range of orthodontic anomalies. These include in childhood and adolescence (1) the prevention of misalignment of teeth and jaws, (2) the treatment of malpositions of the jaws caused by wear and control of endogenous growth and (3) the correction of misaligned teeth. A special focus of the Department of Orthodontics is the treatment of adult patients using specific fixed treatment techniques based on the particular periodontal and prosthetic situation.
In addition, patient care in the Department of Orthodontics is characterized by interdisciplinary cooperation with specialties associated with dentistry. In particular, there is a close clinical collaboration with the Oral, Maxillary and Plastic Facial Surgery in the treatment of patients with complex craniofacial deformities (cleft lip and palate, syndromes), pronounced malocclusions (dysgnathia) and condylar neck fractures. The treatment of newborns with a non synostotic plagiocephaly caused by unilateral positioning by a molding helmet therapy is conducted in close cooperation with the Department of Paediatric Neurosurgery and the Oral, Maxillary and Plastic Facial Surgery.
Reorientation of the teeth is performed in collaboration with Dental Prosthetics and Restorative Dentistry/Periodontology. This therapeutic measure is indicated as preparation prior to restorative rehabilitation of the entire stomatognathic system.
In the Department of Orthodontics, around 1500 patients from all age groups are treated annually, with check-ups every 3 to 6 weeks. Approximately 600 patients a year attend the department for an orthodontic consultation.

Major Research Interests

Three-dimensional stereophotogrammetric diagnostics of the skull and progress analysis in children with positional plagiocephaly or sagittal suture synostosis taking into account psychomotor development.
Establishing and 3D evaluation of a non-invasive dynamic treatment method by means of individually adjusted head orthosis.
(F. Kunz (Orthodontics), H. Böhm, C. Linz (Oral, Maxillary and Plastic Facial Surgery), T. Schweitzer (Neurosurgery)

In a clinical research project involving the Department of Neurosurgery, the Department of Oral, Maxillary and Plastic Facial Surgery and the Department of Orthodontics, a valid, non-invasive method is to be developed in order to record and analyze the form and development of children's skulls three-dimensionally. The interdisciplinary project is supported by the research funding of the interdisciplinary center of clinical research. The results are expected to help resolve unanswered questions about the treatment of children with cranial deformities (with/without surgery or with/without helmet therapy).
The contribution of the Department of Orthodontics is: Longitudinal 3D data acquisition and the morphometric analysis from the neurocranium and viscerocranium of healthy children and children with cranial deformities. This project was honored with the first prize of the German Society of Orthodontics (DGKFO) in 2011.
In recent years, numerous national and international studies had been published in this context.

Influence of malposition of the jaws and the teeth on the oral health related quality of life of adolescents
(A. Stellzig-Eisenhauer, F. Kunz in cooperation with the Department of Clinical Psychology)

Within the last years, the interest of research in oral health related quality of life is increasing. In an interdisziplinary collaboration with the Department of Clinical Psychology, the Department of Orthodontics is carrying out a multicenter investigation using validated questionnaires to evaluate the influence of (1) malposition of the jaws and the teeth and (2) the correction of these malformations on

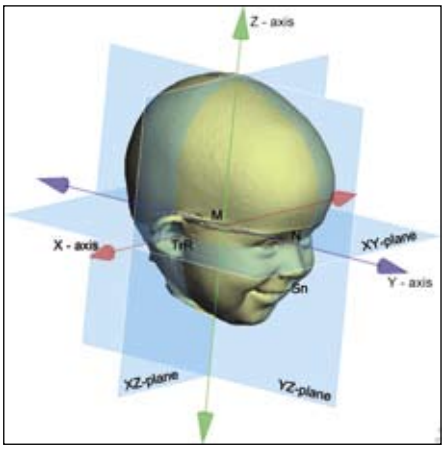


Fig. 1: Three-dimensional analysis of baby's heads.

Fig. 2: Superimposition of three-dimensional data of a patient with positional plagiocephaly before- and after successful head orthesis therapy.

the oral health related quality of life of orthodontic patients.
This interdisciplinary multicentre study was funded in 2017 by the German Society of Orthodontics. The first results have already been presented at the annual conference of the German Society of Orthodontics. This lecture had been honoured with the price for the best lecture of a junior scientist.

Recording prespeech or early speech development in children with and without cranial deformities
(K. Wermke in cooperation with the Pediatric Clinic and the Department of Educational Psychology)

Primary Failure of Eruption (PFE) – clinical and molecular genetic analysis
(A. Stellzig-Eisenhauer in cooperation with the Institute of Human Genetics)

The molecular basis of a disturbance in the eruption mechanism of primary, non-ankylosed teeth is so far unknown. Three heterozygous mutations in the PTH1R gene in diseased patients were first described in an interdisciplinary clinical and molecular genetic study. A part of these results was honored with the prize of the best publication in the „Journal of Orofacial Orthopedics" in 2011.
Since then, more than 30 new mutations of the PTH1R gene were identified being involved in primary failure of tooth eruption (PUBLICATION Roth et al.). A recent research project funded by the IZKF could establish a cell culture model that allows characterizing cellular and functional changes of mutated PTH1 receptors. First results show changes in the cellular localisation of mutated receptors and reduced activation of subsequent signalling pathways. While wild type receptor localizes primarily to the cell membrane, mutants are often found next to the cell nucleus and the endoplasmatic reticulum. This induces changes in the activation of PTH-regulated signaling pathways (PUBLICATION Subramanian). A new study funded by the German Society of Orthodontics develops methods to characterize functional changes of PTH1R mutants using a blood sample from patients with failure of tooth eruption.s
An application for research funding is submitted to the German Research Society (DFG).

Teaching

The orthodontic courses aim to convey knowledge about the nature, extent and pathogenesis of positional defects of the teeth and jaws and to present possible preventive methods and orthodontic treatment options.
The lecture "Introduction to Orthodontics" is intended to provide an overview of the nature, extent and pathogenesis of various jaw anomalies.
The principal lecture "Orthodontics I and II" focuses on preparing students to perform treatment on patients.
The "Course on Orthodontic Technology" aims to provide knowledge about the type, indications, mode of action and fabrication of orthodontic appliances.
The "Course on Orthodontic Treatment I and II" explores theoretical knowledge in depth in small groups and accompanying seminars. In addition, students draw up diagnostic records on patients and learn to use and check therapeutic equipment.

SELECTED PUBLICATIONS

Kunz F, Platte P, Keß S, Geim L, Zeman F, Proff P, Hirschfelder U, Stellzig-Eisenhauer A. (2018) Correlation between oral health-related quality of life and orthodontic treatment need in children and adolescents-a prospective interdisciplinary multicentre cohort study. J Orofac Orthop 79:297-308.

Kunz F, Schweitzer T, Große S, Waßmuth N, Stellzig-Eisenhauer A, Böhm H, Meyer-Marcotty P, Linz C. (2019) Head orthosis therapy in positional plagiocephaly: longitudinal 3D-investigation of long-term outcomes, compared with untreated infants and with a control group. Eur J Orthod 41:29-37.

Kunz F, Schweitzer T, Kunz J, Waßmuth N, Stellzig-Eisenhauer A, Böhm H, Meyer-Marcotty P, Linz C. (2017) Head Orthosis Therapy in Positional Plagiocephaly: Influence of Age and Severity of Asymmetry on Effect and Duration of Therapy. Plast Reconstr Surg 140:349-358.

Roth H, Fritsche LG, Meier C, Pilz P, Eigenthaler M, Meyer-Marcotty P, Stellzig-Eisenhauer A, Proff P, Kanno CM, Weber BHF. (2014) Expanding the spectrum of PTH1R mutations in patients with primary failure of tooth eruption. Clin Oral Investig 18:377-384.

Subramanian H, Döring F, Kollert S, Rukovatkina N, Sturm J, Gambaryan S, Stellzig-Eisenhauer A, Meyer-Marcotty P, Eigenthaler M, Wischmeyer E. (2016) PTH1R mutants found in patients with Primary Failure of Tooth Eruption disrupt G-protein signalling. PLoS One 11:e0167033.

Department of Oral and Maxillofacial Surgery

CONTACT DETAILS

Professor Dr. med. Dr. med. dent.
Alexander Kübler
(Head of the Department)

Pleicherwall 2
97070 Würzburg
Phone: 0931/201-72720
Fax: 0931/201-72700
E-mail: mkg@mail.uni-wuerzburg.de
www.ukw.de/mund-kiefer-und-plastische-gesichtschirurgie

Mission and Structure

The clinic provides 40 permanent beds and covers the whole spectrum of oral and maxillofacial plastic surgery. The main focus here is on reconstructive surgery by microsurgical tissue transfer. Beside inpatient care (about 1,800 patients annually), approximately 19,000 patients are treated in the outpatient clinic. Furthermore, the clinic provides comprehensive consultant support, particularly to the paediatric clinic (craniofacial dysplasia and cleft-lip-palate patients) and within the interdisciplinary emergency treatment and intensive care of trauma patients. Together with the adjacent specialties, in particular orthodontics, neurosurgery, paediatrics and ENT, the interdisciplinary treatment of patients with complex malformations and trauma is ensured. The clinic is part of the *Comprehensive Cancer Center Mainfranken* and is certified as organ center for head and neck tumours as well. Furthermore, the Department belongs to the *Musculoskeletal Center Würzburg*, the *Craniofacial Center Würzburg* and the *Center for Rare Diseases Würzburg*.

Within the framework of inpatient treatment as well as the surgery hours for outpatients, we treat patients with:

- tumours of the head and neck
- trauma of the jaws and face
- craniofacial deformities (esp. cleft-lip-palate)
- plastic-aesthetic reconstruction
- dental implants including bone augmentation
- oral surgery (e.g. cysts, abscesses, osteomyelitis)
- diseases of the salivary glands
- TMJ disorders

Major Research Interests

Tumour biology of oral squamous cell carcinoma
(U. Müller-Richter, S. Hartmann, R. Brands, C. Linz, A. Seher, A. Kübler)

Focus of the research is the identification of mechanisms of tumour development and progression. Here special attention is paid to signal transduction pathways and their intracellular switching points. In addition, modern therapy strategies in treatment of oral squamous cell carcinoma and its precursor lesions are investigated. In this, additional points of attack like tumour antigens play an outstanding role. In cooperation with CCC Mainfranken, research is performed at protein and genetic level to discover mutations in proteins of the tumour metabolism in order to utilize them for tumour therapy. This research lays the foundations for participation in pharmaceutical drug trials (esp. immuno-oncology), which are provided to our patients in cooperation with our ambulatory care for solid tumours.

Bisphosphonate-related necrosis of the jaw
(U. Müller-Richter, J.-F.Dehner, A. Seher, A. Kübler)

The therapy unit "multiple myeloma" of the "Sander Stiftung" is an interdisciplinary concept that summarizes the clinical and scientific expertise of many institutes of the University Hospital Würzburg. The focus of our group is the analysis of bisphosphonate-induced (BION) necrosis of the jaw in multiple myeloma patients. By means of prospective and retrospective monitoring, risk factors and a strategy for the prevention of BION are to be outlined. These molecular biological approaches to therapy that affect bone metabolism are promoted by German Cancer Aid (Deutsche Krebshilfe).

Regeneration of oral mucosa
(C. Linz, A. Fuchs, U. Müller-Richter, A. Kübler, P. Dalton (Department of Functional Materials in Medicine and Dentistry))

The main focus was the development of a melt-electrospun membrane for the intraoral rehabilitation of hard and soft-tissue defects. This membrane consists completely of medical-grade polycaprolactone and provides the following properties: ideal growth conditions for oral mucosa, a bacteria-tight core layer and best regeneration conditions for a bony graft site. In the future, biofunctionalisation of the membrane is the main goal.

Three dimensional stereophotogrammetric diagnosis and treatment evaluation of children with craniofacial anomalies
(H. Böhm, C. Linz, F. Kunz (Department of Orthodontics), T. Schweitzer (Department of Neurosurgery)

This clinical study examines children with all kinds of cranial deformities (premature closure of the cranial sutures or positional plagiocephaly). Areas of interest are self and awareness of others, cognitive development and performance of these children as well as the concerns of their parents. Another aspect

deals with different scanning methods and their improvement to optimize the timing of interventions and treatment algorithms.

Bone regeneration and bone substitution
(A. Fuchs, C. Linz, U. Gbureck (Department of Functional Materials in Medicine and Dentistry)

The focus of the research group is on the development and testing of novel ways of application of resorbable bone replacement materials with a faster potential of bony regeneration compared to up-to-date clinically available materials. Here, pastes and granules with calcium phosphate chemistry are tested in a scheduled animal experiment by implanting in orthotopic, potentially load-bearing defect situations. The behaviour of these materials in direct contact with a bony transplant site should be evaluated. degradation of the pastes/granules and their remodelling into functional, local bone are to be observed in particular.

Modern imaging
(C. Linz, R. Brands, U. Müller-Richter, C. Lapa C., A. Buck (Nuclear Medicine), A. Kübler)

For the initial diagnosis (staging) and continuous aftercare of people with cancer in the head and neck region, different imaging techniques are required. In prospective studies, the significance and best combination of techniques in clinical routine (ultrasound, CBT, MRI and CT) are compared. Diagnostic specificity and sensitivity of neck-lymph-node staging can be increased via FDG-PET/CT. Aims of this study are diagnostic improvement, early identification of relapses or metastasis, and the reduction of radiation exposure with simultaneous cost reduction.

Impact of HGF/Met-pathway on glucose metabolism in head and neck cancer
(IZKF-grant Z-2/59, S. Hartmann)

Targeted therapy of head and neck cancer, which aims mostly at epidermal growth factor receptor (EGFR), is marked by high rates of resistance. This is due on the one hand to tumours being genetically highly heterogenic on the other hand to activation of alternate signalling pathways (HER2, HER3, HER4, cMet, AXL etc.). Especially the RTK cMet is considered for changes in tumour micromilieu (e.g. glucose, PD-L1). The aim of the research is to evaluate the impact of cMet on tumour-cell metabolism and PD-L1-expression on these cells. The findings will later on be evaluated in co-cultured T-cell models.

Basic research into the induction of apoptosis in oral squamous cell carcinoma
(Clinician Scientist Programme/CCC Mainfranken, R. Brands)

Within the framework of targeted therapy of tumours of the head and neck region, tyrosine kinase inhibitors (TKI), which inhibit intracellular signalling pathways selectively, play an important role. So-called SMAC mimetics are pro-apoptotic molecules with the potential to inhibit intracellular inhibitors of apoptosis. The aim of the project is to investigate the efficacy of different TKIs and SMAC mimetics in monotherapy as well as in combination with conventional chemotherapy on oral squamous cell carcinoma. Therefore, in vitro studies with tumour cell lines are performed.

Employment of BMP2-derivates in multiple myeloma
(A. Seher, U. Müller-Richter, J. Nickel (Tissue Engineering & Regenerative Medicine)

As a malignancy of the bone marrow, multiple myeloma (MM) demonstrates a pathological proliferation of antibodies and a progressive destruction of the bony structure. Consecutive treatment with bisphosphonates can lead to a further progression of this destruction, especially in the mandible. Using genetically modified proteins of the BMP-family (bone morphogenetic protein), a novel therapeutic approach in the treatment of MM is evaluated. Through its osteoinductive potential, BMP can lead to a restoration of bone homeostasis on the one hand. On the other hand, its apoptotic effect on neoplastic B-cells of MM can also be utilized in treatment.

Teaching

The clinic ensures theoretical and practical teaching within both the medicine and the dentistry courses.
For medical students, the clinic provides opportunities within multidisciplinary lessons and clinical traineeships. In the context of interdisciplinary oncological lectures, typical tumorous lesions of the oral cavity, jaw, and face are presented. Within dentistry, the fields of oral structure biology, oral pathology, oral and maxillofacial surgery, as well as dental radiology are taught. That includes local dental anaesthetic techniques. These various fields are communicated in both theoretical as well as in practical courses and clinical traineeships.
Furthermore, the clinic is involved in the further education of qualified doctors and dentists through the organisation of certified meetings and courses, e.g. an annual international course on orthognathic surgery.

SELECTED PUBLICATIONS

Brand TM, Hartmann S, Bhola NE, Peyser ND, Li H, Zeng Y, Isacsson Wechsler E, Ranall MV, Bandyopadhyay S, Duvvuri U, Lavallee T, Jordan R, Johnson DE, Grandis JR. (2017) Human papillomavirus regulates HER3 expression in head and neck cancer: implications for targeted HER3 therapy in HPV(+) patients. Clin Cancer Res 23:3072-3083.

Hartmann S, Bhola NE, Grandis JR. (2016) HGF/Met signaling in head and neck cancer: impact on the tumor microenvironment. Clin Cancer Res 22:4005-4013.

Hartmann S, Sayehli CM, Maurus K, Bhola NE, Brands RC, Kübler AC, Müller-Richter UDA. (2018) Plattenepithelkarzinome des Kopf-Hals-Bereichs. MKG-Chirurg 11:30-37.

Lagler C, El-Mesery M, Kübler AC, Müller-Richter UDA, Stühmer T, Nickel J, Müller TD, Wajant H, Seher A. (2017) The anti-myeloma activity of bone morphogenetic protein 2 predominantly relies on the induction of growth arrest and is apoptosis-independent. PLoS One 12: e0185720.

Linz C, Kunz F, Böhm H, Schweitzer T. (2017) Positional Skull Deformities. Dtsch Arztebl Int 114:535-542.

Department of Prosthodontics

CONTACT DETAILS

Professor Dr. med. dent. Marc Schmitter
(Head of the Department)

Pleicherwall 2
97070 Würzburg
Phone: 0931/201-73020
Fax: 0931/201-73000
E-mail: schmitter_m@ukw.de
www.ukw.de/zahnaerztliche-prothetik

Mission and Structure

The Department of Prosthodontics currently about 50 employees and is one of five departments in the Dental University Clinic. Its main mission is to provide theoretical and hands-on education to students in material sciences as well as medical fields. The ambulatory care covers all fields with main focus on prosthetic-restorative dentistry. Classic restorations like crowns, bridges or removables are supported as are current techniques, such as metal-free-, implant-, perioprosthodontics and facial prostheses, in addition to which treatment of cranio-mandibular dysfunctions and myofacial pain syndroms is offered.

Major Research Interests

In the department of prosthodontics, in-vivo and in-vitro studies deal with the following areas: tooth-colored dental materials, imaging, biomechanical aspects, and temporomandibular disorders.

Tooth-colored materials

Decayed teeth can be restored using innovative ceramic materials produced using CAD/CAM technology. In the department of prosthodontics, several in-vitro and in-vivo studies in this area are conducted or planned. A project, which is financed by the DFG, assesses the survival and complication rates of all-ceramic crowns in bruxers. Another project studies the influence of surface treatment on the fracture strength of all ceramic restorations. All ceramic restorations allow to restore teeth on a high aesthetic and functional level, both with and without dental implants. In order to broaden the clinical application of all ceramic restorations, minimal invasive techniques are tested, both in-vitro and in-vivo.

Imaging

An interdisciplinary working group (experimental physics, Prof. Dr. P. Jakob) works since 2006 on the development of dental magnetic resonance imaging (dMRI). The aim of this cooperation was to supplement conventional x-ray techniques with dMRI. By using this technique, detailed anatomic structure of the teeth, the alveolar ridge, etc. could be gained supporting orthodontic, implant, and prosthodontic treatment.
Another interdisciplinary project (in cooperation with the Ludwig-Bolzman-Institute in Graz) investigated the correlation between dMRI and radiographic images and the biological age of subjects (forensic age estimation). About 300 datasets could be included in that study.

Postendodontic restorations

Decayed teeth can be restored using posts and cores. Although there are numerous szudies about that issue, severl questions are still not answered. Thus, several systematic reviews have been performed in 2018 together with the department of restorative dentistry, leading to unexpected results.

Biomechanical aspects

At this time, several interdisciplinary studies on this issue are prepared or in progress.
Both kinetic and kinematic data of mandibular movements should be collected in a DFG project. This DFG-project is in cooperation

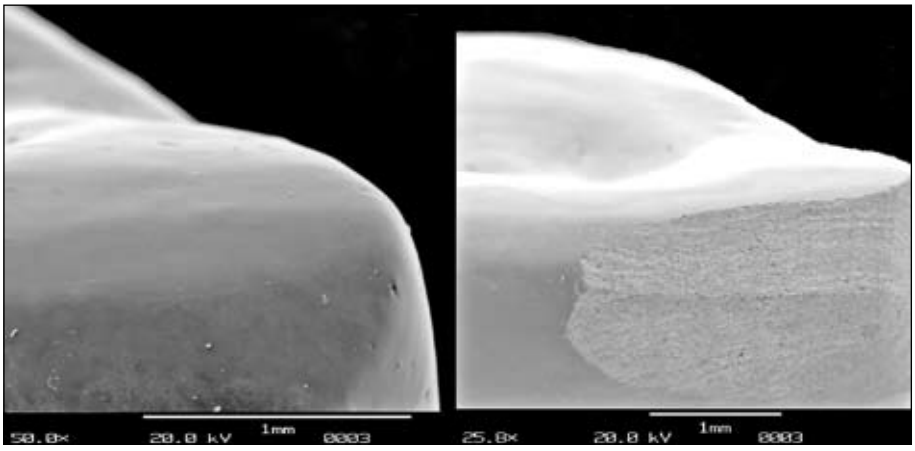


Fig. 1: Surface of a ceramic restoration. Left hand side: untreated. Right hand side: after occlusal adjustment.

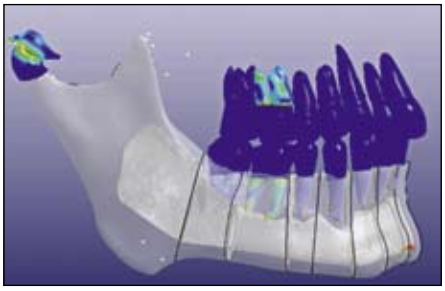


Fig. 2: FEA during clenching on the molars. The colors represent different levels of strain in the periodontal region and the temporomandibular joint.

with the Karlsruher Institute for Technology (KIT), simulating strain and loading using finite element analysis (FEA). This technique allows to look inside anatomical structures and to analyze strain/stress: different occlusion concepts, jaw positions, and dental materials can be tested using FEA. Furthermore, the manufacturing of artificial crowns can be optimized using the results of the FEA analysis.

Temporomandibular disorders (TMD)

Pain, discomfort, dysfunction, clicking and crepitus of the temporomandibular joint, and tensed muscles can be signs/symptoms of TMD. The causes for TMD are multifactorial: bruxism, psychosocial aspects, age, trauma etc. Several projects deal with these aspects in order to develop new therapeutic approaches. Electromyographic recordings are a fundamental technique in these projects, often in combination with clinical examination, and/or imaging. In the working group "oral physiology and experimental biomechanics" the impact of bruxism on pain development in the face and the neck is examined.

Teaching

The premedical curriculum comprises two classes (technical propaedeutics, 60 students and Phantom I, 60 students). The six week Phantom II course takes place annually during the summer off-term. A total of ca. 360 students participated in the medical courses, aided by 8 instructional videos, 4 written instructional booklets and two scripts for material sciences. 2018, close to 400 students attended premed courses. Material science classes span two semesters. All materials are also made available as digital downloads. As of summer 2010, a supplementary eLearning project has been created in cooperation with the VHB.

Two clinical courses are being offered as part of the medical curriculum for fourth and fifth year students, during which the trainees treat own patients under close supervision of professors and assistant doctors. Ca. 55 students are trained per class. The lecture (Prof. Dr. M. Schmitter) on prosthodontics covers general fields of prosthetic dentistry relevant to the dental curriculum. Both lectures span two semesters.
On average, each student performs between two and three restorations which are subject to individual grades. In 2018 this equated to almost 800 prosthetic restorations which were made per class, as well as about 300 during the ten-day final state examinations. In each course there are either one or two written tests, summing up to roughly six exams yielding 300 corrections and gradings!

Eight movies, four clinical instructory scripts and two material science booklets have been made available to students, who also have download access to pdf files of lecture content.

SELECTED PUBLICATIONS

Giannakopoulos NN, Rauer AK, Hellmann D, Hugger S, Schmitter M, Hugger A. (2018) Comparison of device-supported sensomotor training and splint intervention for myofascial temporomandibular disorder pain patients. J Oral Rehabil 45:669-676.

Naumann M, Schmitter M, Krastl G. (2018) Postendodontic restoration: endodontie post-and-core or no post at all? J Adhesive Dent 20:19-24.

Paterakis K, Schmitter M, Said Yenta-Michael S. (2018) Efficacy of epinephrine-free articain compared to articain with epinephrine (1:100 000) for maxillary infiltration. A randomized clinical trial. J Oral Rehabil 45:467-475.

Schmitter M, Kares-Vrincianu A, Kares H, Falsch C, Schindler HJ. (2018) Chronic stress and temporomandibular muscle activity in TMD patients and controls during sleep: a pilot study in females. Cain Oral Investig doi: 10.1007/s00784-018-2474-2.

Zenthöfer A, Rues S, Krisam J, Rustemeyer R, Rammelsberg P, Schmitter M. (2018) Debonding forces for two-piece zirconia abutments with implant platforms of different diameter and use of different luting strategies. Int J Oral Maxillofac Impants 33:1041-1046.

Department of Conservative Dentistry and Periodontology

CONTACT DETAILS

Professor Dr. med. dent. Gabriel Krastl (Head of the Department)

Pleicherwall 2
97070 Würzburg
Phone: 0931/201-72420
Fax: 0931/201-72400
E-mail: krastl_g@mail.uni-wuerzburg.de
www.ukw.de/zahnerhaltung-und parodontologie

Mission and Structure

The Department of Operative Dentistry and Periodontology (16 dentists - 4 of them in the section of periodontology-, 12.5 dental assistants -2.5 of them in the section of periodontology-, 2 dental technicians) is equipped with 10 dental chairs - 3 of them in the section of periodontology-, 2 working centers for the dental technicians and facilities for taking radiographs. For the practical part of the students, education 24 dental chairs are available, 40 working stations for dental technicians as well as 55 dummies for preclinical traning. The area of responsibility of the Department of Conservative Dentistry and Periodontology covers prevention, diagnostics and therapy of diseases of the enamel and dentine (caries, abrasion, erosion and trauma) as well as of the pulp (pulpitis, trauma) and to the periodontal ligament (periodontitis) and their sequelae. Each year approximately 4000 outpatients are treated. In co-operation with the Department of Paediatrics, the Department of Anaesthesiology and the Department for Oral and Maxillofacial Surgery patients can be treated under general anaesthesia.
In patient-care special emphasis is placed on minimally invasive cavity preparation and on adequate restoration of these cavities using adhesive techniques: Due to micro-mechanical bonding of restorative materials to conditioned enamel and dentine, the preparation of macro-mechanical cavities with the inherent further loss of healthy tooth substance can be avoided. Further emphasis is placed on Aesthetic Dentistry: Bonded resin-based composites enable adjustments of contour-, colour- and position-anomalies with non-invasive or minimally-invasive techniques. In the majority of cases there is no more need to prepare the teeth for veneers or full crowns. Preserving healthy tooth substance and dispensing with lab-made restorations are obvious advantages in biological and financial terms. If the dental pulp is affected by caries or tooth injuries vital pulp therapy methods or regenerative endodontic procedures are prefered over conventional root canal treatment. Endodontic treatment is usually performed under the operating microscope. In 2015 the Center of Dental Traumatology in Würzburg was founded as the first interdisciplinary center of excellence for dento-alveolar trauma in Germany. The adequate treatment of complex dental injuries remains a challenge in modern dentistry. Using current therapeutic concepts, severely compromised teeth can be saved in most cases. Particularly in children and young people affected by a dental trauma, treatment must include aesthetic rehabilitation and should aim to avoid any negative impact on the jaw growth.

Major Research Interests

The current research projects of the Department of Conservative Dentistry focus on restorative dentistry, endodontology and dental traumatology. Depending on the area of expertise, the various projects are supervised or co-supervised by the senior physicians of the department (PD Dr. N. Hofmann, Dr. R. Krug, Dr. S. Soliman, Dr. A Schubert).

Laboratory studies

Research at the Department of Conservative Dentistry and Periodontology is focused on the evaluation of restorative materials, appliances and devices required for conservative restorative therapy. In the dental materials area, the interactions between restorative materials and dental hard tissues and the interactions among different restorative materials are studied. A universal testing machine allows the determination of mechanical properties (compressive strength, flexural strength, tensile bond strength, shear bond strength, extrusion shear bond strength). The deformation of teeth under load and during photo-activated polymerization of resin-based composite restorations can be studied using displacement transducers. Additional experimental designs permit the evaluation of the kinetics and the total amount of polymerization shrinkage of restorative resin-based composites, as well as the spectral irradiance of dental light curing units. The marginal seal of restorations is evaluated using dye penetration techniques and computer-based image analysis. The margin fidelity of restorations in vivo and in vitro is monitored

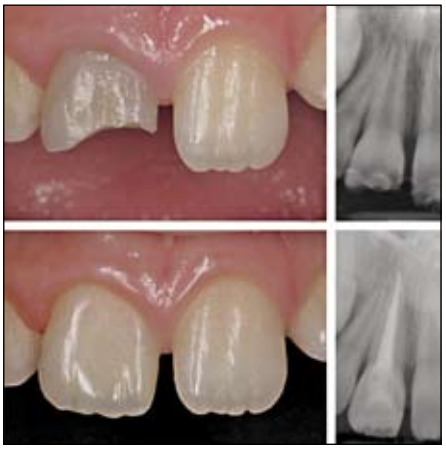


Fig. 1: Esthetic, minimal invasive treatment of a traumatized incisor.

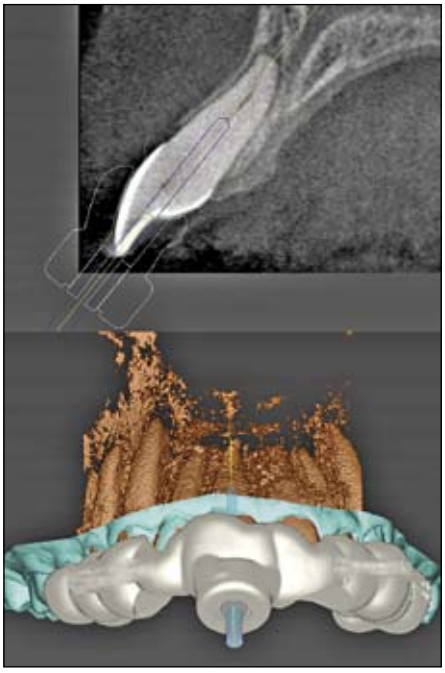


Fig. 2: "Guided Endodontics" a new treatment approach for teeth with pulp canal obliteration.

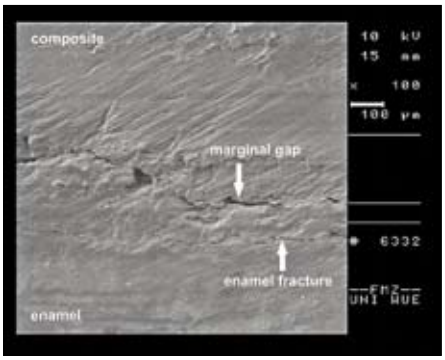


Fig. 3: Marginal analysis of a composite restoration using a scanning electron microscope.

morphologically by the replica technique and a scanning electron microscope. The discoloration potential of different endodontic materials is currently investigated using an in vitro model in a collaborative research project with the University Dental Clinic in Basel, Switzerland. In a further joint research project "Guided Endodontics" a new treatment approach for teeth with pulp canal obliteration utilizing printed templates for drill guidance was developed.

Clinical studies

The purpose of the current clinical studies is to compare newly developed restorative materials and procedures with those previously considered to be the gold standard in the past. Currently, endodontic treatments, performed during the students' courses 10 years ago, are clinically and radiographically examined. Modern root canal preparation and filling techniques are well established in the student treatment courses for five years. The impact of contemporary techniques on the technical quality of root fillings and the success rates of the affected teeth has been determined in recent studies.

The survival of laboratory-fabricated restorations is evaluated in different clinical studies. In the aesthetically sensitive anterior region, these studies include the evaluation of fibre reinforced bonded bridges after a period of up to ten years. In the posterior region, the prognosis of indirect restorations made of ceramic or high-gold alloys is currently investigated approximately eight to ten years after placement.

In the field of dental traumatology, complex dental trauma cases treated at the Center of Dental Traumatology are followed up on long-term. The focus lies on the development of tooth-preserving strategies for heavily compromised teeth. Cases of crown-root fractures, which are considered as difficult to treat due to the subcrestal fracture course are assessed in a clinical study using modern imaging techniques. The long-term survival and the marginal quality of the interface are evaluated up to twelve years after fragment reattachment. Alternative methods such as interalveolar transposition enhance the therapeutic range for this type of injury, and will be systematically examined.

Teaching

Dental education plays a key role in the Department of Conservative Dentistry and Periodontology. The practical training is conducted in 3 parallel courses. In the Phantom Head Course all clinical procedures needed in the field of conservative dentistry can be trained. In the two clinical courses of Conservative Dentistry and Periodontology, patients are treated. The close student supervision by assistants, senior physicians and professors and the generous treatment times guarantee a high-quality treatment. The clinical training corresponds to modern standards. The treatment facilities for students were completely renewed in 2015 and 24 cutting-edge dental treatment units were installed. Two mobile dental microscopes are available for complex endodontic treatments. Digital impressions with intraoral scanners and CAD / CAM fabricated ceramic restorations are also part of the clinical training. The fabrication of indirect restorations is performed in a fully equipped laboratory. All critical operations are reviewed by dental technicians and are corrected if necessary to ensure a high quality level.

SELECTED PUBLICATIONS

Connert T, Krug R, Eggmann F, Emsermann I, ElAyouti A, Weiger R, Kühl S, Krastl G. (2019). Guided Endodontics vs. conventional access cavity preparation: A comparative study about the substance loss using 3D printed teeth. J Endod 45:327-331.

Krug R, Kremeier K, Krastl G. (2019) Long-term retention of avulsed maxillary permanent incisors replanted after prolonged non-physiological storage. Dent Traumatol 35:147-152.

Krug R, Connert T, Soliman S, Syfrig B, Dietrich T, Krastl G. (2018) Surgical extrusion with an atraumatic extraction system: A clinical study. J Prosthet Dent 120:879-885.

Naumann M, Schmitter M, Frankenberger R, Krastl G. (2018) "Ferrule Comes First. Post Is Second!" Fake News and Alternative Facts? A Systematic Review. J Endod 44:212-219.

Soliman S, Meyer-Marcotty P, Hahn B, Halbleib K, Krastl G. (2018) Treatment of an Adolescent Patient with Dentinogenesis Imperfecta Using Indirect Composite Restorations - A Case Report and Literature Review. J Adhes Dent 20:345-354.

Division of Periodontology

CONTACT DETAILS

Professor Dr. med. dent. Ulrich Schlagenhauf (Head)

Pleicherwall 2
97070 Würzburg
Phone: 0931/201-72630
Fax: 0931/201-72680
E-mail: schlagenha_u@ukw.de
www.ukw.de/zahnerhaltung-und parodontologie

Mission and Structure

Next to Prof. Schlagenhauf the staff of the division comprises further four dentists and three dental assistants. The Division of Periodontology forms part of the Department of Conservative Dentistry and Periodontology and is a clinical center for referrals of patients suffering from severe periodontal disease beyond the scope of an average practicing dentist. Especially the therapy of refractory aggressive periodontitis and gingivoperiodontal manifestations of systemic diseases is at the focus of the special competence provided by the division to referring dentists and the public in the region of Lower Franconia and beyond. In collaboration with 7 other periodontal competence centers in Germany the efficacy of anti-infectious strategies for the therapy of aggressive periodontitis and perimplantitis has been evaluated in a major clinical multi-center study. According to established knowledge the onset of periodontal disease is favoured by a proinflammatory dysbiosis of the oropharyngeal microbiota, which in itself is decisively modulated by an increase of systemic inflammation induced e.g. by malnutrition, obesity, stress, smoking as well as by other acquired or hereditary risk factors. Thus a variety of research collaborations has been established with other medical specialties amongst others internal medicine, medical microbiology, pediatrics, osteology and gynecology. Results for example in the field of nutritional modifications and guidance have already entered clinical practice. Also surgical interventions for the minimally invasive resolution and regeneration of soft-tissue and bone lesions within the periodontium are part of the clinical standard procedures provided by the division.

Research Foci

The main research projects of the Division. of Periodontology are listed below. All of them are joint efforts in collaboration with other institutes and clinics of the University of Wuerzburg and the Wuerzburg University Hospital as well as other national or international partners.

Adjunctive use of systemic antibiotics in the therapy of severe periodontal disease

(Y. Jockel-Schneider, U. Schlagenhauf)

The evaluation of the usefulness of adjunctive systemic antibiosis in the course of anti-infective periodontal therapy has been a research focus of the division since several years. Next to preceding clinical trials realized in collaboration with the Institute of Hygiene and Microbiology the Division of Periodontology was a major contributor to a multicenter intervention study on this topic sponsored by the German Research Foundation (DFG). Results of the trial have been published in a series of publications so far. Furthermore the trial data formed the foundation for the establishment of a S3 guideline

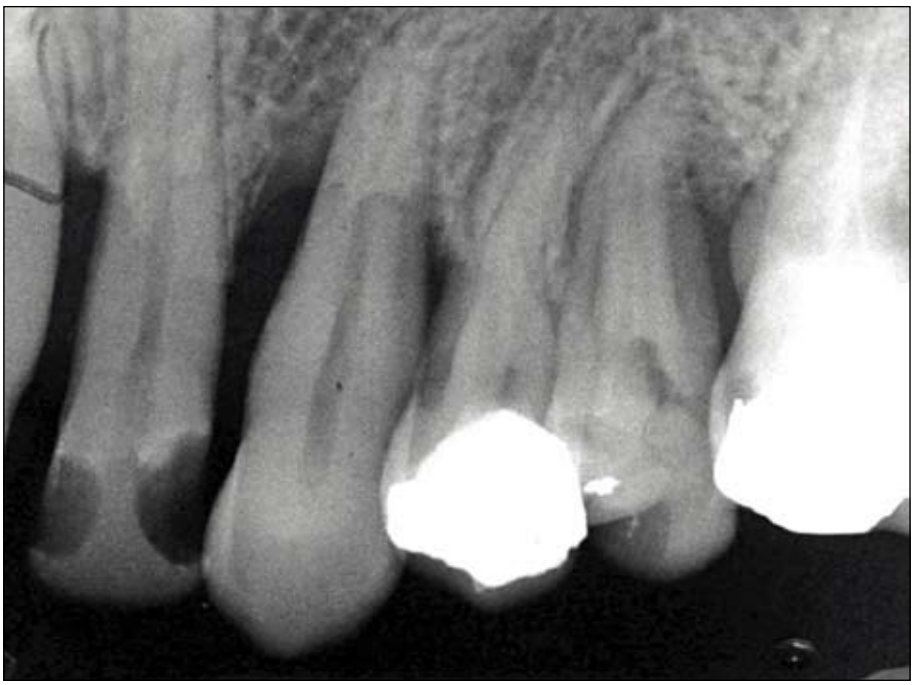


Fig. 1: Deep vertical alveolar lesion at tooth 23 in untreated severe periodontitis.

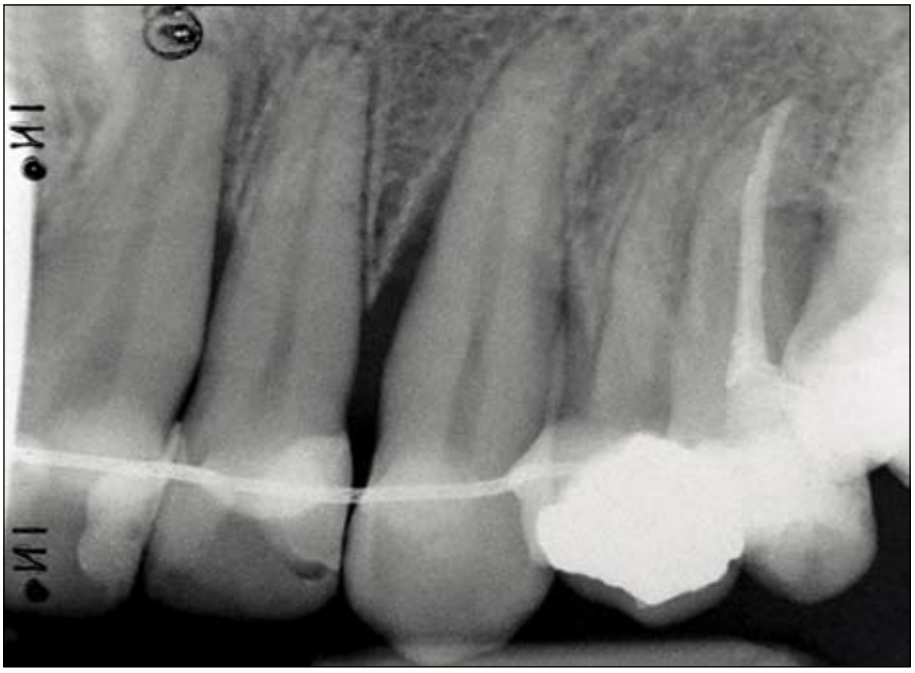


Fig. 2: Regeneration of alveolar bone at tooth 23 two years after anti-infective non-surgical periodontal therapy.

on the adjunctive use of systemic antibiotics in non-surgical periodontal therapy coauthored by Dr. Y. Jockel-Schneider.

Socket preservation after tooth extraction
(S. Fickl)

Subsequent to the extraction of a tooth the neighbouring alveolar bone tends to be resorbed to an extent, which frequently endangers a functionally and esthetically inconspicuous rehabilitation of the defect by a fixed bridge or a dental implant without additional surgical augmentative interventions. Preliminary clinical studies proved that a preferably tight seal of the alveolar bone defect by the placement of a mucosal connective tissue graft significantly reduced the extent of alveolar bone resorption. The identification of further co-factors is the subject of current investigations.

Periodontal diseases and cardiovascular health
(Y. Jockel-Schneider, S. Störk, U. Vogel, M. Eigenthaler, U. Schlagenhauf)

The recently published results of a controlled clinical intervention trial performed in collaboration with the Clinic for Internal Medicine I demonstrated, that the successful elimination of periodontal inflammation has a significant impact on the resolution of vascular dysfunction. Additional *in vitro*-studies performed in collaboration with the Institute of Hygiene and Microbiology of the University of Wuerzburg evaluated the variability of platelet activation among different wild-type strains of *Porphyromonas gingivalis* isolated from periodontitis patients. The data analysis revealed major interindividual differences regarding the speed of activation as well as the followed pathways and the resistance to common activation inhibitors like acetylsalicylic acid and nitroprusside. The data suggest, that periodontitis-associated bacteremia enabling the penetration of virulent strains of *P. gingivalis* into the blood stream may significantly contribute to the development of atherosclerotic lesions.

Teaching

Dental undergraduate training comprises the clinically most relevant aspects of periodontal diagnosis and therapy. It follows the guidelines for the improvement and harmonization of undergraduate periodontal training in Europe established by the European Federation of Periodontology (EFP) as well as the learning objectives in periodontology of the German national competency-based catalogue of learning objectives in dental medicine (NKLZ) established in 2015 by a working-group led by Prof. Schlagenhauf. Subsequent to the intensive teaching of the basic principles of periodontology nonsurgical minimally invasive periodontal therapy procedures are instructed and trained under the close supervision of experienced clinicians firstly in dummy heads and subsequently in real patients. The basic facts of periodontal surgery are also demonstrated and practically instructed in a pig jaw model. After graduation junior staff members of the Division of Periodontology are given the opportunity to acquire a formal postgraduate specialization in periodontology by following a three-year postgraduate training program specified by the guidelines of the German Society of Periodontology (DG PARO).

SELECTED PUBLICATIONS

Fickl S, Fischer K, Petersen N, Happe A, Schlee M, Schlagenhauf U, Kebschull M. (2017) Dimensional Evaluation of Different Ridge Preservation Techniques: A Randomized Clinical Study. Int J Periodontics Restorative Dent 37:403-410.

Jockel-Schneider Y, Bechtold M, Haubitz I, Stork S, Fickl S, Harks I, Eigenthaler M, Vollrath O, Baulmann J, Schlagenhauf U. (2018) Impact of anti-infective periodontal therapy on parameters of vascular health. J Clin Periodontol 45:354-363.

Jockel-Schneider Y, Kobsar A, Stellzig-Eisenhauer A, Vogel U, Stork S, Frantz S, Schlagenhauf U, Eigenthaler M. (2018) Wild-type isolates of Porphyromonas gingivalis derived from periodontitis patients display major variability in platelet activation. J Clin Periodontol 45:693-700.

Kocher T, Holtfreter B, Petersmann A, Eickholz P, HoffmannT, Kaner D, Kim TS, Meyle J, Schlagenhauf U, Doering S, Gravemeier M, Prior K, Rathmann W, Harks I, Ehmke B, Koch R. (2018) Effect of Periodontal Treatment on HbA1c among Patients with Prediabetes. J Dent Res doi: 10.1177/0022034518804185. [Epub ahead of print].

Pretzl B, Salzer S, Ehmke B, Schlagenhauf U, Dannewitz B, Dommisch H, Eickholz P, Jockel-Schneider Y. (2018) Administration of systemic antibiotics during non-surgical periodontal therapy-a consensus report. doi: 10.1007/s00784-018-2727-0. [Epub ahead of print].

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Research Centers

Comprehensive Cancer Center Mainfranken (CCC MF)

Comprehensive Cancer Center Mainfranken

CONTACT DETAILS

Professor Dr. med. Ralf Bargou
(Director)

Josef-Schneider-Str. 6
97080 Würzburg
Phone: 0931/201-35150
Fax: 0931/201-35952
E-mail: anmeldung_CCC@ukw.de
www.ccc.uni-wuerzburg.de

Professor Dr. med. Michael Flentje
(Deputy Director)
Phone: 0931/201-28890

Professor Dr. phil. Martin Eilers
(Deputy Director - Research)
Phone: 0931/31-84111

Dr. med. Manfred Welslau
(Deputy Director - Outreach)
Phone: 06021/4527300

PD Dr. rer. biol. hum. Jutta Riese
(Managing Director)
Phone: 0931/201-35151

Mission and Structure

The Comprehensive Cancer Center Mainfranken (CCC MF) is a well-established permanent multidisciplinary institution of the Faculty of Medicine and the University Hospital headed by a full professor on the level of a department chair. The Center has evolved from the "Interdisziplläres Tumorzentrum der Universität Würzburg", which was founded in 1983. In 2008 the "Tumorzentrum" was transformed into the CCC MF. In 2011, and reconfirmed in 2014 and 2018, the German Cancer Aid awarded the CCC MF the status "Onkologisches Spitzenzentrum". Today, the CCC MF is the central forum for basic, translational and clinical cancer research as well as for state-of-the-art cancer care at Würzburg University, the University Hospital and the region of Mainfranken. Thus, the CCC MF organizes three areas: multi-disciplinary care, translational and clinical research, and the regional cancer care network (outreach). In 2010, the clinical part of the CCC MF was certified as "Oncology Center" by the Deutsche Krebsgesellschaft and successfully passed re-evaluation in 2013 and 2016. The following organ cancer centers and modules have been established and successfully certified under the roof of the CCC MF and the Oncology Center:

(1) Breast Cancer Center (Speaker: Prof. A. Wöckel)
(2) Gynecological Cancer Center (Speaker: Prof. A. Wöckel)
(3) Colorectal Cancer Center (Speaker: Prof. C. Germer)
(4) Pancreas Cancer Center (Speaker: Prof. C. Germer)
(5) Skin Cancer Center (Speaker: Prof. M. Göbeler)
(6) Neuro-oncological Center (Speaker: Prof. R.I. Ernestus)
(7) Head & Neck Cancer Center (Speaker: Prof. R. Hagen, Prof.A. Kübler)
(8) Prostate Cancer Center (Speaker: Prof. H. Riedmiller, Prof. M. Flentje)
(9) Stem Cell Center (Speaker: Prof. H. Einsele, Prof. P.G. Schlegel)
(10) Center for Pediatric Oncology (Speaker: Prof. P.G. Schlegel)
(11) European Center of Excellence for Neuroendocrine Cancers (Speaker: Prof. M. Scheurlen)
(12) European Center for Rare Adults Cancers (ERN EUROCAN, Speaker: Prof. M. Fassnacht)

Multi-disciplinary Care

Medical care of patients suffering from cancer is provided at the University Hospital and its affiliates on an interdisciplinary basis. The CCC MF offers the structural framework for an efficient cooperation. All cancer patients entering the CCC MF are discussed in 17 weekly interdisciplinary tumor conferences and are treated by multi-disciplinary teams. In 2017, the CCC MF has established a bi-weekly molecular tumor board, which integrates the expertise of clinical oncologists, the central clinician scientist team of the Trial Center & ECTU, IT experts & bioinformaticians, geneticists, pathologists and molecular biologists. Furthermore, multidisciplinary outpatient facilities and counselling hours have been established in the field of GI-cancer, endocrine tumors, prostate cancer, lung cancer, gynecological tumors, and head & neck cancer. The central building of the CCC MF (C16) houses the interdisciplinary outpatient chemotherapy ward, the central quality assurance team and cancer registry, the interdisciplinary CCC MF outpatient facility for clinical trials, psycho-oncology, complementary oncology and nutrition counselling.

Additional multi-disciplinary offers for patients, health care professionals, and the community:

- Social service
- Information about self-helpgroups
- Sport and Yoga courses for cancer patients
- Information seminars about cancer therapy and cancer prevention for patients, their relatives and the public.
- Counselling of patients and their families with hereditary cancer
- Numerous training and education programs for physicians, clinician scientists, nurses and other health care professionals

SELECTED PUBLICATIONS

Appenzeller S, Gesierich A, Thiem A, Hufnagel A, Jessen C, Kneitz H, Regensburger M, Schmidt C, Zirkenbach V, Bischler T, Schilling B, Siedel C, Goebeler ME, Houben R, Schrama D, Gehrig A, Rost S, Maurus K, Bargou R, Rosenwald A, Schartl M, Goebeler M, Meierjohann S. (2018) The identification of patient-specific mutations reveals dual pathway activation in most patients with melanoma and activated receptor tyrosine kinases in BRAF/NRAS wild-type melanomas. Cancer doi: 10.1002/cncr.31843. [Epub ahead of print].

Chapuy B, Stewart C, Dunford AJ, Kim J, Kamburov A, ..., Rosenwald A, Thorner AR, Meyerson ML, Golub TR, Beroukhim R, Wulf GG, Ott G, Rodig SJ, Monti S, Neuberg DS, Loeffler M, Pfreundschuh M, Trümper L, Getz G, Shipp MA. (2018) Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med 24:1290-1291.

Dejure FR, Royla N, Herold S, Kalb J, Walz S, Ade CP, Mastrobuoni G, Vanselow JT, Schlosser A, Wolf E, Kempa S, Eilers M. (2017) The MYC mRNA 3'-UTR couples RNA polymerase II function to glutamine and ribonucleotide levels. EMBO J 36:1854-1868.

Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, ..., Gesierich A, Hersey P, Bines SD, Kane JM, Barth RJ, McKinnon G, Farma JM, Schultz E, Vidal-Sicart S, Hoefer RA, Lewis JM, Scheri R, Kelley MC, Nieweg OE, Noyes RD, Hoon DSB, Wang HJ, Elashoff DA, Elashoff RM. (2017) Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med 376:2211-2222.

Gökbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, Faul C, Diedrich H, Topp MS, Brüggemann M, Horst HA, Havelange V, Stieglmaier J, Wessels H, Haddad V, Benjamin JE, Zugmaier G, Nagorsen D, Bargou RC. (2018) Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 131:1522-1531.

Juric D, Rodon J, Tabernero J, Janku F, Burris HA, Schellens JHM, Middleton MR, Berlin J, Schuler M, Gil-Martin M, Rugo HS, Seggewiss-Bernhardt R, Huang A, Bootle D, Demanse D, Blumenstein L, Coughlin C, Quadt C, Baselga J. (2018) Phosphatidylinositol 3-Kinase α-Selective Inhibition With Alpelisib (BYL719) in PIK3CA-Altered Solid Tumors: Results From the First-in-Human Study. J. Clin Oncol 36:1291-1299.

Since 2014 a central entry portal together with a patient guidance system has been implemented to help patients navigate the different aspects of interdisciplinary treatment and follow-up care. These personal patient managers act as trusted contacts for the patients, their relatives and also for physicians involved in the treatment. Currently, a concept for a full-fledged central entry port located in one building is being developed for all cancer patients entering the CCC MF.

Outreach/Regional Cancer CareNetwork

In order to better serve patients' needs for high-quality medical care within the vicinity of their residence the CCC MF actively supports the certification of general oncology and organ-specific centers in the regional area (in total: 3 centers for oncology & 27 organ cancer centers). Currently, 11 community hospitals, 8 rehabilitation facilities and 12 private practices are associated with the CCC MF. The CCC MF assures a high standard of medical care in the region by organizing joint tumor board activities, a regional trial & research network (see also below clinical research), central quality assurance, training and education programs, and the cancer registry services. In 2017 more than 10,000 cancer patients of the region of Lower Franconia were discussed in tumorboards of the regional cancer care network (Univ. Hospital + partner institutions), about a third of these patients were discussed in joint cross-institutional tumorboards. The CCC MF also supports some regional partners through schemes for personnel exchange. Thus, currently experts from the University Hospital work part-time in five regional partner institutions.

Major Research Interests

Clinicians work closely together with biologists and other scientists to perform cancer research on an international and competitive level. The focus of translational research at the CCC MF is to identify molecular targets and to develop therapeutic strategies for genetically complex and heterogeneous tumors. Since 2009, the CCC MF has therefore developed translational research programs focusing on (A) the identification of critical regulators of tumor cell metabolism, (B) immuno-oncology and (C) targeted radiotherapy and molecular imaging. Since 2013 a fourth program on tumor genome sequencing & personalized medicine together with a molecular tumor board has been established (program D).

During the past few years, preclinical research from the major research programs has been successfully translated into the clinic. For example, seminal work from scientists and physicians of the CCC MF has demonstrated the first clinical proof-of-concept of T cell engaging BiTE antibodies in patients with refractory B cell malignancies as well as in solid tumors. Based on registration trials chaired by principal investigators of the CCC MF the first-in-class BiTE antibody blinatumomab has been approved for rr ALL (relapsed/refractory acute lymphoblastic leukemia) as well as for molecularly refractory ALL. (program B).
Another highlight is the identification of new target structures making as yet non-druggable key oncogenes accessible to a targeted approach (program A). This research has in parts already progressed to a stage where the concepts are being tested in clinical trials.
The genome-sequencing program (D) is now established for almost all cancer entities and has led to the identification of new pathogenetic pathways and might lay the foundation for the development of personalized and targeted therapies in a series of different cancer entities. First potential new targets identified in this program are currently being tested in early clinical trials (e.g. head & neck cancer, multiple myeloma). Since 2018 the CCC MF is memeber instititution of the National Lung Cancer Genome Network funded by Deutsche Krebshilfe. Aim of the network is to establish modern genome-based diagnostics and to implement innovative personalized therapies into clinical care.
Research from program C (precision radiotherapy and molecular imaging) led to the development of novel therapies and novel imaging techniques for endocrine tumors, lymphomas, prostate cancer and lung cancer. Imaging guided surgery and robot-assisted surgery has led to an innovative program in the field of precision surgery (e.g. In GI cancer, prostate cancer, head & neck cancer).

Clinical Research

In addition to the translational research programs, the CCC MF has developed a broad infrastructure for a comprehensive program in clinical research.

The clinical cancer registry and healthcare research

The cancer registry collects long-term follow-up data and mortality information of tumor diseases. This is an important tool to monitor the quality of treatment and to observe trends in cancer incidence. In cooperation with the population based cancer registry of the federal state of Bavaria (www.krebsregister-bayern.de) the cancer registry of the CCC MF aims to discover regional and temporal differences of cancer incidences and provides useful data for outcome and healthcare research. For example, analysis of follow-up data from the cancer registry showed that the survival probability of patients with colorectal and lung cancer treated at the CCC MF has markedly improved over the past decade. Additional research programs at the CCC MF that focus on patient care are established in the areas of palliative & supportive care, psycho-oncology and breast cancer.

Interdisciplinary Trial Center and Early Clinical Trial Unit

The Interdisiciplinary Trial Center (ITC) of the CCC MF provides the complete infrastructure for planning and conducting phase-I, II, and III trials in all departments of the University Hospital. This comprises study nurse support, documentation assistance, data management, quality management as well as training and education for physicians and study nurses. A particular strength of the CCC MF is the Early Clinical Trial Unit (ECTU, Phase-I Unit). The ECTU is a highly specialized and fully staffed interdisciplinary clinical unit focussing on the conduction of novel cancer therapies within the framework of phase-I, I/II and II clinical trials (early clinical development). The ECTU is one of the country´s largest phase-I units and was the first of its kind in Germany. Since its start in 2007 the number of experimental phase-I trials has continuously increased with currently more than 30 actively recruiting studies per year (2017/18). A focus of these trials is the development of personalized treatments and immuno-oncology Thus, the ECTU is an important structural element for the translation of preclinical research from the four major research programs into the clinic (Fig.1, from-bench-to-bedside).

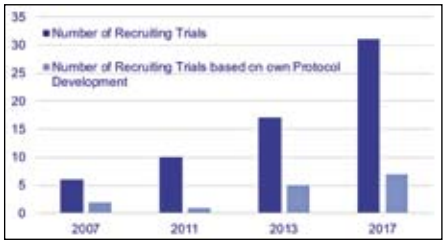


Fig. 1: Increased phase-I trial activity during the last ten years. Parts of the trial program are based on the major research programs of the CCC MF (from-bench-to-bedside).

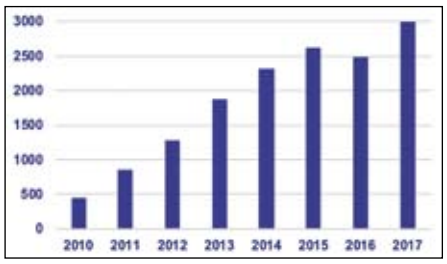


Fig. 2: Increased numbers of patients recruited in trials within the regional trial network during the last years (University Hospital & Partner institutions).

Complementary to the ECTU the CCC MF has established a central interdisciplinary outpatient unit with focus on large phase II and phase III trials mainly for common solid tumors, Based on this infrastructure the CCC MF has established a broad trial program planned and conducted by multi-institutional and multidisciplinary investigator teams comprising gyneco-oncology, uro-oncology, lung cancer, gastro-intestinal cancer and head & neck cancer and other solid tumor entities.

Another important step in the field of clinical research was to integrate external physicians and community hospitals of the regional catchment area into the clinical research programs of the CCC MF and to establish a regional trial network. This has strongly enhanced accrual of patients from the regional area into clinical trials. In 2017, more than 3000 cancer patients of the region Lower Franconia were recruited in clinical trials (Fig. 2).
Based on this infrastructure the CCC MF has initiated a comprehensive program of studies aiming at the improvement and further development of health care standards. Studies are currently running in various fields of clinical oncology. Key trials of this program led to results with practice changing impact in lung cancer, gastro-intestinal cancer, radio-oncology, hemato-oncology, endocrine tumors and supportive care.

Teaching, Training, and Career Development

In 2015, the CCC MF has implemented a new master degree program in molecular & clinical oncology for students in life sciences (biochemistry, biomedicine, biology). Complementary to this program for basic scientists in 2017 the Faculty of Medicine together with the CCC MF has started a new program for medical students in Translational and Personalized Medicine within the Elite Network of Bavaria. Since 2018, the CCC MF organizes the teaching module interdisciplinary oncology as mandatory part of the course of studies human medicine at Würzburg University. Furthermore, the CCC MF organizes a broad multidisciplinary training program for physicians, clinician scientists and study nurses of the University Hospital and partner institutions. In 2018, with strong management support of the Interdisciplinary Center for Clinical Research (IZKF), the CCC MF has established an interdisciplinary cancer research center with a broad career program for both medical and clinician scientists (Mildred-Scheel-Nachwuchszentrum, funded by Deutsche Krebshilfe). Aim of this program is to educate and to interest talented young scientists and clnicians in translational and clinical cancer research.

SELECTED PUBLICATIONS

Juric D, Janku F, Rodón J, Burris HA, Mayer IA, Schuler M, Seggewiss-Bernhardt R, et al. (2018) Alpelisib Plus Fulvestrant in PIK3CA-Altered and PIK3CA-Wild-Type Estrogen Receptor-Positive Advanced Breast Cancer: A Phase 1b Clinical Trial. JAMA Oncol 13:e184475.

Kantarjian H, Stein A, Gökbuget N, Fielding AK, ..., Topp MS. (2017) Blinatumomab versus Chemotherapy for Advanced Scute Lymphoblastic Leukemia. N Engl J Med 376:836-847.

Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR1, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Theelen WS, Lee CK, Sebastian M, Templeton A, Mann H, Marotti M, Ghiorghiu S, Papadimitrakopoulou VA; AURA3 Investigators. Collaborators: ..., Deschler-Baier B, et al. (2017) Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 376:629-640.

Schäfer R, Strnad V, Polgár C, Uter W, Hildebrandt G, ..., Polat B; Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). (2018) Quality-of-life results for accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breast-conserving surgery (GEC-ESTRO): 5-year results of a randomised, phase 3 trial. Lancet Oncol 19:834-844.

Schmitz R, Wright GW, Huang DW, Johnson CA, Phelan JD, ... Rosenwald A, et al. (2018) Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. N Engl J Med 378:1396-1407.

Wegert J, Vokuhl C, Collord G, Del Castillo Velasco-Herrera M, Farndon SJ, ..., Rosenwald A, Gessler M, Behjati S. (2018) Recurrent intragenic rearrangements of EGFR and BRAF in soft tissue tumors of infants. Nat Commun 9:2378.

Comprehensive
Heart Failure Center

CONTACT DETAILS

Am Schwarzenberg 15
97080 Würzburg
Phone: 0931/201-46333
Fax: 0931/201-646333
E-mail: dzhi@ukw.de
www.dzhi.de

Professor Dr. med. Christoph Maack
(Spokesperson)
Department Translational Reseach
Phone: 0931/201-46502

Professor Dr. med. Stefan Frantz
(Deputy Spokesperson)
Department of Internal Medicine I
Phone: 0931/201-39000

Professor Dr. rer. nat. et med. habil. Laura Schreiber, MBA
Department Cardiovaskular Imaging
Phone: 0931/201-46365

Professor Dr. med. Stefan Störk
Department Clinical Research
& Epidemiology
Phone: 0931/201-46363

Professor Dr. med. Brenda Gerull
Department Cardiovaskular Genetics
Phone: 0931/201-46457

Professor Dr. med. Jürgen Deckert
(Member of Board of Directors)
Department of Psychiatry, Psychosomatics and Psychotherapy

Professor Dr. med. Peter Heuschmann
(Member of Board of Directors)
Institute for Clinical Epidemiology and Biometry

Professor Dr. med. Rainer Leyh
(Member of Board of Directors)
Department of Thoracic and Cardiovascular Surgery

Dr. Sebastian Ziegaus
(Managing Director)
Phone: 0931/201-46330

General Information

Heart failure is a rapidly growing health care problem with major socio-economic implications worldwide. Numbers are rising dramatically. Currently, about 3.2 Mio patients with heart failure live in Germany. The syndrome affects approximately one out of ten subjects above the age of 70 years. Heart failure is the most common cause for hospital admissions, and cardiovascular diseases are by far the most frequent causes of death. Due to the complex pathology of the syndrome, quality of life of patients with heart failure is severely compromised. Various comorbidities like diabetes or renal failure predispose to the development of heart failure. Stroke, depression, cerebral dysfunction and sudden cardiac death are frequent consequences of heart failure. Therefore, heart failure is an interdisciplinary health issue. The underlying mechanisms for these bidirectional relationships are not fully resolved yet but involve neuroendocrine activation, inflammation and altered metabolism. Therefore, adequate and effective strategies to improve the understanding of the causes of the disease, for therapies and longtime diseases management are of utmost medical importance.

A major problem for the development of new therapies is the fact that promising discoveries in the preclinical experimental field never make it to the actual treatment of patients (translation). The reasons are manifold: insufficient collaboration between preclinical and clinical institutions, lack of incentives for researchers, decreasing numbers of clinician-scientists and increasing economic constraints for university clinics.

The Comprehensive Heart Failure Center (CHFC) faces these challenges. The German Federal Ministry of Education and Research supports the CHFC as one of eight integrated research and treatment centers for the period 2010 to 2020. The unique selling point of the CHFC is the extensive collaboration of medical basic scientist, clinical scientists and imaging experts (especially physicists) in interdisciplinary teams under one roof. An ultra-modern research building was built and has been operable since January 2017. The buildings fosters the interaction of different disciplines and the translation into clinical concepts. The building provides about 5000 m² of effective floor space of which 90% are dedicated to research.

The organizational structure comprises four research professorships: Cardiovascular Genetics (Prof. Dr. Brenda Gerull), Translational Research (Prof. Dr. Christoph Maack), Molecular and cellular Imaging (Prof. Dr. Laura Schreiber,) and Clinical Research and Epidemiology (Prof. Dr. Stefan Störk) (fig. 2, left).

The investigation of the influence of various comorbidities on the course of heart failure as well as the consequences and complications of heart failure for other organs is realized by close collaboration with clinical departments (internal medicine with cardiology, nephrology, pneumology, endocrinology und intensive care, neurology, psychiatry, surgery and cardiac surgery, radiology and neuroradiology, nuclear medicine) and basic research institutes that are associated with the CHFC. All collaborations are organized in three research areas:

- Project Area „Myocardium“ investigates the role of the myocardium in the cardiovascular continuum for the progression of heart failure through basic, translational and patient oriented research and multidisciplinary imaging.
- Project Area „Heart and Brain“ focuses on the bidirectional interactions between heart and brain in the context of heart failure. Especially the relation between heart failure and depression is under investigation, as well as the identification of functio-

Fig. 1: Group photo Retreat 2018 Kloster Schöntal.

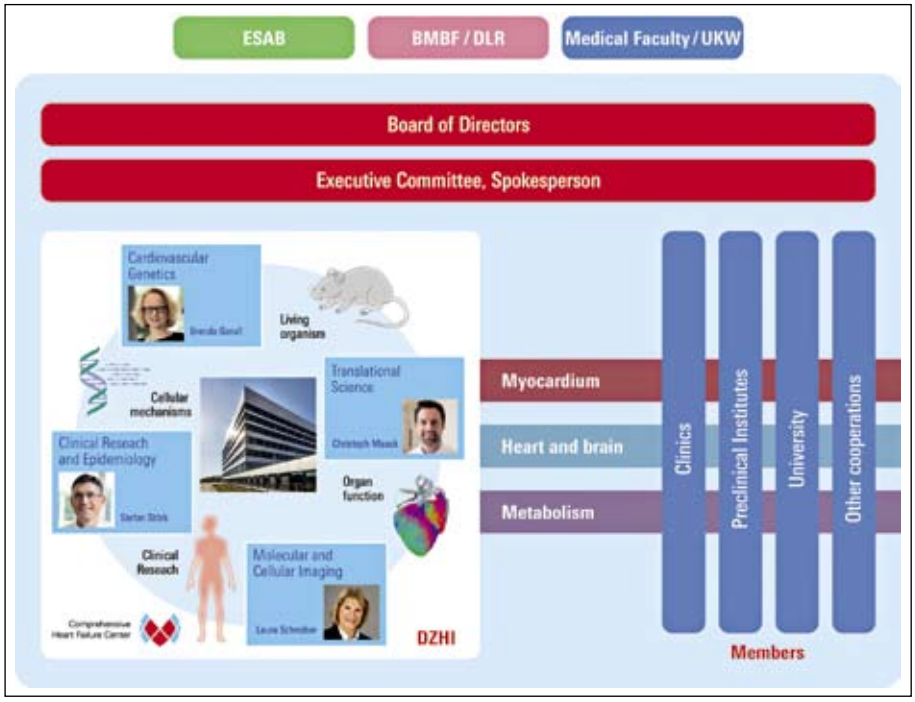


Fig. 2: The four research professorships reside in the new research building. They are closely linked to the clinical departments and preclinical institutes at the University of Würzburg.

nal and structural deficits in patients with advanced heart failure and the progression of systolic dysfunction in patients with ischemic cerebral infarcts.
- Project Area „Heart, Metabolism, and other Organs" investigates the impact metabolic comorbidities on pathogenesis of heart failure.

The main structural innovation and the internationally visible and unique property of the CHFC is the **interdisciplinary integration of different areas of medicine and science** (e.g. from medicine, patient care, physics, psychology) and in particular, the interdisciplinary collaboration between cardiology and other medical areas (nephrology, endocrinology, psychiatry, neurology, surgery etc.). The CHFC supports excellent researchers on all career stages, e.g. in the context of start-up projects, rotational positions, junior groups and research professorships.

In collaboration with the Graduate School of Life Sciences (GSLS), the CHFC organizes subsidiary courses on clinical research, a Master's course in Clinical Sciences and Epidemiology and the Curriculum Translational Medicine (Clinical Research for assistant physicians). Furthermore, the CHFC and its departments contributed significantly to the acquisition of third party funding for a new Clinician Scientist Program (Union CVD).

Focus Areas

Department of Translational Research
Head: Prof. Dr. med. Christoph Maack

The research of the Department of Translational Science focuses on the pathophysiology of heart failure and the development of novel therapeutic strategies, with a particular emphasis on the interaction between cardiac excitation-contraction coupling and mitochondrial function under physiological or pathological conditions. Heart failure is characterized by 1) a defective regulation of intracellular calcium handling, 2) energetic deficit and 3) oxidative stress. Mitochondria play a central role in this interplay, since they are the major cellular source of the energy-carrying molecule ATP and harmful reactive oxygen species (ROS), and calcium is an essential regulator of their function.

In the failing heart, alterations in calcium handling in cardiac myocytes underlie the decrease in cardiac contractile performance. Our previous studies revealed that these abnormalities are also causative for energetic deficit and oxidative stress. A crucial defect in the failing myocardium is the decrease in mitochondrial calcium uptake and the consequent loss of the calcium-dependent stimulation of the citrate (Krebs) cycle, which provides precursors for ATP production and maintains the anti-oxidative capacity of mitochondria. In recent studies, we discovered that pathological increases in cardiac afterload, such as the ones associated with arterial hypertension or heart failure, can exacerbate the overflow of ROS from mitochondria. Furthermore, we investigate the therapeutic potential of drugs that reduce the production of ROS in mitochondria. In animal models of heart failure, these agents decreased cell death, cardiac dysfunction, arrhythmias and mortality. Some of these agents are currently further evaluated in clinical trials in heart failure patients.

The Department of Translational Science hosts two Core Facilities and one Junior Group. The Core Facility for „Cellular Electrophysiology" (head: Dr. Michael Kohlhaas) covers a wide spectrum of methods that allow the integrative analysis of excitation-contraction coupling as well as mitochondrial function and bioenergetics in beating cardiac myocytes. A key technique for this Facility is fluorescent microscopy that can be combined with the patch-clamp technique and/or the measurement of force development in isolated cardiac myocytes. The Core Facility for „Mitochondrial Function" (head: Dr. Alexander Nickel) also harbors a wide array of methods for the assessment of mitochondrial respiratory capacity and other parameters of mitochondrial function.

The Junior Group of Dr. Jan Dudek investigates how defects in mitochondrial function lead to the development of cardiomyopathy. Since several key mitochondrial functions are coupled to the mitochondrial membranes, the Junior Group is particularly interested in the abnormalities in the biosynthesis of membrane lipids and their consequences on cellular metabolism. Therapeutic strategies targeting mitochondrial defects and metabolism are also under investigation. Moreover, the Group investigates the role of mitochondria in the transduction of intracellular signals, and in particular the activation of adaptive signaling pathways in response to mitochondrial dysfunction (the so-called "retrograde signaling pathways").

Department of Cardiovascular Imaging

Head: Prof. Dr. rer. nat. et med. habil. Laura M. Schreiber

Ultrahighfield- (7T) MRI:
The main focus of research is the establishment of the basic mechanisms and of a fundamental understanding of cardiac magnetic resonance imaging (MRI) physics at ultra-

high magnetic field strength of 7T. On this basis, innovative imaging methods are developed for functional, microstructural, metabolic, cellular and molecular imaging of cardiac disease in general, and of heart failure in particular. The complex translational imaging infrastructure commissioned in the new CHFC research building during the last two years in the CHFC allows the full translational path to be used, i.e. from small animals (mouse, rat), large animals (i.e., pigs) towards the patient.

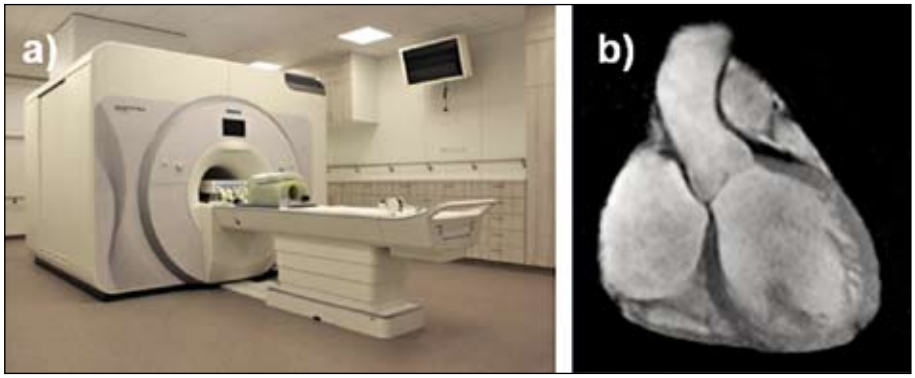


Fig. 3: a) 7T-MRI device at the CHFC; b) MRI-Image of the left ventricular outflow tract at 7T.

Special Contrast Techniques and Hyperpolarization:
Stabilized nitroxyl radicals (TEMPOL) are used as contrast agent for the visualization of oxidative stress in the heart and nearby vessels. Furthermore, the development of polarization techniques for the generation of hyperpolarized fluids for highly sensitive MRI of the metabolism is promoted as well as the development of methods to study the myocardial microstructure.

Hardware Development:
Dedicated multichannel radiofrequency and shim coils are essential for ultrahigh field MRI of the heart. New concepts for this purpose are developed and tested with the aim of obtaining the ultimate image quality and resolution achievable in-vivo.

Computational Cardiology:
An in-silico-model of intracoronary mass transport on high-performance compute clusters has been developed and is deployed now to analyze intracoronary transport of substances dissolved in the blood (i.e. drugs, contrast agents). Machine and deep learning methods are combined with numerical simulations and in-vivo MRI data to predict heterogeneity of substance delivery, and to enable the MRI-based prediction of the outcome of cardiac disease, e.g. in patients with ventricular tachycardia.

Department of Cardiovascular Genetics

Head: Prof. Dr. med. Brenda Gerull

Major Research Interests
Inherited cardiomyopathies often lead to heart failure and sudden cardiac death. Current clinical management is limited because (1) the causative gene remains unknown, (2) our understanding of the molecular mechanisms is limited and (3) the evidence for safe and effective preventive treatments is lacking. Given those challenges, the main research focus is to enhance our understanding of the complex molecular, cellular and genetic framework leading to genetic forms of heart failure.

From novel genes to function – the zebrafish heart as a model system for cardiomyopathies
This project aims at the identification of novel disease-causing genes and the discovery of novel pathways for inherited cardiomyopathies. Whole exome sequencing (WES) in suited families with cardiomyopathies is used for primary gene discovery. Novel gene variants are selected for disease modelling in zebrafish (Danio rerio). Transgenic fish lines for several candidate genes (ILK, TMEM43, PTPLA, etc.) have been generated using the Tol2 transposon system and CRISPR/Cas9 technology and are characterized for signs of heart failure and sudden death using a broad spectrum of phenotypic assays. The goal is to identify molecular pathways involved in the pathogenesis of cardiomyopathies and potentially select novel target molecules.

Disturbed cell-cell junctions in the pathogenesis of arrhythmogenic cardiomyopathy
Cardiac desmosomes are cellular adhesion structures located at the intercalated discs that provide the mechanical attachment between cells. Recent studies on different mouse models lacking or overexpressing desmosomal components have shown that cardiomyocyte adhesion mediated by desmosomal proteins is a sensitive regulated biological process. For example, it has been shown in a mouse model overexpressing DSC2 that changes of the homeostasis of desmosomal cadherins induce a cascade of different cell-cell interactions mediated by a complex network of various extracellular signaling molecules which leads to profound cardiac remodeling and heart failure in mice. However, important questions addressing signaling cascades initiating the remodeling process, inflammatory processes, metabolic signaling as well as the selection of target molecules for specific therapies remain open and are the current research focus.

The role of LEMD2 in the pathogenesis of cardiomyopathy
Recently, a mutation in LEMD2 (p.L13R) was identified, a nuclear envelope protein which is leading to severe cardiomyopathy with sudden cardiac death and juvenile cataract. The presence of massive interstitial fibrosis and abnormal nuclei in diseased myocardial tissue was shown. So far, the *in vitro* data on mutant tissue, cells and recombinant expressed proteins demonstrate that the mutation disrupts protein interactions, cell cycle progress and leads to a premature aging phenotype. A newly generated *in vivo* knock-in mouse model by CRISPR/Cas9 technology carrying the p.L13R mutation will help to further explore the molecular events leading

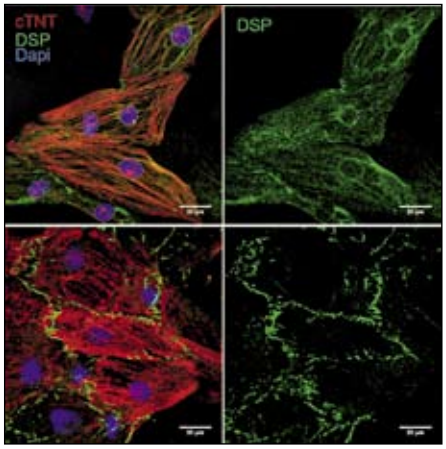


Fig. 4: Confocal microscopy of immunofluorescent images of hiPSC derived cardiomyocytes (CMs) at day 60. Top panel shows CM lacking plakophilin-2 (PKP2); bottom panel indicates the isogenic control. The intermediate linker protein desmoplakin (DSP) demonstrates disturbed localization within the cytoplasm (top) compared to normal at the cell membrane in control cells (bottom). Cardiac Troponin T (cTNT).

to LEMD2 associated cardiomyopathy. The long-term goal is to translate our mechanistic findings into therapeutic approaches targeting specific pathways in the cardiac disease process.

Human iPSC derived cardiomyocytes in inherited cardiomyopathies

Patient-specific model systems, such as human induced pluripotent stem cell (hiPSC) derived cardiomyocytes (CMs), provide new insights into the pathogenesis of heart failure and help to individualize therapeutic approaches. In this project, iPSCs from reprogrammed dermal fibroblasts of different patients with inherited cardiomyopathies were established. To compare the effects of the specific mutations within the patient-specific genetic background, isogenic controls are generated by using CRISPR/Cas9 technology. Two desmosomal proteins were knocked-out: plakophilin-2 (PKP2) and desmoglein-2 (DSG2) in iPSCs for mimicking arrhythmogenic cardiomyopathy (ACM). CM derived from those iPSCs at day 60 lacking PKP2 have been characterized and show disturbed expression of the intermediate linker protein DSP (Fig.1) as well as a higher sensitivity towards increasing extracellular Ca^{2+}-levels resulting in more arrhythmic events. Ongoing work is focusing on the characterization of CMs with mutations in LEMD2 and DNAJC19.

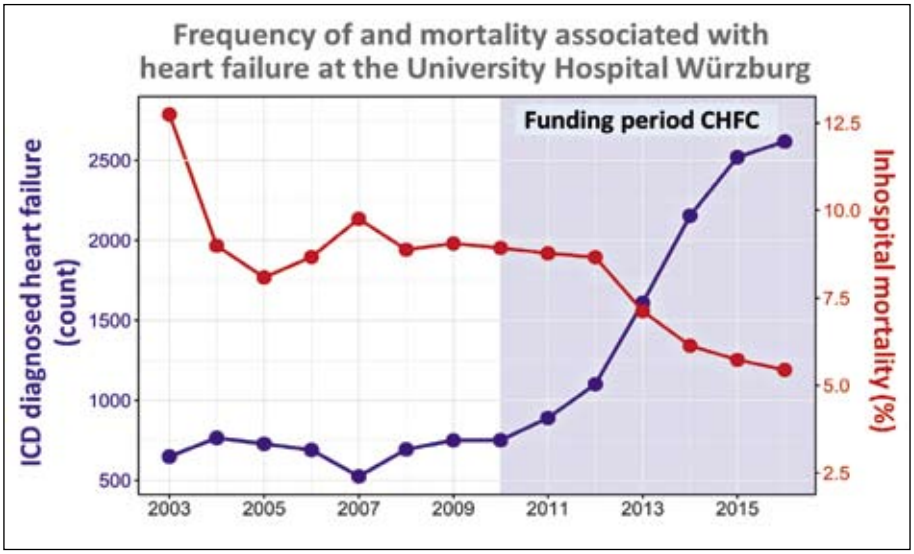


Fig. 5: Hospitalisations of heart failure patients (blue) and hospital mortality rate for heart failure (red) between 2003 und 2015 at the University Hospital Würzburg. The blue layer highlights the funding period of the CHFC.

Department of Clinical Research & Epidemiology

Head: Prof. Dr. med. Stefan Störk

The Department integrates clinical research with optimized ambulatory heart failure care. Structures are developed that aim to directly serve patient care. The utility of these structures is tested in supraregional projects or included into standard care. The following modules are located in the Department: CHFC outpatient clinics, study outpatient clinics, Joint Survey Unit for population-based studies, Clinical Trial Office for (inter-) national studies, Academic Echocardiography Core Lab, CHFC DataWareHouse, ibdw Biobank Subunit. These structures are closely interlinked with various cooperation partners at the University Hospital and the University through jointly financed positions and cooperation projects.

The CHFC outpatient clinics cover a broad interdisciplinary spectrum and are connected to the Medical Dept. I. The outpatient clinics serve about 3,600 patients per year, many of whom also participate in clinical trials. Besides general cardiology clinics, the focus is on specialized outpatient clinics for therapy-resistant hypertension, genetic heart disease, morbid obesity, terminal heart failure and heart transplantation, cardiac amyloidosis and sarcoidosis.

The Clinical Study Unit characterizes all patients in CHFC studies with the harmonized standardized CHFC dataset and serially follows these patients with examinations and endpoint assessments. Currently, about 40 clinical trials are ongoing, most of them with follow-up periods of several years. In 2018, the recruitment rate into clinical trials was 70 to 90 patients per month. In addition to the clinical routine, about 14 study visits are performed each day. The so-called Clinical Trial Office organizes the Germany-wide conduct of multinational studies, recruits and supervises study centers, recruits patients, monitors the progress of studies and communicates with the Trial Committees, – currently in 7 major projects. The Joint Survey Unit, which is operated jointly with the Institute of Clinical Biometry and Epidemiology (Prof. P. U. Heuschmann), conducts population-based studies. In the interdisciplinary STAAB program, 5,000 Würzburg citizens are followed repetitively at 4-year intervals to characterize the factors predisposing to heart failure.

The Department runs a certified Academic Echocardiography & Cardiovascular Core Lab, which organizes and quality-controls the standardization of echocardiography of the Hospital campus. In the Core Lab, training is provided to echo technicians to perform standardized, harmonized echocardiographic examinations and the respective eva-

SELECTED PUBLICATIONS

Angermann CE, Frantz S, Maack C. (2018) The Comprehensive Heart Failure Centre in Wurzburg, Germany. Eur Heart J 39:1757-1760.

Anand SS, Bosch J, Eikelboom JW, ..., Störk S, ...; COMPASS Investigators. (2018) Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 391:219-229.

Bertero E and Maack C. (2018) Metabolic remodelling in heart failure. Nat Rev Cardiol 15:457-470.

Brodehl A, Rezazadeh S, Williams T, ..., Gerull B. (2019) Mutations in ILK, encoding integrin-linked kinase, are associated with arrhythmogenic cardiomyopathy. Transl Res 2019 Feb 15. pii:S1931-5244(19)30036-2.

Chowdhury A, Aich A, Jain G, ..., Dudek J. (2018) Defective Mitochondrial Cardiolipin Remodeling Dampens HIF-1alpha Expression in Hypoxia. Cell Rep 25:561-570 e6.

Edelmann F, Knosalla C, Mörike K, Muth C, Prien P, Störk S. (2018) Chronic Heart Failure – The German Care Guideline Heart Failure. Dtsch Ärztebl Int 115:124-130.

Elabyad IA, Herrmann T, Bruns C, Bernarding J, Erni D. (2019). RF Shimming and Improved SAR Safety for MRI at 7 T With Combined Eight-Element Stepped Impedance Resonators and Traveling-Wave Antenna. IEEE Trans Microw Theo Tech 66:540 - 555.

Elabyad IA, Terekhov M, Stefanescu MR, Lohr D, Fischer M, Schreiber LM. (2019). Design and Evaluation of a Novel Symmetric Multichannel Transmit/Receive Coil Array for Cardiac MRI in Pigs at 7 T. IEEE Trans Microw Theo Tech, in press

luation of these scans, both for routine and research.

Furthermore, the Department is responsible for the further education of specialized heart failure staff, developed in cooperation with the European Society of Cardiology (ESC). From 2020 onwards, this specially trained staff must be present in all centers, clinics and practices involved in a heart failure network (HF-NET) certified by the German Society of Cardiology (DGK). Further training initiatives include physician assistants (MFAs) for heart failure, training as a clinician scientist via Curriculum Clinical Research, and the Heart Failure Specialist based on the DGK model.

The Data Warehouse captures systematically and pseudonymises the information of all outpatients and inpatients and offers faculty-wide an evaluation interface to all employees (PaDaWaN). Hypotheses can thus be tested on large numbers of patients, and new clinical trials can be planned reliably.

The diagnosis of heart failure has steadily increased after setting up the CHFC at the University Hospital and initiating its specialized care programs (see Figure 4, blue curve). At the same time, hospital mortality of patients with heart failure at the University Hospital steadily declined (red line). These two key figures are in the top segment compared with the German-wide average.

Other Research Groups

Junior Group Clement Cochain

Inflammation plays a critical role in ischemic heart disease, being involved both in the development of atherosclerotic lesions that trigger cardiac ischemia, and in the repair process taking place in the ischemic myocardium after infarction. We employed recently developed methods of immune cell profiling, namely single-cell RNA-sequencing, to analyze inflammation at an unprecedented resolution in mouse models of atherosclerosis and myocardial infarction. In atherosclerosis, we could establish the transcriptional landscape of arterial macrophages with potentially important functional implication in disease development. In a mouse model of myocardial infarction, we revealed potential new regulators of macrophage-mediated cardiac repair in the ischemic heart. These results could pave the way towards a better understanding of immune mediated cardiac repair, and new immune modulatory therapeutic strategies for ischemic heart disease.

Immunocardiology Lab
(Junior Group Gustavo Ramos)

The Immunocardiology Lab approaches the infarcted heart from a “wound healing” perspective and address how heart-specific immune responses develop after myocardial infarction (MI) and how they contribute to the tissue repair process. The primary focus is dissecting the specificity and the molecular profile of post-MI T-cell responses, for the sake of developing novel immunological tools to monitor and foster the myocardial healing process.

Cardiac Molecular Imaging
(Junior Group G. Ramos)

The research group Cardiac molecular imaging mainly focuses on pre- and clinical evaluation of novel radiopharmaceuticals to monitor various metabolic conditions of the heart. In this regard, the latest state-of-the-art small animal molecular imaging scanners are used, such as a Siemens Inveon PET or a recently installed MILabs E-class SPECT/CT. Due to close collaboration with the radiochemistry of the Department of Nuclear Medicine (Head: Professor A. K. Buck), the research group has access to a broad range of radiopharmaceuticals, which can be tested in dedicated small animal models. For instance, a rat model of myocarditis has been utilized to monitor the disease course non-invasively and to further corroborate the derived PET signal with immunohistochemistry (1). Moreover, Professor Higuchi and his team have also a strong focus on cardiac innervation imaging using novel F18 labeled PET radiotracers, e.g. by investigating the exact underlying uptake mechanism of these PET radiotracers at the sympathetic nerve terminal. Such an approach allows investigating whether these novel cardiac innervation radiotracers indeed mimic the behavior of physiologic norepinephrine at the nerve terminal (2).

Heart Brain Interaction
(Research Group A. Frey/U. Hofmann)

PD Dr. Anna Frey (Medical Clinic 1) focusses in close operation with colleagues from Neurology, Neuroradiology, Psychiatry and Neurobiology on the interaction of brain and heart. Main emphasis is the influence of heart failure on brain functioning. To further analyze those questions, we examine a cohort of patients with heart failure in a long-term manner over the duration of 5 years. Moreover, a novel optogenetic mouse model is under development to further analyze if modulation of cardiac function is able to regulate networking processes in the brain.

The group of Prof. Dr. Ulrich Hofmann (Medical Clinic 1) addresses the interaction of the cells of adaptive immunity (lymphocytes) and monocytes/macrophages representing innate immunity in myocardial diseases. The projects receive funding from the German Research Foundation (DFG) and the Deutsche Stiftung für Herzforschung. There is a close cooperation with the junior research

SELECTED PUBLICATIONS

Kolokotronis K, Kühnisch J, Klopocki E, Dartsch J, Rost S, Huculak C, Mearini G, Störk S, Carrier L, Klaassen S, Gerull B. (2019) Biallelic mutation in MYH7 and MYBPC3 leads to severe cardiomyopathy with left ventricular non-compaction phenotype. Hum Mutat. 2019 Mar 29. doi:10.1002/humu.23757.

Lohr D, Terekhov M, Weng AM, Schroeder A, Walles H, Schreiber LM. (2019) Spin echo based cardiac diffusion imaging at 7T: An ex vivo study of the porcine heart at 7T and 3T. PLoS One 14: e0213994.

Maack C, Lehrke M, Backs J, ..., de Boer RA, Heymans S. (2018) Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. Eur Heart J 39:4243-4254.

Martens J, Panzer S, van den Wijngaard JPHM, Siebes M, Schreiber LM. (2017) Analysis of coronary contrast agent transport in bolus-based quantitative myocardial perfusion MRI measurements with computational fluid dynamics simulations. Functional Imaging and Modelling of the Heart, Springer 10263:369-380.

Nickel AG, Kohlhaas M, Bertero E, Wilhelm D, Wagner M, Sequeira V, Kreusser MM, Dewenter M, Kappl R, Hoth M, Dudek J, Backs J, Maack C. (2019) CaMKII Does not Control Mitochondrial Ca(2+) Uptake in Cardiac Myocytes. J Physiol. 2019. Online ahead of print.

Sheldon R, Rose S, Ritchie D, Martens K, Connor M, Jagers J, Parboosingh J, Gerull B. (2019) Genetic Association Study in Multigenerational Kindreds with Vasovagal Syncope. Circ Arrhythm Electrophysiol. 12:e006884.

Schulz SM, Ritter O, Zniva R, Nordbeck P, Wacker C, Jack M, Groschup G, Deneke T, Puppe F, Ertl G, Angermann C, Störk S, Pauli P. (2019) Efficacy of a web-based intervention for improving psychosocial well-being in patients with implantable cardioverter-defibrillators: the randomized controlled ICD-FORUM trial. Eur Heart J pii: ehz134. doi: 10.1093/eurheartj/ehz134. [Epub ahead of print]

Störk S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, Hupfer S, Klebs S. (2017) Epidemiology of heart failure in Germany: a retrospective database study. Clin Res Cardiol 106:913-922.

group of Dr. Gustavo Ramos. Moreover, Dr. Ulrich Hofmann is the principal investigator of a clinical study which analyzes the interaction between heart-specific T-cells and myocardial infarction (KAMI study). Together with the Department of Cardiovascular Imaging of the CHFC led by Prof. Dr. Laura Schreiber, a model of myocardial infarction in pigs was established. The pig model will be further used to perform therapeutical translational studies and for the development of new MR-based imaging techniques.

Cellular Cardiology and Molecular Membrane Biology
(Research Group P. Eder-Negrin)

The Eder-Negrin research group examines the function of TRPC (Transient Receptor Potential-C-type) ion channels in chronic pathological situations (increased afterload and myocardial infarction) that lead to heart failure. The regulation of these ion channels in the heart is still elusive. We have found a mechanistic link between TRPC channels and the signaling protein calcineurin that is tightly regulated by the protein FK506-binding protein 52 (FKBP52), a member of the immunophilin family. FKBP52 inhibits a TRPC3-dependent Ca^{2+} influx in cardiomyocytes, prevents calcineurin activation and hypertrophic cardiomyocyte growth. As part of another project, the group examines the relationship between Na^{+}, the release of aldosterone and the fibrotic infiltration in the course of heart failure.

Members of the Board of Directors

Prof. Dr. Wolfgang Bauer, Prof. Dr. Martin Faßnacht-Capeller (Endocrinology), Prof. Dr. Stefan Frantz (Director), Dr. Anna Frey (all Clinic of Internal Medicine I, respectively), Prof. Dr. Thorsten Bley (Clinic of Radiology), Prof. Dr. Andreas Buck (Clinic of Nuclear Medicine), Prof. Dr. Jürgen Deckert (Clinic of Psychiatry, Psychosomatics and Psychotherapy), Dr. Petra Eder-Negrin (CHFC), Prof. Dr. Süleyman Ergün (Institute of Anatomy and Cell Biology), Prof. Dr. Georg Ertl (Medical Director, UKW), Prof. Dr. Alfred Forchel (President, University of Würzburg), Prof. Dr. Matthias Frosch (Dean, Faculty of Medicine), Prof. Dr. Peter Jakob (Institute of Experimental Physics V), Prof. Dr. Brenda Gerull (Department of Cardiovascular Genetics, CHFC), Prof. Dr. Matthias Goebeler (IZKF), Prof. Dr. Peter Heuschmann (Institute for Clinical Epidemiology and Biometry), Prof. Dr. Michaela Kuhn (Institute of Physiology), Prof. Dr. Rainer Leyh (Clinic for Thoracic and Cardiovascular Surgery), Prof. Dr. Kristina Lorenz (Institute for Pharmacology and Toxicology), Prof. Dr. Christoph Maack (Department of Translational Science, CHFC), Prof. Dr. Bernhard Nieswandt (Rudolf Virchow Center), Prof. Dr. Paul Pauli (Institute of Psychology), Prof. Dr. Laura Schreiber (Department of Cardiovascular Imaging, CHFC), Anja Simon (Business Director, UKW), Prof. Dr. Guido Stoll (Department of Neurology), Prof. Dr. Stefan Störk (CHFC), Prof. Dr. Jens Volkmann (Clinic of Neurology), Prof. Dr. Alma Zernecke-Madsen (Institute of Experimental Biomedicine).

SELECTED PUBLICATIONS

Cochain C, Vafadarnejad E, Arampatzi P, Pelisek J, Winkels H, Ley K, Wolf D, Saliba AE, Zernecke A. (2018) Single-Cell RNA-Seq Reveals the Transcriptional Landscape and Heterogeneity of Aortic Macrophages in Murine Atherosclerosis. Circ Res. 122:1661-1674.

Eder P. (2017) Cardiac Remodeling and Disease: SOCE and TRPC Signaling in Cardiac Pathology. Adv Exp Med Biol 993:505-521.

Frey A, Saxon VM, Popp S, Lehmann M, Mathes D, Pachel C, Hofmann U, Ertl G, Lesch KP, Frantz S. (2016) Early citalopram treatment increases mortality due to left ventricular rupture in mice after myocardial infarction. J Mol Cell Cardiol 98:28-36.

Frey A, Sell R, Homola GA, Malsch C, Kraft P, Gunreben I, Morbach C, Alkonyi B, Schmid E, Colonna I, Müllges W, Ertl G, Heuschmann P, Solymosi L, Schmidt R, Störk S, Stoll G. (2018) Cognitive deficits and related brain lesions in patients with chronic heart failure. JACC Heart Fail 6:583-592.

Keppner L, Heinrichs M, Rieckmann M, Demengeot J, Frantz S, Hofmann U, Ramos G. (2018) Antibodies aggravate the development of ischemic heart failure. Am J Physiol Heart Circ Physiol 315: H1358-H1367.

Kirschmer N, Bandleon S, von Ehrlich-Treuenstätt V, Hartmann S, Schaaf A, Lamprecht AK, Miranda-Laferte E, Langsenlehner T, Ritter O, Eder P. (2016) TRPC4α and TRPC4β Similarly Affect Neonatal Cardiomyocyte Survival during Chronic GPCR Stimulation. PLoS One. 11:e0168446.

Ramos GC, van den Berg A, Nunes-Silva V, Weirather J, Peters L, Burkard M, Friedrich M, Pinnecker J, Abeßer M, Heinze KG, Schuh K, Beyersdorf N, Kerkau T, Demengeot J, Frantz S, Hofmann U (2017) Myocardial aging as a T-cell-mediated phenomenon. Proc Natl Acad Sci USA 114: E2420-E2429.

Werner RA, Wakabayashi H, Bauer J, Schütz C, Zechmeister C, Hayakawa N, Javadi MS, Lapa C, Jahns R, Ergün S, Jahns V, Higuchi T. (2018) Longitudinal 18F-FDG PET Imaging in a Rat Model of Autoimmune Myocarditis. Eur Heart J Cardiovasc Imaging doi: 10.1093/ehjci/jey119. [Epub ahead of print].

Werner RA, Kobayashi R, Javadi MS, Köck Z, Wakabayashi H, Unterecker S, Nakajima K, Lapa C, Menke A, Higuchi T. (2018) Impact of Novel Antidepressants on Cardiac Metaiodobenzyl-guanidine (mIBG) Uptake: Experimental Studies in SK-N-SH Cells and Healthy Rabbits. J Nucl Med 59:1099-1103.

Winkels H, Ehinger E, Vassallo M, Buscher K, Dinh HQ, Kobiyama K, Hamers AAJ, Cochain C, Vafadarnejad E, Saliba AE, Zernecke A, Pramod AB, Ghosh AK, Anto Michel N, Hoppe N, Hilgendorf I, Zirlik A, Hedrick CC, Ley K, Wolf D. (2018) Atlas of the Immune Cell Repertoire in Mouse Atherosclerosis Defined by Single-Cell RNA-Sequencing and Mass Cytometry. Circ Res 122:1675-1688.

Interdisciplinary Center for Clinical Research (IZKF)

IZKF Würzburg

CONTACT DETAILS

Professor Dr. med. Matthias Goebeler
(Spokesperson)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/201-56431
Fax: 0931/201-656430
E-mail: izkf@uk-wuerzburg.de
www.med.uni-wuerzburg.de/izkf

Professor Dr. med. Hermann Einsele
(Deputy Spokesperson)
Phone: 0931/201-40001

Dr. Andrea Thelen-Frölich
(Managing Director)
Phone: 0931/201-56430

Assignments and Structure

The IZKF Würzburg organizes the internal research funding for the Faculty of Medicine. Its aim is to strengthen clinical research by funding interdisciplinary cooperation between clinical research and biomedical basic research.

Three key instruments characterise its work:
- to support interdisciplinary research projects within the center's scientific focus (Project Grants).
- to advance the systematic promotion of young researchers in medicine (Early Career Grants).
- to implement core facilities as well as flexible funding instruments to improve local structural conditions (Structural Funding).

Peer-reviewed application procedures and transparent fund management are prerequisites for the IZKF's internal research management. It is steered by three governance boards:
- the General Assembly (meeting of all IZKF members),
- the Executive Board that is responsible for the coordination of all programmes and the funding decisions
- the External Scientific Advisory Board that accompanies the Center's activities and is involved in the evaluation of project proposals.

The IZKF Würzburg was established in 1996 as part of the BMBF's "Health Promotion 2000" programme and has been fully financed by the Free State of Bavaria since 2004.
Since 2010, the annual budget has been ~5 Mill. Euros.

Project Grants

The IZKF's main research areas are particularly represented in the IZKF Project Grants. The aim of this topic-focussed funding is to align the Faculty's existing scientific priorities and to explore and enhance new topics. A close collaboration between clinical and basic research is required to receive funding. After up to three years of IZKF funding, it is expected that the projects are ready to be transferred into external third-party funds. All IZKF Project Grants are selected through an internal and external review process. The IZKF invites proposals every 18 months and receives an average of 30-35 project proposals with each call. Ten to twelve projects receive funding. In 2017 and 2018, the IZKF supported 34 projects in six project areas with the participation of 30 clinical departments and institutes.

Table 1: Overview IZKF Career Programmes

New Funding Module	Target Audience	Programme
CAREER I	… at the outset of scientific training	**MD/PhD-Fellowship Programme** The MD/PhD programme is a three-year postgraduate scientific qualification for physicians to obtain a Dr. rer. nat. (PhD). The programme was established by the IZKF and transferred to the GSLS in 2012. Since then, it has been accompanied by the IZKF's fellowship programme.
		Clinician-Scientist Programme (newly established in 2017) The programme offers a three-year structured and integrated training syllabus for physicians to obtain additional qualifications. It is integrated into the specialty training for physicians. A key element is a research rotation of 50 % for 36 months.
		Rotation Positions Young physicians working in clinic are exempted from patient care duties to take up research for up to 12 months. **RotationPLUS (newly established in 2016)** After a successful rotation, when returning to the clinical routine, it is possible to apply for this follow-up funding.en.
CAREER II	…taking the first steps towards scientific independence	**First-Time-Applicant Programme** This programme targets the commitment, creativity, and interest of talented physicians who have completed their medical doctoral theses and gained their first scientific experience. Its purpose is to support the ability to obtain third-party funding by setting up one's own working group.
		Returnee Programme (newly established in 2016) The Returnee Programme provides highly qualified young scientists from abroad with the opportunity to establish their own research project and research group in Würzburg to obtain further qualifications.
		SPECIAL PROGRAMME: Habilitation Programme for Female Physicians (integrated into the IZKF since 2017) The programme is intended to support highly qualified female physicians on their way to their habilitation and, thus, allow a greater number of women to pursue a scientific career in university medicine.
CAREER III	…with extensive research experience	**IZKF-research groups** The aim is to strengthen research in the clinical departments. The group leader positions were advertised internationally and were open to basic researchers as well as physicians. The groups receive funding for 3+2 years with up to 200,000 euros per year. In total, the Centre has supported seven IZKF research groups since 2012. In the reporting period, the funding for three groups expired as planned. Three new groups were incorporated into the funding programme: In 2017, the IZKF and the Musculoskeletal Centre jointly established a research group, headed by Dr. Marietta Herrmann, to investigate tissue regeneration in musculoskeletal diseases. In 2018, two IZKF research group leaders started their work at the DZHI: Dr. Clement Cochain and his research group are working on the topic „Determinants of macrophage function and immune cell interactions in cardiac repair." Dr. Gustavo Ramos is investigating the role of antigen-specific CD4+ T cells in myocardial infarction and its healing processes.

Fig. 1: IZKF-research group leaders (left to right) Marietta-Herrmann group, Clement Cochain, Gustavo Ramos.

Career Programmes

Scientifically active physicians represent an indispensable link between basic sciences, clinical research, and patient care. The increasing complexity and demands both in healthcare and research, with scarce resources and strong competitive pressure, leave less and less room for a career as a clinician scientist. The IZKF and the Faculty of Medicine have worked intensively on a solution to this situation and have decided to take complementary as well as new paths in the career support of young physicians by establishing the Rotation PLUS, returnee, and clinician scientist programmes. A successful DFG application to establish the clinician scientist programme UNION CVD focussed on cardiovascular disease has underlined these efforts.
With the upcoming funding period 2019 to 2021, new and existing career programmes are combined and reorganised regarding structure and budget, to ensure efficient demand-oriented funding.

Infrastructure and Structural Support

The third key instrument of the IZKF funding is to support the research infrastructure at the Faculty of Medicine. This particularly includes the possibility of establishing core facilities at the IZKF (see table 2) in which important methods, techniques, or special services for (clinical) research are bundled, enhanced, and offered.

In recent years, the development of increasingly complex and cost-intensive technologies in university medicine has posed ever-greater challenges to faculties and universities. The advancement of core facilities was a key priority of the IZKF during the reporting period. The Research Commission of the Faculty of Medicine and the IZKF are working on a local cross-faculty concept for service facilities and technology platforms.
In addition to the core facilities, the IZKF offers central funding as supporting measures for scientific routine. This includes a central fund for the support of scientific exchange

Table 2: Overview of the IZKF Core facilities

Core facility	Contact person	Service offered
Core Unit Systems Medicine	Dr. Kristina Döring	Nucleic-acid sequencing, microarray-based techniques, bioinformatics and single-cell analysis
Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw) Sub-area: Tissue	Prof. Dr. Roland Jahns Prof. Dr. Andreas Rosenwald	Safe storage and use of biomaterials (The ibdw was established in 2011, as one of five national BMBF-funded biobanks, as a central service platform of the Faculty of Medicine.)
Service Unit for Confocal Microscopy and Flow-Cytometry-Based Cell Sorting	Prof. Dr. Andreas Beilhack Prof. Dr. Wolfgang Kastenmüller	Application of fluorescence techniques (systems introduction, support, and consulting on experimental designs and optional data analysis)

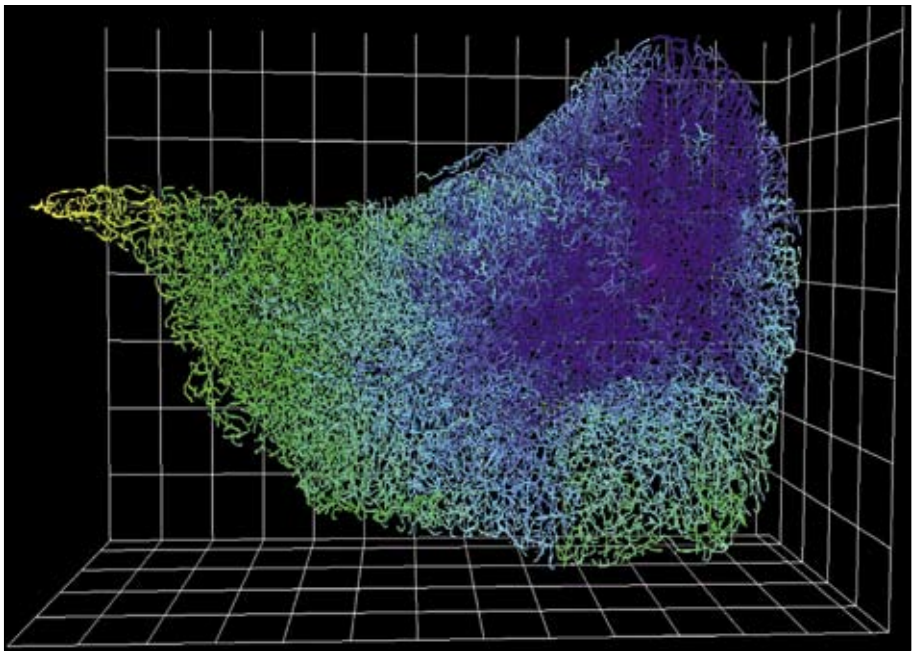


Fig. 2: 3D light sheet microscopy for the determination of molecular mechanisms in thymus regeneration. (Beilhack et al., Science Immunology 3(19), 2018)

Fig. 3: Participants of the IZKF Retreat 2018 at Kloster Banz.

and qualification activities as well as a central fund for start-up and interim financing. Here, innovative and promising projects, which can also lie outside the IZKF main research areas, can be funded for a shorter period, providing they are oriented towards third party funding. The start-up and interim financing is open to all members of the Faculty of Medicine who are eligible to apply in accordance with the regulations. The Executive Board decides on the grants to ensure efficient and flexible funding. In 2017 and 2018, a total of seven start-up and interim financing projects were supported.

SELECTED PUBLICATIONS

See also: Annual report of the IZKF (can be obtained from the IZKF office)

Cochain C, Ait-Oufella H, Zernecke A. (2018) Neutrophils promote atherosclerotic plaque destabilization in a mouse model of endotoxinaemia. Cardiovasc Res 114:1573-1574.

Duell J, Dittrich M, Bedke T, Mueller T, Eisele F, Rosenwald A, Rasche L, Hartmann E, Dandekar T, Einsele H, Topp MS. (2017) Frequency of regulatory T cells determines the outcome of the T-cell-engaging antibody blinatumomab in patients with B-precursor ALL. Leukemia 134:4341-4349.

Gogishvili T, Danhof S, Prommersberger S, Rydzek J, Schreder M, Brede C, Einsele H, Hudecek M. (2017) SLAMF7-CAR T cells eliminate myeloma and confer selective fratricide of SLAMF7+ normal lymphocytes. Blood 130:2838-2847.

Kittel-Schneider S, Hilscher M, Scholz CJ, Weber H, Grünewald L, Schwarz R, Chiocchetti AG, Reif A. (2017) Lithium-induced gene expression alterations in two peripheral cell models of bipolar disorder. World J Biol Psychiatry 27:1-14.

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

Rudolf Virchow Center for Experimental Biomedicine (RVZ)

RUDOLF VIRCHOW ZENTRUM

CONTACT DETAILS

Professor Dr. rer. nat. Caroline Kisker and Professor Dr. rer. nat. Bernhard Nieswandt (Directors of the RVZ and Speakers of the Board of Directors)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-80330
Fax: 0931/31-83255
E-mail: rvz@virchow.uni-wuerzburg.de
www.uni-wuerzburg.de/rvz

Research groups active during reporting period (2017/2018):

Professor Dr. Bettina Böttcher (since 2018) (Structural Dynamics of Biological Complexes)

Dr. Davide Calebiro (until 2018) (Single Molecule Pharmacology of G Protein-Coupled Receptors)

Dr. José Pedro Friedmann Angeli (since 2018) (Cell Death Regulation)

Professor Dr. Katrin Heinze (Molecular Microscopy)

Professor Dr. Dr. h.c. Martin Heisenberg (Brain and Behaviour)

Professor Dr. Carsten Hoffmann (until 2017) (G Protein-Coupled Receptors)

Professor Dr. Caroline Kisker (DNA Repair and Structure-Based Drug Design)

Dr. Sonja Lorenz (Molecular Mechanisms of Ubiquitin Signaling)

Dr. Hans Maric (since 2018) (Microarray-Based Development of Protein Super Binders)

Professor Dr. Bernhard Nieswandt (Vascular Biology)

Professor Dr. Hermann Schindelin (Protein Structure and Function)

Dr. Andreas Schlosser (Mass Spectrometric Analysis of Posttranslational Protein Modifications)

Dr. Grzegorz Sumara (Hormonal Regulation of Metabolism)

Dr. Ingrid Tessmer (Single Molecule Studies of DNA Repair)

Dr. Ann Wehman (Molecular Membrane Dynamics)

General Information

In 2001, the University of Würzburg won the approval in the first nationwide competition of the German Research Foundation (DFG) to establish a Research Center. The concept of the Rudolf Virchow Center (RVZ) was chosen from among 80 submitted proposals. After reconstruction of temporary accommodation, the Center was founded in 2002. In July 2009, researchers of the Rudolf Virchow Center and the Center for Infectious Disease Research moved together into a new building, the former surgical hospital. Almost 10,000 m^2 of space with excellent facilities have since been available for research, teaching and training as well as for events for the scientific community and the public. The Center received funding as the DFG Research Center for Experimental Biomedicine for 12 years until June 2013; since then it has been continued as a Central Research Institution of the University of Würzburg with funds from the State of Bavaria, the University and the Faculty of Medicine.

The Center is a central institution of the University. The professors in the Center are affiliated to the Faculty of Medicine or have a dual membership also with another faculty. The Rudolf Virchow Center is composed of different elements in research and teaching. Its interdisciplinary research projects focuses on "target proteins", central regulatory biomolecules derived from diverse cell types with a causal connection to human health.

Right from the beginning, the Rudolf Virchow Center aimed to create innovative structures within the University. Junior Research Groups were established, providing junior scientists complete independence with the option of extension into temporary research professorships for excellent group leaders. The RVZ also comprises permanent groups, often with the need for specific research infrastructure. Excellent established scientists have the possibility to concentrate on a five-year, high-risk project as Research Professors according to the model of American Howard Hughes professorships. In addition to its major focus on research, the Rudolf Virchow Center was also involved in planning and establishing the new Bachelor and Master's Program in Biomedicine, initiated in the winter term 2001/02 at the University of Würzburg. In addition, the RVZ is involved in the more recently established programs in Biochemistry (BSc/MSc), the MSc program Translational Medicine and the FOKUS Program Life Sciences. At the level of PhD students, a program for Biomedicine was established that served as the nucleus for a large-scale reform of graduate training at the University culminating in the foundation of the Graduate School of Life Sciences. This school won approval twice in two successive rounds of the national Excellence Initiative (2006/2012). The Public Science Center of the Rudolf Virchow Center is in close contact with the media and informs the public about current research projects. The Center also offers a variety of laboratory projects and events for school kids and adults, providing an opportunity to explore science first-hand.

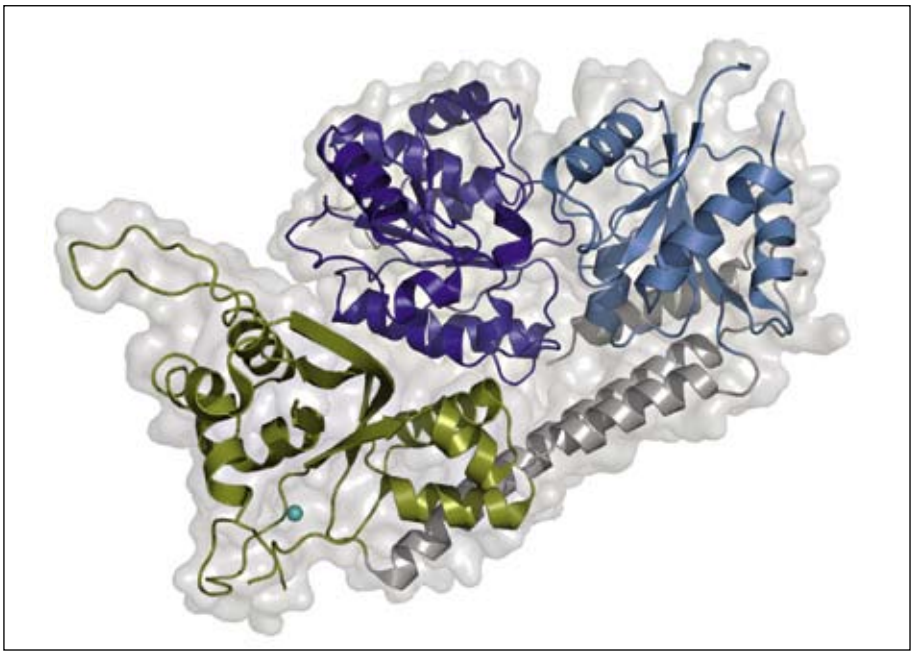


Fig. 1: Human RecQ4 helicase structure (amino acids 449-1111) involved in the the maintenance of genomic integrity. Picture: Group Kisker/RVZ

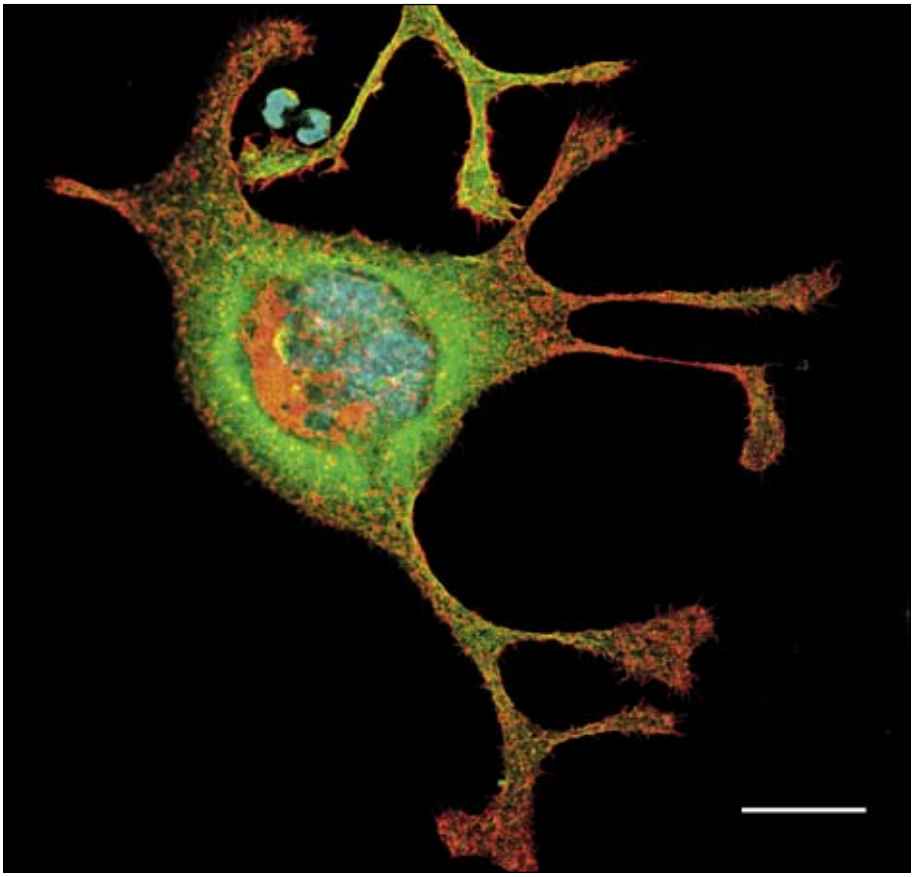


Fig. 2: A cultured bone marrow megakaryocyte forming proplatelets. Picture: Group Nieswandt/RVZ

Major Research Interests

During the reporting period 2017/2018 fifteen research groups were established at the Rudolf Virchow Center. Research at the RVZ focuses on "target proteins" covering four broad research fields with multiple overlap: (1) Protein Structure and Function, (2) Proteins in Cellular Signalling, (3) Nucleic Acid Binding Proteins and (4) Proteins in Cell-Cell Interactions and Motility.

Structural Dynamics of Biological Complexes
(B. Böttcher)
Research in Bettina Böttcher's group addresses the structural basis of how biological complexes utilize modular architectures to fulfil their diverse functions and how structural dynamics enhance this functionality. The main focus of the group is on higher-order protein complexes which adds extra functionality to proteins beyond catalysis and which includes scaffolding, provision of protective environments and control of multi-step reaction pathways. Methodologically, the Böttcher group uses electron cryo-microscopy and image processing, always adapted to the needs of the specific research projects.

Single Molecule Pharmacology of G Protein-Coupled Receptors
(D. Calebiro)
G protein-coupled receptors (GPCRs) mediate the effects of several hormones and are major drug targets. To investigate receptor nanodomains the Calebiro laboratory develops and uses advanced optical methods such as fluorescence resonance energy transfer (FRET) and single-molecule microscopy. With such approaches the group focuses on GPCRs active not only at the plasma membrane, but also – contrary to classical models of GPCR signaling – at intracellular sites. The overall goal is to contribute to the development of novel drugs with improved efficacy and fewer side effects for a variety of human diseases based on newly discovered principles of GPCR signaling.

Cell Death Regulation
(J. P. Friedmann Angeli)
The overall goal of the Friedmann group is to understand how cells cope with and adapt to oxidatively induced damage to their phospholipid membranes. In this context research is primarily devoted to characterizing a novel form of cell death – ferroptosis. In particular, the focus is on how metabolic conditions predispose cells to premature oxidation and ultimately cell death - a cellular event that is at the root of a number of degenerative diseases. Ultimately, understanding the molecular events underlying ferroptosis may lead to new strategies which would help us to modulate the cell and its life decisions.

Molecular Microscopy
(K. Heinze)
The Heinze lab develops 3D fluorescence microscopic and spectroscopic methods that allow for either spatiotemporal super-resolution or whole organ imaging with subcellular details. In an interdisciplinary approach high-resolution concepts of fluorescence microscopy are combined with tricks from the material sciences. This involves designing and producing nano-coated biocompatible surfaces, which create a signal enhancing effect and thereby increase the resolution of the imaging process. Light Sheet Fluorescence Microscopy in combination with novel computational modelling concepts is used to visualize cell-cell interactions in the larger tissue context of mouse organs.

Brain and Behaviour
(M. Heisenberg)
Research of the Heisenberg group focuses on the fruit fly *Drosophila melanogaster* with the overall goal to understand how brains organize behaviour. No other organism offers similar tools to manipulate the brain in the living, behaving organism and to relate behaviour to its underlying substrate. The group analyses operant behaviour and in particular operant learning, selective attention as well as endogenously changing perceptual hypotheses. Special attention is paid to initiating activity and the adaptive role of chance in the brain. The understanding of brain function at the behavioural level is still in its infancy.

G Protein-Coupled Receptors
(C. Hoffmann)
To transduce a signal of a hormone or prescription drug across the plasma membrane, G protein-coupled receptors (GPCRs) need to undergo conformational changes. The focus of the Hoffmann group is to investigate such conformational changes during GPCR activation and deactivation. FRET-based probes have been developed for GPCRs to image their conformational changes in living cells and in millisecond time resolution. The use of such FRET-based sensors facilitates the study of receptor-ligand interactions directly at the level of the receptor itself. This allows direct monitoring of the ef-

fects of potential future drugs at the protein level.

DNA Repair and Structure-Based Drug Design
(C. Kisker)
The Kisker laboratory uses high resolution structural biology in combination with state-of-the-art biochemical and biophysical analyses to address fundamental questions in DNA repair mechanisms as well as other mechanisms, which are important for the maintenance of genomic integrity. The Kisker group focuses mainly on the nucleotide excision repair (NER) machinery, as well as on de-ubiquitination cascades. The overall goal of these studies is to understand the underlying molecular mechanisms, which provide the basis for highly targeted structure-based drug design approaches, to combat cancer and infectious diseases more effectively and specifically.

Molecular Mechanisms of Ubiquitin Signaling
(S. Lorenz)
Cells regulate the abundance, localization, conformational dynamics and activity of proteins in response to a myriad of stimuli. A major way to accomplish this challenging task is through posttranslational protein modifications. Research in the Lorenz lab is directed at understanding the structural basis and functional consequences of posttranslational modifications with a particular focus on the enzymes of the ubiquitin system. The Lorenz group pursues an interdisciplinary approach by combining X-ray crystallography, cryo-EM, and NMR spectroscopy with various other biophysical, biochemical and cell biological techniques. Mechanistic insights are used to devise novel avenues towards targeting the ubiquitin system therapeutically in cancer and infectious diseases.

Microarray-Based Development of Protein Super Binders
(H. Maric)
The Maric group has established a highly advanced technology setup to study the molecular action of proteins with highest throughput. The research goal is to create compact, high affinity protein super binders with optimal selectivity profiles as universal molecular tools to uncover novel therapeutic principles and visualize healthy and pathophysiological processes with molecular resolution. The protein super binders obtained from robotic peptide microarrays are used to study blood coagulation, brain function as well as the onset of cancer. They are also promising labels with high binding efficacies for super-resolution fluorescence microscopy.

Vascular Biology
(B. Nieswandt)
At sites of vascular injury blood platelets come into contact with the subendothelial extracellular matrix, which triggers their activation and the formation of a hemostatic plug. This process is crucial to limit posttraumatic blood loss, but may also lead to pathological thrombus formation causing diseases such as myocardial infarction or stroke. Research of the Nieswandt group focuses on platelet biogenesis and the role of platelets in thrombotic and thrombo-inflammatory diseases with the aim to identify novel therapeutic targets for cardiovascular diseases. The group uses genetically modified mouse lines in combination with disease models to identify new strategies to inhibit the thrombotic and/or pro-inflammatory activity of platelets while preserving their hemostatic function.

Protein Structure and Function
(H. Schindelin)
Knowledge of the three-dimensional structure of biological macromolecules provides insights into their functions. Following this key principle of structural biology research activities of the Schindelin group focus on a mechanistic understanding of protein properties and functions. Using structural studies augmented with biochemical, biophysical and cell-based approaches the group concentrates on proteins modified with ubiquitin or ubiquitin-like modifiers with a focus on the activating enzymes and selected ubiquitin ligases as well as on neuronal signal transmission via inhibitory neurotransmitter receptors such as the glycine and GABA(A) receptors as well as anchoring and transport of these receptors.

Mass Spectrometric Analysis of Post-translational Protein Modifications
(A. Schlosser)
Proteins typically do not act as isolated entities. To fulfil their cellular functions they extensively interact with other proteins, either by forming stable protein complexes and molecular machines with distinct cellular functions or by transient interactions with other proteins and protein complexes. Posttranslational Protein Modifications (PTMs) such as phosphorylation, acetylation or ubiquitination are another important cellular way for regulating protein functions. The Schlosser group uses mass spectrometry to study protein-protein interactions, PTMs as well as neuropeptides and peptides presented to the immune system by the major histocompatibility complex (MHC peptides).

Hormonal Regulation of Metabolism
(G. Sumara)
Adapting to changing levels of nutrient availability is pivotal for the survival of organisms. Specific responses to fasting and feeding are regulated by a complex array of hormonal cues. Research of the Sumara lab combines genetic and biochemical approaches to understand these intricate signalling events occurring in different organs (e.g. liver and adipose tissue) during fasting, feeding and other physiological conditions and, if dysregulated, how they contribute to the development of metabolic diseases such as obesity, type 2 diabetes and non-alcoholic fatty liver disease.

SELECTED PUBLICATIONS

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

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

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

Group Heinze:
Stegner D, van Eeuwijk JMM, Angay O, Gorelashvili MG, Semeniak D, Pinnecker J, Schmithausen P, Meyer I, Friedrich M, Brede C, Beilhack A, Schulze H, Nieswandt B, Heinze KG. (2017) Thrombopoiesis is spatially regulated by the bone marrow vasculature. Nat Commun 8:127.

Group Heisenberg:
Toepfer F, Wolf R, Heisenberg M. (2018) Multistability with ambiguous visual stimuli in Drosophila orientation behavior. PLoS Biol 16: e2003113.

Group Hoffmann:
Agnetta L, Kauk M, Alonso Canizal MC, Messerer R, Holzgrabe U, Hoffmann C, Decker M. (2017) A photoswitchable dualsteric ligand controlling receptor efficacy. Angewandte Chemie International Edition 56: 7282-7287.

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

Single Molecule Studies of DNA Repair
(I. Tessmer)
Ingrid Tessmer's group aims at elucidating mechanisms of DNA processing systems. Protein-protein and protein-DNA interactions involved in DNA repair and replication are investigated using single molecule atomic force microscopy (AFM) in combination with other biophysical and biochemical techniques. AFM allows the direct visualization of molecular assemblies at the level of the individual molecules. The Tessmer group is particularly interested in understanding different DNA damage recognition strategies developed by various DNA repair mechanisms as well as their pathological disturbances.

Membrane Biology
(A. Wehman)
Throughout life cells communicate to coordinate the organism's response to stimuli. Cells release extracellular vesicles that carry signals and repair membranes. The Wehman group aims to discover how vesicles bud from the surface of cells and to reveal how cells interact with released vesicles. This research is an essential first step to induce or suppress vesicle formation, which is similar to viral budding, and to monitor or influence disease severity, especially cancer and autoimmune diseases.

Teaching

All groups offer internships and lectures for students of the Bachelor and Master's Program in Biomedicine as well as other programs. International symposia and conferences are held for scientists from the life sciences and related disciplines. PhD students of the Center are enrolled in the Virchow Graduate Program, which is part of the section Biomedicine of the Graduate School of Life Sciences (GSLS).

SELECTED PUBLICATIONS

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

Gruppe Maric:
Maric HM, Hausrat TJ, Neubert F, Dalby NO, Doose S, Sauer M, Kneussel M, Strømgaard K. (2017) Gephyrin-Binding Peptides Visualize Post-Synaptic Sites and Modulate Neurotransmission. Nat Chem Biol 13:153-160.

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

Gruppe Schindelin:
Hines RM, Maric HM, Hines DJ, Modgil A, Panzanelli P, Nakamura Y, Nathanson AJ, Cross A, Deeb T, Brandon NJ, Davies P, Fritschy JM, Schindelin H, Moss SJ. (2018) Developmental seizures and mortality result from reducing GABAA receptor α2-subunit interaction with collybistin. Nat Commun 9:3130.

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

Gruppe Sumara:
Löffler MC, Mayer AE, Trujillo Viera J, Loza Valdes A, El-Merahbi R, Ade CP, Karwen T, Schmitz W, Slotta A, Erk M, Janaki-Raman S, Matesanz N, Torres JT, Marcos M, Sabio G, Eilers M, Schulze A, Sumara G. (2018) Protein kinase D1 (PKD1) deletion in adipocytes enhances energy dissipation and protects against adiposity. EMBO J 37: pii:e99182.

Gruppe Tessmer:
Gross J, Wirth N, Tessmer I. (2017) Atomic Force Microscopy Investigations of DNA Lesion Recognition in Nucleotide Excision Repair. J Vis Exp 24: doi:10.3791/55501.

Gruppe Wehman:
Beer KB, Rivas-Castillo J, Kuhn K, Fazeli G, Karmann B, Nance JF, Stigloher C, Wehman AM. (2018) Extracellular vesicle budding is inhibited by redundant regulators of TAT-5 flippase localization and phospholipid asymmetry. Proc Natl Acad Sci U S A 115:E1127-E1136.

Research Center for Infectious Diseases (ZINF)

CONTACT DETAILS

Professor Dr. rer. nat. Cynthia Sharma
(Spokesperson since 2018)

Professor Dr. rer. nat. Jörg Vogel
(Spokesperson until 2017)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-82560
E-mail: cynthia.sharma@uni-wuerzburg.de
www.zinf.uni-wuerzburg.de/

Petra Thomas
(Office)
Phone: 0931/31-82441
E-mail: petra.thomas@uni-wuerzburg.de

General Tasks and Organization

The Research Center for Infectious Diseases (ZINF) is a central institution of the University of Würzburg that is dedicated to the research on infectious diseases, which severely impact human health. The ZINF facilitates interdisciplinary and cross-faculty communication, initiation of joint research activities as well as recruitment of extramural funding. It also fosters the joint organization of international conferences and meetings. It includes researchers from four institutes within the Faculty of Medicine, the Department of Internal Medicine II of the university hospital, as well as five departments from the faculties of Biology, Chemistry, and Pharmacy. Recently, the ZINF has grown to include new members from the recently established Helmholtz Institute for RNA-based Infection research (HIRI) and the Max-Planck-Research Groups on Systems Immunology in Würzburg. An important element of the ZINF are the independent Young Investigator groups (described below), whose work focuses on current emerging topics in microbiology and infectious diseases. The Young Investigator groups are associated with and physically located at the Institute of Molecular Infection Biology (IMIB). Notably, the Young Investigator programme has been identified as a role model for the promotion of junior scientists throughout Germany and on the international level. Based on the high scientific output and international reputation of the ZINF, it was awarded the status of a central and permanent institution of the University in 2009. In 2018, together with the Institute of Molecular Infection Biology, the ZINF celebrated its 25th anniversary. The celebrations included a one-day scientific symposium on November 14th, 2018, that allowed for exchanges between current and former ZINF members, friends and colleagues, and alumni of the Young Investigator programme. The symposium was an opportunity to reflect upon the accomplishments of ZINF, get to know the research of our current young investigators, and discuss the future of molecular infection biology research at both the University of Würzburg and the international research community.

Research Foci of ZINF Young Investigator Groups

Epigenetic gene regulation in *Trypanosoma brucei*

(N. Siegel, 2012 – 2017)

Trypanosomes are small unicellular eukaryotic parasites of insects, birds, fish, and mammals that have been around for more than 300 million years. Most species of trypanosomes are non-pathogenic but infamous exceptions exist: *Trypanosoma brucei* causes sleeping sickness in Sub-Saharan Africa and *Trypanosoma cruzi* causes Chagas disease in Central and South America. Yet, many aspects of trypanosome biology remain poorly understood, which includes the regulation of gene expression. Using the protozoan parasite *T. brucei*, the Siegel group studies epigenetic mechanisms involved in establishing transcriptional-permissive and -repressive chromatin structures. One key question is how changes in chromatin structure can help the parasite to evade the host immune response via antigenic variation. Our group is interested in how epigenetic factors such as posttranslational histone modifications, histone variants, and non-coding RNAs interact to form chromatin structures that modulate transcription. Central to this work is the use of deep sequencing technology to determine the genome-wide distribution of the various epigenetic factors.

Regulatory networks in pathogenesis

(J. C. Pérez, since 2014, joint ZINF-IZKF group)

The human body harbours a large variety of non-bacterial microbes. While these microorganisms are mostly harmless to us, some do occasionally cross the mucosal barrier and cause disease. Despite their obvious medical importance, little is known about the mechanisms whereby commensal non-bacterial microbes turn into deadly pathogens and cause disease. *Candida albicans* is the most prominent fungal species residing on various human mucosal surfaces. The majority of healthy adults carry *C. albicans* as part of their normal gut microbiota. In addition to being a human commensal, *C. albicans* is a common cause of mucosal disease in healthy people, particularly females. It is also the major cause of life-threatening fungal infections. The Pérez group seeks to gain insights into the biology of this unicellular eukaryotic organism through the study of its transcriptional regulatory circuitry. Using a combination of full-genome molecular biology methods and genetic screens in mouse models that recapitulate commensal and pathogenic niches of *C. albicans*, we have identified regulators, circuits, and target genes needed explicitly for *C. albicans* to colonize different environments of the mammalian host. The group has also established a gnotobiotic mouse model of gut colonization to investigate the

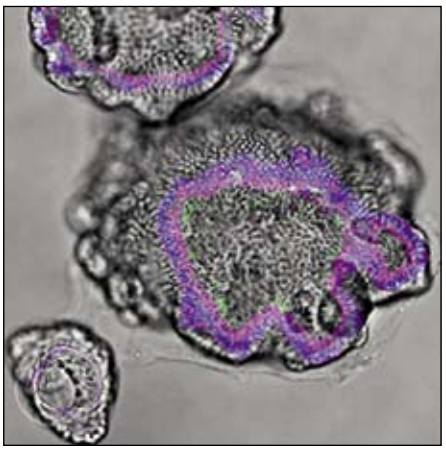


Fig.: A human stomach organoid infected with Helicobacter pylori. Grey: bright-field, green: Helicobacter pylori, pink: actin, blue: cell nucleus.

host response to commensal fungi as well as the interplay between *C. albicans* and intestinal bacteria. Our findings illustrate the general strategies employed by members of the microbiota to proliferate as harmless commensals and how some of these microbes become life-threatening pathogens.

Organoids as host models
(S. Bartfeld, since 2015)

In order to understand disease development and advance our possibilities for therapeutic interventions, advanced models for human tissues and their diseases are needed. In the past decade, the development of new cell culture technologies has facilitated the culture of adult tissue-resident stem cells. Provided with the right cocktail of growth factors that mimic their *in vivo* niche, stem cells can divide *in vitro* and form miniature versions of the organs from which they are derived, so called organoids. One organoid contains stem cells as well as differentiated cells. The cells are primary and non-transformed, but can be renewed indefinitely in the lab due to the natural regenerative capacity of the stem cells. Organoids therefore present unprecedented possibilities for the culture of patient-derived primary cells for experiments in the lab. In close collaboration with the University Hospital Würzburg, we initiate organoids from adult stem cells resident in resection material from patients (Fig.). We focus on the gastrointestinal tract, and are particularly interested in gaining a better understanding of the barrier function of the epithelium and the interplay between infection and inflammation in cancer development. We continue to build biobanks of gastrointestinal organoids and advance our disease models for gastric cancer and infection with gastric pathogens. We also combine organoid technology with systematic approaches such as RNA sequencing and targeted approaches such as CRISPR/Cas9-mediated genetic modifications to better understand the cells and their interaction with infectious agents.

RNA Biology of *Clostridium difficile*
(F. Faber, since 2018)

Clostridioides difficile (formerly: *Clostridium difficile*) is a Gram-positive, anaerobic, spore-forming bacterium that is a leading cause of antibiotic-associated diarrhea in industrialized countries. Infection with this toxin producer causes a spectrum of pathologies ranging from mild diarrhea to fulminant and often lethal pseudomembranous colitis. The intestinal life cycle of *C. difficile* proceeds in an ever-changing gut environment, from the antibiotic-induced disruption of the microbiota to the pathogen-induced inflammatory host response, which is reflected in the complex regulatory network connecting environmental gut signals with the expression of central virulence factors. We are particularly interested in how small regulatory RNA molecules (sRNAs) are involved in the regulation of the infection process. Our knowledge of the RNA biology of *C. difficile* is lagging far behind what we know in other intestinal pathogens. To get insights into post-transcriptional regulation in *C. difficile*, we have mapped its primary transcriptome and have identified a repertoire of sRNA molecules. We are now working on the functional characterization of these new candidates and their associated RNA-binding protein partners. In addition, we plan to establish an *in vitro* 3D-tissue model based on human mucus-producing colonocytes to study the underlying molecular mechanisms of RNA-based regulation in the context of an infection. Here, we further plan to use the "Dual RNA-seq" method to uncover how the activity of the sRNAs might impact host signaling pathways during infection.

Teaching

ZINF members organize practical courses and lectures for undergraduate students in biology, medicine, and biomedicine, and also supervise Bachelor's and Master's students' thesis projects. In addition, ZINF members are also members of the Graduate School of Life Sciences (GSLS) and are involved in graduate student supervision and training. The Center also regularly organises seminars, workshops, and conferences covering current topics in medicine and microbiology.

SELECTED PUBLICATIONS OF THE ZINF YOUNG INVESTIGATOR GROUPS

Bartfeld S, Koo BK. (2017) Adult gastric stem cells and their niches. Wiley Interdiscip Rev Dev Biol. 6(2). doi: 10.1002/wdev.261.

Böhm L, Torsin S, Tint SH, Eckstein MT, Ludwig T, Pérez JC. (2017) The yeast form of the fungus Candida albicans promotes persistence in the gut of gnotobiotic mice. PLoS Pathog 13:e1006699.

del Olmo Toledo V, Puccinelli R, Fordyce PM, Pérez JC. (2018) Diversification of DNA binding specificities enabled SREBP transcription regulators to expand the repertoire of cellular functions that they govern in fungi. PLoS Genet 14:e1007884.

Meir J, Hartman E, Eckstein MT, Guiducci E, Kirchner F, Rosenwald A, LeibundGut-Landmann S, Pérez JC. (2018) Identification of Candida albicans regulatory genes governing mucosal infection. Cell Microbiol 20:e12841.

Müller LSM, Cosentino RO, Förstner KU, Guizetti J, Wedel C, Kaplan N, Janzen CJ, Arampatzi P, Vogel J, Steinbiss S, Otto TD, Saliba AE, Sebra RP, Siegel TN. (2018) Genome organization and DNA accessibility control antigenic variation in trypanosomes. Nature 563:121–125.

Pompaiah M, Bartfeld S. (2017) Gastric Organoids: An Emerging Model System to Study Helicobacter pylori Pathogenesis. Curr Top Microbiol Immunol 400:149-168.

Renz H, Adkins BD, Bartfeld S, Blumberg RS, Farber DL, Garssen J, Ghazal P, Hackam DJ, Marsland BJ, McCoy KD, Penders J, Prinz I, Verhasselt V, von Mutius E, Weiser JN, Wesemann DR, Hornef MW. (2018) The neonatal window of opportunity-early priming for life. J Allergy Clin Immunol 141:1212-1214.

Vasquez JJ, Wedel C, Cosentino RO, Siegel TN. (2018) Exploiting CRISPR-Cas9 technology to investigate individual histone modifications. Nucleic Acids Res 46:e106.

Wedel C, Förstner KU, Derr R, Siegel TN. (2017) GT-rich promoters can drive RNA pol II transcription and deposition of H2A.Z in African trypanosomes. EMBO J 36:2581–259.

Westmeier D, Posselt G, Hahlbrock A, Bartfeld S, Vallet C, Abfalter C, Docter D, Knauer SK, Wessler S, Stauber RH. (2018) Nanoparticle binding attenuates the pathobiology of gastric cancer-associated Helicobacter pylori. Nanoscale 10:1453-1463.

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Associated extra-mural institution

Helmholtz Institute for RNA-based Infection Research (HIRI)

Helmholtz Institute for RNA-based Infection Research (HIRI)

HIRI
HELMHOLTZ
Institute for RNA-based Infection Research

CONTACT DETAILS

Professor Dr. rer. nat. Jörg Vogel
(Director)

Josef-Schneider-Str. 2
97080 Würzburg

Phone: 0931/31-89587
E-mail: info@helmholtz-hiri.de
www.helmholtz-hiri.de

Alice Hohn
(Head of Administration)

Dr. rer. nat. Tim Schnyder
(Scientific Coordinator)

Mission and Structure

The Helmholtz Institute for RNA-based Infection Research (HIRI) was established in May 2017 as joint venture between the Helmholtz Centre for Infection Research (HZI) and the Julius Maximilian University of Würzburg (JMU). Located on the Würzburg medical campus, it is the first research institution worldwide to exclusively address the role of ribonucleic acids (RNAs) in infection processes. Based on novel findings, the HIRI will pioneer an integrative approach to advance RNA-based therapeutics such as anti-infectives.

Rising antimicrobial resistance, chronic infections, and (re-) emerging pathogens are among the major challenges facing humanity. RNA is increasingly understood to contribute to key regulatory and sensory processes in the cell, but the role of RNA in infection biology remains understudied. HIRI therefore combines interdisciplinary expertise with cutting-edge research infrastructure to exploit the vast potential of RNA as a diagnostic molecule, target, and drug to combat infectious diseases.

Research at HIRI focuses on four areas – bacterial infections, viral infections, host response and RNA delivery – complemented by the strategic pursuit of emerging topics in RNA research. Collaboration between groups is core to our mission and provides a vibrant research environment for our scientists and trainees. In this sense, HIRI's physical location on the historic campus of the University Hospital fosters collaboration and exchange with scientists of other institutions such as the Institute for Molecular Infection Biology (IMIB), the Rudolf Virchow Center for experimental biomedicine (RVZ) or the University Hospital Würzburg itself.

Since HIRI's establishment in May 2017, seven research group leaders from five nations have started their work at the interface of RNA and infection. As of early 2019 almost 50 scientific and administrative staff are employed by HIRI with numbers set to grow. In order to be able to accommodate additional employees in the future, a new building will be constructed at the site of the former department of Urology. The winners of an architectural competition have designed the building to fit well into the existing campus. Once finished, the new HIRI will house state-of-the-art facilities and provide space for up to 150 scientific and administrative staff. Building work will start in 2021 at the earliest. The

Fig. 1: The building of the former department of Urology will soon make way for the new HIRI. The winners of an architectural competition have designed the building to fit well into the existing campus. Once finished, it will house state-of-the-art facilities and up to 150 scientific and administrative staff. Building work will start in 2021 at the earliest.

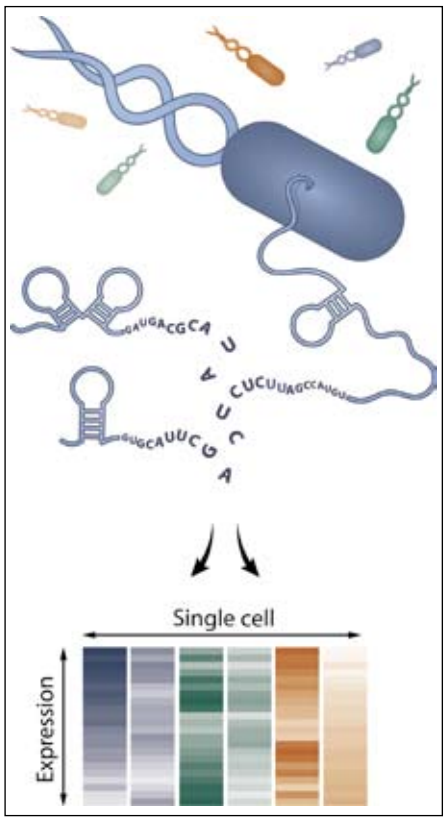


Fig. 2: A combination of single-cell analysis and RNA sequencing methods of pathogenic bacteria such as Salmonella is one of the major research interests at HIRI.

HIRI thus plays a key role in a long-term strategy to boost the impact of Würzburg as a scientific hub.

Teaching

HIRI provides an interactive and stimulating environment for students and young scientists of various disciplines. In addition to supervising undergraduate, Master and PhD students, group leaders at HIRI organize short courses on both basic and emerging topics in the fields of RNA and infection biology. These courses take place twice a year and are open to interested students from the whole of Würzburg University. Furthermore, HIRI has established the "RNA Seminar" lecture series, which takes place every other Tuesday during the semester. International high-profile scientists are invited to Würzburg to present their work to a growing and diverse audience. The RNA Seminar provides students with the opportunity to learn from experienced speakers, discuss their results and bounce their ideas.
In a collaborative effort with both HZI and JMU graduate schools HIRI established the new graduate training program "RNA and Infection" in 2018. While all HIRI PhD students are fully funded, exceptional students can apply for a Dr. Eckernkamp Fellowship, which is a dedicated studentship granted by the Vogel Foundation. The HIRI graduate program offers young scientists the opportunity to work at the interface of RNA and infection biology using state-of-the-art methods and infrastructure. Structured mentoring, central funding and three initial lab rotations are integral to the new graduate program. In particular, lab rotations make sure students get an overview of the research carried out at HIRI before embarking on the PhD journey. A first call for applications led to the recruitment of several outstanding students who start in spring 2019.

Major Research Interests

RNA Biology of Bacterial Infections
(Prof. Jörg Vogel)

HIRI's founding director, Professor Jörg Vogel, established the first HIRI group in June 2017. The aim of his work is to develop novel procedures to understand the RNA world of bacterial pathogens and use RNA-centric approaches to target pathogens and manipulate the microbiota.
The Vogel lab strives to chart the diversity of noncoding RNA functions and RNA-binding proteins in major bacterial pathogens and in the hundreds of different bacteria that make up the human microbiome. The lab develops new RNA deep sequencing-based techniques to capture the RNA world of any microbe, ideally at the single cell level. Researchers want to understand how and why bacteria use RNA as a regulator during infection and exploit this knowledge to target pathogens and edit the microbiota with precision. Projects focus on several bacteria from our major workhorse *Salmonella Typhimurium* to anaerobic microbes that are associated with colorectal cancer such as *Fusobacterium nucleatum*.

Single-Cell Analysis
(Dr. Antoine-Emmanuel Saliba)

The research of Dr Antoine-Emmanuel Saliba and his group is dedicated to using single-cell RNA-seq approaches to study heterogeneity in host responses to infections and its impact on disease outcome.
Pathogenic bacteria can reside in a mammalian host for a life-long period and chronic carriers form a reservoir leading to recurrent infections. Despite the importance of chronic infections for public health, how subsets of pathogens escape the host's immune surveillance and how the host contains the spread of bacteria are still poorly understood. Scientists within the Single-cell Analysis group develop and use single-cell transcriptomics and computational approaches to decipher the microenvironments of individual pathogens and ultimately their functional consequences on infection outcome.

SELECTED PUBLICATIONS

Cochain C, Vafadarnejad E, Arampatzi P, Pelisek J, Winkels H, Ley K, Wolf D, Saliba AE, Zernecke A. (2018) Single-cell RNA-seq reveals the transcriptional landscape and heterogeneity of aortic macrophages in murine atherosclerosis. Circ Res 122:1661-1674.

Heidrich N, Bauriedl S, Barquist L, Li L, Schoen C, Vogel J. (2017) The primary transcriptome of Neisseria meningitidis and its interaction with the RNA chaperone Hfq. Nucleic Acids Res 45:6147-6167.

Michaux C, Holmqvist E, Vasicek E, Sharan M, Barquist L, Westermann AJ, Gunn JS, Vogel J. (2017) RNA target profiles direct the discovery of virulence functions for the cold-shock proteins CspC and CspE. Proc Natl Acad Sci U S A 114:6824-6829.

Müller LSM, Cosentino RO, Förstner KU, Guizetti J, Wedel C, Kaplan N, Janzen CJ, Arampatzi P, Vogel J, Steinbiss S, Otto TD, Saliba AE, Sebra RP, Siegel TN. (2018) Genome organization and DNA accessibility control antigenic variation in trypanosomes. Nature 563:121-125.

Sharan M, Förstner KU, Eulalio A, Vogel J. (2017) APRICOT: an integrated computational pipeline for the sequence-based identification and characterization of RNA-binding proteins. Nucleic Acids Res 45:e96.

Papenfort K, Sun Y, Miyakoshi M, Vanderpool CK, Vogel J. (2013) Small RNA-mediated activation of sugar phosphatase mRNA regulates glucose homeostasis. Cell 153:426-437.

RNA Synthetic Biology
(Prof. Chase Beisel)

The lab of Prof Chase Beisel investigates and harnesses the functional diversity of CRISPR-Cas immune systems for the development of new technologies. They aim to develop a new generation of CRISPR technologies that can be employed to better understand, diagnose, and combat human infections.
The discovery of RNAs involved in adaptive immune systems in bacteria and archaea called CRISPR-Cas systems represents a milestone in molecular biology. These systems use RNA to recognize matching genetic material from selfish genetic elements bent on infecting these microbes. However, this property was quickly co-opted to form powerful tools that easily and selectively cut matching DNA sequences, which is revolutionizing our ability to edit DNA sequences at will —whether in industrial bacteria to overproduce therapeutic compounds or in humans to cure otherwise untreatable genetic diseases. These same CRISPR technologies are also being applied to rapidly and cheaply diagnose viral infections and to serve as tailored-spectrum antimicrobials that can selectively eradicate pathogens while sparing our commensal microbiota.
CRISPR technologies hold incredible potential, yet they are derived from immune systems that we are still trying to understand. The Beisel lab is exploring the full diversity of these immune systems in nature and how their functions have evolved to protect microbes against foreign invaders. Researchers are also using these insights to advance the work on infectious diseases and multidrug-resistant infections.

Recoding Mechanisms in Infections
(Jun. Prof. Neva Caliskan)

The research of Jun Prof Neva Caliskan's group aims to identify and characterize the mechanisms and regulatory implications of translational recoding in RNA viruses and pathogenic bacteria.
RNA is the central molecule that transfers genetic information into functional proteins of host cells and pathogens. The message encoded in the RNA can be read in multiple ways through alternative translation strategies. This adds a hidden-layer to post transcriptional gene expression and alters the proteome composition significantly during infections. The versatility of RNA molecules allows for a dynamic translational regulation in time and space and enables the pathogen and the host to respond faster to changes upon infection. With the outbreak of superbugs and emerging viruses, there is an urgent need to develop new therapeutic strategies to combat infections. Can targeting alternative translation pathways be an option to combat deadly pathogens? Can we specifically interfere with mRNA structures as a novel anti-infective strategy? The Caliskan lab seeks answers to these questions by developing methods to investigate RNA structure and translation in real time using a multidisciplinary approach ranging from single molecules to cells.

Integrative Informatics in Infection Biology
(Jun. Prof. Lars Barquist)

The group of Jun Prof Lars Barquist will develop systems approaches to RNA and infection, using modern visualization, data sci-

Fig. 2: HIRI group leaders, JMU President Prof. Forchel, Dean Prof. Frosch, HZI Director Prof. Heinz and Dr. Schunk of the Vogel Foundation gather for a photo at HIRI's first birthday. This occasion also marks the implementation of the Dr. Eckernkamp Fellowship of the Vogel Foundation for exceptional doctoral students at HIRI.

ence, and machine learning technologies to integrate large-scale functional genomics data.
The lab analyses and integrates genomic and post-genomic data to provide insight into bacterial pathogenesis. Researchers have been active in developing bioinformatics techniques to analyze and interpret the results of experiments using high-throughput sequencing, including transposon-insertion sequencing, CLIP-seq, and dual RNA-seq. Scientists are actively developing new algorithms and statistical approaches to these kinds of data to provide insight into both host-microbe interactions and RNA-based regulation in bacterial pathogens. Furthermore, the Barquist lab has also been active in applying machine learning tools to the evolution of bacterial pathogens using genome sequencing data. By dissecting the architecture of these machines, lab members have been able to extract new insights into how pathogens adapt to their hosts. The lab is currently investigating ways to incorporate additional layers of information, such as gene expression information and mutations in non-coding RNA, into such models to provide a more comprehensive view of pathogen behavior.

Host-Pathogen-Microbiota Interactions
(Jun. Prof. Alexander Westermann)

The group of Jun Prof Alexander Westermann focuses on investigating molecular RNA-based mechanisms that allow infecting pathogens to outcompete the resident microbiota. Their research centers on the identification and functional characterization of non-coding RNA molecules in pathogens, microbiota members and the host, to identify those RNAs that may serve as biomarkers for diagnostics or as therapeutic targets.
Bacterial infections of mammalian hosts are arguably among the most complex biological processes, often comprising a multitude of interacting organisms from different kingdoms. How do bacterial pathogens promote infection and what defense mechanisms do they have to overcome in order to colonize? What molecular mechanisms manifest the protective role of the microbiota against pathogenic attack? And what is the role of noncoding RNAs in host-microbiota-pathogen crosstalk? These and related questions are addressed by the Westermann lab. Using cutting-edge RNA-sequencing-based techniques, research centers on the identification and functional characterization of noncoding RNA molecules in the enteric pathogen *Salmonella Typhimurium*, the important intestinal microbiota member *Bacteroides thetaiotaomicron*, and the human host, to identify those RNAs that may serve as biomarkers for diagnosis or as therapeutic targets in the future. In addition to contributing to the field by the development of novel RNA-seq-based technologies for complex infection settings, researchers aim to increase the knowledge about functions of regulatory RNA molecules and RNA-binding proteins in bacterial pathogenesis and symbiosis, by gaining biological insights from mechanistic studies.

Genome Architecture and Evolution of RNA Viruses
(Jun. Prof. Redmond Smyth)

The Helmholtz Young Investigator Group of Jun Prof Redmond Smyth investigates how RNA viruses regulate their replication and evolution using non-coding RNA structures within their genomes.
RNA viruses are a major threat to human health and responsible for millions of deaths each year. Their replication is orchestrated by the RNA genome, which encodes for viral proteins needed to hijack the host cell. Traditionally, infectious disease research has focused on blocking viral replication by inhibiting these proteins. However, we now appreciate that the genomes of RNA viruses are not just passive carriers of protein coding information, but active participants in the viral infection process through the action of non-coding RNA. The lab studies the structure and function of viral non-coding RNA, with the goal of harnessing the resulting knowledge in the design of next generation RNA-based therapies.

SELECTED PUBLICATIONS

Caliskan N, Wohlgemuth I, Korniy N, Pearson M, Peske F, Rodnina MV. (2017) Conditional Switch between Frameshifting Regimes upon Translation of dnaX mRNA. Mol Cell 66:558-567.e4.

Caliskan N, Katunin VI, Belardinelli R, Peske F, Rodnina MV. (2014) Programmed-1 frameshifting by kinetic partitioning during impeded translocation. Cell 157:1619-1631.

Dugar G, Leenay RT, Eisenbart SK, Bischler T, Aul BU, Beisel CL, Sharma CM. (2018) CRISPR RNA-Dependent Binding and Cleavage of Endogenous RNAs by the Campylobacter jejuni Cas9. Mol Cell 69:893-905.e7.

Holmqvist E, Li L, Bischler T, Barquist L, Vogel J. (2018) Global Maps of ProQ Binding In Vivo Reveal Target Recognition via RNA Structure and Stability Control at mRNA 3' Ends. Mol Cell 70:971-982.e6.

Marshall R, Maxwell CS, Collins SP, Jacobsen T, Luo ML, Begemann MB, Gray BN, January E, Singer A, He Y, Beisel CL, Noireaux V. (2018) Rapid and Scalable Characterization of CRISPR Technologies Using an E. coli Cell-Free Transcription-Translation System. Mol Cell 69:146-157.e3.

Smyth RP, Smith MR, Jousset AC, Despons L, Laumond G, Decoville T, Cattenoz P, Moog C, Jossinet F, Mougel M, Paillart JC, von Kleist M, Marquet R. (2018) In cell mutational interference mapping experiment (in cell MIME) identifies the 5' polyadenylation signal as a dual regulator of HIV-1 genomic RNA production and packaging. Nucleic Acids Res 46:e57.

Smyth RP, Despons L, Huili G, Bernacchi S, Hijnen M, Mak J, Jossinet F, Weixi Li, Paillart Jean-Christophe, von Kleist M, Marquet R. (2015) Mutational Interference Mapping Experiment (MIME) for studying the relationship between RNA structure and function. Nat Methods 12:866-872.

Stapels DAC, Hill PWS, Westermann AJ, Fisher R, Thurston TL, Saliba A-E, Blommestein I, Vogel J, Helaine S. (2018) Salmonella persisters undermine host immune defences during antibiotic treatment. Science 362:1156-1160.

Wheeler NE, Gardner PP, Barquist L. (2018) Machine learning identifies signatures of host adaptation in the bacterial pathogen Salmonella enterica. PLoS Genet 14:e1007333.

Westermann AJ, Förstner KU, Amman F, Barquist L, Chao Y, Schulte LN, Müller L, Reinhardt R, Stadler PF, Vogel J. (2016) Dual RNA-seq unveils noncoding RNA functions in Salmonella-host interplay. Nature 529:496-501.

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Collaborative Research Centers and Transregios

Collaborative Research Center 688, Mechanisms and Imaging of Cell-Cell Interactions in the Cardiovascular System

CONTACT DETAILS

Professor Dr. rer. nat. Bernhard Nieswandt (Speaker)

Institute of Experimental Biomedicine University Hospital and Rudolf Virchow Center
Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-80406
Fax: 0931/31-61652
E-mail: sfb688@ukw.de
www.sfb688.de

Professor Dr. med. Georg Ertl (Vice-Speaker)
Phone: 0931/201-39001

Professor Dr. med. Michaela Kuhn (Vice-Speaker)
Phone: 0931/31-82720

Dr. rer. nat. David Stegner (Scientific Secretary)
Phone: 0931/31-80419

Kerstin Siegmann (Office)
Phone: 0931/31-81457

Mission and Structure

Cardio- and cerebrovascular diseases account for most fatalities worldwide. The SFB 688 collaborative research center, founded in 2006, ended in December 2017 after 12 successful years. It created a unique research network involving scientists and clinicians from four faculties and eleven institutes and clinics of the University of Würzburg. The aim was to understand central pathophysiological processes in vascular disorders with a clear focus on identification of new signaling molecules and cell-cell interactions to create innovative concepts for prevention and treatment of cardio- and cerebrovascular diseases.
Of special importance was the development of innovative imaging techniques such as magnetic resonance (MR) imaging methods, positron-emission tomography (PET) and *in vivo* fluorescence microscopy that allow *in vivo* monitoring of disease progression in experimental models and patients with vascular disorders.

Major Research Interests

This integrated approach united complementary areas of research including molecular biology, physiology, biophysics, proteomics and bioinformatics, with clinical medicine. Molecular and pharmacological murine disease models generated in the SFB 688 allowed clinically-orientated groups to gain new insights into the development of thrombosis, myocardial infarction and stroke. Additional emphasis was put on secondary complications such as edema and scar formation that strongly influence heart and brain function. The use of novel MR contrast agents and high field MR imaging (up to 17.6 Tesla), PET tracers as well as advanced fluorescence microscopy imaging in animal models of thrombosis, myocardial infarction and stroke allow for better surveillance of heart, brain and vascular function in the living organism and provide new links to clinical medicine.

Project Area A (Fundamentals and mechanisms of vascular cell-cell interactions)

This project area investigated the initiation of pathological cell-cell interactions especially of platelets, monocytes, leukocytes and endothelial cells within the vascular system. These cells play a central role in primary hemostasis and immune defense, but also in vascular thrombosis and inflammation often leading to organ dysfunction. During the last year of the SFB 688 the following important new insights were obtained in the field of vascular cell-cell interactions:
Blood platelets are produced by large bone marrow (BM) precursor cells, megakaryocytes (MKs), which extend cytoplasmic protrusions (proplatelets) into BM sinusoids. The molecular cues that control MK polarization towards sinusoids and limit transendothelial crossing to proplatelets remained unknown. Groups from the SFB 688 identified the small GTPases Cdc42 (go-signal) and RhoA (stop-signal) as a regulatory circuit downstream of the MK-specific mechanoreceptor GPIb to coordinate polarized transendothelial plate-

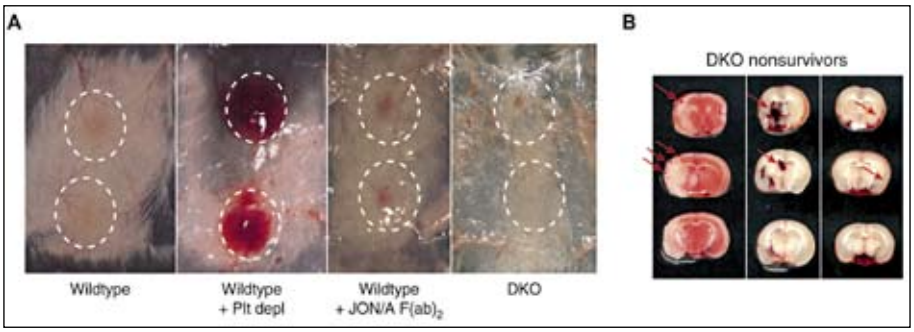


Fig. 1: Platelet degranulation is essential for hemostasis during ischemic stroke, but not during inflammation of the skin. (A) Mice were subjected to the reverse passive Arthus reaction to trigger inflammation of the skin. Platelet-depleted wildtype mice showed massive intradermal hemorrhage at the site of inflammation, whereas control mice or mice pretreated with GPIIbIIIa-blocking JON/A-F(ab)2 displayed edema formation, but no bleeding. Strikingly, no bleeding was observed in mice whose platelets are unable to release their granule content due to deficiencies of Nbeal2 and Munc13-4 (DKO). (B) In a model of experimental stroke, however, these double-deficient mice showed significantly increased mortality (50%), which was due to intra-cranial hemorrhages with microbleedings, intraparenchymal and subarachnoid hemorrhage present in the infarcted areas.

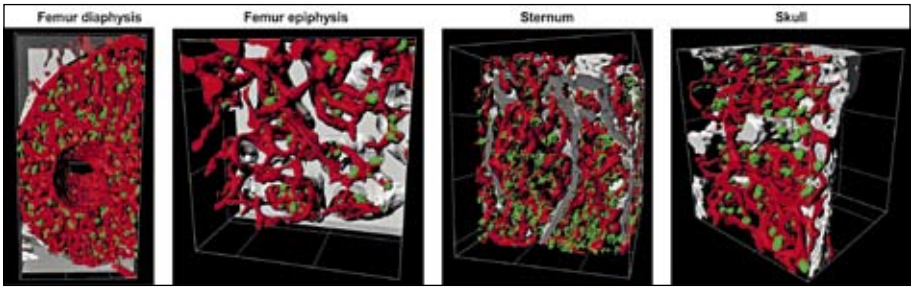


Fig. 2: The inter-bone space is fully vascularized and contains megakaryocytes (MKs). The reconstruction of bone marrow (BM) along with bone structures for different types of bone revealed that the entire BM contains MKs (green, GPIX) and blood vessels (red, CD105). Grid square = 200 µm.

let biogenesis (Dütting *et al.*, Nat Commun 2017).
It is well recognized that platelets maintain hemostasis after injury, but also during inflammation of the skin or lung as well as in the ischemic brain. The exact contribution of platelets to maintain hemostasis upon ischemic stroke was, however, unclear. Using transgenic mouse models, it could be shown that platelet granule constituents are not required to maintain hemostasis during experimental inflammation of the skin or lung (Fig. 1A; Deppermann *et al.*, Blood 2017). However, in the context of ischemic stroke defective platelet degranulation results in intracranial hemorrhages (Fig. 1B). These results uncover vascular bed-specific differences in the prevention of inflammatory bleeding.

Project Area B and Z02 (Molecular and functional imaging of the cardiovascular system and its cell-cell interactions)

Imaging techniques played a pivotal role in the SFB 688, allowing the investigation of cardiovascular diseases in rodents and humans. Here, Magnetic Resonance Imaging (MRI) and nuclear imaging (PET, SPECT and autoradiography) have been central imaging modalities. Mathematical modeling of MR parameters served as the basis for new MR methods for measuring microcirculation or quantification of microcompartments. This resulted in a new method for perfusion measurement. Local aortic pulse wave velocity (PWV) is a measure for vascular stiffness and has a predictive value for cardiovascular events. Ultra high field CMR scanners allow the quantification of local PWV in mice, however these systems are yet unable to monitor the distribution of local elasticities. In a recent study we provided a new accelerated method to quantify local aortic PWV in mice at 17.6 T, showing that total measurement time could be reduced by a factor of 6. This study demonstrated novel methods to non-invasively quantify the spatial variations in local PWV along the aorta of mice as a relevant model of atherosclerosis (Herold *et al.*, J Cardiovasc Magn Reson 2017).
Commentary to MRI and PET also fluorescence imaging has been widely used within the consortium. This is exemplified by a recent study of the SFB 688 that combined 4-color light sheet fluorescence microscopy (LSFM), a technique that can be used to scan whole organs at subcellular resolution, with multi-color two-photon microscopy (2PM), which can be used to study dynamic processes deep in the tissue of living mice. The combination of LSFM and 2PM to image the BM provided new insights into platelet biogenesis: As already indicated, platelets are released from MKs in the BM. Previous concepts suggested that MKs migrate from an endosteal niche towards vascular sinusoids during their maturation. However, LSFM revealed that the BM vasculature is an extremely dense network within which MKs are homogenously distributed and the majority of MKs is in close contact with the vasculature (Fig. 2). Slow MK migration and limited intravascular space disprove the previous concept of thrombopoiesis (Stegner *et al.,* Nat Commun 2017).

Imaging of cardiovascular cell-cell interactions was also applied to the ischemic brain to elucidate the role of platelets in secondary infarct development. It could be shown that blocking platelet glycoprotein (GP) receptor Ib resulted not only in an improved stroke outcome, but also inhibited the local inflammatory response in the ischemic brain as indicated by lower numbers of infiltrating T cells and macrophages (Schuhmann *et al.*, J Neuroinflammation 2017). These results further support the concept of thrombo-inflammation, which has been developed within our SFB 688, and underscore that thrombotic activity and inflammation are closely intertwined in acute ischemic stroke. The cell-cell interaction of immune cells, such as monocytes/macrophages or T cells, with platelets and endothelial cells facilitates microvascular dysfunction leading to secondary infarct growth.

SELECTED PUBLICATIONS

Deppermann C, Kraft P, Volz J, Schuhmann MK, Beck S, Wolf K, Stegner D, Stoll G, Nieswandt B. (2017) Platelet secretion is crucial to prevent bleeding in the ischemic brain but not in the inflamed skin or lung in mice. Blood 129:1702-1706.

Dütting S, Gaits-Iacovoni F, Stegner D, Popp M, Antkowiak A, van Eeuwijk JMM, Nurden P, Stritt S, Heib T, Aurbach K, Angay O, Cherpokova D, Heinz N, Baig AA, Gorelashvili MG, Gerner F, Heinze KG, Ware J, Krohne G, Ruggeri ZM, Nurden AT, Schulze H, Modlich U, Pleines I, Brakebusch C, Nieswandt B. (2017) A Cdc42/RhoA regulatory circuit downstream of glycoprotein Ib guides transendothelial platelet biogenesis. Nat Commun 8:15838.

Herold V, Herz S, Winter P, Gutjahr FT, Andelovic K, Bauer WR, Jakob PM. (2017) Assessment of local pulse wave velocity distribution in mice using k-t BLAST PC-CMR with semi-automatic area segmentation. J Cardiovasc Magn Reson 19:77.

Schuhmann MK, Guthmann J, Stoll G, Nieswandt B, Kraft P, Kleinschnitz C. (2017) Blocking of platelet glycoprotein receptor Ib reduces „thrombo-inflammation" in mice with acute ischemic stroke. J Neuroinflammation 14:18.

Stegner D, vanEeuwijk JMM, Angay O, Gorelashvili MG, Semeniak D, Pinnecker J, Schmithausen P, Meyer I, Friedrich M, Dütting S, Brede C, Beilhack A, Schulze H, Nieswandt B, Heinze KG. (2017) Thrombopoiesis is spatially regulated by the bone marrow vasculature. Nat Commun 8:127.

Transregio-Collaborative Research Center 34, Pathophysiology of Staphylococci in the Post-genomic Era

CONTACT DETAILS

Professor Dr. rer. nat. Thomas Rudel
(Speaker Würzburg)

Chair of Microbiology, Biocenter
Am Hubland
97074 Würzburg
Phone: 0931/31-84401
Fax: 0931/31-84402
E-mail: Thomas.rudel@biozentrum.uni-wuerzburg.de
www.staphaureus.org

PD Dr. rer. nat. Knut Ohlsen
(Deputy Speaker Würzburg)

Institut of Molecular Infection Biology
Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-82155
Fax: 0931/31-82578
E-mail: knut.ohlsen@uni-wuerzburg.de

Professor Dr. med. Barbara Bröker
(Coordinating Speaker)

University Medicine Greifswald
Department of Immunology
Ferdinand-Sauerbruch-Str. DZ7
17475 Greifswald
Phone: 03834/865595
E-mail: broeker@uni-greifswald.de

Professor Dr. rer. nat. Andreas Peschel
(Speaker Tübingen)

Eberhard-Karls-University Tübingen
Interfaculty Institute of Microbiology and Infection Medicine (IMIT)
Elfriede-Aulhorn-Straße 6
72076 Tübingen
Phone: 07071/2981515
E-mail: andreas.peschel@uni-tuebingen.de

General Information

It was the aim of this SFB/Transregional collaborative research center (TR34) to take advantage of the great opportunities offered by the post-genome era to achieve a new quality of understanding of the life processes of the important human pathogen *Staphylococcus aureus*. To reach this ambitious aim the expertise of groups in Tübingen, Münster and Würzburg in cell physiology/biochemistry and infection biology of *Staphylococcus aureus* in general was combined with the established expertise in proteomics of Gram-positive bacteria in Greifswald.

Project leader Würzburg:

PD Dr. K. Ohlsen (A2, Z3)
Prof. Dr. T. Dandekar (A8, Z1)
PD Dr. W. Ziebuhr (B4)
Prof. Dr. J. Vogel (C6)
Prof. Dr. T. Rudel (C11)
Dr. M. Fraunholz (C11)

Major Research Interests

The research projects were grouped in four parts: in part A (4 projects), the general physiology of *S. aureus* was considered, dealing with such essential chapters as the regulation of metabolism, and the stress and starvation responses with a tight connection to its pathophysiology, a theme that has frequently been underestimated. The regulation of cell-surface-bound and extracellular virulence factors was the focus of part B (3 projects). Project area C (11 projects) dealt with the behaviour of the pathogen in the host and provided new information on the host-pathogen interaction. Part Z (4 projects) offered state of the art technologies to all projects to discover and analyze *S. aureus* metabolism and pathogenicity. The projects of the groups in Würzburg dealt especially with different aspects of host-pathogen interactions. Project part A2 studied eukaryotic-type serine/threonine protein kinases (ESTPKs) and protein phosphatases that are probably involved in the regulation of several physiological pathways. In the A8 and Z1 project, functional genomics technologies, and systems biology approaches were applied to create new insights into physiology and pathophysiology of *S. aureus*. In project part B4 the impact of methionine metabolism on fitness and virulence of staphylococci has been studied. Project part C6 was interested in the cellular response of host cells after internalization of *S. aureus* by using proteomics and RNAseq technology. The aim of project C11 was the molecular definition of host signaling pathways responsible for cytotoxic effects during *S. aureus* internalization (Fig. 1). In project Z3 in vivo imaging platform techniques (bioluminescence, fluorescence, magnetic resonance imaging) have been implemented to visualize the dynamics of *S. aureus* infections and corresponding morphological and physiological changes in host tissues.

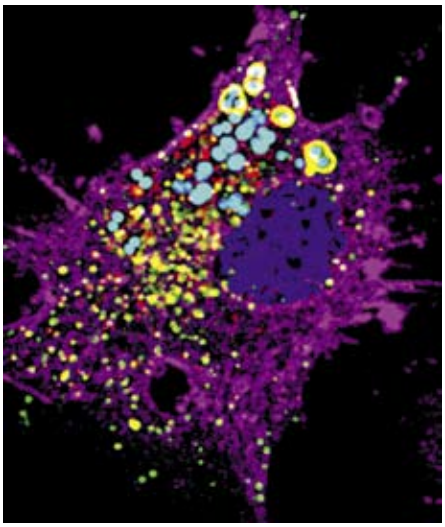


Fig.: Mammalian endothelial cells (magenta, with blue nucleus) are efficiently infected with Staphylococcus aureus (cyan). Some of the bacteria localise to autophagosomes. Image recorded by Kerstin Paprotka.

The funding period of the Transregio-Collaborative Research Center 34 ended in June 2018.

SELECTED PUBLICATIONS

Balasubramanian S, Skaf J, Holzgrabe U, Bharti R, Forstner KU, Ziebuhr W, et al. (2018) A New Bioactive Compound From the Marine Sponge-Derived Streptomyces sp. SBT348 Inhibits Staphylococcal Growth and Biofilm Formation. Front Microbiol 9:1473.

Horn J, Klepsch M, Manger M, Wolz C, Rudel T, Fraunholz M. (2018) Long Noncoding RNA SSR42 Controls Staphylococcus aureus Alpha-Toxin Transcription in Response to Environmental Stimuli. J Bacteriol 200:e00252-18.

Horn J, Stelzner K, Rudel T, Fraunholz M. (2018) Inside job: Staphylococcus aureus host-pathogen interactions. Int J Med Microbiol 308:607-624.

Jarick M, Bertsche U, Stahl M, Schultz D, Methling K, Lalk M, Stigloher C, Steger M, Schlosser A, Ohlsen K. (2018) The serine/threonine kinase Stk and the phosphatase Stp regulate cell wall synthesis in Staphylococcus aureus. Sci Rep 8:13693.

Ohlsen K, Hertlein T. (2018) Towards clinical application of non-invasive imaging to detect bacterial infections. Virulence 8:1-10.

Transregio-Collaborative Research Center 58, Fear, Anxiety, Anxiety Disorders

Fear, Anxiety, Anxiety Disorders
Furcht, Angst, Angsterkrankungen
SFB / TRR 58

CONTACT DETAILS

Professor Dr. phil. Paul Pauli
(Speaker Würzburg)

Center of Mental Health
Institute of Psychology, Chair I – Biological Psychology, Clinical Psychology and Psychotherapy
Marcusstr. 9-11
97070 Würzburg
Phone: 0931 31- 82843
Fax: 0931 31-82733
E-mail: pauli@psychologie.uni-wuerzburg.de
www.medizin.uni-muenster.de/sfbtrr58/the-project

Professor Dr. rer. nat. Hans-Christian Pape
(Coordinating Speaker)

Institute of Physiology I
Westfälische Wilhelms-University Münster
Robert-Koch-Str. 27a
48149 Münster

Professor Dr. med. Christian Büchel
(Speaker Hamburg)

Mission and Structure

The Transregio-SFB 58 was initiated in 2008 and after the second successful review in 2016 was extended until 2020. It comprises work groups of the Universities of Münster, Hamburg, and Würzburg. The speakers are H.-C. Pape (Münster, speaker), C. Büchel (Hamburg, deputy speaker), and P. Pauli in Würzburg (deputy speaker). Altogether, over 80 scientists collaborate in 18 subprojects of the SFB-TRR 58 in an interdisciplinary way, and numerous graduates and Ph.D. students undergo research training in structured Ph.D. programs, at Würzburg in the context of the GSLS and the GK1253.
Fear and anxiety, the two phylogenetic oldest emotions, are the focus of the research. These emotions may emerge in pathological anxiety states in humans and as anxiety disorders are important precursors of depressive disorders, both being the two most common mental disorders. Together with colleagues from the other two universities, the scientists in Würzburg explore the development of anxiety in its physiological as well as pathological form on a comprehensive and integrative basis from the gene over the single cell and complex cell networks to human behaviour and back. Obtaining a better understanding of the underlying complex molecular and psychological mechanisms of the development and remission of pathological anxiety will hopefully lead to innovative and individualized treatment strategies.

Research topics

Aim of the Transregio-SFB is to explore the pathogenesis of physiological and pathological anxiety from the gene level to humans suffering from anxiety disorders in a translational approach. While in the first funding period mechanisms of conditioning and extinction were in the center of interest, the projects of the subsequent funding periods focus on the mechanisms of sustained fear and fear generalization. To do so, neurobiologists and neurophysiologists, physicists and psychologists, neurologists and psychiatrists closely work together in an interdisciplinary manner. Results from model organisms like knock-out mice are validated in humans (*reverse phenotyping*) by innovative experimental approaches (*imaging genomics, epigenomics). G*enetic findings in humans are in turn be experimentally verified in animal models (*reverse genetics*). To achieve these aims, the TRR-SFB 58 consists of three closely connected areas of research with participation of scientists from Würzburg in 10 of the 19 subprojects:

Research area A- **basic science** - explores the molecular mechanisms of the development of fear in animal models. Studies of serotonin-transporter knock-out mice as best-established animal model of fear exploring the mismatch hypothesis as well as coping mechanism and the role of epigenetic programming in mediating them (A01 and A05; Lesch, vandenHove, Schmitt) are complemented by studies on the role of hippocampal BDNF in the context regulation of fear and anxiety (A10; Blum and Sendtner). As one significant result for the first time the role of tryptophan hydroxylase 2 could be defined for anxiety behaviour (Waider et al. 2017).

In research area B – **behavioral science**- healthy subjects are investigated on multiple levels with experimental psychophysiological paradigms for fear and anxiety. In each subproject, the role of genetic modulation of the behavioural response is scrutinized. Studies on context fear conditioning and generalisation in virtual reality (B01; Pauli and Wieser) and studies on the role of BDNF as mediator of the effects of stress on fear conditioning and extinction are performed. Here the role of BDNF variation for generalization could be further elaborated (Andreatta et al. 2019).

Research area C – **translational science** - focuses on the investigation of pathomechanisms which are relevant for anxiety disor-

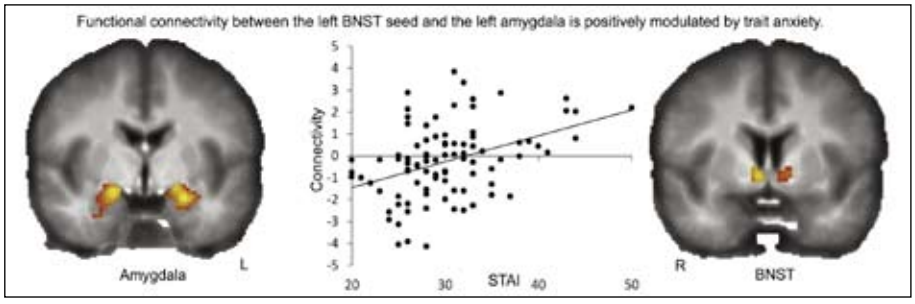


Fig. 1: Modulation of functional connectivity between the left BNST and the left amygdala by trait anxiety (kindly provided by M.Herrmann based on Brinkmann et al. 2018).

Fig. 2: Comprehensive Anxiety Center and A-Center Anxiety Disorders 12/2018.

ders and their treatment and prevention. Epigenetic experimental designs (C02; Domschke, Neufang), functional magnetic resonance imaging experimental designs (C06 and C10; Herrmann and Gamer) and machine learning (C09; Lüken) are employed. As important results the reversibility of methylation by psychotherapeutic intervention could be confirmed (Schiele et al., 2018) and for the first time the effect of anxiety traits on bed nucleus striae terminalis and amygdala connectivity could be shown (Brinkmann et al. 2018; figure 1).

The large (n=4500) cross-sectional cohort with ex ante phenotypically according to RDOC criteria and genetically well-defined control subjects for the studies of areas B and C is completed by the **central project Z02** (Domschke, Dannlowski, Lonsdorf, Lüken, Romanos, Pauli, Reif). A genome-wide association study is performed as basis for the definition of polygenic risk scores. It has already delivered new candidate molecules for research area A in the 3rd funding period, e.g. GLRB (Deckert et al. 2017). To allow for the investigation of developmental and preventive aspects the cross-sectional adult cohort is complemented by a longitudinal cohort (n=500) of children and adolescents (Romanos). The dimensional intermediate phenotype generalization is investigated as a risk factor for the development of anxiety disorders and as a target for preventive interventions.

A paradigmatic example for the interdisciplinary and synergistic research of the 1st and 2nd funding period of the SFB is the research on the novel Neuropeptide S and its receptor. Its role for fear and anxiety was studied in animal models, experimental human studies employing functional imaging techniques and in clinical human studies employing molecular genetic techniques. Results were published in more than 20 publications so far. As a translational offspring NPSR agonists are being investigated clinically as novel anxiolytics. This serves as a model for other molecular targets.

At the University of Würzburg, the following institutions currently are involved:

Faculty of Medicine, Center of Mental Health, Department of Psychiatry, Psychosomatics and Psychotherapy (project leaders: J. Deckert, M. J. Herrmann, K. P. Lesch, D. van den Hove, A. Schmitt), Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (M.Romanos) and Institute of Clinical Neurobiology (R. Blum, M. Sendtner).
Faculty of Human Sciences, Center of Mental Health, Chair of Psychology I (project leaders: P.Pauli. M.Andreatta, M.Gamer).
A. Fallgatter, A. Reif, K. Domschke, B. Gerber, A. Mühlberger and U. Lüken left for W3 chairs at Tübingen, Frankfurt and Freiburg resp. (Departments of Psychiatry and Psychotherapy), Leipzig (Institute of Neurobiology, Genetics), Regensburg and Berlin (Institutes of Psychology) respectively, but are still associated with the SFB.
To continue the successful research after the end of funding the SFB in 2020 at Würzburg, a Comprehensive Anxiety Center and an A-Center for anxiety disorders were established in 2017 (figure 2).

Symposia:

1. International Symposium on Fear, Anxiety, Anxiety Disorders; Münster, 10.-12.12.2009
2. International Symposium on Fear, Anxiety, Anxiety Disorders; Würzburg, 15.-17.9.2011
3. International Symposium on Fear, Anxiety, Anxiety Disorders; Hamburg, 11.-13.10.2013
4. International Symposium on Fear, Anxiety, Anxiety Disorders; Würzburg, 25.-27.9.2015
5. Internationales Symposium on Fear, Anxiety, Anxiety Disorders together with the 1. Congress of the World Association on Stress-related and Anxiety Disorders; Würzburg, 14.-17.9. 2017

SELECTED PUBLICATIONS

Andreatta M, Neueder D, Genheimer H, Schiele MA, Schartner C, Deckert J, Domschke K, Reif A, Wieser MJ, Pauli P. (2019) Human BDNF rs6265 polymorphism as a mediator for the generalization of contextual anxiety. J Neurosci Res 97:300-312.

Brinkmann L, Buff C, Feldker K, Neumeister P, Heitmann CY, Hofmann D, Bruchmann M, Herrmann MJ, Straube T. (2018) Inter-individual differences in trait anxiety shape the functional connectivity between the bed nucleus of the stria terminalis and the amygdala during brief threat processing. Neuroimage 166:110-116.

Deckert J, Weber H, Villmann C, Lonsdorf TB, Richter J, Andreatta M, Arias-Vasquez A, Hommers L, Kent L, Schartner C, Cichon S, Wolf C, Schaefer N, von Collenberg CR, Wachter B, Blum R, Schümann D, Scharfenort R, Schumacher J, Forstner AJ, Baumann C, Schiele MA, Notzon S, Zwanzger P, Janzing JGE, Galesloot T, Kiemeney LA, Gajewska A, Glotzbach-Schoon E, Mühlberger A, Alpers G, Fydrich T, Fehm L, Gerlach AL, Kircher T, Lang T, Ströhle A, Arolt V, Wittchen HU, Kalisch R, Büchel C, Hamm A, Nöthen MM, Romanos M, Domschke K, Pauli P, Reif A. (2017) GLRB allelic variation associated with agoraphobic cognitions, increased startle response and fear network activation: a potential neurogenetic pathway to panic disorder. Mol Psychiatry 22:1431-1439.

Schiele MA, Ziegler C, Kollert L, Katzorke A, Schartner C, Busch Y, Gromer D, Reif A, Pauli P, Deckert J, Herrmann MJ, Domschke K. (2018) Plasticity of Functional MAOA Gene Methylation in Acrophobia. Int J Neuropsychopharmacol 21:822-827.

Waider J, Popp S, Lange MD, Kern R, Kolter JF, Kobler J, Donner NC, Lowe KR, Malzbender JH, Brazell CJ, Arnold MR, Aboagye B, Schmitt-Böhrer A, Lowry CA, Pape HC, Lesch KP. (2017) Genetically driven brain serotonin deficiency facilitates panic-like escape behavior in mice. Transl Psychiatry 7:e1246.

Transregio-Collaborative Research Center 124, Pathogenic Fungi and their Human Host: Networks of Interaction - FungiNet

– FungiNet –

CONTACT DETAILS

Professor Dr. med. Hermann Einsele
(Speaker Würzburg)
University Hospital Würzburg
Department of Internal Medicine II
Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-40000
Fax: 0931/201-640001
E-mail: einsele_h@ukw.de
www.funginet.de

Professor Dr. rer. nat. Axel Brakhage
(Speaker Jena)

Institute of Microbiology
Dept. of Microbiology and Molecular Biology
Friedrich-Schiller-University Jena
Beutenbergstr. 11 a
07745 Jena
Phone: 03641/532-1001
Fax: 03641/532-0802
E-mail: Axel.brakhage@hki-jena.de

General Information

The Transregio CRC124 Jena-Würzburg was initiated and established in 2013 by the Deutsche Forschungsgemeinschaft (DFG) and is now in its second funding period. The long-term goal of this research consortium is to gain new insights into the pathophysiology of invasive mycoses by combining research activities in mycology and immunology. With the application of modern high-throughput techniques knowledge should be created as a basis for an improved diagnosis and treatment of fungal infections. Since the data acquisition requires a comprehensive data analysis and interpretation, system biology and structured bioinformatics expertise in data processing, data management and data interpretation from both sites are realized in project area B. This expertise is being used to connect the experimental projects of project areas A and C and to support a translational approach to fungal research. Project areas A and C focus on two important pathogens, *Aspergillus fumigatus* and *Candida albicans*, respectively, to investigate the interactions of the fungi with the innate and adaptive immune system. The translational approach in the Collaborative Research Center is supported by the existing infrastructure at both sites, including the Center for Sepsis Control in Jena and the Early Clinic Trial Unit and the Interdisciplinary GMP Facility in Würzburg.

Major Research Interests

Project Area A – *Aspergillus fumigatus*: From environmental microorganism to pathogen

In project area A, "*Aspergillus fumigatus*: From environmental microorganism to pathogen", the infection-relevant networks of *Aspergillus fumigatus* and host cells are being analysed employing functional genomics, transcriptomics and proteomics. Transcriptional programs and protein signalling networks of the pathogen as well as the host innate and adaptive immunity are investigated.

Aims of the project area A are: (1) to systematically investigate all levels of infection biology starting with the pathogen, via its interaction with single cell types (epithelial cells, DCs, alveolar macrophages, neutrophils, natural killer (NK) cells), more complex infection models involving several cell types at the same time, mouse models up to clinical samples, (2) to elucidate the regulatory circuits in both the pathogen and the host cells using methods of functional genome analysis, (3) to clarify the relevance of single genes / proteins in this process by applying functional analyses (generation of knock-out mutants, biochemical analysis, cell culture and animal models, RNAi), (4) to analyze material from patients based on these data, to prove the hypotheses generated in experimental (primary cells, cell cultures, animal models) and computational models. Consequently, the effects of defined cytokines on the motility, recruitment and function of tissue-resident alveolar macrophages and neutrophils after an *Aspergillus* infection with high-resolution microscopy techniques are examined. The findings are intended to improve immune reconstitution in stem cell transplant patients in the future. We will not only elucidate pathogenicity mechanisms, but also identify diagnostic biomarkers and potential targets for new antimycotic approaches, including the development of protocols for GMP-grade generation of DCs, NK and Treg cells suitable for clinical use.

Project Area B – Bioinformatics / Computational systems biology of infection

Project area B connects the project areas A and C and is essential for the comparative approach of this research consortium. In project area B data of different origin and structure will be analyzed to construct dynamic network models and, finally, to compare the networks representing both pathogens in interaction with the host. Additionally, the project INF will contribute to and guarantee a standardized acquisition and management of data from the pathogenic fungi and host cells. This standardization will be supported using both an already established data warehouse and by establishing Standard Operating Procedures. The harmonization of experiments for the pathogenic fungi, immune cells and their interaction ensures the generation of comparable and thus valuable data sets that will allow to draw significant conclusions and to construct models with high predictive power with the perspective to assist the diagnosis and personalized therapy of fungal infectious diseases. The aim is to construct network models followed by network model analysis, to support the optimal and standardized design of further experi-

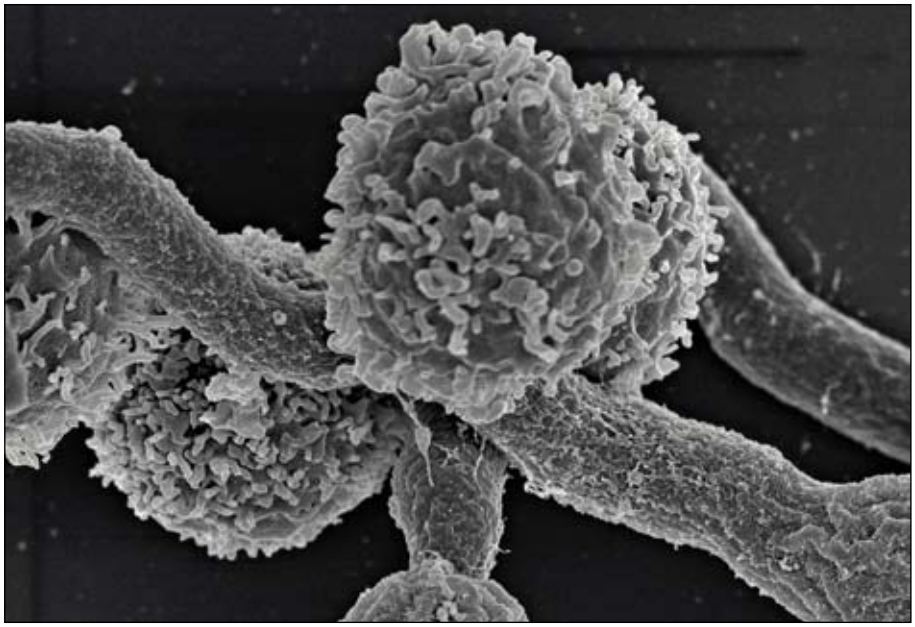


Fig. 1: Aspergillus fumigatus hyphae and activated human natural killer cells (Project A02).

ments and to draw predictions for novel strategies for diagnostics (biomarker design) and therapy.
The aims of the TR124 are: (1) Transcriptome data obtained from immune effector cells and host tissues as well as from the pathogenic fungi with the aim to investigate niche- and stage-specific expression profiles. (2) Proteome data acquired from host and pathogens. (3) Genetic, microbiological and biochemical data as well as data from clinical investigations will be received and analysed. (4) Data will be also generated in a spatiotemporal resolution to describe and model the infection process in both time and space. This will be achieved by using techniques already established by the project partners, such as confocal laser scanning microscopy (several partners), time-lapse fluorescence microscopy, light-sheet fluorescence microscopy, *in vivo* imaging and MALDI-imaging. Complementary bioinformatic methods to understand host-pathogen interactions are the metabolic reconstruction, game theory and bottom-up analyses of signalling molecules, knowledge-based networks, Boolean as well as top-down strategies such as reconstruction of dynamic gene regulatory networks and image data analysis and agent-based spatial modelling.

Project Area C – *Candida albicans*: From commensal to pathogen

Project area C focuses on the transition of *C. albicans* from commensal growth to the early stages of severe, life-threatening infections. Key aspects will be the investigation of regulatory networks governing translocation of *C. albicans* from the gut as the main reservoir to the bloodstream and consequent responses of human innate and adaptive immunity. In addition to high-throughput tools for proteome and transcriptome analysis, mutant libraries partially generated by FungiNet PIs and modern imaging technologies will be used to analyse networks of pathogen-host interplay.
Aims of the project area C are (1) to identify the molecular networks enabling and regulating tissue invasion of *C. albicans* by systematically analysing the stepwise processes preceding dissemination of the fungal pathogen, (2) to use high-throughput methods and advanced imaging tools to elucidate and functionally analyse mechanisms of the host response during interaction of different host cells and tissues (epithelium, neutrophils, monocytes, macrophages) with *C. albicans* in a range of models from infection of cell lines to more complex set-ups integrating primary human cells and *in vivo* models, (3) to characterize the mutual communication between *C. albicans* and the human host, focusing on the role of mediators secreted by both pathogen and host cells in triggering, modulating or enhancing antifungal immune responses, (4) to allocate data and information for future translational approaches to diagnosis and therapy of fungal infection, using clinical material from local biobanks to evaluate the potential of identified markers for clinical application.

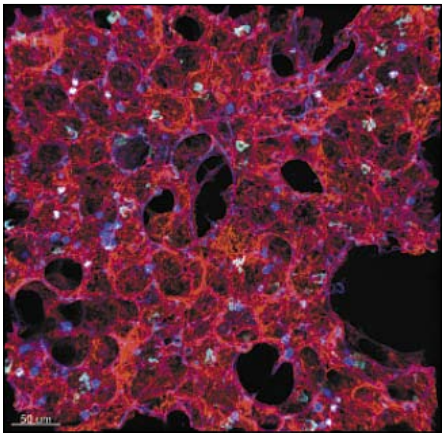


Fig. 2: The research network focuses on the interaction of the immune system with human-pathogenic fungi. Depicted is a lung with alveolar macrophages and lung epithelial cells (in red) (Project A03).

The following projects of Würzburg are included in the CRC/TR124:

A2 Prof. Dr. Hermann Einsele and Prof. Dr. Jürgen Löffler, Internal Medicine II, University Hospital Würzburg
A3 Prof. Dr. Dr. Andreas Beilhack, Internal Medicine II, University Hospital Würzburg, PD Dr. Ulrich Terpitz, Institute of Biotechnology and Prof. Dr. Katrin Heinze, Rudolf-Virchow-Center, University of Würzburg
A4 Prof. Dr. Max Topp, Internal Medicine II, University Hospital Würzburg
B1 Prof. Dr. Thomas Dandekar, Dept. of Bioinformatics, University of Würzburg
B2 Prof. Dr. Thomas Dandekar, Dr. Dr. Marcus Dittrich, Dept. of Bioinformatics, University of Würzburg
C2 Prof. Dr. Joachim Morschhäuser, Institute for Molecular Infection Biology, University of Würzburg
C6 PD Dr. Niklas Beyersdorf, Institute for Virology and Immunobiology, University of Würzburg and Prof. Dr. Peter Zipfel, Department of Infection Biology, Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute, Jena.

SELECTED PUBLICATIONS

Bergfeld A, Dasari P, Werner S, Hughes TR, Song WC, Hortschansky P, Brakhage AA, Hünig T, Zipfel PF, Beyersdorf N. (2017). Direct binding of the pH-regulated protein 1 (Pra1) from Candida albicans inhibits cytokine secretion by mouse CD4+ T cells. Front Microbiol 8:844.

Chopra M, Biehl M, Steinfatt T, Brandl A, Kums J, Amich J, Vaeth M, Kuen J, Holtappels R, Podlech J, Mottok A, Kraus S, Jordán Garrote AL, Bäuerlein CA, Brede C, Ribecchini E, Fick A, Seher A, Polz J, Ottmüller K, Baker J, Nishikii H, Ritz M, Mattenheimer K, Schwinn S, Winter T, Schäfer V, Krappmann S, Einsele H, Mueller TD, Reddehase MJ, Lutz MB, Männel DN, Berberich-Siebelt F, Wajant H, Beilhack A. (2016) Exogenous TNFR2 activation protects from acute GvHD by induction of host Treg expansion. J Exp Med 213:1881–1900.

Hellmann A, Lother J, Wurster S, Lutz M, Schmitt A, Morton O, Eyrich M, Czakai K, Einsele H, Loeffler J. (2017) Human and murine innate immune cell populations display common and distinct response patterns during their in vitro interaction with the pathogenic mould Aspergillus fumigatus. Front Immunol 8:1716.

Kalleda N, Amich J, Arslan B, Poreddy S, Mattenheimer K, Mokhtari Z, Einsele H, Brock M, Heinze KG, Beilhack A. (2016) Dynamic Immune Cell Recruitment After Murine Pulmonary Aspergillus fumigatus Infection under Different Immunosuppressive Regimens. Front Microbiol 7:1107.

Lupiañez CB, Canet LM, Carvalho A, Alcazar-Fuoli L, Springer J, Lackner M, Segura-Catena J, Comino A, Olmedo C, Ríos R, Fernández-Montoya A, Cuenca-Estrella M, Solano C, López-Nevot MÁ, Cunha C, Oliveira-Coelho A, Villaescusa T, Fianchi L, Aguado JM, Pagano L, López-Fernández E, Potenza L, Luppi M, Lass-Flörl C, Loeffler J, Einsele H, Vazquez L; PCRAGA Study Group, Jurado M, Sainz J. (2015) Polymorphisms in Host Immunity-Modulating Genes and Risk of Invasive Aspergillosis: Results from the AspBIOmics Consortium. Infect Immun 84:643-657.

Marischen L, Englert A, Schmitt AL, Einsele H, Loeffler J. (2018) Human NK cells adapt their immune response towards increasing multiplicities of infection of Aspergillus fumigatus. BMC Immunol 19:39.

Ramírez-Zavala B, Mottola A, Haubenreißer J, Schneider S, Allert S, Brunke S, Ohlsen K, Hube B, Morschhäuser J. (2017) The Snf1-activating kinase Sak1 is a key regulator of metabolic adaptation and in vivo fitness of Candida albicans. Mol Microbiol 104:989-1007.

Voltersen V, Blango MG, Herrmann S, Schmidt F, Heinekamp T, Strassburger M, Krüger T, Bacher P, Lother J, Weiss E, Hünniger K, Liu H, Hortschansky P, Scheffold A, Löffler J, Krappmann S, Nietzsche S, Kurzai O, Einsele H, Kniemeyer O, Filler SG, Reichard U, Brakhage AA. (2018) Proteome Analysis Reveals the Conidial Surface Protein CcpA Essential for Virulence of the Pathogenic Fungus Aspergillus fumigatus. MBio 9:pii: e01557-18.

Ziegler S, Weiss E, Schmitt A, Schlegel J, Burgert A, Terpitz U, Sauer M, Moretta L, Sivori S, Leonhardt I, Kurzai O, Einsele H, Loeffler J. (2017) CD56 Is a Pathogen Recognition Receptor on Human Natural Killer Cells. Sci Rep 7:6138.

Transregio-Collaborative Research Center 166, High-end Light Microscopy Elucidates Membrane Receptor Function – ReceptorLight

CONTACT DETAILS

Professor Dr. rer. nat. Markus Sauer
(Deputy Speaker)

Department of Biotechnology and Biophysics
Biocenter
Am Hubland
97074 Würzburg
Phone: 0931/31-88687
Fax: 0931/31-84509
E-mail: m.sauer@uni-wuerzburg.de
www.receptorlight.uni-jena.de

General Information

Participating Institutions:
Friedrich Schiller University Jena
Julius Maximilian University Würzburg
Jena University Hospital
University Hospital of Würzburg
Rudolf Virchow Center Würzburg
Participating non-university institution:
Leibniz Institute of Photonic Technology

The Transregio Collaborative Research Center (Transregio 166) was established 2015 by the DFG and started its scientific activities on July 01, 2015. In the CRC/TR ReceptorLight, high-end light microscopy techniques with highest spatial and time resolution are applied and further developed to gain deeper insight into the function of membrane receptors. Following the binding of so-called ligands, membrane receptors generate specific signals that control the cells of an organism in a multifaceted manner. In the past years new light microscopy methods have provided essentially new insights into the function of membrane receptors, for example into the rates of ligand binding to and the conformational changes within the membrane receptors. Concerning the localization of the receptors, a spatial resolution in the range of 20 nm has been reached, which is far below the optical diffraction limit of Ernst Abbe. The working groups in Jena and Würzburg contributing to ReceptorLight bundle their methodological expertise in the field of high-end microscopy with that in the fields of physiology and biophysics of membrane receptors.

Major Research Interest

This collaboration aims to generate new insight into the function and distribution of diverse membrane receptors, and in parallel, to induce the development of new high-end light-microscopy methods. The 22 projects use e.g. super-resolution microscopy, 3 dimensional two photon calcium imaging, single-molecule strategies, tip-enhanced Raman spectroscopy, confocal patch-clamp fluorometry, Förster resonance energy transfer analyses, fluorescence correlation spectroscopy and also combinations of these methods. The participants of ReceptorLight use these methods and complex mathematical algorithms for the analysis of the data in close collaboration.

The research program is grouped in three areas:

- A Methodological developments
- B Ligand-gated ion channels
- C GPCRs and other membrane receptors

The following projects of Würzburg are included in the CRC/TR 166:

A3 Prof. Dr. Georg Nagel, Julius von Sachs Institute of Biosciences, Department of Molecular Plant Physiology and Biophysics, University Würzburg
A4 Prof. Dr. Markus Sauer, Department of

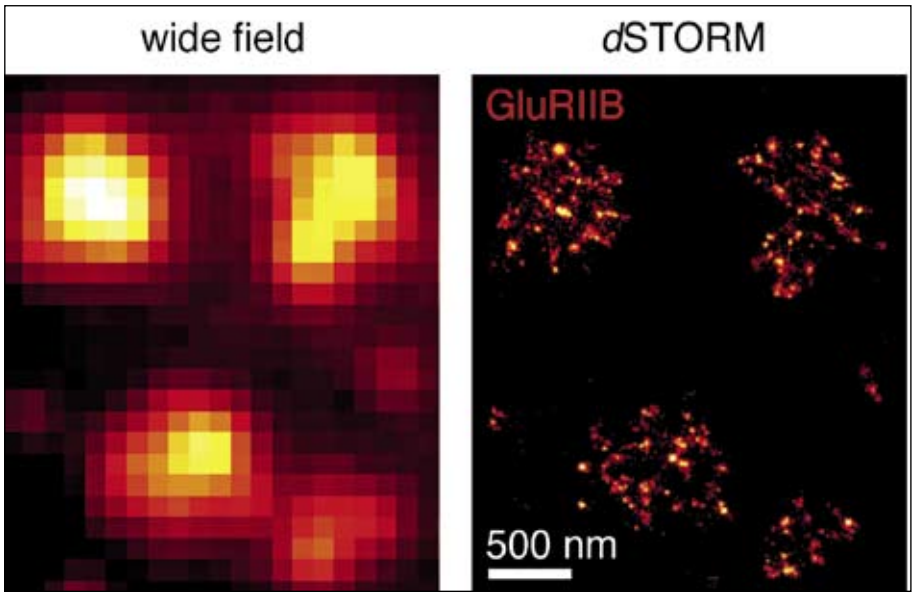


Fig. 1: Antibody staining against an ionotropic glutamate receptor subunit (GluR-IIB) at neuromuscular synapses of Drosophila illustrates the higher spatial resolution delivered by super-resolution microscopy (dSTORM, right) compared to conventional wide field microscopy (left). Images from project B4 Kittel/Sauer.

Biotechnology and Biophysics, Biocenter, University Würzburg in cooperation with Prof. Dr. Rainer Heintzmann, Institute of Physical Chemistry, University Leipzig

B2 PD Dr. Sören Doose, Department of Biotechnology and Biophysics, Biocenter, University Würzburg in cooperation with Prof. Dr. Christian Geis, Department of Neurology Hans Berger, Jena University Hospital

B4 Dr. Robert J. Kittel, Institute of Physiology, Department of Neurophysiology University Würzburg in cooperation with Prof. Dr. Markus Sauer, Department of Biotechnology and Biophysics, Biocenter, University Würzburg

B6 Prof. Dr. Manfred Heckmann, Institute of Physiology, Department of Neurophysiology University Würzburg in cooperation with Prof. Dr. Anna-Leena Sirén, Department of Neurosurgery, University Hospital of Würzburg

B8 Prof. Dr. Rainer Hedrich, Julius von Sachs Institute of Biosciences, Department of Molecular Plant Physiology and Biophysics, University Würzburg in cooperation with Prof. Dr. Dietmar Geiger, Julius von Sachs Institute of Biosciences, Department of Molecular Plant Physiology and Biophysics, University Würzburg

C1 Dr. Davide Calebiro, Institute of Pharmacology and Toxicology, Department of Pharmacology, Rudolf Virchow Center and Bio-Imaging Center, University Würzburg

C2 Prof. Dr. Carsten Hoffmann, Institute of Pharmacology and Toxicology, Department of Pharmacology, Rudolf Virchow Center and Bio-Imaging Center, University Würzburg

C3 PD Dr. Tobias Langenhan, Institute of Physiology, Department of Neurophysiology University Würzburg

C4 Prof. Dr. Martin Lohse, Institute of Pharmacology and Toxicology, Department of Pharmacology, Rudolf Virchow Center and Bio-Imaging Center, University Würzburg in cooperation with Prof. Dr. Klaus Benndorf, Institute of Physiology II, Jena University Hospital

C6 Dr. Katrin Heinze, Rudolf Virchow Center and Bio-Imaging Center, University Würzburg in cooperation with Prof. Dr. Martin Lohse, Institute of Pharmacology and Toxicology, Department of Pharmacology, Rudolf Virchow Center and Bio-Imaging Center, University Würzburg

C7 Prof. Dr. Michaela Kuhn, Institute of Physiology, Department of Cardiovascular Physiology – Physiology I, University Würzburg

SELECTED PUBLICATIONS

Gambarotto D, Zwettler FU, Le Guennec M, Schmidt-Cernohorska M, Fortun D, Borgers S, Heine J, Schloetel JG, Reuss M, Unser M, Boyden ES, Sauer M, Hamel V, Guichard P. (2019) Imaging cellular ultrastructures using expansion microscopy (U-ExM). Nat Methods 16:71-74.

Heil HS, Schreiber B, Emmerling M, Dabauvalle MC, Krohne G, Hoefling S, Kamp M, Sauer M, Heinze KG. (2018) Sharpening emitter localization in front of a tuned mirror. Light Sc Appl 7:99.

Neubert F, Beliu G, Terpitz U, Werner C, Geis C, Sauer M, Doose S. (2018) Bioorthogonal Click Chemistry Enables Site-specific Fluorescence Labeling of Functional NMDA Receptors for Super-Resolution Imaging. Angew Chem Int Ed Engl 57:16364-16369.

Sauer M, Heilemann M. (2017) Single-molecule localization microscopy in eukaryotes. Chem Rev 117:7478-7509.

Scholz N, Guan C, Nieberler M, Grotemeyer A, Maiellaro I, Gao S, Beck S, Pawlak M, Sauer M, Asan E, Rothemund S, Winkler J, Prömel S, Nagel G, Langenhan T, Kittel RJ. (2017) Mechano-dependent signaling by Latrophilin/CIRL quenches cAMP in proprioceptive neurons. Elife doi:10.7554/eLife.28360.

Transregio-Collaborative Research Center 205, The Adrenal: Central Relay in Health and Disease

CONTACT DETAILS

Professor Dr. med. Martin Fassnacht
(Spokesperson Würzburg,
Vice-Spokesperson CRC 205)

Department of Internal Medicine I
University Hospital Würzburg
Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-39200
E-mail: fassnacht_m@ukw.de

Professor Dr. med. Stefan R. Bornstein
(Spokesperson Dresden + CRC 205)

Department of Internal Medicine III
Carl Gustav Carus Faculty of Medicine
Technical University Dresden
Fetscherstr. 74
01307 Dresden
Phone: 0351/458-5955
E-mail: stefan.bornstein@uniklinikum-dresden.de

Professor Dr. med. Martin Reincke
(Spokesperson Munich, Vice-Spokesperson CRC 205)

Medical Clinic and Polyclinic IV
Ludwig-Maximilian-University Munich
Ziemssenstr. 1
80336 Munich
Phone: 089/4400-5-2101
E-mail: martin.reincke@med.uni-muenchen.de

General Information

The Collaborative Research Center (CRC) 205 was initiated and established in February 2017 by the Deutsche Forschungsgemeinschaft (DFG) and began its work on July 1st, 2017. It combines the complementary expertise of researcher from the Technical University Dresden, the Ludwig-Maximilian-University Munich and the Julius-Maximilian-University Würzburg. The research efforts of CRC/TRR 205 aim to elucidate the etiology of primary adrenal diseases and to unravel how disruption of adrenal function may contribute to common systemic diseases.
The combination of multidisciplinary expertise and the translational connection between basic and clinical areas focus on several objectives and are summarized in two directionally interconnected parts. This includes in project area A the cellular interaction within the microenvironment of the adrenal as well as the entire organism. The additional project area B focuses on the comprehensive exploration of cellular and molecular causing adrenal tumors and the translation and implementation of novel diagnostic and therapeutic strategies for the management of adrenal-related diseases.

Major Research Interests

Project Area A – Adrenal and Systemic Disease

The adrenal gland has a central role in adaptation to acute and chronic stress. It coordinates a variety of highly dynamic processes and multiple biological functions, including (neuro)endocrine, metabolic, cardiovascular and immune responses to external challenges.
Adrenal plasticity that enables rapid adjustments to external stimuli requires continuous cellular renewal, which not only enables correct sensing of the physiological demands for adrenal hormones, but also facilitates rapid organ remodeling in response to these demands. Adrenocortical, neuroendocrine and neural cells are functionally integrated within the gland and closely interact with endothelial and immune cells in the adrenal environment. This multicellular crosstalk further emphasizes the complexity characterizing adrenal biology and function. Several common pathological conditions - cardiovascular disease, depression, Alzheimers disease, metabolic syndrome and inflammatory disorders - are associated with abnormal adrenal function and blunted corticosteroid rhythmicity.

The nine research projects included in A focus on three main research parts.
(1) The adrenal function in health and disease depends on intra- and extra-adrenal modulators, including a variety of systemic stress responses. The focus lies on inflammatory and hypoxia-signaling pathways and immune-related adrenal dysfunction of adrenocortical tissue as a result of autoimmunity. (2) In addition, mechanisms regulating adrenal plasticity and regeneration is addressed elaborately; with major emphasis on therapeutic strategies for chronic adrenal insufficiency as well as congenital hyperplasia and studies concerning adrenomedullary and –cortical progenitor/stem cells in adults. (3) The central regulatory role of the gland in major systemic diseases, including metabolic-cardiovascular disorders, such as obesity, diabetes and hypertension constitutes the last main research area.

Project Area B – Adrenal-related Tumors

Adrenal tumors are among the most frequently detected neoplasms in humans and are detectable in up to 10% of elderly populations. Most of these tumors are hormonally inactive benign adrenocortical adenomas. Functional or malignant adrenal tumors, such as pheochromocytomas, neuroblastomas, adrenocortical carcinoma and aldosterone- or cortisol-producing adrenal adenomas are more rarely encountered, but accompanied by a significant disease burden.
Project area B consisting of eight projects focusing on the pathogenesis, diagnostics and promising novel therapies of adrenal-related tumors. Dysregulated adrenal function and secretion of hormones not only contributes to the highly heterogeneous disease manifestations of these tumors but also to more common disease processes (e.g., high blood pressure, obesity, inflammation) and pathologies (e.g., diabetes, heart disease, sepsis).

The eight projects of research area B focus on four of the most clinically relevant tumors of the sympatho-adrenalmedullary systems and the hypothalamic-pituitary-adrenal axis: (1) Studies about pheochromocytomas and paragangliomas respectively address the elucidation of tumorigenic mechanisms and the identification of therapeutic targets and biomarkers. (2) Aldosterone-producing adenomas or bilateral hyperplasia of the zona glomerulosa are leading to primary aldosteronism and are associated with higher morbidity. An improvement of diagnostic and therapeutic outcome by subtype stratification is an essential prerequisite for appropriate

therapeutic intervention. Studying the genetic causes leading to pathogenetic mechanisms of hyperplasia and adenomas is crucial for characterization of the disease pattern. (3) Within the wide range of adrenal tumors, the rare adrenocortical carcinoma has some unique feature. By applying multiple-omics studies, we identified two distinct subgroups based on their steroidogenic activity and expression of immune activation marker, which is along with prognosis. Additionally, putative tumor-specific (neo-)antigens using exome sequencing and innovative treatment concepts of immune modulators (e.g. checkpoint inhibitors) and blockers of adrenal steroidogenesis, will be investigated. (4) At last, the study on ACTH-dependent Cushing's syndrome aims to understand the mechanism underlying impaired negative glucocorticoid feedback on ACTH release and subsequent cortisol excess characteristics.

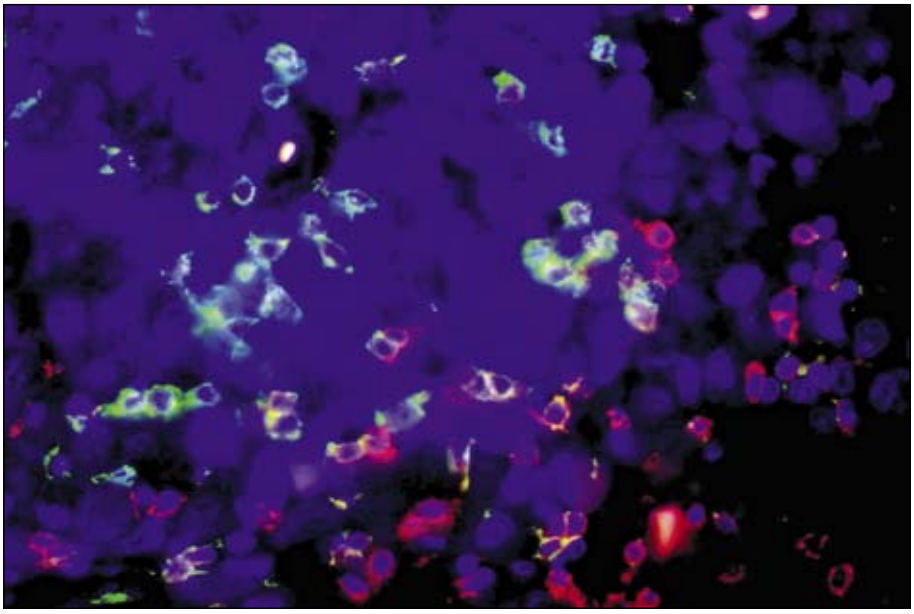


Fig.: Immunofluorescent CD3+/CD8+ lymphocytes infiltrated in adrenocortical carcinoma (red: CD3-positive T-lymphocytes, green: CD8-positive T-lymphocytes), project B16.

Associated projects C

Furthermore, there are currently five projects that are closely related to the CRC 205, but funded by other DFG sources.

The following projects of Würzburg are included in the CRC 205:

B13: **Establishment of a non-invasive, examiner-independent molecular imaging tool for aldosterone-producing tissue.** Prof. Dr. med. Stefanie Hahner, Dept. of Internal Medicine I, Div. of Endocrinology, University Hospital Würzburg

B16: **Steroid hormones and immune tolerance – learning from adrenocortical carcinoma.** Prof. Dr. med. Martin Fassnacht and PD Dr. rer.nat. Dr. med. Matthias Kroiß, Dept. of Internal Medicine I, Div. of Endocrinology, University Hospital Würzburg

C03: **Deciphering the molecular pathogenesis of Cushing's disease.** Dr. rer. nat. Silviu Sbiera, Dr. med. Timo Deutschbein, and Prof. Dr. Martin Fassnacht, Dept. of Internal Medicine I, Div. of Endocrinology, University Hospital Würzburg

C05: **At the interface between ER and mitochondria: inhibition of SOAT1 as a new treatment strategy against adrenocortical carcinoma.** PD Dr. rer.nat. Dr. med. Matthias Kroiß and Prof. Dr. med. Martin Fassnacht, Dept. of Internal Medicine I, Div. of Endocrinology, University Hospital Würzburg

S02: **Patient cohorts, biobanks and registries.** Prof. Dr. med. Martin Fassnacht, Dept. of Internal Medicine I, Div. of Endocrinology, University Hospital Würzburg

INFO1: **Infrastructure for adrenal research.** Prof. Dr. med. Martin Fassnacht, Dept. of Internal Medicine I, Div. of Endocrinology, University Hospital Würzburg

SELECTED PUBLICATIONS

Fuss CT, Treitl M, Rayes N, Podrabsky P, Fenske WK, Heinrich DA, Reincke M, Petersen TO, Fassnacht M, Quinkler M, Kickuth R, Hahner S. (2018) Radiation Exposure of Adrenal Vein Sampling - a German Multicenter Study. Eur J Endocrinol 179:261-267.

Heinze B, Fuss CT, Mulatero P, Beuschlein F, Reincke M, Mustafa M, Schirbel A, Deutschbein T, Williams TA, Rhayem Y, Quinkler M, Rayes N, Monticone S, Wild V, Gomez-Sanchez CE, Reis AC, Petersenn S, Wester HJ, Kropf S, Fassnacht M, Lang K, Herrmann K, Buck AK, Bluemel C, Hahner S. (2018) Targeting CXCR4 for Molecular Imaging of Aldosterone-Producing Adenoma. Hypertension 71:317-325.

Lippert J, Appenzeller S, Liang R, Sbiera S, Kircher S, Altieri B, Nanda I, Weigand I, Gehrig A, Steinhauer S, Riemens RJM, Rosenwald A, Müller CR, Kroiss M, Rost S, Fassnacht M, Ronchi CL. (2018) Targeted molecular analysis in adrenocortical carcinomas: a strategy towards improved personalized prognostication. J Clin Endocrinol Metab 103:4511-4523.

Megerle F, Herrmann W, Schloetelburg W, Ronchi CL, Pulzer A, Quinkler M, Beuschlein F, Hahner S, Kroiss M, Fassnacht M. (2018) Mitotane monotherapy in patients with advanced adrenocortical carcinoma. J Clin Endocrinol Metab 103:1686-1695.

Schweitzer S, Kunz M, Kurlbaum M, Vey J, Kendl S, Deutschbein T, Hahner S, Fassnacht M, Dandekar T, Kroiss M. (2019) Plasma steroid metabolome profiling for the diagnosis of adrenocortical carcinoma. Eur J Endocrinol 180:117-125.

Sun N, Wu Y, Nanba K, Sbiera S, Kircher S, Kunzke T, Aichler M, Berezowska S, Reibetanz J, Rainey WE, Fassnacht M, Walch A, Kroiss M. (2018) High resolution tissue mass spectrometry imaging reveals a refined functional anatomy of the human adult adrenal gland. Endocrinology 159:1511-1524.

Transregio-Collaborative Research Center 221, Modulation of Graft-versus-Host and Graft-versus-Leukemia Immune Responses after Allogeneic Stem Cell Transplantation

G>H
G>L
sfb transregio 221

CONTACT DETAILS

Professor Dr. med. Hermann Einsele
(Deputy Speaker)

Department of Internal Medicine II
University Hospital Würzburg
Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-40000
Fax: 0931/201-640001
E-mail: einsele_h@ukw.de
www.gvhgvl.de

Professor Dr. med. Wolfgang Herr
(Speaker)

University Hospital Regensburg
Department of Internal Medicine III
Franz-Josef-Strauß-Allee 11
93053 Regensburg
Phone: 0941/944-5501
Fax: 0941/944-5502
E-mail: wolfgang.herr@ukr.de

Professor Dr. med. Andreas Mackensen
(Deputy Speaker)

University Hospital Erlangen
Department of Medicine 5
Ulmenweg 18
91054 Erlangen
Phone: 09131/85-35954
Fax: 09131/85-35958
E-mail: andreas.mackensen@uk-erlangen.de

General Information

In the Collaborative Research Center Transregio 221 scientists of the Universities and the University Hospitals Regensburg, Erlangen and Würzburg will develop innovative immunotherapeutic strategies to improve the outcome of allogeneic hematopoietic stem-cell transplantation.

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is a curative treatment option for patients with high-risk leukemia and lymphoma and for some inherited or acquired hematopoietic deficiencies. Around half a million transplantations have been performed to date and approximately 28 million voluntary stem cell donors are currently registered world-wide. The curative potential of allo-HSCT is based on the replacement of the patient´s hematopoiesis by hematopoietic stem cells derived from a healthy donor and the immunologic eradication of residual patient hematopoietic cells by co-transplanted lymphocytes. This graft-versus-hematopoiesis reaction is mainly mediated by alloreactive donor T cells and affects malignant hematopoietic cells, thereby evoking potent graft-versus-leukemia / lymphoma (GvL) effects. Although allo-HSCT offers a unique chance to rescue patients with otherwise incurable hematologic malignancies, a significant proportion of allo-HSCT recipients develop disease relapse or progression after transplantation. Thus, there is an urgent need to better understand and ultimately strengthen GvL responses to prevent tumor escape. However, GvL-promoting strategies carry the inherent risk of inducing graft-versus-host disease (GvHD), where donor T cells attack and damage non-hematopoietic tissues. The efficient prevention and treatment of severe GvHD is a pivotal prerequisite to benefit from allo-HSCT and its potent GvL effects. Hence, the elucidation of basic mechanisms in tissue-directed graft-versus-host responses is essential to reduce the high treatment-related morbidity and mortality in allo-HSCT. GvHD-free allo-HSCT is then an ideal immunotherapy platform to boost GvL responses for the cure of patients, including those with residual disease or relapse after transplantation.

The Collaborative Research Center/ Transregio (CRC/TR) 221 takes an interdisciplinary approach to device complementary strategies to separate GvHD from GvL effects by exploring and exploiting cell signaling pathways, immune regulatory cell populations and networks and by retargeting immune effector cells against malignant cells. Ultimately, this concerted research endeavor aims to enhance the clinical safety and efficacy for patients undergoing allo-HSCT in the future.

Major Research Interests

Area A of the consortium explores T cell redirection tools (i.e. T cell receptors, chimeric antigen receptors, minor histocompatibility antigens, multi-specific antibodies) for the augmentation of hematopoiesis-specific GvL activity, and examines the reactivation of silenced GvL responses by checkpoint inhibition and through enhanced metabolic “fitness” of donor immune cells.

The projects in area B investigate cell signaling pathways (i.e. TNFR2, CD28, Wnt, NFAT, IL-7R/Batf/CSF2) and immune regulatory/ suppressive cells and networks including regulatory T cells, mesenchymal stromal cells and dendritic cells to prevent and/or treat acute and chronic GvHD. They also study the modulation of GvHD-promoting co-factors such as tissue inflammation, microbiome alterations, epithelial and endothelial damage for effective prophylaxis and therapy of severe GvHD. Promising strategies in GvL projects will be evaluated with respect to their influence on GvHD (and vice versa) and all participating institutions support translational studies evolving from the CRC/TR projects if considered sufficiently robust for clinical testing.

Project A03 - Michael Hudecek, Hermann Einsele
„CAR-engineered T cells that augment the graft-versus-leukemia effect of allogeneic HSCT”
In this project, we apply the chimeric antigen receptor (CAR) technology to augment the GvL effect of HSCT. CARs are synthetic designer receptors that redirect the specificity of T cells to recognize malignant cells. We will pursue two novel CAR targets, i.e. FLT3 in acute myeloid leukemia and SLAMF7 in multiple myeloma, and apply cutting-edge strategies to increase their efficacy (e.g. through metabolic arming) and safety (e.g. with enhanced suicide genes). To avoid GvHD, we will generate CMV-specific (endogenous TCR) CAR-T cells and employ novel in vivo models to evaluate their ability to concomitantly battle against leukemia/myeloma and CMV infection.

Project A04 - Thomas Bumm, Ralf Bargou
„Novel bi-molecular T-cell activating antibodies for personalized graft-versus-leukemia therapy.”
We aim to develop novel bi-molecular hemibody constructs that address antigen combinations instead of single target molecules for high precision immunotherapy in the context of allogeneic HSCT.

Project B01 - Friederike Berberich-Siebelt
„Selective inhibition of the transcription factor NFAT in graft-versus-host disease”
Calcineurin inhibitors block NFAT activation and protect patients from graft-versus-host disease during bone marrow transplantation. On the other hand, they exert adverse side effects and interfere with the valuable graft-versus-leukemia effect. In contrast, NFAT deficiency maintains graft-versus-leukemia activity, although still protecting from graft-versus-host disease in mouse models. Therefore, it is planned to evaluate new NFAT inhibitors in vitro, on engineered human skin and in mouse models, as well as to ablate NFAT family members by CRISPR/Cas9 ahead of cell transfer.

Project B02 – Harald Wajant
„Targeting of TNFR2 and related molecules to separate GvHD from the GvL effect"
Previously, we demonstrated in mice that targeting of TNFR2 and Fn14 allows GvL effect-sparing inhibition of GvHD by different mechanisms. Now, we will clarify whether co-targeting of TNFR2 and Fn14 yields additive or even synergistic therapeutic activity. To facilitate clinical translation of TNFR2 targeting on Tregs, we will also develop human TNFR2-specific antibody variants with Fcγ-receptor-independent agonistic activity and various IL-2 receptor targeted TNFR2 agonists. These reagents will be tested and evaluated in a variety of in vitro models but also in knock-in mice in which the ectodomain of murine TNFR2 has been replaced by the corresponding domain of human TNFR2.

Project B09 - Andreas Beilhack
„Non-classical monocyte-derived intestinal myeloid cells in allo-HSCT - Biology and therapeutic applications"
Based on our recent findings on the spatio-temporal kinetics of graft-versus-host disease (GvHD) pathophysiology we discovered a regulatory myeloid cell population that exerts protective functions during the intestinal GvHD effector phase. Employing preclinical mouse models for GvHD and GvL we will interrogate the identity, mechanism of action, and therapeutic potential of this immune-protective myeloid cell subset to improve allo-HSCT.

Project B11 - Alma Zernecke, Andreas Beilhack
„Targeting the reciprocal interaction of GvHD and atherosclerosis after allogeneic HSCT"
Patients undergoing allogeneic HSCT have an increased risk of cardiovascular disease. To address the interconnection between GvHD and atherosclerosis, we will use a GvHD-atherosclerosis mouse model and analyze GvHD activity, plaque development, as well as local and systemic immune responses. We will further focus on monocytes/macrophages and CD8+ T cells in mediating vascular inflammation and GvHD using relevant knockout mice and/or cell depletion strategies. In addition, we will investigate the potential of immunosuppressive drugs to improve GvHD-related atherosclerosis. It is our aim to define novel approaches to reduce cardiovascular events after HSCT.

Project Z01 –Andreas Rosenwald
„Pathology work-up of GvL and GvHD in mice and men"
GvHD diagnosis remains a challenge even for experienced transplant pathologists due to its variable clinical and histological manifestation and the still insufficient validity and reproducibility of diagnostic histopathological criteria. In this service project, expert (immuno-)histological evaluation of human and murine tissues is provided. Furthermore, a digital histology archive will be established that includes consensus reports generated in virtual microscopy conferences and that are linked to clinical data bases for the evaluation of transplant outcome, complications and prognostic histology biomarkers.

Project Z02 - Andreas Beilhack
„Generation of genetically modified animals and complex transplant models"
Due to the complexity of graft-versus-recipient (GvH) and graft-versus-leukemia (GvL) responses, appropriate preclinical in vivo models are needed to study fundamental biological processes as well as new intervention strategies. In addition to providing general support in research design and implementation, the Z02 service project will generate important new genetically engineered mouse lines as well as provide GvHD models in germ-free mice. The aim is to carry out comparable, reproducible and reliable in vivo studies at all three sites of the CRC/TR 221.

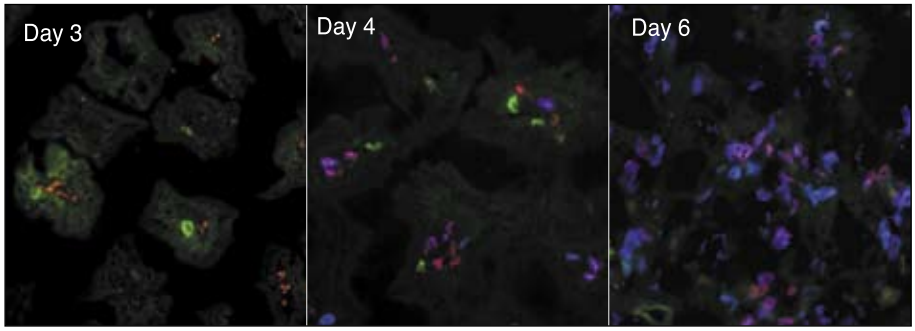


Fig.: Progression of intestinal acute graft-versus-host disease after allogeneic hematopoietic cell transplantation. After T cell priming in secondary lymphoid organs, alloreactive T cells infiltrate in a concerted action lamina propria of the intestinal tract and attack intestinal epithelial cells (donor CD4 T cells in magenta, donor CD8 T cells in blue). Credit: A. Beilhack, Medizinische Klinik & Poliklinik II

SELECTED PUBLICATIONS

Chopra M, Biehl M, Steinfatt T, Brandl A, Kums J, Amich J, Vaeth M, Kuen J, Holtappels R, Podlech J, Mottok A, Kraus S, Jordán-Garrote AL, Bäuerlein CA, Brede C, Ribechini E, Fick A, Seher A, Polz J, Ottmüller KJ, Baker J, Nishikii H, Ritz M, Mattenheimer K, Schwinn S, Winter T, Schäfer V, Krappmann S, Einsele H, Müller TD, Reddehase MJ, Lutz MB, Männel DN, Berberich-Siebelt F, Wajant H, Beilhack A. (2016) Exogenous TNFR2 activation protects from acute GvHD via host T reg cell expansion. J Exp Med 213:1881-1900.

Chopra M, Brandl A, Siegmund D, Mottok A, Schäfer V, Biehl M, Kraus S, Bäuerlein CA, Ritz M, Mattenheimer K, Schwinn S, Seher A, Grabinger T, Einsele H, Rosenwald A, Brunner T, Beilhack A, Wajant H. (2015). Blocking TWEAK-Fn14 interaction inhibits hematopoietic stem cell transplantation-induced intestinal cell death and reduces GvHD. Blood 126:437-444.

García-Guerrero E, Gogishvili T, Danhof S, Schreder M, Pallaud C, Pérez-Simón JA, Einsele H, Hudecek M. (2017) Panobinostat induces CD38 upregulation and augments the antimyeloma efficacy of daratumumab. Blood 129:3386-3388.

Gogishvili T, Danhof S, Prommersberger S, Rydzek J, Schreder M, Brede C, Einsele H, Hudecek M. (2017) SLAMF7-CAR T cells eliminate myeloma and confer selective fratricide of SLAMF7+ normal lymphocytes. Blood 130:2838-2847.

Jetani H, Garcia-Cadenas I, Nerreter T, Thomas S, Rydzek J, Meijide JB, Bonig H, Herr W, Sierra J, Einsele H, Hudecek M. (2018) CAR T-cells targeting FLT3 have potent activity against FLT3-ITD+ AML and act synergistically with the FLT3-inhibitor crenolanib. Leukemia 32:1168-1179.

Monjezi R, Miskey C, Gogishvili T, Schleef M, Schmeer M, Einsele H, Ivics Z, Hudecek M. (2017) Enhanced CAR T-cell engineering using non-viral Sleeping Beauty transposition from minicircle vectors. Leukemia 31:186-194.

Ullrich E, Abendroth B, Rothamer J, Huber C, Büttner-Herold M, Buchele V, Vogler T, Longerich T, Zundler S, Völkl S, Beilhack A, Rose-John S, Wirtz S, Weber GF, Ghimire S, Kreutz M, Holler E, Mackensen A, Neurath MF, Hildner K. (2018) BATF-dependent IL-7RhiGM-CSF+ T cells control intestinal graft-versus-host disease. J Clin Invest 128:916-930.

Vaeth M, Bäuerlein CA, Pusch T, Findeis J, Chopra M, Mottok A, Rosenwald A, Beilhack A, Berberich-Siebelt F. (2015) Selective NFAT targeting in T cells ameliorates GvHD while maintaining anti-tumor activity. Proc Natl Acad Sci U S A 112:1125-1130.

Transregio-Collaborative Research Center 225, From the Fundamentals of Biofabrication towards Functional Tissue Models

CONTACT DETAILS

Professor Dr. rer. nat. Jürgen Groll
(Spokesman)

Julius-Maximilians-University of Würzburg
Department for functional materials in medicine and dentistry
Pleicherwall 2
97070 Würzburg
Phone: 0931/201-73610
E-mail: trr225@fmz.uni-wuerzburg.de
www.trr225biofab.de

Professor Dr.-Ing. habil. Aldo R. Boccaccini
(Site-Speaker Erlangen-Nuremberg)

Friedrich-Alexander-University
Erlangen-Nuremberg
Institute of Biomaterials
Cauerstr. 6
91058 Erlangen
Phone: 09131/85-28601
E-mail: aldo.boccaccini@fau.de

Professor Dr. rer. nat. Thomas Scheibel
(Site-Speaker Bayreuth)

University of Bayreuth
Biomaterials research group
Universitätsstr. 30
95447 Bayreuth
Phone: 0921/55-7360
E-mail: thomas.scheibel@bm.uni-bayreuth.de

Dr. rer. nat. Jennifer Ritzer
(Scientific Coordinator)
Phone: 0931/201-73657
E-mail: trr225@fmz.uni-wuerzburg.de

Mission and Structure

The SFB/TRR 225 "From the fundamentals of biofabrication towards functional tissue models" started its activities in January 2018 and includes working groups from the Universities of Erlangen-Nuremberg, Bayreuth and Würzburg. The organization of the SFB/TRR 225 is carried out via the organs: Board, Spokesman, General Assembly and Young Scientist Committee. PhD programs of the different graduate schools in Würzburg (GSLS), Erlangen-Nuremberg (Life@FAU) and Bayreuth (BayNAT) guarantee a structured training for the PhD students within the research network. In addition, summer schools and symposia adapted to the specific research focus of the SFB/TRR 225 provide subject-specific education and knowledge.
As part of this transregional research center, more than 80 scientists from 18 subprojects are collaborating on a cross-location, complementary and interdisciplinary basis within the still young but rapidly growing research field of biofabrication. In the medium term, the SFB/TRR 225 aims to develop functional human *in vitro* tissue models for biomedical research in the field of regeneration or disease development, as well as long-term regenerative therapy options for the clinic.

Sub-project leader Würzburg:
UKW
Prof. Dr. Jürgen Groll (A06, B02, B04, Z01)
Prof. Dr. Torsten Blunk (A02, C02)
Prof. Dr. Paul Dalton (A04, B01)
Dr. habil. Jörg Teßmar (A02)
Prof. Dr. Carmen Villmann (B01)
Dr. Jan Hansmann (B03)
Dr. Krystyna Albrecht (B07)
Prof. Dr. Dr. Andreas Beilhack (B08)
Prof. Dr. Harald Wajant (C04)
JMU
PD Dr. Tessa Lühmann (A03)
Prof. Dr. Robert Luxenhofer (A03)
Prof. Dr. Süleyman Ergün (B04)
PD Dr. Regina Ebert (B05)
Prof. Dr. Jürgen Seibel (B05)

Major Research Interests

Content of the SFB/TRR 225 is the exploration of the fundamentals of biofabrication and its systematic exploitation with the aim and vision to generate functional human tissue models.
The SFB/TRR 225 initially (first funding period: 2018 – 2021) focusses on the development of materials and methods as well as the exploration of cellular behavior during and after the printing process. As a starting point, recently established bioinks will be processed to generate first tissue models serving as a benchmark for further improvements and completely novel approaches.

The application of automated 3D-printing-processes for the generation of constructs in which cells and materials are positioned simultaneously in a tissue-like structure holds the promise for a standardized generation of so far unreached functional tissue models. These would be of tremendous value for replacing animal models for pharma- and cancer research and as regenerative therapeutic option.

Combining innovations in technologies and bioinks, the consortium aims at the identification and further development of synergetic strategies to biofabricate functional tissues. This will be accompanied by an extensive analysis and characterization at all levels - from the bioinks material properties to the biological function of printed tissue models *in vitro* and *in vivo*.

The progress of the young research field of biofabrication is currently limited mainly by a lack of bioinks, which guarantee the survival of the cells during the printing process and also positively influence their behavior after printing or ideally even control it. In order to counteract this, the SFB/TRR 225 is focused to develop suitable bioinks which, in addition to the survival of the cells, should not adversely affect or even control their behavior after printing. The understanding of the relationships between process parameters and cell reactions is also part of the research within the SFB/TRR 225. Methods for a more precise fabrication, integration of the printing process in the subsequent cultivation step and finally for continuous monitoring of cell behavior during and after the printing process form the focus of our research and development.

Within the first funding phase, the SFB/TRR 225 is thus divided into the three project areas A (Bioinks), B (Processes and Methods) and C (Biofabricated Models).

Fig.: The SFB / TRR 225 is divided into the three project areas A (Bioinks), B (Processes and Methods) and C (Biofabricated Models).

A: Bioinks - Aim: New Functional and Responsive Bioinks

- **Projects A01-A04: Joint approach - Homogenous Bioinks**
- **Projects A05-A07: Joint approach - Disperse Bioinks**

The project area A develops new bioinks - divided into homogeneous systems, based on molecularly dissolved polymers, and disperse systems in which the cell-loaded component is used as a disperse phase in a homogeneous phase. Within these two areas, the projects mainly interact to investigate the parameters which not only ensure the short-term survival of cells during the printing process, but also influence or even control the long-term behavior of cells after the printing process.

B: Processes and Methods - Aim: Precise and Reproducible Manufacturing Processes and Methods

- **Projects B01-B04: Joint approach - Precision and Supply**
- **Projects B05-B08: Joint approach - Monitoring and Modelling**

Project area B is designed to better understand and control the printing process itself as well as the basic behavior of cells in biofabricated constructs during and after printing, through material and method development. On this basis, very sensitive cells should become printable in medium and long term. On this basis reproducible functional tissue models will be produced.

C: Biofabricated Models - Aim: Construction of first Tissue Models

Projects of the area C are using already established bioinks of the network to build and test the first tissue models, which afterwards serve as benchmarks for the new developments in the further course of the network. The focus is on the production and investigation of models of myocardial tissue, vascularization models and 3D tumor models.

Based on available bioinks, models and understanding of the process, selected bioinks and methods will be further developed in the following funding phases in order to biofabricate, characterize and finally validate tissue models for functional parameters *in vitro* and *in vivo*.

SELECTED PUBLICATIONS

Böck T, Schill V, Krähnke M, Steinert AF, Tessmar J, Blunk T, Groll J. (2018) TGF-β1-Modified Hyaluronic Acid/Poly(glycidol) Hydrogels for Chondrogenic Differentiation of Human Mesenchymal Stromal Cells. Macromol Biosci 18:e1700390.

Gutmann M, Braun A, Seibel J, Lühmann T. (2018). Bioorthogonal Modification of Cell Derived Matrices by Metabolic Glycoengineering. ACS Biomater Sci Eng 4:1300-1306.

Roshanbinfar K, Vogt L, Greber B, Diecke S, Boccaccini A, Scheibel T, Engel FB. (2018) Electroconductive Biohybrid Hydrogel for Enhanced Maturation and Beating Properties of Engineered Cardiac Tissues. Adv Funct Mater 28:1803951.

Schneidereit D, Schürmann S, Friedrich O. (2018) PiezoGRIN: a high-pressure chamber incorporating GRIN lenses for high-resolution 3D-microscopy of living cells and tissues. Adv Sci 2018:1801453.

Stafiej P, Küng F, Kruse FE, Schubert DW, Fuchsluger TA. (2018) Mechanical and Optical Properties of PCL Nanofiber Reinforced Alginate Hydrogels for Application in Corneal Wound Healing. Biomater Med Appl 2:2.

Steiner D, Lingens L, Fischer L, Köhn K, Detsch R, Boccaccini AR, Fey T, Greil P, Weis C, Beier J, Horch RE, Arkudas A. (2018) Encapsulation of mesenchymal stem cells improves vascularization of alginate-based scaffolds. Tissue Eng Part A 24:1320-1331.

Transregio-Collaborative Research Center 240, Platelets – Molecular, Cellular and Systemic Functions in Health and Disease

CONTACT DETAILS

Professor Dr. rer. nat. Bernhard Nieswandt (Speaker)

University Hospital Würzburg and Rudolf Virchow Center
Institute of Experimental Biomedicine, Chair I
Josef-Schneider Str. 2
97080 Würzburg
Phone: 0931/31-80405
Fax: 0931/201-61652
E-mail: bernhard.nieswandt@virchow.uni-wuerzburg.de
www.tr240.de

Professor Dr. med. Meinrad Gawaz (Vice-Speaker)
Phone: 07071/29 83 68 8

Dr. rer. nat. David Stegner (Scientific Secretary)
Phone: 0931/31-80419

Kerstin Siegmann (Office)
Phone: 0931/31-81457

Mission and Structure

The aim of the DFG-funded collaborative research center CRC/TR 240 "Platelets – molecular, cellular and systemic functions in health and disease" is to decipher the complex and insufficiently understood functions of platelets. Led by the Institute of Experimental Biomedicine Würzburg, together with the University Hospital Tübingen, the "ISAS" Dortmund and the University of Greifswald, the CRC has started its work in July 2018 with a total funding of 13.7 Mio € from the German Research Foundation (DFG). The CRC focuses on mechanisms of platelet biogenesis and the role of platelets beyond thrombosis and hemostasis in (patho)physiological conditions, such as heart attack, stroke, acute lung failure and cancer with the aim to develop novel treatment concepts. The strength of this network is the pronounced translational character that unites cutting edge basic, translational and clinical research.

Major Research Interests

Platelets are anuclear cell fragments that derive from bone marrow precursor cells called megakaryocytes and are essential for the maintenance of vascular integrity. Basic, translational and clinical platelet research has advanced considerably in recent years. A deepened understanding of the role of platelets in cardio- and cerebrovascular diseases has led to improvements in therapy and reduced morbidity and mortality, but often at the expense of bleeding complications. In addition, recent studies have revealed unexpected functions of platelets in (patho)physiological conditions beyond their "classical" role in thrombosis and hemostasis, such as inflammation, wound healing and cancer. However, the molecular mechanisms and therapeutic relevance of these novel platelet functions are largely unexplored.
The CRC investigates the diverse roles of platelets by focusing on (A) *Cell biology of megakaryocytes and platelets* to understand their basic functions and (B) *Platelets as regulators and effectors in disease*. The unique network of basic, translational and clinical scientists within the CRC combines expertise in mouse genetics, *in vivo* disease models, advanced imaging techniques, systems biology/omics and clinical research. We follow a comprehensive approach starting out from *in vitro* systems and animal models to clinical research with large patient cohorts and biobanking.

ADAP deficiency impairs megakaryocyte polarization with ectopic proplatelet release and causes microthrombocytopenia

Megakaryocytes situated in the bone marrow generate platelets by extending proplatelets into sinusoidal blood vessels. Defects in the process of platelet biogenesis can lead to thrombocytopenia and bleeding. *Congenital autosomal recessive small-platelet thrombocytopenia* (CARST) is a platelet disorder caused by mutations in the Adhesion and degranulation-promoting adapter protein (*ADAP*) gene that is associated with microthrombocytopenia (reduced platelet count with small platelet size). In this study, we used mice with constitutive ADAP deficiency ($Adap^{-/-}$) to investigate the mechanisms underlying the microthrombocytopenia in CARST. We could show that $Adap^{-/-}$ mice display a phenotype similar to CARST patients, including moderate thrombocytopenia and smaller-sized platelets. By using 3D immunofluorescence confocal imaging and intravital 2 photon microscopy (2P-IVM), we could show that the morphology of $Adap^{-/-}$ megakaryocytes in the bone marrow was altered,

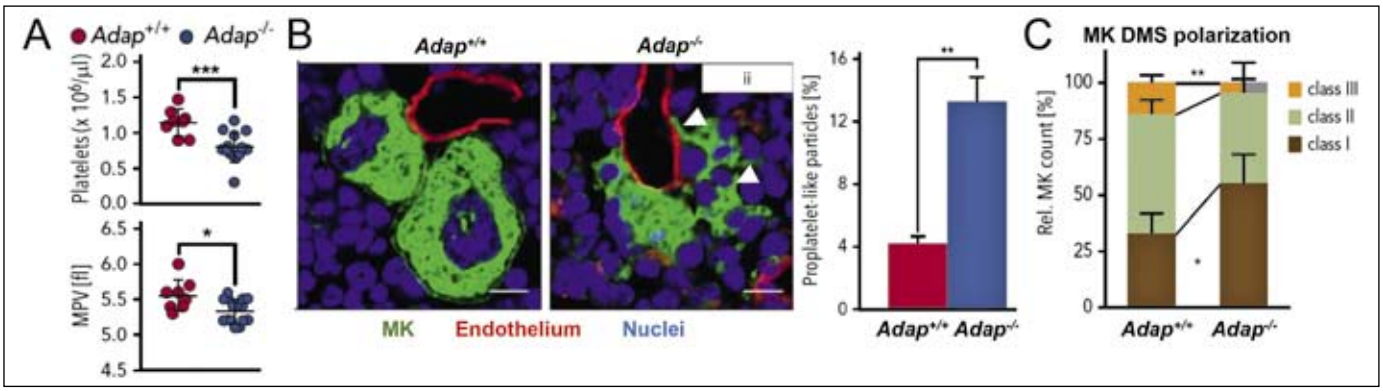


*Fig. 1: Microthrombocytopenia caused by ectopic (pro)platelet release and defective megakaryocyte (MK) polarization in ADAP-deficient mice. (A) Platelet count (upper) and platelet size (MPV, lower) were determined in $Adap^{+/+}$ and $Adap^{-/-}$ mice by a hematology analyzer (n≥8). (B) Release of (pro)platelet-like particles into the bone marrow compartment of $Adap^{-/-}$ mice. Left: Representative confocal microscopy images of immunostained cryosections of femura from $Adap^{+/+}$ and $Adap^{-/-}$ mice. Sinusoids (red, CD105), MKs (green, GPIX), and nuclei (blue, DAPI). Arrows indicate (pro)platelet-like structures. Scale bar: 10 µm. Right: Analysis of (pro)platelet-like particles in the bone marrow by flow cytometry (n=3). (C) Defective DMS polarization of $Adap^{-/-}$ MKs in vitro. Quantitative analysis of the distribution of 3 MK classes in vitro on day 5 of cultivation. (n=500 MKs per genotype). Values are mean ± SD, ***P<0.001, **P<0.01, *P <0.05.*

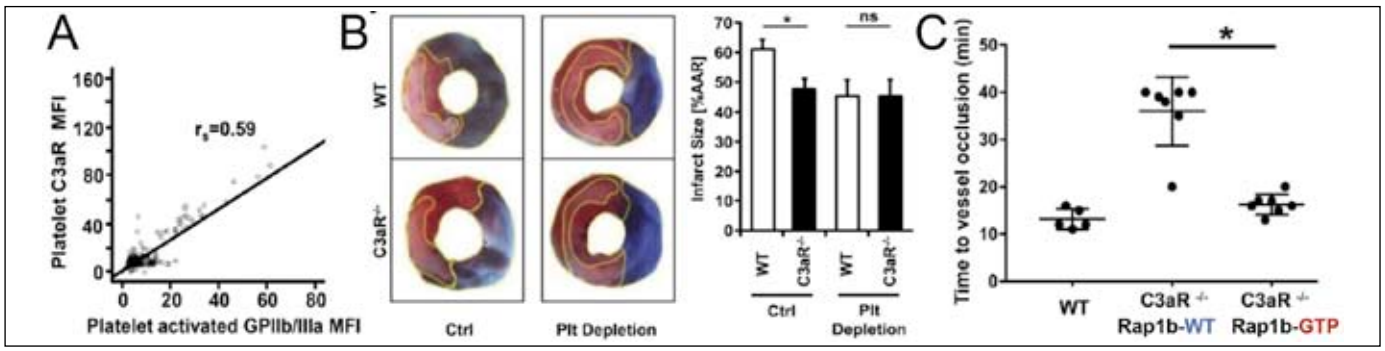


*Fig. 2: Functional relevance of C3aR in platelets. (A) Expression of C3aR and activated integrin GPIIbIIIa (PAC-1 antibody) were measured by flow cytometry in patients with coronary artery disease (n=501). The correlation of C3aR with activated GPIIbIIIa is depicted. Spearman rank coefficient rs=0.59, ***P<0.001. (B) Platelet-derived C3aR contributes to experimental myocardial infarction. Left: Representative Monolite blue/triphenyltetrazolium chloride staining pictures of infarcts in WT and C3aR$^{-/-}$ mice after injection of platelet-depleting or control serum. Right: Reduced area of necrosis in C3aR$^{-/-}$ animals vs WT littermates treated with control serum. This difference was no longer present when platelets were depleted (n=7/8). Values are presented as percent of infarct size of the area at risk (AAR) vs WT littermate controls. (C) Role of Rap1b in C3aR-mediated thrombus formation. $FeCl_3$-induced thrombus formation of mesenteric arterioles was analyzed in C3aR$^{-/-}$ mice expressing normal, endogenous Rap1-GTP levels ("Rap1-WT") and in C3aR$^{-/-}$ mice with constitutively active Rap1 ("Rap1-GTP"). Time to vessel occlusion was significantly shorter in C3aR$^{-/-}$ Rap1-GTP mice compared to C3aR$^{-/-}$ Rap1-WT littermates (n=5-7). Data represent mean ± SEM. *P<0.05.*

characterized by fragmentation and ectopic release of (pro)platelet-like fragments into the bone marrow compartment. Furthermore, cultured *Adap*$^{-/-}$ bone marrow megakaryocytes exhibited reduced spreading, as well as impaired β1 integrin activation and podosome formation on extracellular matrix proteins. Finally, polarization of the megakaryocyte demarcation membrane system (DMS), a characteristic membraneous network formed exclusively in mature megakaryocytes, was defective in *Adap*$^{-/-}$ megakaryocytes. Together, our findings demonstrate that the abnormal platelet biogenesis in *Adap*$^{-/-}$ mice is a megakaryocyte-intrinsic defect and point to a novel role of ADAP in the process of megakaryocyte polarization and platelet formation (Spindler *et al.,* Blood 2018).

Functional relevance of the anaphylatoxin receptor C3aR in platelets marks an intersection point between innate immunity and thrombosis

Platelets are the major mediators of thrombosis, but also critical for vascular integrity, and players in vascular inflammatory conditions. The complement system acts as the first line of defense against invading microorganisms and is a key mediator of inflammation. Whereas the existent crosstalk between the complement and the coagulation system, including platelets, is well established, the resulting pathophysiological implications are still poorly understood. By taking advantage of patient samples and transgenic mice, we analyzed the importance of the complement receptor C3aR for platelet function *in vitro*, as well as for hemostasis, intravital thrombosis, myocardial infarction and stroke *in vivo*. We found a strong positive correlation of platelet C3aR expression with activated integrin GPIIbIIIa in patients with coronary artery disease. Exogenous addition of C3aR promoted platelet adhesion, spreading and calcium mobilization of wild-type platelets *in vitro* while, conversely these processed were reduced in C3aR-deficient (*C3aR*$^{-/-}$) platelets. In line with a positive role of C3aR in regulating platelet function, *C3aR*$^{-/-}$ mice exhibited prolonged tail bleeding times and were partially protected in experimental models of myocardial infarction and stroke. Platelet depletion and reconstitution experiments demonstrated that the observed defects were specifically caused by platelet C3aR. Mechanistically, we found that C3aR-mediated signaling regulates the activation of the GTPase Rap1b, and thereby bleeding arrest and thrombus formation *in vivo*. Together, our findings reveal a novel function of C3aR for platelet thrombus formation and highlight a detrimental role of imbalanced complement activation in cardiovascular disease.

SELECTED PUBLICATIONS

Droppa M, Borst O, Katzenberger T, Krause R, Bramlage K, Bramlage P, Lausberg HF, Schlensak C, Grasshoff C, Gawaz M, Geisler T. (2018) Clinical and economical impact of the presence of an extended heart team throughout the balloon-expandable transcatheter aortic valve implantation procedure. Clin Res Cardiol doi: 10.1007/s00392-018-1359-3.

Manukjan G, Eilenberger J, Andres O, Schambeck C, Eber S, Schulze H. (2018) Functional classification of pediatric patients with non-syndromic delta-storage pool deficiency. Hämostaseologie doi: 10.1055/s-0038-1675574.

Peng B, Geue S, Coman C, Münzer P, Kopczynski D, Has C, Hoffmann N, Manke MC, Lang F, Sickmann A, Gawaz M, Borst O, Ahrends R. (2018) Identification of key lipids critical for platelet activation by comprehensive analysis of the platelet lipidome. Blood 132:e1-e12.

Sauter RJ, Sauter M, Reis ES, Emschermann FN, Nording H, Ebenhöch S, Kraft P, Münzer P, Mauler M, Rheinlaender J, Madlung J, Edlich F, Schäffer TE, Meuth SG, Duerschmied D, Geisler T, Borst O, Gawaz M, Kleinschnitz C, Lambris JD, Langer HF. (2018) A Functional Relevance of the Anaphylatoxin Receptor C3aR for Platelet Function and Arterial Thrombus Formation Marks an Intersection Point Between Innate Immunity and Thrombosis. Circulation 138:1720-1735.

Spindler M, van Eeuwijk JMM, Schurr Y, Nurden P, Nieswandt B, Stegner D, Reinhold A, Bender M. (2018) ADAP deficiency impairs megakaryocyte polarization with ectopic proplatelet release and causes microthrombocytopenia. Blood 132:635-646.

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Scientific Infrastructure

Core Unit Systems Medicine (CU SysMed)

CONTACT DETAILS

Dr. rer. nat. Tobias Heckel
(Head since 04/2019)
Phone: 0931/31-82893

Dr. rer. nat. Kristina Döring
(Interim Head until 03/2019)

Dr. rer. nat. Konrad Förstner
(Head until 08/2018)

Josef-Schneider-Str. 2
97080 Würzburg
E-mail: cu_sysmed_order@uni-wuerzburg.de
www.sysmed.uni-wuerzburg.de

General Information

The Core Unit Systems Medicine (CU SysMed) is a shared facility of the Faculty of Medicine of the University of Würzburg and the Interdisciplinary Center for Clinical Research (IZKF) of the University Hospital of Würzburg. The CU SysMed provides its services especially to the researchers in Würzburg and helps with the application and development of high-throughput technologies for handling systems biological and systems medical questions.

Key activities of the CU SysMed comprise basic research-oriented functional genomics research projects (e.g. RNA-based regulatory mechanisms and epigenetic phenomena) as well as medically relevant projects (e.g. decoding of genetic or gene-regulatory mechanisms with relevance in disease-associated processes in e.g. cancer, diabetes and infectious diseases). A special focus thereby lay and still lies on the development and application of highly parallel single-cell sequencing analyses in collaboration with the group of Dr. Antoine-Emmanuel Saliba at the newly founded Helmholtz Institute for RNA-based Infection Research (HIRI) in Würzburg.

In addition to supporting the research of scientists of all departments of the University and the University Hospital in Würzburg, the CU SysMed collaborated with external scientists from Germany and abroad to solve demanding systems biological/medical research questions. In 2017 and 2018 the CU SysMed conducted more than 170 projects including the preparation of more than 1200 sequencing libraries (without the single-cell sequencing libraries) and more than 200 sequencing runs on the Illumina NextSeq 500 sequencing platform. Since the middle of 2018, we have completely substituted our microarray approaches with high-throughput sequencing technologies.

Services and Structure

The CU SysMed offers user-oriented services. These range from help with the design of the sequencing experiment, the RNA quality control, the preparation of sequencing libraries, the actual sequencing of samples, to the bioinformatical analysis of sequencing data (Fig. 1). Our main aim in this process is good consultation of our users and finding quick, affordable, and flexible solutions for all projects. For the sequencing of the vast majority of samples, we use our in-house NextSeq 500 sequencing platform. This machine is very versatile, with a possible read length of 75 to 300 nt, 130 M or 400 M reads per run and comparatively short running times. For projects with high sequencing demands, we send the ready libraries to the Helmholtz Centre for Infection Research (HZI) in Braunschweig to have them sequenced on their Illumina NovaSeq 6000 sequencing platform. This is possible through the collaboration with the HIRI in Würzburg.

In general, the CU SysMed was mainly working on establishing new sequencing applications and executing sequencing projects as well as bioinformatical data analysis and integration (Fig. 2). In addition, we were engaged in the development of (open source) bioinformatics tools in close collaboration with experimentally oriented researchers. Furthermore, in 2018, the CU SysMed started working on 3rd generation sequencing technologies (Nanopore) to expand its sequencing portfolio also to full-length transcripts.

The method portfolio of the CU SysMed currently covers exome- and genome-sequencing, transcriptome sequencing (mRNA, lnRNA, miRNAs, total RNA), special RNA-sequencing methods for example to analyze host-pathogen interactions (dual RNA-seq) or to study RNA-protein complexes (e.g. CLIP-seq, RIP-seq, Grad-seq), as well as single-cell RNA-sequencing (scRNA-seq). For

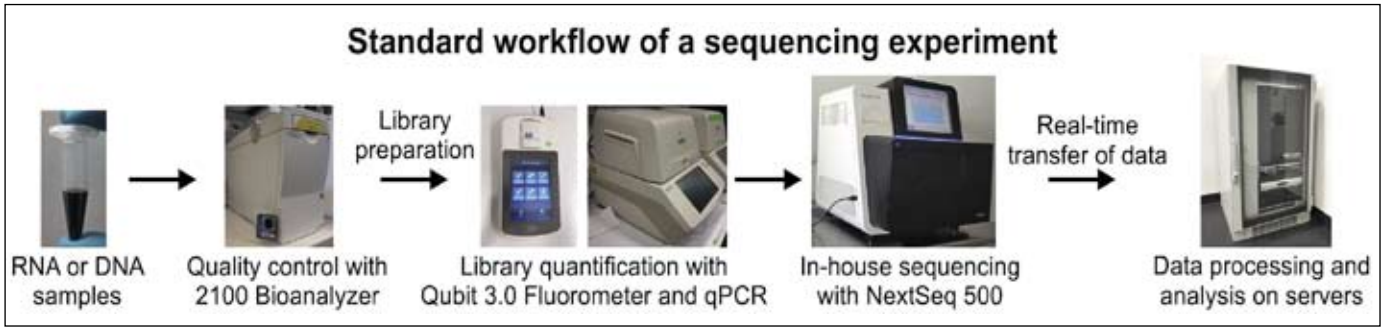


Fig. 1: Standard workflow of a sequencing experiment displaying the individual steps. The CU SysMed can perform all of these steps or only individual ones, depending on the user preference.

single-cell RNA-sequencing we mainly use two approaches that both require polyadenylated RNAs. For the analysis of a couple of FACS-sorted single cells or small cell populations, a similar approach as for standard RNA-seq is used. In contrast to this, for the analysis of a large number of single cells (up to 10,000) we use a droplet-based approach for library preparation from 10X Genomics. In order to use this technique, a specialized device, the 10X Genomics Chromium Controller, was purchased. On demand, new methods can be established in collaboration with the respective research groups (e.g. ATAC-seq, which is a method to investigate the accessibility of the chromatin via high-throughput sequencing).

Moreover, the CU SysMed was committed to teaching by supporting various IT and bioinformatics courses. The team consisted/consists of following people: Dr. Panagiota Arampatzi, Dr. Richa Bharti (until 09/2018), Dr. Thorsten Bischler, Dr. Sascha Dietrich (since 11/2018), Dr. Kristina Döring (since 09/2017), Dr. Konrad Förstner (until 08/2018), Margarete Göbel and Elena Katzowitsch.

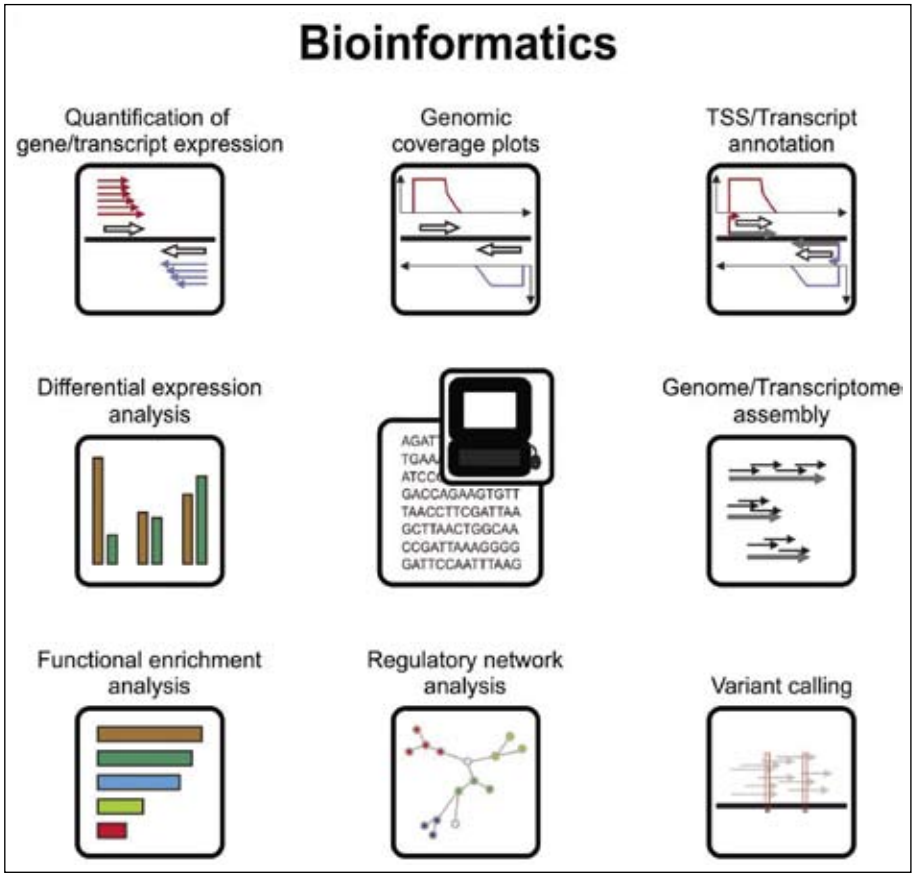


Fig. 2: Overview of the offered bioinformatics services.

SELECTED PUBLICATIONS

Bury S, Soundararajan M, Bharti R, von Bünau R, Förstner KU, Oelschlaeger TA. (2018) The Probiotic Escherichia Coli Strain Nissle 1917 Combats Lambdoid Bacteriophages Stx and λ. Front Microbiol 9:929.

Cochain C, Vafadarnejad E, Arampatzi P, Pelisek J, Winkels H, Ley K, Wolf D, Saliba AE, Zernecke A. (2018) Single-Cell RNA-Seq Reveals the Transcriptional Landscape and Heterogeneity of Aortic Macrophages in Murine Atherosclerosis. Circ Res 122:1661-1674.

Holmqvist E, Li L, Bischler T, Barquist L, Vogel J. (2018) Global Maps of ProQ Binding In Vivo Reveal Target Recognition via RNA Structure and Stability Control at mRNA 3' Ends. Mol Cell 70:971-982.e6.

Müller LSM, Cosentino RO, Förstner KU, Guizetti J, Wedel C, Kaplan N, Janzen CJ, Arampatzi P, Vogel J, Steinbiss S, Otto TD, Saliba AE, Sebra RP, Siegel TN. (2018) Genome organization and DNA accessibility control antigenic variation in trypanosomes. Nature 563:121-125.

Wedel C, Förstner KU, Derr R, Siegel TN. (2017) GT-rich Promoters Can Drive RNA Pol II Transcription and Deposition of H2A.Z in African Trypanosomes. EMBO J 36:2581–2594.

Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw)

INTERDISZIPLINÄRE BIOMATERIAL- UND DATENBANK WÜRZBURG ibdw

CONTACT DETAILS

Professor Dr. med. Roland Jahns
(Head)

Straubmühlweg 2a
97078 Würzburg
Phone: 0931/201-47 000
Fax: 0931/201-647 000
E-mail: ibdw@ukw.de
www.ukw.de/interdisziplinaereeinrichtungen/interdisziplinaerebiomaterial-und-datenbank-wuerzburg

Professor Dr. med. Andreas Rosenwald
(Head of the Institute of Pathology)
Phone: 0931/31-81199

Dr. sc. hum. Michael Neumann
(Head IT, Vice-head ibdw)
Phone: 0931/201-45 040

Madeline Starke
(Office Manager)
Phone: 0931/201-47 001

General Information

Medical research based on human biochemical, histological, or genetic data analysed in conjunction with (longitudinal) clinical information is essential to foster improvements in the detection, diagnosis, treatment, and prevention of common as well as so-called rare (multi-factorial) diseases.

Embedded in the National Biobank Initiative of the Federal Ministry of Education and Research (BMBF) since its set-up in 2011 and grand opening in 2013 as one (out of five) centralized National Biobanks, the *Interdisciplinary Bank of Biomaterials and Data Würzburg* (ibdw) systematically collects and stores long term and under strict quality control both liquid (blood/DNA/serum/urine) and solid biomaterials (BM) (tissues and biopsies, hosted in the ibdw/CCCM tissue-bank under the auspices of the Institute of Pathology) donated by patients and study participants of the Medical Campus Würzburg for medical research purposes on a strictly voluntary basis.

In the developmental concept of the ibdw as an *independent central service unit* of the Faculty of Medicine, priority has been set towards a concerted establishment and sharing of resources for medical research comprising clinical core data, human bio-samples, and biochemical, histological, genetic and/or clinical information derived from their analysis (which will all be available through the currently implemented clinical data warehouse). With this aim, the ibdw has put into practice a systematic, simultaneous, and sequential collection of both liquid and solid BM from patients and study participants of all clinical departments of the University Hospital.

To secure integrity and long-term quality of the collected biomaterials, as one of its paramount tasks the ibdw has implemented highest quality standards according to current OECD- and ISBER-recommendations and has been certified according to DIN ISO 9001:2015 since 08/2016. Because there are no restrictions regarding storage duration and/or the purpose of (medical) research, all biomaterials and data hosted by the ibdw must strictly adhere to the legal framework (including privacy protection and data protection according to the new European Data Protection Regulation (GDPR)) and all current ethical principles. For each stored human BM, the ibdw provides the corresponding core annotation data and, through the clinical data warehouse, access to expandable disease-specific clinical datasets in accordance with current data protection and safety regulations (multi-level authenticated data access model).

Structure, aims, and major research interests of the ibdw

The ibdw is composed of a central database and two central biosample repositories, one for liquid and the other for solid/tissue BM, and a limited number of specialized decentralized subunits, all adhering to ibdw standards and rules. The Faculty of Medicine, that is, the Julius-Maximilians-University and the University Hospital together hold full responsibility for the ibdw, which is governed by its own steering committee. Each central and decentralized collection of data and BM meets the highest quality standards according to DIN ISO 9001:2015 and the current OECD/ISBER recommendations.

Implementation of the ibdw concept is currently achieved jointly with the Service Center Medical Informatics (SMI) by a establishing an uniform IT-structure across all departments and institutes of the Medical Research Campus (also linked with e.g., the pathology information system and the tumour databank of the CCCM) tracking the ibdw-conform labelled and processed individual liquid and/or solid biosamples in order to link them with the patient-specific pseudonymized clinical datasets, which are collected along the patient management paths and stored in the clinical data warehouse. However, clinical information and/ or information derived from the analysis of the patients' biosamples will be accessible only on request by a specified data and privacy protecting regulation.

To secure high degree of automation and thus high quality of ibdw-hosted biomaterials (BM) for liquid biosamples (blood, urine, ascites, cerebrospinal fluid) there is tight cooperation with the Hospital's central laboratory. For tissue samples (tissues, biopsies) there is very tight collaboration with the Institute of Pathology and, of course, all surgical departments of the University Hospital. Consequently, the tissue bank of the ibdw/CCCM under guidance of the Institute of Pathology has been installed next door to the operating theatres and the corresponding rapid section laboratories.

Pre-existing high-quality biosample collections within the University Hospital have been identified to be integrated into the ibdw systematically. In addition, the ibdw manages and operates human biomaterials contributed by existing national and international publicly funded basic and clinical research programmes at the University and the University Hospital of Würzburg, and, through the clinical data warehouse, provides access to corresponding clinical and laboratory (analytical) data. These include - but are not limited to - the Interdisciplinary Center for Clinical Research (IZKF), the Comprehensive Cancer Center Mainfranken (CCCM), the Comprehensive Heart Failure Center (CHFC),

Fig. 1: Public visibility of the ibdw: biobank action day during the Bavarian Plant Exposition 2018.

the Research Center for Infectious Diseases (RCID) an the Center for Rare Diseases North Bavaria (ZESE).
Since the official grand opening of the ibdw facilities in 06/2013, equipped with two fully automated cryostores each having a capacity of about 0.5 Mio liquid biosamples, the ibdw has gained national and international visibility as work package leader for both ethical, legal, and social (ELSI)-issues and public relations (see also Fig. 1) in the BMBF-funded German Biobank Node (GBN), and from 2017 on equally within the BMBF-funded German Biobank Alliance (GBA). Aims of GBN/GBA are to coordinate and harmonize all biobank-activities on a national level, comprising –amongst others– harmonization of data acquisition and exchange (to achieve biobank interoperability), standardization of quality criteria (ring-trials, see Fig. 2) and rules for the certification of biobanks, but also to develop a joint (national) strategy regarding ELSI matters of German biobanks, including public visibility and involvement (Fig. 3). The ibdw actively participates in all these fields, thereby offering an ideal interdisciplinary platform for future national, European (BBMRI), and global networking in medical research.

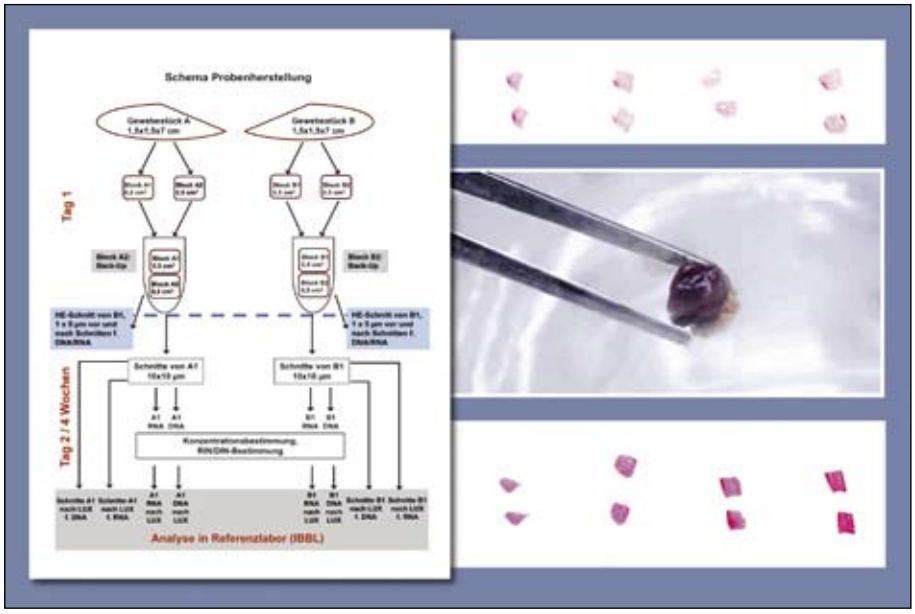


Fig. 2: Successful participation of the ibdw in the GBA ring-trials (here: liver-tissue sectioning).

Main principles of the IBDW comprise:

- Concurrent sampling of liquid and solid human biomaterials using a consistent biosample labelling, registration, tracking, storage, and retrieval system enabling parallel analysis of matching blood and tissue samples along the course of the respective disease(s);
- Short term storage of biosamples for 2-5 years (-80°C, immediate access, rapid sample read out, rapid sample compilation for medical research purposes);
- Long-term storage for >10 years (-160°C, gas phase liquid nitrogen) for pre-specified liquid BM;
- Implementation and faculty-wide harmonization of biobanking-SOPs and handling guidelines for BM;
- Achieved in 08/2016: certification according to DIN ISO 9001:2015, since then annual maintenance of certificate;
- Implementation of a multi-level data storage and access concept ensuring consistency of data and biosample identity adopting all current data and privacy protection regulations;
- Implementation of hierarchical pseudonymized clinical datasets (core data, and harmonized disease-specific/study-specific datasets available through the clinical data warehouse);
- Active participation in the German Biobank Registry, the German Biobank Node (GBN, Berlin), and the German Biobank Alliance (GBA);
- Project-based cooperation with the biobank of the Bavarian Blood Donors (BioKEP project, funded by the TMF);
- Project-based cooperation and networking on a national, European (BBMRI-ERIC, Horizon 2020 funded ADOPT project), and international level (ISBER).


Fig. 3: Conceptual contribution and active participation of the ibdw in the National Poster Campaign of GBN/GBA to foster visibility of German hospital-based biobanks and their paramount importance for biomedical research.

SELECTED PUBLICATIONS

Appenzeller S, Gesierich A, Thiem A, Hufnagel A, Jessen C, Kneitz H, Regensburger M, Schmidt C, Zirkenbach V, Bischler T, Schilling B, Siedel C, Goebeler ME, Houben R, Schrama D, Gehrig A, Rost S, Maurus K, Bargou R, Rosenwald A, Schartl M, Goebeler M, Meierjohann S. (2019). The identification of patient-specific mutations reveals dual pathway activation in most patients with melanoma and activated receptor tyrosine kinases in BRAF/NRAS wild-type melanomas. Cancer 125:586-600.

Betsou F, Bilbao R, Case J, Chuaqui R, Clements JA, De Souza Y, De Wilde A, Geiger J, Grizzle W,Guadagni F, Gunter E, Heil S, Kiehntopf M, Koppandi I, Lehmann S, Linsen L, Mackenzie-Dodds J, Aguilar Quesada R, Tebbakha R, Selander T, Shea K, Sobel M, Somiari S, Spyropoulos D, Stone M, Tybring G, Valyi-Nagy K, Wadhwa L. (2018). Standard PREanalytical Code version 3.0. Biopreserv Biobank 16 doi:10.1089/bio.2017.0109.

Geiger J, Both S, Kircher S, Neumann M, Rosenwald A, Jahns R. (2018) Hospital-integrated biobanking as a service - The interdisciplinary Bank of Biomaterials and Data Würzburg. Open J Bioresources 5:6. DOI:http://doi.org/10.5334/ojb.

Jahns R, Schirmacher P. (2018) The current ethical and legal framework for human biobanks (Ethik und Rechtslage von humanen Biobanken). Pathologe 39:445-448.

Morbach C, Gelbrich G, Tiffe T, Eichner F, Wagner M, Heuschmann PU, Störk S; STAAB consortium, Frantz S, Maack C, Ertl G, Fassnacht M, Wanner C, Leyh R, Volkmann J, Deckert J, Faller H, Jahns R. (2018) Variations in cardiovascular risk factors in people with and without migration background in Germany - Results from the STAAB cohort study. Int J Cardiol doi:10.1016/j.ijcard.2018.10.098.

Clinical Trial Center Würzburg (CTCW)

CONTACT DETAILS

Professor Dr. med. Peter U. Heuschmann
(Scientific Director)

Klemens Hügen
(Managing Director)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/201-39342
Fax: 0931/201-639342
E-mail: zksw@ukw.de
www.ukw.de/interdisziplinaere-einrichtungen/zentrale-fuer-klinische-studien-zksw/startseite

Research Portfolio

The Clinical Trial Center Würzburg (CTCW) is the central academic clinical research organization (ACRO) of the Faculty of Medicine in Würzburg and is integrated in the University Hospital Würzburg (UKW).
The CTCW allows for activities and competencies of the Faculty of Medicine in Würzburg with respect to clinical studies to be pooled and regionally expanded. Infrastructure aimed at the conduct of local and regional studies in particular will be further professionalized and the recruitment of patients in clinical studies improved.
The CTCW focuses specifically on the conduct of Phase I to IV investigator-initiated clinical studies. The CTCW´s goal is to support scientific partners throughout all steps of a clinical trial, starting with the initial idea, the development of a viable concept, the joint application of research funding, the preparation and conduct of the clinical study, and also includes data evaluation and publication of results. The interdisciplinary team of the CTCW has all required competencies in the areas of biometric planning and analysis, legal and regulatory aspects, monitoring, data management, IT and databases as well as study coordination and project management.

Services

The CTCW is specialized in the conduct of academic Phase I to IV investigator-initiated clinical studies. It offers clinical study support within the scope of novel drug development, the development of medicinal products and therapies for national and international research projects, and provides personnel and logistic resources for medical research. Through close cooperation and continuous dialogue with the investigators, our services can be customized to fit the individual requirements of the clinical study. In consultation with the project manager, CTCW services can entail the support of the entire study or of particular processes or modules, e.g. data management, biometrics, clinical monitoring or project management. In addition to other research projects, the CTCW supports and supervises Phase I to IV clinical trials according to the German Medicines Act and medicinal product trials according to the Act on Medical Devices (MPG) starting with their conception and including planning, execution, and data analysis following the principles of good clinical practice. The CTCW also supports the University Hospital Würzburg (UKW) in the exercise of their activities as sponsor according to the German Medicines Act and Act on Medical Devices, and is part of the sponsor quality management (Sponsor-QA) and sponsor commission of the UKW.
In the period from 2017 to 2018, 34 study projects were carried out with the participation of the CTCW and seven study projects were supported in the planning phase. A total of 137 consulting activities were provided regarding individual planning, study design, study implementation, legal requirements, biometric-statistical evaluation of clinical studies, as well as submission of applications to the health authorities.

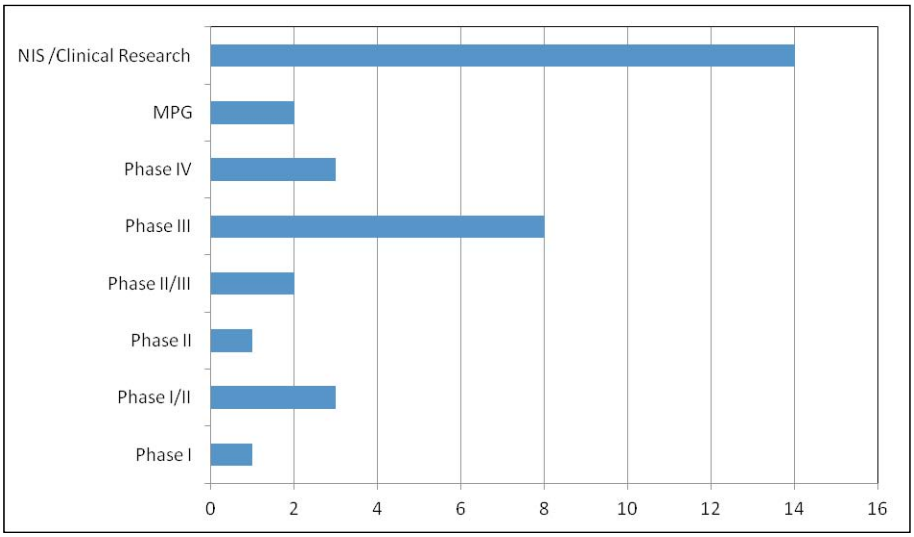


Fig. 1: Distribution of studies with the participation of the Clinical Trial Center Würzburg by type and phase in the years 2017/2018. Drug studies correspond to Phases I to IV, Medical Device Studies (MPG), and Clinical Research Projects (Non-Interventional Studies (NIS) or, for example, studies on new surgical procedures).

Cooperations

The CTCW cooperates with national and international institutions, researchers, and physicians, who intend to plan and conduct a clinical trial. Close relationships are maintained between the CTCW and other German universities and nationwide study groups. Within Würzburg, the University Hospital AöR as well as the academic teaching hospitals are important collaboration partners of the CTCW.
In 2017 and 2018, the CTCW supported 10 hospitals, two interdisciplinary research centers and three clinical profile centers to coordinate their study projects successfully and to realize high-quality studies according to international standards. The CTCW also supports decentralized operational study facilities at the University Hospital Würzburg and three external hospitals.
It is closely cooperating with the German Comprehensive Heart Failure Center (DZHI), the Comprehensive Cancer Center Mainfranken (CCCMF), the Nephrological Study Center Würzburg (NSZ), the Service Center Medical Informatics (SMI), as well as the Institute for Clinical Epidemiology and Biometry (ICE-B). The CTCW also maintains trial cooperations with the University of Oxford, Imperial College London, Hospital of the City of Ludwigshafen and the University Hospital Essen.

Education and Training

Other services of the CTCW include the development of competencies in the area of clinical studies by offering qualification and training programmes. The CTCW offers seminars and educational courses for investigators, study managers, and study nurses.

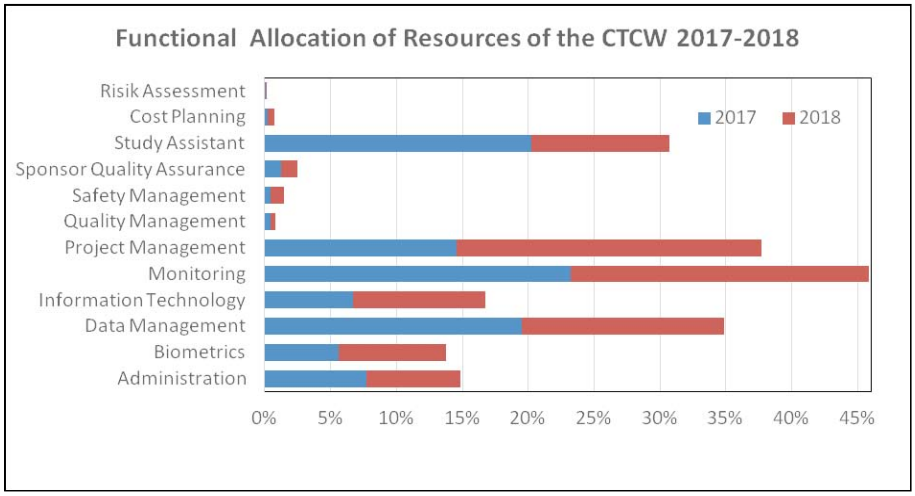


Fig. 2: Distribution of resources of individual services by the Clinical Trial Center Würzbug (CTCW) in the years 2017 and 2018 taking into account the effective working time [%]

SELECTED PUBLICATIONS

Fenske W, Refardt J, Chifu I, Schnyder I, Winzeler B, Drummond J, Ribeiro–Oliveira A, Jr., Drescher T, Bilz S, Vogt D R, Malzahn U, Kroiss M, Christ E, Henzen C, Fischli S, Tönjes A, Mueller B, Schopohl J, Flitsch J, Brabant G, Fassnacht M, Christ–Crain M. (2018) A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus. NEJM 379:428-439.

Hammer F, Malzahn U, Donhauser J, Betz Ch, Schneider M, Grupp C, Pollak N, Störk S, Wanner Ch, Krane V, MiREnDa Study Group. (2018) Effect of spironolactone on left ventricular mass in hemodialysis patients: the MiREnDa study – a randomized controlled trial. Kidney Int 95:983-991.

Korompoki E, Del Giudice A, Hillmann S, Malzahn U, Gladstone DJ, Heuschmann P, Veltkamp R. (2017) Cardiac monitoring for detection of atrial fibrillation after TIA: A systematic review and meta-analysis. Int J Stroke 12:33-45.

Korompoki E, Filippidis FT, Nielsen PB, Del Giudice A, Lip GYH, Kuramatsu JB, Huttner HB, Fang J, Schulman S, Martí-Fàbregas J, Gathier CS, Viswanathan A, Biffi A, Poli D, Weimar C, Malzahn U, Heuschmann P, Veltkamp R. (2017) Long-term antithrombotic treatment in intracranial hemorrhage survivors with atrial fibrillation. Neurology 89:687-696.

Wachter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, Seegers J, Wasser K, Schulte A, Jürries F, Messerschmid A, Behnke N, Gröschel S, Uphaus T, Grings A, Ibis T, Klimpe S, Wagner-Heck M, Arnold M, Protsenko E, Heuschmann PU, Conen D, Weber-Krüger M; Find-AF(randomised) Investigators and Coordinators. (2017) Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial. Lancet Neurol 16:282-290.

Center for Experimental and Molecular Medicine (ZEMM)

CONTACT DETAILS

Professor Dr. rer. nat. Albrecht Müller
(Head)

Zinklesweg 10
97078 Würzburg
Phone: 0931/201-45848
Fax: 0931/201-45147
E-mail: albrecht.mueller@uni-wuerzburg.de
www.zemm.uni-wuerzburg.de

Dr. med. vet. Heike Wagner
(Head of Animal Facility)
Phone: 0931/201-44077

Professor Dr. rer. nat. Michael R. Bösl
(Head of Transgenic Technology)
Phone: 0931/201-44078

Mission and structure

The ZEMM is a facility of the Faculty of Medicine available for temporary use by thematically clearly defined research projects requiring animal husbandry. In addition to the laboratory division, the ZEMM houses the central animal husbandry unit of the University of Würzburg.
The animal facility comprises three similarly sized divisions: experimental animal husbandry, the breeding division, and the division for SPF breeding and care of animals under perfect hygienic conditions. The housing rooms are equipped with extensive holding areas and complex venting and climate control systems, allowing for animal husbandry fulfilling the greatest demands of cleanliness.
Scientists working in the fields of medicine and biomedicine also have access to a number of small-animal and one large-animal operating room. Animals may be transferred to the experimental husbandry unit, as long as specifics relating to animal care do not necessitate decentralized housing.
In 2018, the ZEMM hosted an average of 19,000 mice belonging to around 85 different user groups, the different transgenic mouse lines involved numbering 650 in total. During the course of the past year, these user groups were working on a variety of approved animal experimentation projects, of which circa 80 continue to run in 2019.

The ZEMM occupies around 900m^2 of office and laboratory space, which may be allocated on the basis of applications for third-party-funded projects. Currently, workgroups from Medical Clinics I and II, as well as the stem-cell-biology workgroup headed by Professor Albrecht Müller are located in the ZEMM. Since October 2018, animal research laboratories of the Neurology Clinic have been positioned in the building for experimental work.

Transgenic Technology

The mouse is the most important mammalian model system in biomedical research. Its importance to Wüzburg as a center of research is substantiated by continuously increasing numbers of animals housed.
Research with genetically engineered mouse models does not only need a state-of-the-art animal facility, but also relies on artificial reproductive technologies (ARTs), which are provided by the Transgenic Technology lab as a central platform. Our lab focuses on providing the following scientific services:

- Rederivation of freshly harvested mouse embryos from mouse lines imported from external animal facilities in order to maintain the local hygiene level
- Rederivation of cryopreserved embryos
- Rederivation of cryopreserved mouse sperms via *in-vitro* fertilization

Fig. 1: View of an individually ventilated cage system for housing immunocompromised animals.

- Cryopreservation of mouse lines as sperms or embryos

The international exchange and import of mouse lines is almost exclusively accomplished through the shipment of cryopreserved embryos and sperms.

After the local quarantine station was closed down, the import of mouse lines from sources with high-risk infections is now only feasible through the rederivation of cryopreserved embryos or sperms.

Owing to the formation of new groups using the mouse as research model, the number of rederivations of mouse lines has tripled in the last two years. In order to meet the increased demand, the laboratory capacity will be expanded with the support of the Dean of the Faculty of Medicine.

The *de novo* generation of genetically engineered mouse models is offered in collaboration with the Rudolph Virchow Center or the Chair of Experimental Biomedicine I.

Fig. 2: CRISPR/Cas9 ribonucleoprotein complexes are injected into the pronucleus of a fertilized mouse oocyte for gene editing.

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Teaching and Promotion of Young Academics

CONTACT DETAILS

Professor Dr. med. Christoph-Thomas Germer
(Dean of Studies in Medicine)

Professor Dr. med. Dr. med. dent. Alexander Kübler
(Vice-Dean of Teaching and Research in Dentistry)

Professor Dr. med. Manfred Gessler
(Dean of Studies for B.Sc./M.Sc. Degrees in Medicine)

Implementation of completely electronic examinations (e-exams)

The Faculty of Medicine purchased 200 iPads in order to implement written examinations on tablets connected by Wi-Fi. The winter semester of 2016/17 saw the introduction of e-exams for semester cohorts of 160-180 students in clinical medical school. Thanks to the electronic examination format, innovative question types that assess clinical decision-making and procedural knowledge, as well as minimize the probability of guessing, may be employed alongside the classic multiple-choice questions for the first time. Moreover, the new format enables the incorporation of images, which is particularly beneficial to the subject fields employing visual diagnostics (e.g. radiology, pathology). Automatically exporting the examination results will reduce the rate of errors in post-processing and reduce the time needed to mark and evaluate the examinations. Along with the new examinations, opportunities for prompt post-examination follow-up discussions have been established with the spokespersons for each semester as well as those responsible for the examination. The summer semester of 2018 saw the electronic infrastructure extended through the purchase of a further 60 tablets for the degree course in dentistry.

New WueCampus platform in preparation of the internal Faculty examinations

A new course room on the University's e-learning platform WueCampus has been set up for students preparing to sit examinations. The aim is to make available the content from the most recent examinations in each and every subject to students for study purposes while maintaining copyright. The creation of adaptively combinable examination scenarios as well as a search and commenting function are currently in development.

Expansion of the course "Practical Clinical Examination Methods" (PKU) and quality assurance for the final examination (objective structured clinical examination (OSCE))

The foundations of basic medical skills and communication are laid in the compulsory course PKU in the fifth semester of medical school. Basing on the National Competency-Based Catalogue of Learning Objectives in Medicine (NKLM), the learning objectives have now been formulated explicitly and identified to students, and to which examination content has been adapted strictly. The course was expanded by adding the module titled "Consolidation of Examination Techniques", which now allows more time for practical exercise and revision. In order to utilize the resource-intensive time in small-group teaching as effectively as possible, the theoretical proportion of each course day was reduced to a minimum. Students prepare for the course in their own time, in the sense of the flipped-classroom concept. The statistical evaluation of the final OSCE could be shifted to probabilistic test theory. Mathe-

Fig. 1: Mentoringprogramm MED 5Plus1.

Fig. 2: The neurology module in the practical clinical examination course.

matical models of the examination results can now be called upon to identify confounders, which, once corrected, can be added back to the results. Thus not only the quality but also the fairness of the test is improved for students.

New training placements in bedside teaching

From the beginning of the winter semester in 2017/18 in reinforcement of the practical training already available and to increase patient contact, two additional weeks of bedside teaching have been introduced as a compulsory element to the sixth semester of clinical medical school. Students may select any of the clinics at UKW and broaden their training in any field toward which they are inclined.

Evaluating the teaching and addressing the results

Thanks to the assistance of the Council of Students' Representatives and a rise in the appreciation of comments for improvement, we have been able to increase the response rates in the regular evaluations carried out for all compulsory courses. The evaluation allows participants to grade the course globally, enter how often they participated, and invites participants to enter free-text comments. Furthermore, the evaluation platform EvaSys provides the opportunity for individual surveys for more focussed questions or teacher-related surveying. The titles of the most highly rated courses in medicine were published for the first time in an edition of the employees' magazine of UKW in 2018. Good teaching performance should be honoured visibly in this manner.

The awarding of teaching prizes

The Albert-Koelliker Teaching Prize for advancement and improvement in teaching at the Faculty of Medicine in Würzburg has been awarded twice annually since autumn 2003. The Prize is valued at €10,000; the prize money limited to a specific purpose. Within the framework of the graduation ceremonies in the spring and autumn of 2017, the Prize went to the Fachschaftsinitiative Medizin e.V. (Action Group of the Council of Students' Representatives in Medicine) for their perennial commitment to the Faculty of Medicine, as well as Prof. Dr. Michael Bohnert from the Institute of Forensic Medicine and Prof. Dr. Angelika Stellzig-Eisenhauer from the Orthodontics Outpatients' Clinic for their excellent performance in teaching. In spring 2018, the Prize was awarded to the teaching staff of the Department of Anaesthesiology headed by the Department Director Prof. Dr. med. Dr. h.c. Norbert Roewer, whose teaching was commended as being particularly varied and clear in nature. Autumn 2018 saw the former Head of the Teaching Department of General Practice Dr. Hellmuth, as representative of all the general practice contract lecturers and teaching practices at the University of Würzburg, decorated with the Prize.

New academic teaching hospital

The circle of academic teaching hospitals was expanded with the inclusion of Main-Spessart Hospital in Lohr in 2017. The Faculty Board of Management agreed to the addition following a visit of the facilities by a delegation from Würzburg and the extensive verification of all the documents submitted. Practical Year placements in the fields of surgery, internal medicine, anaesthesiology, and neurology are available in Lohr.

Permanent adoption of the Competence Network of Medical Teaching in Bavaria

After expiry of the nine-year-long period of funding the Competence Network of Medical Teaching in Bavaria by the former Bavarian State Ministry for Education, Culture, Science, and Art (now Ministry for Education and Culture and Ministry for Science and Art), the collaboration has now been adopted permanently by the faculties. The position paper on the legal framework requirements when crediting digital teaching formats towards the teaching load may be named as an exemplary product of the working group on e-learning. Moreover, common criteria and content relating to the recognition of medical didactics qualification processes were compiled by the workgroup on faculty development.

Qualification through postgraduate master's programme in medical education

During the reporting period, four members of the Faculty of Medicine or University Hospital have been accepted onto the postgraduate programme "Master of Medical Education" in Heidelberg. They should contribute to the further professionalization of teaching and are funded through state study subsidies. One teacher from Würzburg already managed to graduate from the MME degree programme successfully in 2017.

Paul-Ehrlich Contest

The team of medical students from Würzburg won the competitive Paul-Ehrlich Contest in

2017. Diagnoses at lightning speed following a look at a photograph, proposals of treatment in tricky cases, and manual skills on the treatment table were the order of the day. Thirteen teams from faculties of medicine in Germany and Austria competed against each other in the competition in Frankfurt in 2017. At the end of the day, the team from Würzburg under the supervision of Prof. Dr. Nentwich (ophthalmology) and Prof. Dr. Knop (internal medicine) were able to win through. Numerous evening seminars took place in preparation, during which the most important clinical pictures were consolidated.

System accreditation of the University and fields of study audit

During the meeting on 19 March 2018, the Agency for Quality Assurance of Accredited Degree Courses (AQAS) came to the decision that the University of Würzburg should receive unconditional system accreditation. In its report, the expert panel certifies that the University of Würzburg possesses an ideal system of quality management (QM) in the field of study and teaching. The Faculty of Medicine follows the University-wide QM structures and takes up the challenge of continuous compliance as well as further development of the QM cycles. System accreditation was certified for the duration of six years.

The aims of qualification and curriculum mapping with the NKLM

A process of reaching a consensus with respect to qualification aims of degree courses took place within the framework of system accreditation. Such target competencies are best understood as a higher-ranking summary as well as prioritisation. For the first time for the degree in medicine, they were formulated as "ability to take a qualified position of employment", "scientific ability", ability to be committed socially", and "development of personality". They span all of the learning objectives defined by the NKLM like an umbrella and have been published on the Faculty's website since the summer semester of 2018.

Furthermore, all the courses taught in both preclinical and clinical medical school have already been mapped with the NKLM on the level of the operationalised learning objectives since the winter semester of 2016/17. This has the aim of assigning the competency-based learning objectives to the respective courses and individual periods or modules, as well as providing both students and teachers with an aid to orientation.

New mentoring programme MED 5Plus1

The MED 5Plus1 programme that was renewed in the winter semester of 2017/18 is targeted at students of the Faculty as a group mentoring programme during their studies. It supports students in decisions and questions relating to their studies and careers. An experienced physician or scientist respectively accompanies a group of five mentees throughout the course of one year. The mentoring itself is based on the concept of student mentoring practised at the University of Medicine in Vienna.

Students may select which mentoring group they wish to join on the basis of the mentors' profiles. In monthly meetings, mentors afford the groups valuable insight into their working life and the respective field of research. Moreover, numerous different offers and strategies of support may be discussed, focussed projects explored, and new teaching concepts tried out collectively.

Internationalisation

Following an invitation from the Faculty of Medicine in Würzburg, a delegation from our Japanese partner institution Nagasaki University visited the Siebold-Collegium in Würzburg for a two-day symposium on radiotherapy from 28 September to 1 October 2017 (sessions: Biological Impacts of Radiation as Cause of Disease; Diagnostic and Therapeutic Use of Radiation, Prevention and Treatment of Radiation-induced Injury and Palliative Care). During the symposium and in addition to the technical debate, the opportunity was taken to lay the foundations of closer research collaboration with colleagues in Würzburg.

In November 2017, the Faculty of Medicine in Würzburg signed a memorandum of understanding with respect to collaboration with University Medical Center Utrecht. Cooperation between Utrecht and Würzburg already exists on a number of levels, including teaching, for example through the involvement of both universities in the international double master's degree in biofabrication (www.biofabdegree.net), as well as research projects, such as the EU consortium project HydroZONES (www.hydrozones.eu). This current focus on the field of biofabrication is to be reinforced and serves as a breeding ground for cooperation in other topics.

April 2018 saw a delegation from the Faculty of Medicine in Würzburg travelling to the Technion – Israel Institute of Technology in Haifa, where a cooperation agreement on student exchange with the Ruth and Bruce Rappaport Faculty of Medicine was signed.

In 2017/18, new Erasmus Agreements could be entered into with Vilnius University in Lithuania, the University of Ljubljana in Slovenia, and Stradins University Riga in Latvia. This now increases the number of Erasmus faculty partnerships to 39.

In the academic year of 2017/2018, a total of 31 medical students spent a period of study abroad generally lasting one semester via partnership programmes, with 27 by means of the Erasmus Programme. The exchange programmes (primarily with Japan, Tanzania, and China) were used by a total of 14 Würzburg students in 2017 and 17 in the following year for a Practical Year placement or a clinical elective at one of the partner universities abroad. In return, 14 students from partner universities in 2017 and a total of 21 in 2018 came to Würzburg to complete a practical placement for one to two months.

The master's degree course in translational neuroscience as an English-language elite programme has been supported by the Bavarian Ministry of Science since October 2018. Practical placements at universities abroad are explicitly foreseen on the programme.

Dentistry

The clinical curriculum is organized according to the currently valid Medical Licensure Act for dentistry students and requires an extensive vocational education and training. The dental education program is mainly based on sciences and dental techniques and medicine. The clinical education program deals with diagnosis and therapy of dental and dentofacial anomalies and jaw diseases, restorative dentistry, oral and maxillofacial surgery, prosthetics, orthodontics, as well as periodontics. During their course of studies, students practice, develop and enhance their manual skills at simulation units with training dolls. Beginning with the 7th semester students start to treat patients. Interactive training concepts and problem-based learning integrated in the clinical education are offered. The department of dental prosthetics focus on the practice-oriented education by providing the latest research results. Innovative teaching through exercises on 3D-printed model teeth are performed in the Restorative Dentistry course of the first clinical semester. Lectures and exercises on digit-

ally manufactured ceramic restoration (CAD CAM) present students the most modern therapeutic options in dentistry.
The Students have access to an extensive library with numerous computer workstations with Internet connection for their private studies. Since the winter semester 2013/14 the government grant allotted to the dental clinic is mainly used for the financing of tutors and a full-time teaching coordinator, as well as for the financing of extremely expensive instruments and expendable items for the student courses. The high financial burden, which dental students have to bear today, is thus reduced. The Department of Dentistry awards the Adolf-und-Inka-Lübeck-Prize twice a year to the two best graduates of the final examination. The presentation of prizes takes place in the festive context of the University Church (Neubaukirche) at the awarding of certificates since 1977.
In the winter 2015, a vice dean for teaching and research in dentistry has been appointed, whose aim will be the continuous development and improvement of teaching. The introduction of a new licensing system for dentistry was rejected shortly before the vote in the Federal Council and will hopefully be rethought by the amendment of the Medical Study Program 2020.

Bachelor's and Master's Degree Programmes

B.Sc./M.Sc. Degree Programmes in Biomedicine and Biochemistry

The degrees in biomedicine are offered by the Faculty of Medicine in conjunction with the Faculty of Biology and teach students at the interface between classic science and clinical research. Teaching in close proximity to research with intensive laboratory placements in small groups as well as the early involvement in current research topics comprise core elements. In preparation of the bachelor's or master's thesis written in English, additional placements in individual workgroups are envisaged in order to guarantee that students accomplish their respective dissertations efficiently and productively.
Whereas the syllabus in the bachelor's programme remains rather tight, students enrolled on the master's programme in biomedicine are relatively free to set their own priorities after completing the extensive practical course in model organisms during the first semester. The numerous opportunities to spend time abroad are one of the special features, during which students may broaden both their scientific as well as personal horizons. The Biomedica alumni meetings and the Biomedical Student Symposium, which attracted over 180 participants from 17 universities in 2018, count as particularly important extracurricular activities significantly co-organized by students themselves.
Interest remains consistently high with 108 students enrolled on the bachelor's programme and a further 48 on the master's programme currently. The majority of graduates from previous years have decided predominantly to seek further scientific qualification in the form of a doctorate, with around 40% remaining in Würzburg and the rest moving to other locations either in Germany or abroad.
The Faculty of Medicine has also been offering a degree course towards a Bachelor of Science in Biochemistry in conjunction with the Faculty of Chemistry and Pharmacy since 2009. The demand is also exceptionally high for the 60 places on offer. Within the framework of the consecutive M.Sc. programme, an area of focus on molecular oncology was set up that should appeal in particular to suitable applicants from abroad in search of focussed training at the interface between basic research and clinical oncology.

Master's Degree Programme and Additional Courses of Study in Translational Neuroscience

The elite programme **Translational Neuroscience** is a scientifically oriented M.Sc. degree course offered by the Faculty of Medicine and taught in English. Its strength lies in the tight link between questions relating to basic research into neurobiology and issues relating to clinically oriented research and the applicability to treatment and clinic. The programme has been supported financially as an elite degree course by the Elite Network in Bavaria since the winter semester of 2018/2019 and is now open to medical students as an additional course of study once they have passed Part I of the National Medical Licencing Examination. Enrolment on the programme requires participation in an aptitude assessment procedure. The didactically coordinated programme concentrates on scientific project work and project design, in addition to competency in the fields of neurobiology, neurology and neurosurgery, psychiatry, and psychology. By targeting the synergies between these fields, which have been separated up until now, the competencies developed by students allow them to meet the challenges of developing new methods to treat complex neuropsychiatric diseases and disorders. The aim is to qualify the graduates for positions in clinical science in the field of neuroscience.

Additional Programme and Master's Degree in Translational Medicine

An additional programme by the name of **Translational Medicine** comprising 60 ECTS has been on offer to medical students since the summer semester of 2018. This programme provides participants with sound knowledge from all sub-disciplines involved in translational research. A master's degree in translational medicine comprising an additional six months of work towards a master's thesis (30 ECTS) is open to applicants who have completed their degree in medicine. Both programmes are supported financially within the framework of the Elite Network of Bavaria.

The diversity of topics on offer in courses ranges from experimental fundamental research via clinical trials and all the way up to the implementation of scientific discoveries in the medical care of the population. During research placements at national and international partner institutions, students may consolidate their knowledge and gain insight into current research. Graduates of the programme are thus exceptionally well prepared for the challenges of modern research in medicine.

Bachelor's Degree in Academic Speech and Language Therapy / Logopaedics

The bachelor's degree in academic speech and language therapy / logopaedics was introduced in conjunction with the Würzburg Vocational College of Logopaedics (Caritas-Schulen gGmbH) in the winter semester of 2014/2015. The dual degree programme accepts 25 students annually and successful participants receive two qualifications on graduation. Not only do they sit the national examination to obtain certification as a speech and language therapist, they also receive a Bachelor of Science as an academic qualification.

Graduate School of Life Sciences (GSLS)

Graduate School
Life Sciences

CONTACT DETAILS

Professor Dr. rer. nat. Caroline Kisker (Dean)

Rudolf-Virchow-Center for Experimental Biomedicine
Chair of Structural Biology
Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/31-80381
E-mail: caroline.kisker@virchow.uni-wuerzburg.de
www.graduateschools.uni-wuerzburg.de/life_sciences

Professor Dr. rer. nat. Thomas Rudel
Chair of Microbiology, Theodor-Boveri-Institute for Biosciences
(Vice Dean, GSLS)

Professor Dr. rer. nat. Katrin Heinze
Molecular Microscopy, Rudolf-Virchow-Center for Experimental Biomedicine
(Vice Dean, GSLS)

Dr. rer. nat. Gabriele Blum-Oehler
(Managing Director)
Phone: 0931/31-81474

General Information

For many years, the Faculties of Medicine and Biology have gained extensive experience with structured graduate training through the MD/PhD programme and several DFG-funded graduate research training groups (Graduiertenkollegs) at the University of Würzburg. University-wide discussions as to how to improve graduate training led to the foundation of the "International Graduate School" (IGS) by the University Senate at the end of 2003 which was renamed in subsequent years to Würzburg University Graduate Schools (UWGS). The UWGS covers the university's entire academic spectrum, encompassing separate graduate schools, catering to the specific scientific and training needs and cultures of its diverse disciplines.

Early years

Several programmes and their doctoral researchers joined forces to identify and develop common structures and curricula, to organize joint activities and to set common standards (see box) for their doctoral researchers resulting in the section Biomedicine in 2003. Since then, many generations of basic and clinical scientists have successfully completed this programme.
The section of Biomedicine has not only built up new structures and developed key training elements, but also served as a nucleus for the foundation of the "Graduate School of Life Sciences" (GSLS) which now harbours not only the section Biomedicine but also Infection and Immunity, Neuroscience, Integrative Biology, and Clinical Sciences. The GSLS was twice successful in the "Excellence Initiative of the Federal and State Governments" (2006 and 2012) and obtained funding to support fellowships and other activities within the GSLS.

The growing Graduate School

Increases in size and scope resulting from the progressive integration of further programmes and discussions in the context of the national "Excellence Initiative" called for a number of changes within the UWGS. The UWGS transformed into an umbrella organization for four independent graduate schools in 2006: The Graduate School of the Humanities (GSH), the Graduate School of Science and Technology (GSST), the Graduate School of Law, Economics and Society (GSLES), and the Graduate School of Life Sciences (GSLS).
All four Graduate Schools cater to the needs of their respective broad fields of science, uniting research in the life sciences, the humanities, the natural sciences and social sciences.
The umbrella organization, the UWGS, assures adherence to, and development along common rules. It also provides general services to the individual schools. In this con-

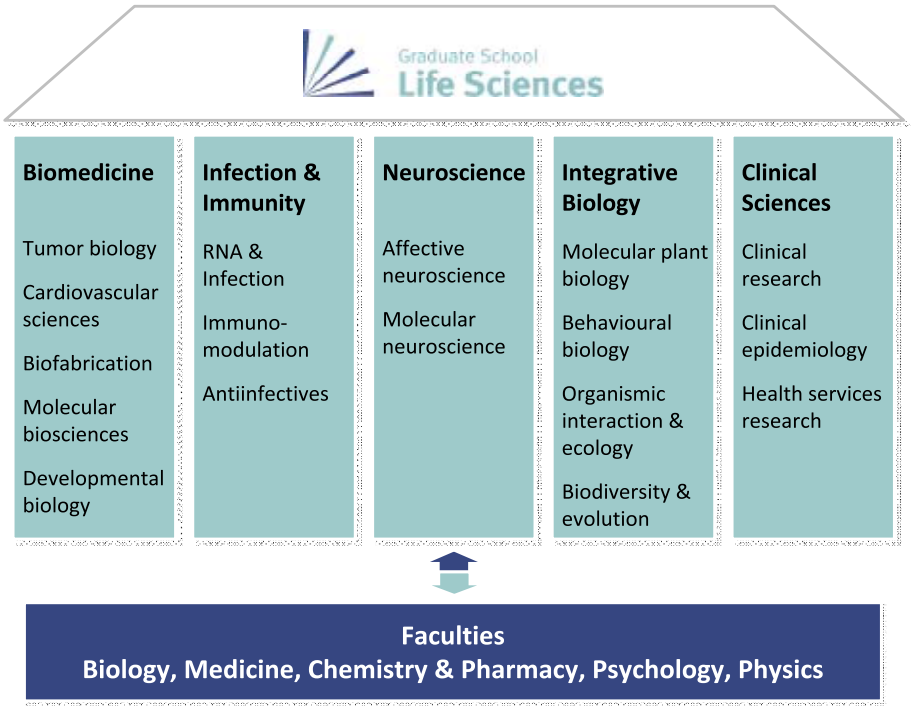


Fig. 1: Structure of the Graduate School of Life Sciences.

text, doctorate degree regulations ("Promotionsordnung") were developed and passed by the University Senate in 2006. These regulations contain a set of common articles along with specific regulations for the individual schools including a mentoring system as well as rules for admissions and formal standards (see box). A common charter for the UWGS and all of the individual graduate schools was passed by the Senate in August 2007, regulating issues of membership and operating procedures. The UWGS has also developed a standard regulation for doctoral study programmes that are easily adaptable to the needs of the individual graduate schools. The study programmes "Life Science" and "Humanities" were approved by the Bavarian State Ministry of Sciences at the end of 2007.

Recent developments in the Graduate School of Life Sciences

The Graduate School of Life Sciences (GSLS) is the largest and most strongly integrated graduate school at the University of Würzburg. The plans for the GSLS were set forth in the successful applications within the framework of the Excellence Initiative.
The GSLS now houses doctoral researchers of collaborative research programmes – such as the DFG-funded collaborative research centers ("Sonderforschungsbereiche"), research training groups ("Graduiertenkollegs"), clinical research groups ("Klinische Forschergruppen"), and other collaborative programmes (funded by the Federal Ministry of Education and Research (BMBF), the European Union, and other sources) as well as individual grant programmes and PhD fellowships. The school is currently divided into five separate sections as described above. Doctoral researchers of the MD/PhD programme are integrated into the respective sections according to their research interests. Each section usually comprises individual programmes which are the scientific as well as social "homes" of the doctoral researchers (see Fig. 1).

GSLS fellowship programme: The fellowship programme of the GSLS is the core element within the graduate school and is funded by the Excellence Initiative. The 12th round of international recruitment was completed in the winter of 2018. To date, more than 3700 standardized written applications have been evaluated in the recruitment rounds, and interviews with more than 550 candidates have been conducted by the GSLS admission board in Würzburg, by means of video conferencing and visits abroad. So far, 146 fellows from 35 different countries have been supported by the GSLS, underlining its particularly international character.
To date, the number of formal members of the GSLS has risen to more than 290 principal investigators from all participating faculties. In 2018, the number of doctoral researchers registered in the doctoral study programmes "Life Sciences" rose to more than 480.

Excellence Programme for Medical Doctoral Researchers: The renewal proposal of the GSLS in the framework of the second phase of the Excellence Initiative was approved in July 2012. Besides establishing an international MSc programme and a programme for postdoctoral fellows to foster their early independence, the introduction of an excellence programme for MD doctoral studies was also envisaged, addressing the top ~20% of medical students (Fig. 2).
Since March 2013, 154 MD students have registered to participate in the structured doctoral training programme of the GSLS; by the end of 2018, 21 doctorates had been awarded. To register, the following criteria have to be fulfilled:

- Receipt of an MD fellowship from the Faculty of Medicine or the GSLS
- The thesis entails an experimental or clinical epidemiological research project
- Successful completion of the First State Examination in medicine is required
- A dedicated phase towards the thesis of at least nine months
- The establishment of a thesis committee with three PIs.

Applications for the MD fellowships can be submitted by two application deadlines per year (1st June and 1st December) to the Faculty of Medicine. The requirements for the successful completion of an MD thesis amount to a third of those for the natural sciences GSLS doctoral researchers, as the programme is expected to last a maximum of one year. The programme comprises seminars, journal clubs, methods courses, workshops, retreats, and the active participation in at least one international conference. MD students can also choose from a great variety of transferable skills courses in the GSLS. An additional requirement is to obtain at least one co-authored peer-reviewed original research publication prior to completion of their thesis.

The FOKUS Master Life Sciences Study Programme: The usual admission requirement for the doctoral study programmes of the GSLS is a master of science degree or a diploma. Previously, students holding a BSc degree could only enter the GSLS after a one-year qualification phase consisting of a mini thesis and three oral examinations. To attract excellent international candidates directly after their BSc, the GSLS and the Faculty of Biology, in cooperation with the other constituent faculties of the GSLS, designed the fast track course 'FOKUS Life Sciences'. Created in 2012 and accredited in 2013, the study programme has attracted excellent students from around the world. Candidates enter a rigorous selection process before being admitted. In the first semester, students are prepared for active research in the life sciences through two specifically designed lecture se-

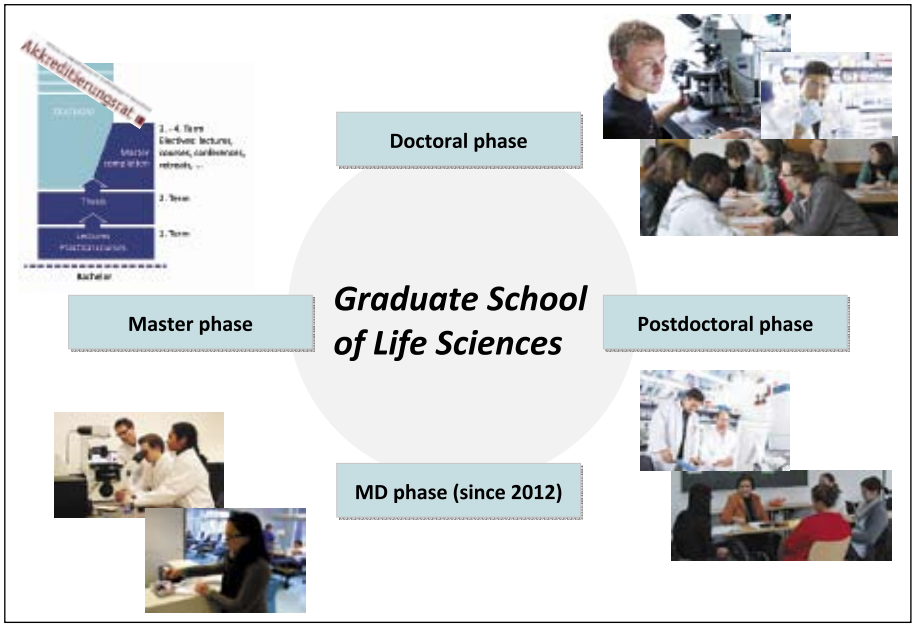


Fig. 2: Programmes of the Graduate School of Life Sciences.

Fig. 3: Annual GSLS retreats offer PhD and MD doctoral researchers interdisciplinary networking opportunities and foster intense discussions.

ries and a multitude of lab-based internships. Only students who attain excellent grades in the first semester are permitted to remain on the fast track and pursue their master's thesis during the second semester. The thesis ideally sets the foundation for a follow-on PhD project, which students can start immediately if their master's thesis is excellent. The remaining ECTS points required for completion of the MSc degree will be earned during the PhD phase. By offering the option to work towards a PhD within a year of a BSc degree and to obtain a master's degree parallel to studying towards the PhD, the FOKUS Life Sciences programme is able to attract even more internationally excellent students to Würzburg.

Since the programme was introduced in the winter term of 2012/13, 45 students have been admitted. In the meantime, 32 students have completed their master's and almost all have entered into a PhD programme in Würzburg or other renowned national and international research institutions. One graduate successfully applied for the Clinician Scientist Programme of the Interdisciplinary Center for Clinical Research in Würzburg. Six students successfully applied for the GSLS fellowship programme, 23 started PhD projects via the fast-track option after the 1st year.

The PostDoc Plus Programme: It is important to support junior researchers on their path to independence. In the course of the 2nd phase of the Excellence Initiative, the GSLS therefore offers postdoctoral researchers a research grant for the duration of one year. This grant was designed to provide the basis for the preparation of their own grant proposals such as the Emmy Noether programme or ERC starting grants. Even though the support was only granted for one year, the GSLS programme has proved to be quite successful; from 2013 to 2018, 32 postdoctoral researchers successfully applied for the GSLS research grants. The funding resulted in several high-quality publications and grant applications (e.g. DFG or EU proposals). Eight candidates meanwhile accepted independent group-leader positions.

Key elements of training in the Graduate Schools

- The traditional single supervisor ("Doktorvater" or "Doktormutter") is replaced by a thesis committee with three principal investigators (PIs).
- A wide range of training activities is offered, from which an individual programme is tailored for each doctoral researcher.
- Doctoral researchers actively participate in the programme by offering and organizing courses and symposia (Fig. 3).
- A common quality standard is assured through the set of requirements.

Mentoring System

Each doctoral researcher is matched with an individual thesis committee, which meets with them at regular intervals to monitor progress and adjust the research and training activities. Additionally, the doctoral researchers report on the status of their project within their research groups and programmes in order to exchange ideas and obtain feedback within their peer-group.

Training activities

The training activities total a minimum of 4-6 hours per week (depending on the specific graduate school) and consist of seminars, journal clubs, programme seminars, methods courses, and transferable skills workshops as well as retreats and international conferences.

Common Graduation Commission

The participating faculties form a Common Graduation Commission within the respective graduate school. The commission is responsible for the conferral of all doctoral degrees within the graduate school. This enforces common standards across disciplines and fosters interdisciplinary cooperation in graduate training.

MENTORING med – Career Programmes at the Faculty of Medicine and University Hospital

CONTACT DETAILS

Sibylle Brückner
(Project Coordination)

Josef-Schneider-Str. 2
97080 Würzburg
Phone: 0931/201-53850
Fax: 0931/201-55222
E-mail: sibylle.brueckner@ukw.de
www.med.uni-wuerzburg.de/fakultaet/karriere

Objectives

MENTORING med is used as a modern instrument in academic career development in order to recruit and support qualified young scientists in pursuit of their career and higher achievements. Female scientists (one-to-one setting) and – since 2016 – also male scientists (peer setting) are brought together with established senior scientists and leaders. Networks are formed so that better career opportunities develop.

Structure

The programme focuses on three elements: on a qualification programme (workshop series), on the building of networks (network meetings) and on meetings between the mentee / peer groups and the mentors (mentoring relationship).

In addition to the seminars of the basic programme (kick off, introduction, interim review and final event), five network meetings as well as 14 workshops and seminars take place. All of them are related to career-relevant topics such as university appointments, third-party funding, and leadership.

History

The MENTORING med programme is a cooperation between the Faculty of Medicine, clinic, and the officer for gender equality issues of the Faculty. The programme was co-financed until the 31 May 2015 by the European Social Fund (ESF), especially in order to promote female scientists to leading positions. The programme started in 2008, thus celebrating its ten-year jubilee in the time frame of this report. In October 2014, the position of the mentoring managing director was perpetuated; MENTORING med was integrated into the permanent budget of the University Hospital in June 2015.
From 2008 until May 2015, four rounds took place, each of them with 18-month duration. A total of 164 female mentees (about 40/round) and 164 female or male mentors participated. Some mentors were involved in more than one round.

A new concept was drafted in 2015:
MENTORING med was renamed to MENTORING med One-to-One and a second programme was established, MENTORING med PEER for female and also for male mentees. The duration of the programmes was extended from 18 to 24 months, respectively. The programmes run in shifts.

Programme variations

MENTORING med One-to-One

The successful programme offers the opportunity to build up a one-to-one mentoring relationship and especially focuses on individual supervision and support of the junior researcher. In tandems, mentees are provided with advice through experienced female and male mentors.

MENTORING med PEER

The new programme particularly focuses on cross-gender and interdisciplinary networking. So-called peers continuously meet in small groups to discuss common career goals. Peer groups invite mentors.

Participants 2017/2018

MENTORING med One-to-One

Mentees: 20 female mentees, among them 14 from medicine, four from natural science, one mentee holding a Dr. med. and a Dr. rer. nat and one holding a Dr. phil.

Mentors: Out of 21 mentors in this round, 13 of them were female and eight male. All were in-house (Faculty of Medicine and University Hospital), among them 15 medical doctors, eight natural scientists, and one veterinarian.

MENTORING med PEER

First round Peer (2016/2017):

Mentees: Out of a total of 20 mentees in this round, ten were female, ten male, two mentees terminated their participation prior to the formal end. Out of the remaining mentees, ten were doctors, one was a dentist, and seven were scientists.

Mentors: In this round, 24 mentors were involved, ten female and 14 male. All were in-house (Faculty of Medicine and University Hospital), 11 of them were medical doctors, nine natural scientists and one veterinarian.

Second round Peer (2018/2019):

Mentees: Out of a total of 17 mentees in this round, 12 were female and five male, of whom two terminated their participation in the project. The remaining mentees were:

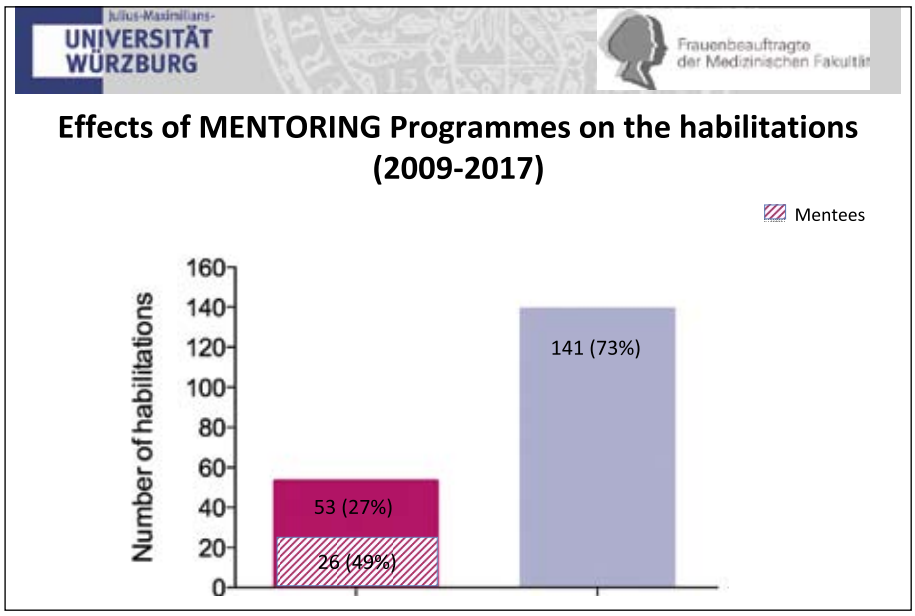


Fig.: Habilitations 2009-2017; Mentees (taken from: report of the main officer for gender equality issues of the Faculty of Medicine, winter 2018; source: Dean's Office of the Faculty of Medicine). Red represents women, blue men.

ten medical doctors, four natural scientists, and two dentists.

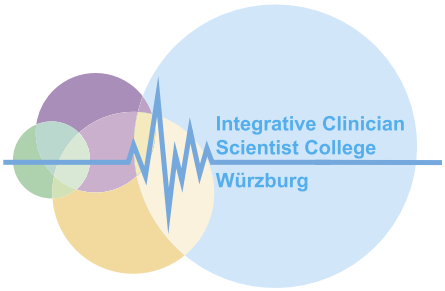
Mentors: In this round, 24 mentors were involved, ten females and 14 males. All were in-house (Faculty of Medicine and University Hospital), 15 of them being medical doctors, eight natural scientists, and one veterinarian.

Results

The following data illustrate the great success of the Mentoring med programmes. The effects on "habilitations" at the Faculty of Medicine in Würzburg are depicted (see Fig.):

The completed habilitations by female mentees have been increasing in number since the programmes were launched in 2009. Between 2009 and 2017, a total of 53 women and 141 men completed their habilitations (27% women). Among the 53 women, 26 of them were mentees in the MENTORING med programme. Out of all the women who completed their "habilitation", 49% did so as members of the Mentoring med programme.

Integrative Clinician Scientist College (ICSC)



CONTACT DETAILS

Interdisciplinary Center for Clinical Research

Professor Dr. med. Stefanie Hahner (Vice dean for the promotion of young scientists and women)

Professor Dr. med. Matthias Goebeler (Spokesperson of the Interdisciplinary Center for Clinical Research and vice dean for the intramural promotion of research)

Dr. Andrea Thelen-Frölich (Manager of the Interdisciplinary Center for Clinical Research)

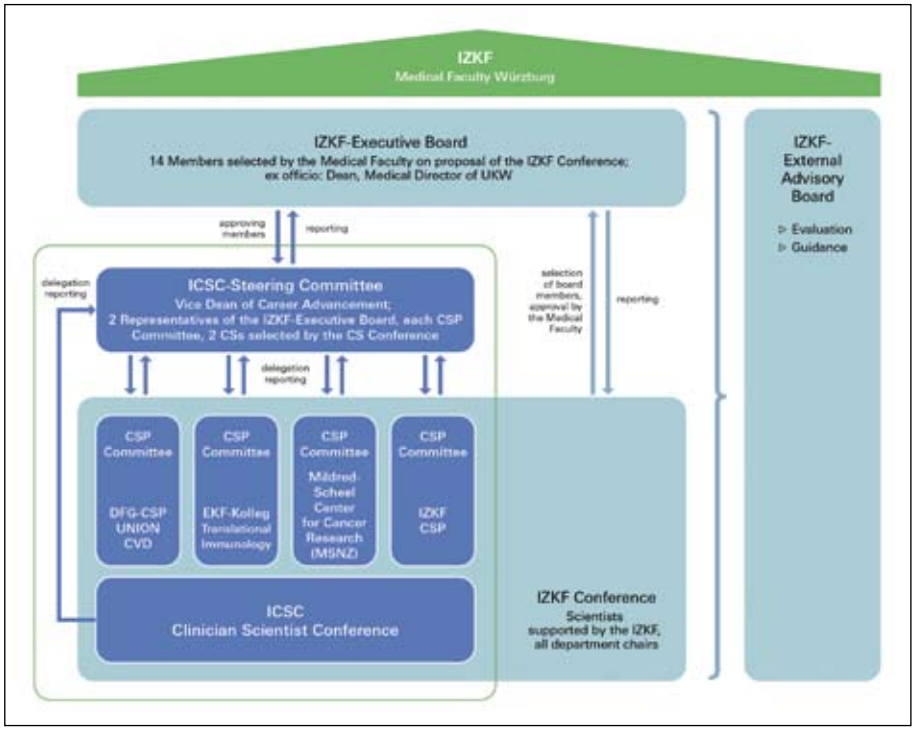


Fig. 1: Governance structure of the ICSC.

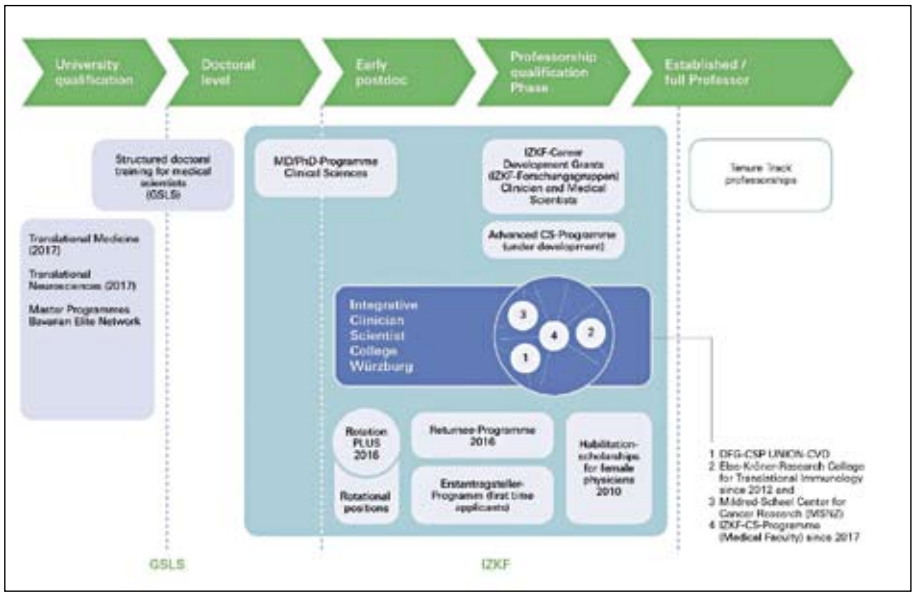


Fig. 2: Integration of the Integrative Clinician Scientist College (ICSC) into the structures for the development of junior physicians at the Faculty of Medicine.

The idea of housing all the clinician-scientist programmes in Würzburg under one roof arose in early 2018, following the establishment of the clinician-scientist programme in the IZKF. This is a structured scientific programme integrated into specialty training, providing a protected research period (cf. IZKF Clinician-Scientist Programme). The Integrative Clinician Scientist College (ICSC) intends to provide a uniform and joint platform for all clinician-scientist programmes or individual funding schemes in the Faculty under the umbrella of the IZKF, in order to:

- establish guidelines for clinician-scientist training at the Faculty of Medicine in Würzburg with the following core elements: a protected research period of 18 months' duration, integration into specialty training, qualification with a mandatory curriculum, mentoring and quality assurance (cf. IZKF Clinician-Scientist Programme);
- promote scientific networking and peer-group development of young scientists in the clinical field;
- use resources efficiently toward the implementation and development of the programmes and to avoid duplication of efforts and infrastructure;
- to ensure unified and consistent governance, transparent selection, and decision-making structures, as well as regular external evaluation of the overall concept within the scope of the IZKF (see Figure 1).

The ICSC is embedded in the junior staff support programmes of the Faculty of Medicine and currently unites the faculty-funded Clinician-Scientist Programme of the IZKF with the following programmes:

- The Else-Kröner College of Translational Immunology, which was founded in 2010 as one of the first three research colleges for young physicians to be funded by the Else-Kröner-Fresenius-Foundation.
- the Clinician-Scientist Programme UNION CVD (Understanding Interorgan Networks in Cardiovascular Diseases) approved and funded by the DFG in 2018, and
- the clinician-scientist branch of the Mildred-Scheel Young Investigators' Center funded by German Cancer Aid, which was approved in 2018.

Scientific coordinator:
Professor Dr. med. Stefanie Hahner, Vice dean for the promotion of young scientists and women, permanent member of the IZKF executive board

Coordination and Administration:
Claudia Elsner-Kunze, IZKF Administrative Office
Phone: 0931 / 201-56433
E-mail: Elsner_C@ukw.de

In contrast to the other rather modular IZKF career programmes, the Clinician-Scientist Programme is the first to offer the opportunity of completing a three-year, structured scientific programme integrated into specialty training with a protected research period lasting 18 months. The programme structure and contents were defined by a task force appointed by the IZKF, based on the DFG recommendations for the establishment of clinician-scientist programmes in 2015, existing programmes in Berlin and Freiburg, as well as the experience gathered from existing IZKF career programmes. The committee is chaired by Professor Hahner who is a permanent executive board member and also the vice dean for the promotion of young scientists and equal opportunities. Professor Hahner is also responsible for the scientific coordination of the Clinician-Scientist Programme.

Together with the protected period of research as a core element of the programme, the complementary curriculum also includes scientific training and peer-group building and networking. Group mentoring and quality-assurance measures such as individual agreements of objectives, written reports, and feedback meetings provide not only individual support for each clinician scientist but also a continuous evaluation of the programme and, if necessary, its readjustment (see Figure 3). It is also possible and encouraged to rotate to a working group abroad. The programme's fundamentals are documented in a white paper, agreements on objectives, and a personal handbook.

The programme was launched in April 2017. Annually, up to five clinician scientists can be admitted to the programme, allowing up to a maximum of 15 participants in any one year to be funded during a three-year period. In contrast to the Else-Kröner Research College, the Mildred-Scheel Center, and the UNION-CDV Clinician-Scientist Programme, the IZKF Clinician-Scientist Programme is not bound to a single scientific focus and is therefore open to physicians from all disciplines and research areas. Practical experience has proven that the one-to-one exchange with colleagues from other clinical departments and research areas during regular meetings, retreats, and training events not only improves scientific exchange and broadens the horizon, but is also of assistance to daily work in clinic.

In addition to the research rotation, the programme curriculum also includes structured scientific and didactic training. Over the last 15 months, the participants of the IZKF Clinician-Scientist Programme have attended joint training courses with the fellows of the Else-Kröner Research College. To date, there have been a warm-up meeting with coaching, a scientific writing seminar, a statistics seminar and a kick-off meeting on team building at the start of the second cohort.

From June 2018 up until the event, the clinician scientists planned and organized the "First Interdisciplinary Network Meeting for Clinician Scientists" at the museum in the "Kulturspeicher " in Würzburg. The symposium took place from 21 - 23 February 2019.

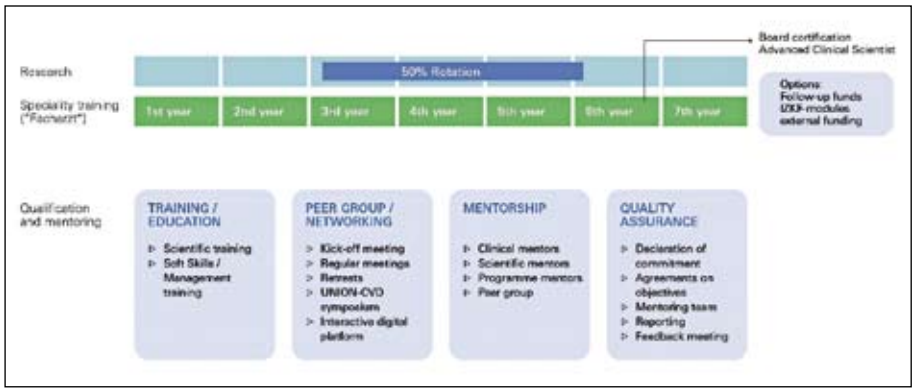


Fig. 3: Programme structure of the Clinician-Scientist Programme.


Fig. 4: The programme currently provides funding for: top row, left to right, Margarete Heinrichs, Jan-Peter Grunz, Sandra Ihne, Johanna Wagner, Anastasia Kuzkina. Bottom row, left to right, Lisa Rauschenberger, Thomas Fischer, Carolin Kastner, Johannes Völker.

Fig. 5: Poster for the First Interdisciplinary Networking Symposium for Clinician Scientists.

Else-Kröner-Forschungskolleg Würzburg

Scientific coordinator:
Professor Dr. Dr. med. Andreas Beilhack, Department of Internal Medicine II

Spokesperson:
Professor Dr. rer. nat. Jörg Wischhusen, Department of Obstetrics and Gynecology

Coordination and Administration:
Claudia Kunze, IZKF Administrative Office
Phone: 0931/201-56433
E-mail: kunze_c@ukw.de

General information and structure

The Würzburg Else-Kröner Research College for Interdisciplinary Translational Immunology for early-career physicians, in receipt of funding since 2012, served as a model for all the clinician-scientist programmes in Würzburg. The interdisciplinary research and education programme, which aims to provide structured, clinic and science-oriented training in the field of immunology, was a catalyst for the other clinician scientist programmes at the Faculty of Medicine. Led by Professor Dr. Dr. Andreas Beilhack (Department of Internal Medicine II) and Professor Dr. Jörg Wischhusen (Department for Gynaecology and Obstetrics), the Research College was funded by the Else-Kröner-Fresenius-Foundation in two three-year funding periods with a total budget of two million euros. It will end on 31 December 2019 after an extension involving no further expenditure. A total of 16 fellows and four associated clinician scientists from seven clinical departments have been funded since 2012.

Scientific focus

(Mal)functions of the immune system have a decisive impact on various diseases throughout many of the classic disciplines in medicine. Improved interconnection between basic immunological research and the translation of those results into clinical applications is imperative for innovative therapeutic approaches.
The Else-Kröner Research College Würzburg takes into consideration the necessity of patient-oriented personalization in immunotherapeutic concepts. Since regulatory mechanisms of the immune system, responsible for insufficient protection against cancer and infectious diseases, may simultaneously be able to weaken excessive immune responses in transplant rejection, autoimmune diseases, and allergies, all these topics are thus integrated into the curriculum of the Else-Kröner Research College Würzburg. In this manner, the parallels between differing diseases can be highlighted beyond the classic borders of single specialties. Although it is a comparatively new programme (2012), the Else-Kröner Research College has already proved highly successful in supporting long-term interdisciplinary cooperation, for example, promoting the translation of therapeutic approaches frequently seen in immunotherapy towards new indications in different contexts.

Structured training towards becoming a *clinician scientist*

College membership lasts three years. During the orientation semester, weekly meetings with clinicians and researchers provided the Else-Kröner fellows with an overview of the programme and contacts with experts from different disciplines. This was complemented by one-week laboratory rotations in up to three different research groups. Then, the fellows worked with their supervisors on an individual programme to ensure that their 12-month research project was with the clinical training coordinated to an optimum. An external mentor, who did not have to take into account any potential conflicts of interest, accompanied the fellows' personal career development.
During the protected research rotation, no clinical obligations were to be assigned to the fellows. In addition to regular (guest) lectures, the training programme offered seminars with a focus on specific topics providing in-depth insight into a number of aspects (statistics, bioinformatics, methods, literature, particular immunology, applied immunology, study design, biobanking, bioethics, etc.). The training at the College also includes the organization of the symposium: Translational Immunology - From Target to Therapy, which will be held for the sixth time in 2019. The fellows recruit top-class researchers from the field of immunology as lecturers and are responsible for the planning and organization of the symposium. An evening programme in a small get-together allows the fellows to discuss their work with the invited scientists and to establish important contacts in Germany as well as abroad. From the very beginning, the international symposium has been a highlight in the Würzburg immunology community.

Long-term objectives and achievements of the programme

The transfer of research results achieved into third-party funding is strongly encouraged and treated as a perspective for fellows. This has already been realized by some of our fellows. Furthermore, First-Time-Applicant-Programme, the RotationPLUS-Programme or, after a stay abroad, the Returnee Programme of the Faculty's Interdisciplinary Center for Clinical Research (IZKF) is also an option. When applying for external funding, the fellows can also seek the support and advice of the IZKF. This will allow successful Else-Kröner fellows to set up their own research group.

Fig. 6: The successful Else-Kröner fellows of the Else-Kröner-Research College for Interdisciplinary Translational Immunology from left to right: Andreas Beilhack (Scientific Coordinator), Torsten Steinbrunn, Markus Krebs, Tanja Stüber, Max Bittrich, Sophia Danhof, Laura Peters, Jörg Wischhusen (Spokesperson), Franziska Grän.

Understanding Interorgan Networks in Cardiovascular Diseases

UNION CVD

Scientific coordinator:
Professor Dr. med. Stefanie Hahner, Vice dean for the promotion of young scientists and women, Department of Internal Medicine II

Coordination and Administration:
Claudia Kunze, IZKF Administrative Office
Phone: 0931/201-56433
E-mail: kunze_c@ukw.de

The clinician-scientist programme „Understanding InterOrgan Networks in Cardiovascular Diseases“ (UNION-CVD), funded by the DFG since 01.01.2019, focusses on translational research on organ interactions in cardiac and vascular diseases and on the cardiac/vascular side effects of non-cardiovascular diseases. The programme is led and supervised by Professor Stefanie Hahner (Internal Medicine I/ Endocrinology/ vice dean for the promotion of young scientists and women), the co-applicants being Professor Jürgen Deckert (Psychiatry), Professor Stefan Frantz (Internal Medicine I/Cardiology), Professor Christoph Germer (Surgery/ vice dean of studies), Professor Matthias Goebeler (Dermatology /Spokesperson of the IZKF), Professor Peter Heuschmann (Epidemiology/ Center for Clinical Studies), Professor Michaela Kuhn (Physiology), Professor Christoph Maack (Spokesperson of the Comprehensive Heart Failure Center), Professor Stefan Störk (Internal Medicine/Cardiology), Professor Alma Zernecke-Madsen (Experimental Medicine).

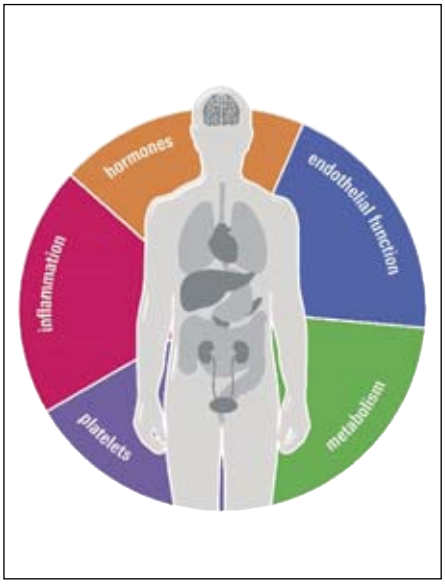


Fig. 7: Projects will investigate interactions (grey) and pathomechanisms (outer circle) of cardiac and vascular diseases affecting multiple organs.

The aim of the programme is to promote multidisciplinary research at the University of Würzburg and the University Hospital Würzburg in the field of the interaction of the cardiovascular system with other organs. For this purpose, the following aspects are relevant:

- the effect of interorgan networks on the pathogenesis and progression of cardiovascular diseases
- the understanding of how the degradation of the cardiovascular system affects comorbidities
- the identification of new strategies towards treating polyaetiological cardiovascular diseases.

The programme is funded by the DFG for an initial period of three years with six clinician scientist positions per year. After a positive interim evaluation, another two years will be funded. The call for applications for the first six positions was closed in January 2019. The programme started officially on 1 April, 2019.
The structure and implementation of the UNION-CVD Clinician-Scientist Programme is based on the IZKF Clinician-Scientist Programme. It is however thematically rooted in the ongoing research focus of cardiovascular research and its interactions. The programme is particularly closely linked to the Comprehensive Heart Failure Center, from where it receives significant input and into which it radiates back as a programme supporting young researchers.

MSNZ Würzburg
Mildred-Scheel-Nachwuchszentrum

Scientific coordinator:
Professor Dr. phil. Martin Eilers, Chair of Biochemistry and Molecular Biology, Biocenter

Coordination and Administration:
Dr. rer. nat. Martin Czolbe,
IZKF Administrative Office
Phone: 0931/201-56439
E-mail: czolbe_m@ukw.de

In July 2018, the Faculty of Medicine in Würzburg received funding approval to establish one of a total of five Mildred-Scheel Centers for Cancer Research (MSNZ) throughout Germany. Initiated by a grant from German Cancer Aid (Deutsche Krebshilfe), the aim of these centers is to maintain the sustainability of national cancer research and thus open up attractive career paths to both clinician and medical scientists. An important concern is maintaining a good work-life balance. For this purpose, German Cancer Aid is providing ten million euros to each site over the period of five years. Prof. Martin Eilers at the Chair of Biochemistry and Molecular Biology in the Biocenter of the University of Würzburg led the application process in Würzburg.
In addition to positions for advanced group leaders of young scientists, the MSNZ also offers a track for clinician scientists. The latter work on their own project for three years, affiliated to an established workgroup, with the aim of establishing an independent research group assisted by a doctorate student. The first such position has already been filled. Physicians are tied in to the ICSC through the IZKF, can profit from training opportunities available, as well as network beyond the realms of the MSNZ.

Habilitation Programme for Female Physicians – Special funding line of the IZKF

Coordination:

Professor Dr. med. Stefanie Hahner
(Committee for the Promotion of Young Scientists and Women)

Department of Internal Medicine I
Oberdürrbacher Str. 6
97080 Würzburg
Phone: 0931/201-39200
E-mail: Hahner_S@ukw.de

Maike Fecher
(IZKF Administrative Office)
Phone: 0931/201-56432

The "Habilitation Programme for Female Physicians" promotes young female scientists in medicine. Its goal is to support female physicians in their postdoctoral research towards their "habilitation" and to increase the number of women in leading positions. The programme funds postdoctoral physicians from all clinical departments and institutes of the Faculty of Medicine who are aiming to obtain the postdoctoral lecturing qualification of habilitation and can already demonstrate their scientific excellence in their respective field. The funding is intended as support for participants to fulfil the requirements of the habilitation regulations. Thus, the extent and duration of the support are adjusted to the individual situation of each candidate.

The programme may fund rotation positions, other personnel, and consumables. The selected candidates also participate in the MENTORING med postdoctoral programme for women.

The programme was initiated by the Faculty of Medicine in 2010 and was added to the IZKF funding portfolio in 2017. The Committee for the Advancement of Young Scientists and Women is responsible for the conception of the programme and the admission process according to the regulations of the IZKF. The final decision on who receives funding is made by the IZKF Executive Board.

By the end of 2018, 18 women had received funding. Nine participants completed their habilitation, while three others started their habilitation procedure. For the new funding period starting in 2019, three of the seven applicants have received a grant. The number of women habilitating at the Faculty of Medicine has increased from 15% (2012-2014) to 38% (2015-2017).

The following participants received funding during the reporting period 2017/2018:

Catharina Bartmann (Department of Gynaecology and Obstetrics): *Hallmarks of cancer in gynaecology and obstetrics*

Susanne Brenner (Department of Internal Medicine I): *Cardiorespiratory aspects in decompensation and recompensation of systolic heart failure.*

Katrin Doppler (Department of Neurology) *The Node of Ranvier as a target in inflammatory neuropathies.*

Anna Frey (Department of Internal Medicine I): *Interactive role of comorbidities in the development, progression, and prognosis of heart failure.*

Kirsten Glaser (Department of Paediatrics): *Neonatal infection and inflammation and the role of immunomodulators in the pathogenesis of foetal and neonatal short- and long-term morbidity.*

Yvonne Jockel-Schneider (Department of Conservative Dentistry / Periodontology): *Modulation of periodontal and vascular inflammations by control of oral biofilms and probiotic and dietary intervention.*

Bettina Kraus (Department of Internal Medicine I): *Local and systemic glucose metabolism in cardiac remodelling and heart failure.*

Fig.: Participants of the Habilitation Programme presented their projects during the External Advisory Board meeting of the IZKF in October 2018.

SELECTED PUBLICATIONS

Brenner S, Christa M, Berliner D, Deubner N, Ertl G, Held M, Marx A, Angermann CE, Störk S, Rutten FH, Güder G. (2017) Frequency and prognostic impact of mid-expiratory flow reduction in stable patients six months after hospitalisation for heart failure with reduced ejection fraction. Int J Cardiol 227:727-733.

Doppler K, Appeltshauser L, Villmann C, Martin C, Peles E, Krämer HH, Haarmann A, Buttmann M, Sommer C. (2016) Auto-antibodies to contactin-associated protein 1 (Caspr) in two patients with painful inflammatory neuropathy. Brain 139:2617-2630.

Glaser K, Silwedel C, Fehrholz M, Henrich B, Waaga-Gasser AM, Henrich B, Claus H and Speer CP. (2018) Ureaplasma species differentially modulate angionic and growth factors and cell adhesion molecules in neonatal and adult monocytes. Cytokine 105:45-48.

Jansen E, Beekhof P, Schupp N, Kreutzmann M, Kraus BJ. (2017) A comparison between two assays for the redox status in plasma. J Anal Bioanal Tech 8:342.

Jockel-Schneider Y, Bechtold M, Haubitz I, Störk S, Fickl S, Harks I, Eigenthaler M, Vollrath O, Baulmann J, Schlagenhauf U. (2018) Impact of Antiinfective Periodontal Therapy on Parameters of Vascular Health. J Clin Periodontol 45:354-363.

Students' Representatives

CONTACT DETAILS

Josef-Schneider-Str. 2
97080 Würzburg

Phone: 0931/201-53859
Fax: 0931/201-53858

E-mail:fachschaft.medizin@uni-wuerzburg.de
www.fi-med.de

The medical students' union is a group of students representing the interests of medical students in Würzburg on a voluntary basis. It is our aim to enhance the conditions for studying and teaching in cooperation with the academics at our faculty in order to establish and create a convenient working atmosphere.
To achieve this, we focus on two major aspects:
We represent the medical students in various committees: In the faculty council, the committee of study affairs, the students' council and in the appointment boards of the faculty. Since the tuition fees have been abolished, we have also been working for a wise and efficient use of the funds in the tuition fees replacement committee.
Besides, we organize several leisure activities, provide students with support regarding university matters and offer counsel where necessary. This includes, but is not limited to the organization of information sessions, parties and live broadcasts of major sporting events like the soccer European championship and World Cup.
At the beginning of each term, we welcome new students in the context of the freshers' days. We believe that these three days offer a unique opportunity to get to know one's new fellow students, the city of Würzburg and the university. In our experience, these days foster first friendships, not to mention the great fun they mean to all of us.
On the first day of their clinical training, we take the now third-year students around the university hospital and introduce them to the different clinical complexes and institutes on the campus. In addition, we publish a booklet containing all information about the faculty, lectures, courses, examinations, books, events etc., most of which can also be found on our homepage. During the lecture time, our office serves as a contact point for all difficulties and questions students have to cope with. Here, we offer a variety of leaflets and information brochures regarding different aspects of medical studies.
To complete our extracurricular offers, there are a number of clubs and courses students can participate in.
To begin with, we offer a course of "Medical English" where students can practice different kinds of medical conversation and enlarge their vocabulary.
Furthermore, we offer in cooperation with the psychological Institute, the "Anamnesegruppen" ("Medical history group") helps both medical and psychology students to acquire better perception and communication skills by leading anamnesis talks with real patients who agreed to take part in the group's sessions.
The sexual education project MSV ("MitSicherheitverliebt") helps high school students to familiarize with contraception and safe dealing with sexuality. The teddy bear clinic aims at taking the fear of young children of seeing a physician by re-enacting the situation of a hospital visit with the children's cuddly toys being treated as patients.
The education project concerning organ donations ("Aufklärung Organspende") was newly added to our portfolio. Their goal is to sensitize high school students and others about transplantation and e.g. brain death diagnostics.
Moreover, other groups use parts of our premises to meet or operate, such as the SEG MED, a nationwide association of medical students offering favourable medical equipment (e.g. stethoscopes), or the local bvmd group. The latter is the department of the national federation of all German medical students' unions in Würzburg and among other things organizes international exchange programs for medical students.
Further, we work together with the societies of emergency medicine, the European Medical Students' Association (EMSA) and support regional social projects. Finally, we initiate "buddy program" for first-year students, due to which older students will encourage them and help to facilitate the beginning of their studies.
In the recent past we have launched a new program especially for visiting students to further enhance their experience at Würzburg University.
There is also a students´ council meeting once every week. It serves the purpose of information exchange and offers room to talk about current activities and future projects. Students and university staff are always welcome to join us! Beyond that, we organize a students' union weekend to discuss special topics that exceed the schedule of our regular meetings once every semester.
Two of our major achievements in the past years are the founding of the working group "teaching coordinators" that strengthened the close cooperation between the individual teaching coordinators to initiate innovative teaching strategies and the PromoMed convention that helps students to find a position for a medical dissertation. Therefore, we have expanded our services by PromoMesse, a fair for research groups to present themselves and inform students so that the progress of searching for a medical thesis project will be facilitated. Moreover, we have created a special part on our website to inform fellow students about the possibilities of graduating.
Within the next semesters, we will further commit ourselves to the improvement of teaching methods. The active use of the university's clinical skills lab, its library, the multitude of practical examination courses, recently established recreation, study and conference rooms and the huge number of optional courses offered by students further emphasis the success of our work.
At this point, we would like to thank the faculty for the ongoing support of our work and are looking forward to a continuous constructive cooperation.

The students' representatives of the Faculty of Medicine

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

The Faculty of Medicine: Basic Data

The Faculty of Medicine: Basic Data

Research Centers

Comprehensive Cancer Center Mainfranken (CCC MF)

Comprehensive Heart Failure Center (CHFC)

Interdisciplinary Center for Clinical Research (IZKF)

Rudolf Virchow Center for Experimental Biomedicine (RVZ)

Research Center for Infectious Diseases (ZINF)

Collaborative Research Centers, Research Training Groups, Research Units

Collaborative Research Center 688, Mechanisms and Imaging of Cell-Cell Interactions in the Cardiovascular System

Transregio-Collaborative Research Center 34, Pathophysiology of Staphylococci in the Post-genomic Era

Transregio-Collaborative Research Center 58, Fear, Anxiety, Anxiety Disorders

Transregio-Collaborative Research Center 124, Pathogenic Fungi and their Human Host: Networks of Interaction - FungiNet

Transregio-Collaborative Research Center 166, High-end Light Microscopy Elucidates Membrane Receptor Function – Receptor-Light

Transregio-Collaborative Research Center 205, The Adrenal: Central Relay in Health and Disease

Transregio-Collaborative Research Center 221, Modulation of Graft-versus-Host and Graft-versus-Leukemia Immune Responses after Allogeneic Stem Cell Transplantation

Transregio-Collaborative Research Center 225, From the Fundamentals of Biofabrication towards Functional Tissue Models

Transregio-Collaborative Research Center 240 - Platelets – Molecular, Cellular and Systemic Functions in Health and Disease

Research Training Group 2157: 3D Tissue Models for Studying Microbial Infections by Human Pathogens

Research Unit 2123: Sphingolipid Dynamics in Infection Control

Research Unit 2314: Targeting Therapeutic Windows in Essential Cellular Processes for Tumor Therapy

Scientific Infrastructure

Core Unit Systems Medicine (CU SysMed)

Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw)

Clinical Trial Center Würzburg (CTCW)

Center for Experimental and Molecular Medicine (ZEMM)

Clinical Treatment Centers

Allergy Center Mainfranken
Breast Center
Center of Dental Traumatology
Center for Developmental Pediatrics
Center for Gynaecological Endocrinology and Reproductive Medicine
Center for Interdisciplinary Pain Therapy
Center for Internal Medicine (ZIM)
Center for Mental Health (ZEP)
Center for Neuromuscular Disorders
Center for Neuro-Oncology (NTZ)
Center for Obesity and Metabolic Surgery
Center for Operative Medicine (ZOM)
Center for Radiology (ZRad)
Center for Rare Diseases - Reference Center Nothern Bavaria (ZESE)
Center for Stem Cell Transplantation and Immunotherapy
Center for Visceral Oncology
Comprehensive Cancer Center Mainfranken (CCC MF)
Comprehensive Hearing Center (CHC)
Comprehensive Heart Failure Center (CHFC)
Gynaecological Cancer Center
Head and Neck Cancer Center
Interdisciplinary Center for Palliative Medicine
Interdisciplinary Center for Thoracic Diseases
Interdisciplinary Cleft Lip and Palate Center
Liver Center
Neuro-oncological Tumour Center
Perinatal Center
Prostate Cancer Center
Regional Center of Radiation Protection (RSZ)
Shock Trauma Center
Skin Cancer Center
Stroke Center
Thyroid Center Würzburg (WSZ)
Transplantation Center
WHO REMPAN Collaborating Center
Würzburg Center for Radiation Incidents
Würzburg Center for Oncology
Würzburg Center for Peritoneal Cancer
Würzburg Heart Center
Würzburg Musculoskeletal Center (MCW)
Würzburg Rheumatism Center
Würzburg Thyroid Center

Virchow-Lectures

1997 Prof. Dr. Melitta Schachner
Hamburg
1997 Prof. Dr. Donald Metcalf
Melbourne, Australien
1997 Prof. Dr. Carlo Croce
Philadelphia, USA
1997 Prof. Dr. Ralph Steinmann
New York, USA
1998 Prof. Dr. Salvador Moncada
London, England
1998 Prof. Dr. Max Perutz
Maryland, USA
1999 Prof. Dr. Heiner Westphal
Cambridge, USA
2000 Prof. Dr. Harald zur Hausen
Heidelberg
2000 Prof. Dr. Rudolf Jänisch
Cambridge, USA
2001 Prof. Dr. Manfred Eigen
Göttingen
2002 Prof. Dr. Axel Ullrich
Martinsried
2002 Prof. Dr. Alfred Wittinghofer
Dortmund
2002 Prof. Dr. Dieter Gallwitz
Göttingen
2003 Prof. Dr. Peter Gruss
München
2004 Prof. Dr. Kai Simons
Dresden
2004 Prof. Dr. Peter Walter
San Francisco, USA
2005 Prof. Dr. Hartmut Michel
Frankfurt
2005 Prof. Dr. Svante Pääbo
Leipzig
2006 Prof. Dr. Günter Blobel
New York, USA
2007 Prof. Dr. Oliver Smithies
Chapel Hill, USA
2007 Prof. Dr. Klaus Rajewsky
Boston, USA
2008 Prof. Dr. Hans C. Clevers
Utrecht, Niederlande
2010 Prof. Dr. Meinrad Busslinger
Wien, Österreich
2011 Prof. Dr. Roger Tsien
San Diego, USA
2014 Prof. Diane E. Griffin
Baltimore, USA
2019 Prof. Dr. Stanley Riddell
Washington, USA

Honorary doctorates awarded by the Faculty of Medicine (since 1948)

1948 Dr. Albert Knoll
Ludwigshafen
1952 Prof. Dr. med. Georg Hohmann
München
1956 Dr. G. Wahl
Würzburg
1961 Prof. Dr. Ernst Freudenberger
Basel, Schweiz
1982 Dr. Johannes von Elmenau
München
1982 Prof. Dr. Wilhelm Feldberg
London, England
1991 Prof. Dr. Arno G. Motulsky
Seattle, USA
1995 Prof. Dr. Peter Vogt
La Jolla, USA
1995 Prof. Alan E.H. Emery
Budleigh Salterton, England
1997 Prof. Dr. Hans Thoenen
München
2000 Prof. Dr. Hermann Bujard
Heidelberg
2001 Prof. Dr. Hermann Wagner
München
2005 Prof. Dr. Volkmar Braun
Tübingen
2007 Prof. Dr. G. Fritz Melchers
Basel/Berlin
2008 Prof. Dr. Harald zur Hausen
Heidelberg
2010 Prof. Dr. Ernst-Theodor Rietschel
Borstel
2011 Prof. Dr. Ernst-Ludwig Winnacker
München
2014 Prof. Dr. Hartmut Wekerle
München
2015 Prof. Dr. Dr. Helmut Remschmidt
Marburg
2017 Prof. Dr. Otmar Wiestler
Bonn

Rinecker-medals awarded by the Faculty of Medicine

1890 Prof. Dr. Robert Koch
Berlin
1891 Prof. Dr. Camillo Golgi
Pavia, Italien
1994 Prof. Dr. Emil von Behring
Marburg
1897 Prof. Dr. Johannes von Kries
Freiburg i. B.
1900 Prof. Dr. Karl Schleich
Charlottenburg
1903 Dr. Ernst Overton
Würzburg
1909 Prof. Dr. Clemens von Pirquet
Breslau
1912 Geheimrat Dr. Max Rubner
Berlin
1917 Prof. Dr. Heinrich Albers-Schönberg
Hamburg
1922 Prof. Dr. Franz Hofmeister
Würzburg
1929 Prof. Dr. Ludolf von Krehl
Heidelberg
1936 Prof. Dr. Adolf Butenandt
Danzig
1943 Prof. Dr. Bernhard Bavink
Bielefeld
1950 Prof. Dr. Georg Sticker
Zell a. Main
1956 Prof. Dr. Erich Grafe
Garmisch-Partenkirchen
1965 Prof. Dr. Hans Rietschel
Würzburg
1973 Prof. Dr. Dr. Viktor Emil Freiherr
v. Gebsattel
Würzburg/Bamberg
1982 Prof. Dr. Loris Premuda
Padua, Italien
1986 Prof. Dr. Shaul G. Massry
Los Angeles, USA
1993 Prof. Dr. Miklos Palkovits
Budapest, Ungarn
1995 Prof. Dr. Ernst J.M. Helmreich
Würzburg
2009 Prof. Dr. Volker ter Meulen
Würzburg
2012 Prof. Dr. Kurt Kochsiek
Würzburg
2016 Prof. Dr. Christoph Reiners
Würzburg

Carl Caspar von Siebold-medals awarded by the Faculty of Medicine

2009 Prof. Dr. Walter Eykmann
Würzburg

2009 Manfred Ach
Margetshöchheim

2011 Renate Schülke-Schmitt
Würzburg

2013 Elterninitiative leukämie- und tumorkranker Kinder e.V. Würzburg

2015 Interessengemeinschaft zur Förderung der Kinder der Würzburger Intensivstation (KIWI e.V.)
Würzburg

Winners of the Albert Koelliker-Award for excellent teaching (of the last 10 years)

Semester	Winners
Spring 2009	Professor Dr. H. Klinker, Department of Internal Medicine II Professor Dr. A. Renk, Department of Prosthodontics
Autumn 2009	Professor Dr. C.-T. Germer, Head of the Department of General, Visceral, Vascular and Pediatric Surgery
Spring 2010	Professor Dr. E.-B. Bröcker, Professor Dr. H. Hamm, Professor Dr. J.C. Becker, Professor Dr. A. Trautmann, Department of Dermatology, Venereology and Allergology
Autumn 2010	Professor Dr. R. Jahns, Department of Internal Medicine I
Spring 2011	Dr. B. van Oorschot, Department of Radiation Oncology – Center for Palliative Medicine Dr. S. Neuderth, Division of Medical Psychology, Medical Sociology, and Rehabilitation Research Herr Professor Dr. Dr. A. Kübler, Head of the Department of Oral and Maxillofacial Surgery
Autumn 2011	Professor Dr. R. Meffert, Head of the Department of Trauma-, Hand-, Plastic and Reconstructive Surgery
Spring 2012	Professor Dr. J. Volkmann, Head of the Department of Neurology
Autumn 2012	PD Dr. S. Knop, Department of Internal Medicine II Professor Dr. B. Klaiber, Head of the Department of Conservative Dentistry and Periodontology
Spring 2013	PD. Dr. U. Dietz, Department of General, Visceral, Vascular and Pediatric Surgery Dr. R. Wagner, Department of Trauma, Hand, Plastic and Reconstructive Surgery
Autumn 2013	Professor Dr. A. Friebe, Institute of Physiology
Spring 2014	Professor Dr. E. Asan, Institute of Anatomy and Cell Biology
Autumn 2014	Professor Dr. K. Brehm, Institute of Hygiene and Microbiology
Spring 2015	Professor Dr. A. Stich, Division of Tropical Medicine, Missionsärztliche Klinik
Autumn 2015	Professor Dr. T. Bley, Head of the Institute for Diagnostic and Interventional Radiology
Spring 2016	Professor Dr. M. Fassnacht, Professor Dr. S. Hahner, Dr. Dr. M. Kroiß, Professor Dr. B. Allolio (posthum). Department of Internal Medicine I
Autumn 2016	Professor Dr. J. Deckert, Professor Dr. Dr. K. Domschke, Departmentof Psychiatry, Psychosomatics and Psychotherapy Professor Dr. M. Romanos, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Spring 2017	Student`s Representatives of the Faculty of Medicine
Autumn 2017	Professor Dr. Michael Bohnert, Director, Institute of Forensic Medicine Professor Dr. Angelika Stellzig-Eisenhauer, Director, Department of Orthodontics
Spring 2018	Lectures of the Department of Anaesthesiology and Critical Care
Autumn 2018	Dr. Hans-Jörg Hellmuth, Head of the Teaching Department of General Practice (2008-2017), and the academic teaching practices

Habilitations

2017

Clinical

Dr. med. Dr. rer. nat. Boelmans, Kai	Neurology
Dr. med. Feuchtenberger, Martin	Internal Medicine
Dr. phil. Jans, Thomas	Clinical Children and Adolescent Psychology
Dr. med. Smul, Thorsten Michael	Anaesthesiology
Dr. med. Winkler, Bernd Erhard	Anaesthesiology
Dr. med. Doppler, Kathrin Janina	Neurology
Dr. med. Blümel, Christina V.	Nuclear Medicine
Dr. med. Haring, Bernhard	Internal Medicine
Dr. med. Holzapfel, Boris Michael	Orthopaedics and Trauma Surgery
Dr. med. Lapa, Constantin F. V.	Nuclear Medicine
Dr. phil. nat. Lückerath, Katharina M.	Experimental Oncology
Dr. rer. nat. Streng, Andrea	Experimental Paediatrics
Dr. med. Ach, Thomas Georg	Ophthalmology
Dr. med. Held, Matthias	Internal Medicine
Dr. med. Kleinert, Stefan	Internal Medicine
Dr. med. Stumpner, Jan Martin	Anaesthesiology
Dr. med. Diessner, Ernst Joachim	Obstetrics and Gynaecology
Dr. med. Dr. med. univ. Petritsch, Bernhard	Radiology

Preclinical

Dr. med. Monoranu, Camelia-Maria	Neuropathology
Dr. rer. nat. Kittel, Robert Johannes	Physiology
Dr. rer. physiol. Krempl, Christine	Virology
Dr. rer. nat. Wagner, Nicole	Anatomy and Cell Biology
Dr. rer. nat. Almanzar, Giovanni	Immunology

2018

Clinical

Dr. med. Polak, Thomas	Psychiatry and Psychotherapy
Dr. med. Schick, Martin	Anaesthesiology
Dr. sc. hum. Metzger, Marco	Regenerative Medicine
Dr. med. Konrads, Christian	Orthopaedics and Trauma Surgery
Dr. med. Schneider, Andreas	Internal Medicine
Dr. med. Rückriegel, Stefan Mark	Neurosurgery
Dr. med. Frey, Anna	Internal Medicine
Dr. med. Herrmann, Sebastian	Internal Medicine
Dr. med. Fluri, Felix	Neurology
Dr. med. Lock, Johan Friso	Surgery
Dr. med. Polat, Bülent	Radiotherapy

Preclinical

Dr. rer. nat. Brändlein, Stephanie	Immunopathology
Dr. med. Barrera, Vera	Forensic Medicine

Admission numbers

Human medicine and Dentistry

Year	Human medicine (m/f)	Dentistry (m/f)
WS 2016/17	157 (64/93)	57 (19/38)
SS 2017	152 (60/92)	53 (20/33)
WS 2017/18	159 (58/101)	53 (15/38)
SS 2018	152 (45/107)	51 (19/32)
WS 2018/19	155 (56/99)	55 (15/40)

Bachelor- and Master Courses

Year	Biomedicine B.Sc. (m/f)	Biomedicine M.Sc. (m/f)	Experimental Medicine M.Sc (m/f)	Biochemistry B.Sc. (m/f)	Biochemistry M.Sc. (m/f)
WS 2016/17	42 (8/34)	15 (6/9)	0	82 (38/44)	32 (10/22)
SS 2017	0	0	0	77 (35/42)	0
WS 2017/18	33 (7/26)	18 (7/11)	0	60 (24/36)	34 (15/19)
SS 2018	0	0	1 (1/0)	1 (0/1)	0
WS 2018/19	48 (7/41)	16 (2/14)	0	70 (26/44)	43 (22/21)

Year	Translational Medicine M.Sc. (m/f)	Translational Neuroscience M.Sc. (m/f)
WS 2016/17	–	9 (3/6)
SS 2017	–	0
WS 2017/18	–	11 (4/7)
SS 2018	0	0
WS 2018/19	0	12 (3/9)

Accompanying Courses

Year	Experimental Medicine (m/f)	Clinical Research and Epidemiology (m/f)	Translational Medicine (m/f)	Translational Neuroscience (m/f)
WS 2016/17	4 (4/0)	8 (7/1)	–	–
SS 2017	0	2 (0/2)	–	–
WS 2017/18	10 (2/8)	6 (5/1)	–	–
SS 2018	–	–	27 (15/12)	0
WS 2018/19	–	–	24 (17/7)	0

Graduations

Human medicine and Dentistry

Year	Human medicine (m/f)	Dentistry (m/f)
Frühjahr 2017	129 (60/69)	40 (21/19)
Herbst 2017	141 (60/81)	47 (17/30)
Frühjahr 2018	156 (56/100)	33 (10/23)
Herbst 2018	177 (61/116)	44 (16/28)

Bachelor- and Master Courses

Year	Biomedicine B.Sc. (m/f)	Biomedicine M.Sc. (m/f)	Experimental Medicine M.Sc (m/f)
Frühjahr 2017	17 (5/12)	4 (0/4)	3 (3/0)
Herbst 2017	5 (0/5)	6 (0/6)	0
Frühjahr 2018	9 (1/8)	1 (0/1)	2 (0/2)
Herbst 2018	5 (1/4)	0	0

Doctorates (without doctorates in natural sciences)

Year	Dr. med (m/f)	Dr. med. dent. (m/f)	Total (m/f)
2017	142 (56/86)	44 (14/30)	186 (70/116)
2018	160 (65/95)	42 (15/27)	202 (80/122)

The deans of the Faculty of Medicine since 1945

1945 to 1947	Professor Dr. med. Dankwart ACKEMANN
1947 to 1948	Professor Dr. med. Jürg ZUTT
1948 to 1949	Professor Dr. med. Max MEYER
1949 to 1951	Professor Dr. med. Curt SONNENSCHEIN
1951 to 1952	Professor Dr. med. Werner WACHSMUTH
1952 to 1953	Professor Dr. med. Hans SCHEUERMANN
1953 to 1954	Professor Dr. med. Hermann WOLF
1954 to 1955	Professor Dr. med. Dr. phil. Wilhelm NEUMANN
1955 to 1957	Professor Dr. med. Heinrich SAAR
1957 to 1958	Professor Dr. med. Georges SCHALTENBRAND
1958 to 1959	Professor Dr. med. Kurt NEUBERT
1959 to 1960	Professor Dr. med. Hans FRANKE
1960 to 1961	Professor Dr. med. Erich BAUEREISEN
1961 to 1962	Professor Dr. med. Ernst WOLLHEIM
1962 to 1963	Professor Dr. med. Horst WULLSTEIN
1963 to 1964	Professor Dr. med. Hans-Werner ALTMANN
1964 to 1965	Professor Dr. med. Horst SCHWALM
1965 to 1966	Professor Dr. med. dent. Rudolf NAUJOKS
1966 to 1967	Professor Dr. med. Wolfgang SCHWERD
1967 to 1968	Professor Dr. med. August RÜTT
1968 to 1969	Professor Dr. med. Erich BAUEREISEN
1969 to 1970	Professor Dr. med. Helmut RÖCKL
1970 to 1971	Professor Dr. med. Theodor Heinrich SCHIEBLER
1971 to 1973	Professor Dr. med. Karl Heinz WEIS
1973 to 1975	Professor Dr. med. Johannes LANG
1975 to 1977	Professor Dr. med. Erich BAUEREISEN
1977 to 1979	Professor Dr. med. Otto SCHRAPPE
1979 to 1981	Professor Dr. med. Karl-Heinrich WULF
1981 to 1983	Professor Dr. med. Karl-August BUSHE
1983 to 1985	Professor Dr. med. Volker ter MEULEN
1985 to 1987	Professor Dr. med. Gerhardt NISSEN
1987 to 1989	Professor Dr. med. Stefan SILBERNAGL
1989 to 1991	Professor Dr. med. Kurt KOCHSIEK
1991 to 1994	Professor Dr. med. Hans Konrad MÜLLER-HERMELINK
1994 to 1996	Professor Dr. med. Klaus WILMS
1996 to 1998	Professor Dr. med. Klaus TOYKA
1998 to 2002	Professor Dr. med. Volker ter MEULEN
2002 to 2004	Professor Dr. med. Stefan SILBERNAGL
2004 to 2006	Professor Dr. med. Georg ERTL
since 2006	Professor Dr. med. Matthias FROSCH

Imprint

Publisher
Faculty of Medicine
Julius-Maximilians-Universität Würzburg
Josef-Schneider-Str. 2
97080 Würzburg
www.med.uni-wuerzburg.de

Editorial staff
Gabriele Gerlach
Matthias Frosch

Image sources
- University Hospital Würzburg / Departments and Institutes
- Faculty of Medicine / Institutes and Scientific Units
- Portrait photos: University Hospital Würzburg (© K. Heyer und © D. Peter) or private
- Page 5: Faculty of Medicine

Design, layout and print
Schimmel Satz & Graphik
Im Kreuz 9
97076 Würzburg

Cover
The cover shows figures related to research projects of the Faculty of Medicine.

Digital version
The research report can be downloaded at:
www.med.uni-wuerzburg.de/forschung/forschungsberichte

Faculty of Medicine
University of Würzburg

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Universitätsklinikum Würzburg

Faculty of Medicine
of the University of Würzburg

Josef-Schneider-Str. 2 · 97080 Würzburg
www.med.uni-wuerzburg.de