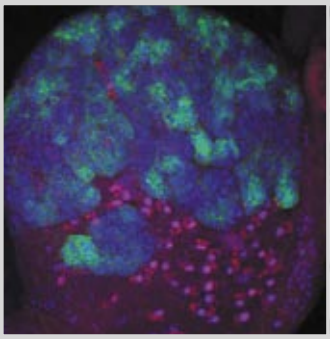
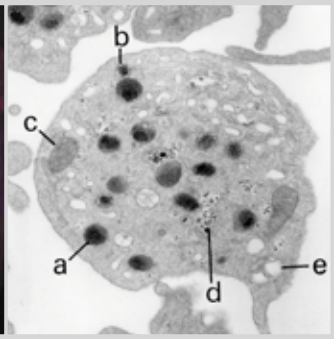
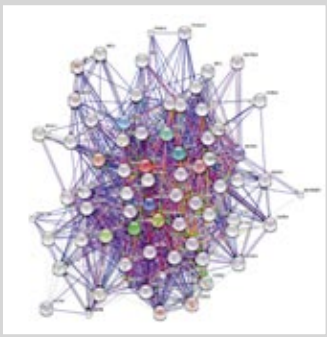
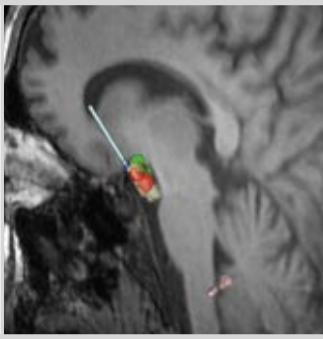
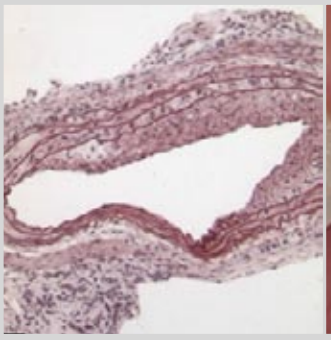
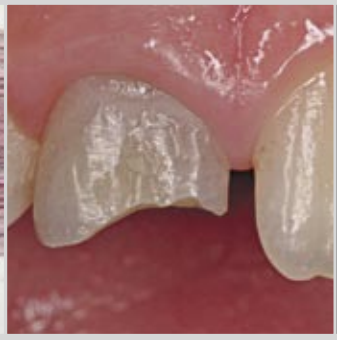
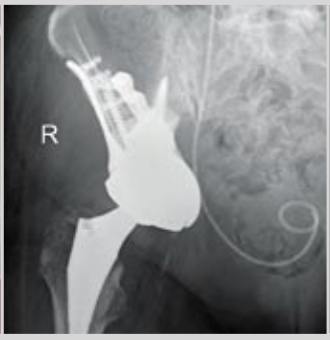
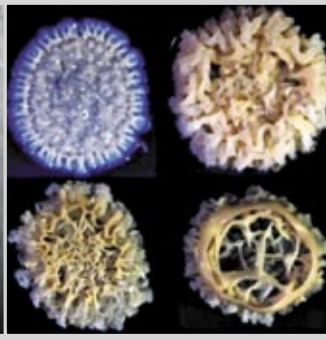
Medical Faculty
University of Würzburg

RESEARCH REPORT 2017

Julius-Maximilians-
UNIVERSITÄT WÜRZBURG



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Foreword

Dear Readers,

Excellent scientists and modern infrastructure guarantee outstanding research, teaching and patient care of the highest calibre. On the following pages, our research report presents the achievements and activities of the institutes, clinics and scientific institutions in the areas of research and training. In this way, we hope to contribute to creating a broad public awareness of our work and our institutions.

First of all, it is a special pleasure to introduce colleagues who have been newly appointed to our faculty. The generation change which will soon be complete, particularly in the clinical facilities, has had a fundamental positive impact on our faculty over the past few years. I should like to draw your attention to the following pages, where you will be introduced to the Department of Conservative Dentistry and Periodontology under the new directorship of *Prof. Dr. G. Krastl*, the Department of Obstetrics and Gynecology under the new directorship of *Prof. Dr. A. Wöckel* and the Department of Ophthalmology under the new directorship of *Prof. Dr. J. Hillenkamp. Prof. Dr. S. König* was appointed to the newly established Institute of Medical Teaching and Medical Education Research. *Prof. Dr. L. Schreiber* was appointed to the newly established Chair in Molecular and Cellular Imaging, one of four research professorships established at the Comprehensive Heart Failure Center (CHFC). *Prof. M. Pham* was appointed to the newly established Department of Diagnostic and Interventional Neuroradiology. *Prof. M. Schmitter* accepted the Chair in the Department of Prosthodontics. Our faculty was also joined by *Prof. Dr. L. Dölken.* He took over the Chair in Virology at the Institute of Virology and Immunobiology from our colleague *Prof. Dr. A. Rethwilm*, who regrettably passed away much too soon, just before his retirement. In all, from 2014 to 2016, there were new appointments to 24 "W2"- professorships and two "W1"- professorships in the clinical and preclinical theoretical field.

The Medical Faculty has continued to successfully advance its strategic objective – the establishment of non-university research facilities. The ongoing recruitment phase for the Max Planck systems immunology research teams and the founding of the "Fraunhofer Translation Center for Regenerative Therapies for Cancer and Musculoskeletal Diseases", which was financed by the Free State of Bavaria, are of key importance for biomedical research in Würzburg.

The "Helmholtz Institute for RNA-based Infection Research (HIRI)", which was founded in the autumn of 2016 and whose construction and start-up phase was funded to the tune of 46 million euros by the Free State of Bavaria, is focused on a particularly important and promising field within translational infection research. The research programme has been assessed as "outstanding" by an international committee of high-calibre experts. Following application and appraisal, an outstanding honour was bestowed on the designated Founding Director, Prof. Dr. Jörg Vogel. In March 2017, he will be awarded the Gottfried Wilhelm Leibniz Prize of the German Research Foundation (DFG) – the most important research development grant in Germany. For his internationally acclaimed work to increase our understanding of the role of regulatory RNA molecules in infection biology.

The Medical Faculty is characterised by numerous other successful funding applications and awards to scientists. Taken as a whole, this is reflected in the DFG's current research atlas, in which Würzburg occupies the third place among German medical faculties with regard to the number of DFG research grants; when one compares the sheer volume of funding, at an average of € 800,000 per professor, we even occupy first place!

The quality of medical doctorates has been the object of intensive public debate over the past few years. For our Medical Faculty, this was an opportunity to scrutinise present-day practices of conferring medical doctorates and to create new structures aimed at guaranteeing the quality of medical doctorates in the future. One essential aspect of these efforts was to open up the University of Würzburg *Graduate School of Life Sciences* (GSLS), which has already been in existence for 10 years and is funded by the "Excellence" initiative, to the conferral of medical doctorates, in order to be able to apply the high qualitative standards established there to medical doctorates as well.

Outstanding medical research is based not least on suitable infrastructure. In order to set future standards here too, the university, clinic and faculty have started the "Masterplan" project. For the very first time, this project is presenting a conceptual plan for the further utilisation of the Grombühl Campus and its enlargement on the "northern tract of land", and offers solutions for the most pressing questions regarding the locations of various new clinical, university and non-university buildings. The highlight of the building development of the Medical Faculty during the reporting period was the construction of the approximately 5,500 square meter research building for the Comprehensive Heart

Fig. 1: Reaching a milestone! The successful expert appraisal of the Helmholtz Institute for RNA-based Infection Research (HIRI) is reflected in the pleased smiles of the participants at the meeting of expert appraisers on 1st June 2016. (from left to right) Prof. Dr. Alfred Forchel (President, JMU), Prof. Dr. Otmar Wiestler (President of the Helmholtz Association), Prof. Dr. Lars Dölken (Chair in Virology, JMU), Prof. Dr. Jörg Vogel (HIRI Founding Director), Prof. Dr. Hermann Einsele (Director of the Department of Internal Medicine II, UKW), Prof. Dr. Matthias Frosch (Dean of the Medical Faculty, JMU), Prof. Dr. Dirk Heinz (Scientific Director, Helmholtz Centre for Infection Research). Photograph: Hilde Merkert.

Failure Center at the end of 2016, with the ceremonial handing over of the key and the inauguration of the building in January 2017.

The implementation of these building measures and the construction of the non-university research facilities has only been possible thanks to support from the political sector. Here, representative of the many supporters and sponsors for whose help we are grateful, special thanks are due to the President of the Bavarian Parliament Barbara Stamm, MdL (Member of the Bavarian Parliament) Oliver Jörg and Minister of State Ilse Aigner, without whose support and commitment the founding of the Helmholtz Institute for RNA-based Infection Research would never have been possible. Above all, I should like to also thank the members of the Medical Faculty, who, thanks to their creativity and tireless dedication to research and teaching, are the bedrock of our faculty's excellent reputation.

Würzburg, February 2017

Prof. Dr. Matthias Frosch
Dean

Fig. 2: The new building for the Comprehensive Heart Failure Center (CHFC). Photograph: State Building Office of Würzburg.

Honours awarded by the Medical Faculty

Prof. Dr. med. Dr. h.c. Hartmut Wekerle *from Munich is pictured receiving an honorary doctorate, presented by the Dean Prof. Dr. M. Frosch (left) during the graduation ceremony in the Neubaukirche on 24 May, 2014. From 1982 to 1987, Prof. Wekerle was the Head of a clinical Max Planck Research Group on multiple sclerosis in Würzburg, which was supported by the Hermann and Lilly Schilling Foundation. From 1988 on, he was Head of the Section for Neuroimmunology at the Max Planck Institute for Neurobiology in Martinsried. Since his appointment as Emeritus Professor in 2011, he has been continuing his research as a senior professor at the Max Planck Institute supported by the Hertie Foundation. The Faculty of Medicine honoured his outstanding scientific achievements especially with respect to the role of T-lymphocytes, his observations on the interaction of autoimmune CD4 T-cells with cellular components of the central nervous system, as well as his fundamental contributions to multiple sclerosis research. Prof. Wekerle has also rendered enormous service in promoting the establishment of the Max Planck Research Groups for systems immunology in Würzburg.*

Prof. Dr. med. Dr. phil. Helmut Remschmidt *from Marburg is pictured here receiving an honorary doctorate presented by the Dean Prof. Dr. M. Frosch (left) during the graduation ceremony in the Neubaukirche on 13 June, 2015. To begin with, Prof. Remschmidt was appointed as Professor in child and adolescent psychiatry and neurology at the Faculty of Medicine of the Free University of Berlin in 1975. In 1980, he was appointed as Professor of Child and Adolescent Psychiatry at the Philipps-University of Marburg, taking on the role of Head of the similarly named clinic. He maintained this professorship until his retirement in the year of 2006. Prof. Remschmidt was and still is a member of many committees i.a. at the World Health Organization, the Federal Government, the Deutsche Forschungsgemeinschaft, the Federal Science Council, and the German Medical Association. From 2000 to 2008, he supported the University Hospital in Würzburg as a member of the Supervisory Board. With Prof. H. Remschmidt, the Faculty of Medicine and University Hospital in Würzburg have honoured an internationally regarded physician and scientist who has influenced child and adolescent psychiatry in many ways and who has made a great contribution to university medicine in Würzburg.*

For his long standing achievements in the Faculty of Medicine of the University of Würzburg, the Rinecker Medal in gold was awarded to **Professor Dr. med. Dr. h.c. (Univ. Minsk) Christoph Reiners** *(born in Mönchengladbach in 1946) during the graduation ceremony of the Faculty in the Neubaukirche on 4 June, 2016. The medal and the certificate were presented by the Dean Prof. Dr. M. Frosch (left) and the President of the University of Würzburg Prof. Dr. A. Forchel (right). In his tribute, Prof. Dr. H. Einsele (second from right) particularly appreciated, apart from his scientific achievements as a specialist in nuclear medicine, his services to the University Hospital of Würzburg, the fortunes of which he coined as Medical Director from 2001 to 2015. As physician, scientist, and Medical Director, Christoph Reiners has achieved the extraordinary and made an exceptional contribution in his service to university medicine in Würzburg.*

The ***Interessengemeinschaft zur Förderung der Kinder der Würzburger Intensivstation*** *(Community for the Support of Children on the Würzburg Intensive Care Unit, KIWI e.V.) was honoured by the Faculty of Medicine and University Hospital with the Siebold Medal on 12 October, 2015. The Siebold Medal honours people and organizations rendering outstanding services to the Faculty of Medicine and University Hospital. On the occasion of the 25th anniversary of KIWI e.V., the Faculty of Medicine and University Hospital thanked the Society for their excellent service in the support of premature babies, severely ill neonates, and children with life-threatening diseases. Expressing their appreciation, the Medical Director Prof. Dr. C. Reiners (4th from left) and the Dean Prof. Dr. M. Frosch (not pictured) presented the Carl Caspar von Siebold Medal to KIWI e.V. From the left: S. Mott, Treasurer, I. Schmolke and O. Hehn, both Chairs of KIWI e.V., Prof. Dr. C. Reiners, Prof. Dr. C. Speer, Head of the Department of Paediatrics of the University Hospital, B. Stamm, President of the State Parliament of Bavaria, PD Dr. J. Wirbelauer, Senior Consultant on the paediatric intensive care units and V. Halbleib, Member of the State Parliament of Bavaria. Photograph: KIWI e.V.*

The History of the Würzburg Medical Faculty

The medical faculty of 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 *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 very subtle and mobile animal spirits in the ventricles rather than with 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. Again, medicine ranked among the University's three higher faculties from the start, though it took several years until the medical faculty 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 invalid, 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 and frequented one 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 Würzburg Medical Faculty 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 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 for the first time. 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 which 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 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, philoso-

phical 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 developped 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 leading representative 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. Thanks to 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 outpatient care as well as work on the wards was 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 a "Zentrum Operative Medizin" (ZOM), a "Zentrum Experimentelle Molekulare Medizin" (ZEMM) and a "Zentrum Innere Medizin" (ZIM).

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

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Institutes and Departments

Preclinical Institutes and Chairs

Institute of Anatomy and Cell Biology, Chair of Anatomy I 10
Institute of Anatomy and Cell Biology, Chair of Anatomy II 12
Institute of Physiology, Chair of Vegetative Physiology 14
Institute of Physiology, Chair of Neurophysiology 16
Biocenter Würzburg, Chair of Physiological Chemistry 18
Biocenter Würzburg, Chair of Biochemistry and Molecular Biology 20
Biocenter Würzburg, Chair of Developmental Biochemistry 22
Institute for the History of Medicine 24
Institute for Medical Radiation and Cell Research (MSZ) 26
Institute of Molecular Infection Biology 28

Theoretical-clinical Institutes

Institute for Hygiene and Microbiology 30
Institute of Clinical Epidemiology and Biometry (ICE-B) 32
Institute of Forensic Medicine 34
Institute of Pathology 36
Institute of Pharmacology and Toxicology, Chair of Pharmacology 38
Institute of Pharmacology and Toxicology, Chair of Toxicology 40
Institute of Virology and Immunobiology, Chair of Immunology 42
Institute for Virology and Immunobiology, Chair of Virology 44
Institute of Human Genetics 46

Center for Operative Medicine (ZOM)

Department of Anaesthesia and Critical Care 48
Department of General, Visceral, Vascular and Pediatric Surgery (Surgery I) 50
Department of Trauma, Hand, Plastic and Reconstructive Surgery 52
Department of Thoracic and Cardiovascular Surgery 54
Department of Urology and Paediatric Urology 56

Center for Internal Medicine (ZIM)

Department of Internal Medicine I 58
Department of Internal Medicine II 61
Division of Molecular Internal Medicine 64
Institute of Transfusion Medicine and Haemotherapy 66

Center for Radiology (ZRAD)

Department of Diagnostic and Interventional Radiology 68
Department of Diagnostic and Interventional Neuroradiology 70
Department of Nuclear Medicine 72
Department of Radiation Oncology 74

Gynecology, Pediatrics, and Dermatology

Department of Obstetrics and Gynecology 76
Department of Pediatrics 78
Department of Dermatology, Venereology and Allergology 80

Neurosensory Center

Department of Oto-Rhino-Laryngology, Plastic, Aesthetic and Reconstructive Head and Neck Surgery 82
Department of Ophthalmology 84
Department of Neurosurgery 86
Department of Neurology 88

Center of Mental Health (ZEP)

Department of Psychiatry, Psychosomatics and Psychotherapy with Division of Forensic Psychiatry 90
Division of Molecular Psychiatry 92
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy 94
Department of Medical Psychology, Psychotherapy, Medical Sociology, and Rehabilitation Research 96

Clinical Institutes and Chairs

Institute of Experimental Biomedicine, Chair of Experimental Biomedicine I 98
Institute of Experimental Biomedicine, Chair of Experimental Biomedicine II 100
Institute of Clinical Neurobiology 102
Chair of Tissue Engineering and Regenerative Medicine (TERM) 104
Department of Orthopedics 106
Institute of Medical Teaching and Medical Education Research 108

Center of Oral Health (ZMKG)

Department for Functional Materials in Medicine and Dentistry 110
Department of Orthodontics 112
Department of Oral and Maxillofacial Surgery 114
Department of Prosthodontics 116
Department of Conservative Dentistry and Periodontology 118
Division of Periodontology 120

Institute of Anatomy and Cell Biology, Chair of Anatomy I

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Professor Dr. med. Stefanie Kürten
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Mission and Structure

At the Department I of the Institute for Anatomy and Cell Biology, the research group Neuroimmunology (head: Prof. Dr. med. Stefanie Kürten) studies B-cell dependent immunopathology of multiple sclerosis (MS), the role of microglial cells and the development of neuroprotective therapy strategies. The research group Tumor angiogenesis 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, 5 Ph.D. students and 3 technical assistants.

Focus of research

B cell dependent immunopathogenesis of multiple sclerosis
(S. Kürten, G. Pommerschein, D. M. Rovituso)

MS is a chronic autoimmune disease of the central nervous system (CNS). The role of B cells in the immunopathogenesis of MS has been taking center stage in MS research in the past years. In addition to producing autoantibodies and presenting antigens, B cells are involved in the disease by the generation of tertiary lymphoid organs in the CNS. The research objective of the group is to illuminate the mechanisms of B cell involvement by analyzing animal models. To this end, a particular form of autoimmune encephalomyelitis is studied which can be triggered in mice by active immunization with a fusion protein consisting of myelin basic protein and proteolipid protein, and which proceeds in a B cell-dependent manner. In this model, key molecules are to be identified that are important for the formation of tertiary lymphoid organs. These key molecules are to be examined also in MS patients and correlated with the course and severity of the disease. This novel research approach may lead to the development of new therapies. We have already identified one of those key molecules – the cell adhesion molecule CEACAM1. Therapeutic blocking of CEACAM1 led to significant reduction of clinical symptoms and CNS histopathology. Mechanistically, these effects were caused by an inhibition of CEACAM1-induced B cell aggregation. An additional research focus is the development of B cell-based biomarkers for MS patients which are not only to be used diagnostically but could also facilitate the decision for a targeted immunomodulatory therapy.

Development of neuroprotective therapy strategies for MS
(S. Kürten, A. Schampel)

Currently available therapies for MS are targeting mainly its inflammatory component. It is known, however, that even at the onset of the disease, patients are affected by neurodegeneration which progresses during the disease course, leading to irreversible destruction of nerve fibers. In analyses of animal models of MS, we were able to show that treatment with the calcium channel antagonist nimodipine decreased axonal damage and demyelination with simultaneous increase of remyelination. In this project the mechanisms of the observed effects are to be studied further. Here our results point to an essential role of microglial cells whose production of toxic effector molecules might be inhibited by nimodipine treatment.

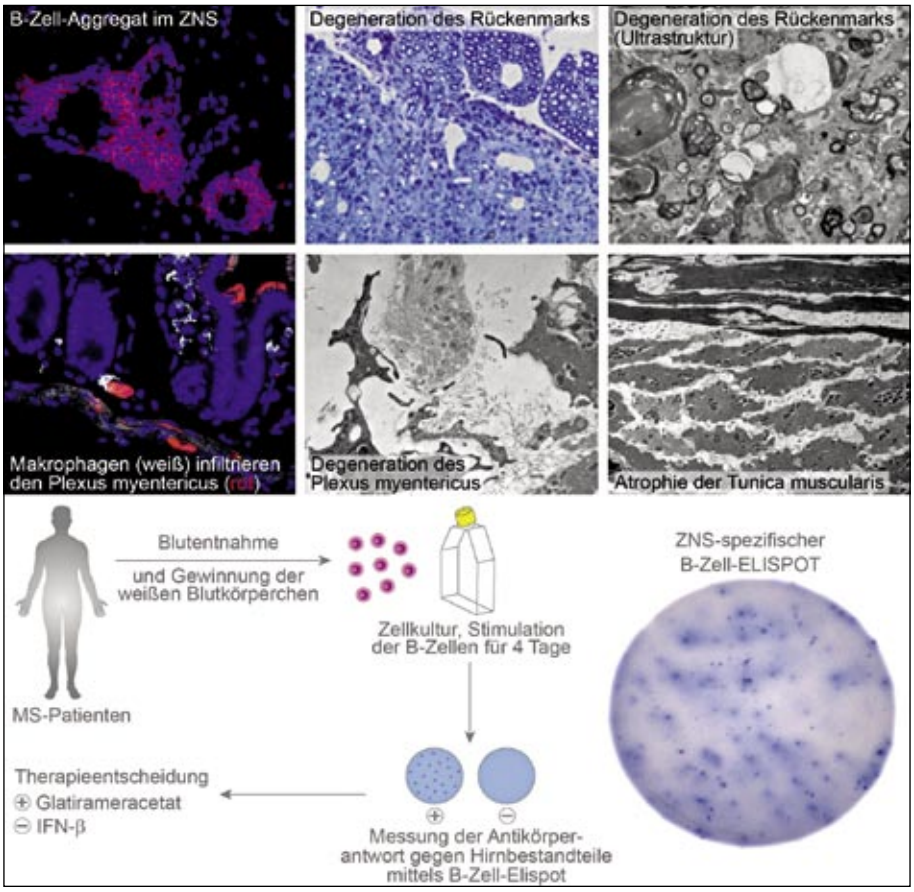

Fig. 1. Research profile of the research group (AG) Neuroimmunology (Prof. Kürten). Among the research foci are the analysis of infiltration, demyelination and axonal degeneration in the central and enteric nervous system (CNS and ENS) in multiple sclerosis (MS). Additionally, biomarker studies are carried out which particularly aim to elucidate the role of B cells in MS.

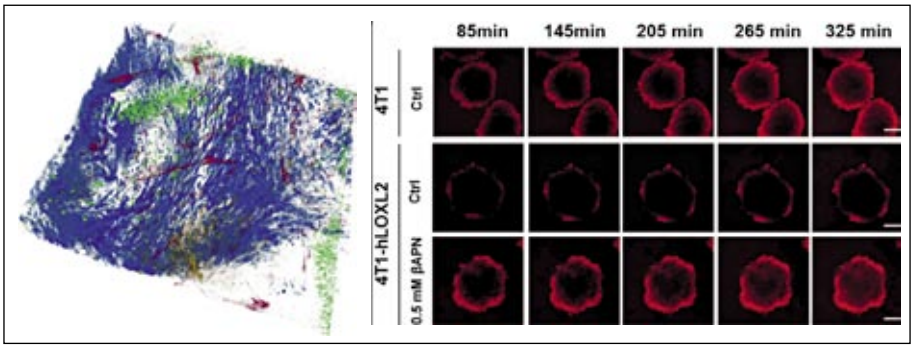

Fig. 2. (A) 3D reconstruction of a tumor region following fluorescence immunohistochemical documentation of different cell populations: fibroblasts (blue), blood vessels (red), CD44+ Tumor cells (green) and macrophages (yellow). (B) Time-dependent illustration of the diffusion of drugs into the center of tumor spheroids. Overexpression of the enzyme LOXL2 (middle panels), which increases the stiffness of the extracellular matrix, reduces the permeability of the spheroids for tumor-therapeutics. This effect is abolished after inhibition of the enzyme via addition of ßAPN (lower panels)

Generation of microglial cells from the vessel wall in the central nervous system
(S. Kürten, T. Königer, S. Ergün)

In addition to the contribution of the adaptive immune system to the pathogenesis of MS, a decisive role of macrophages and microglial cells is undisputed. With this project, we provide the first investigations studying whether microglial cells may be generated directly from the stem cell niche of the vessel wall in the CNS in the course of inflammatory processes. Whether these microglial cells play a detrimental or rather a beneficial role is to be characterized in a second step. The proof of a local generation of microglial cells in patients suffering from MS would stress the necessity of therapeutic strategies which target and are effective within the CNS, and are not only aimed at modulating the immune system in general. It would also be of significance for understanding and treating numerous other diseases, such as brain tumors or Morbus Alzheimer, in which microglia plays an important role.

The enteric nervous system in multiple sclerosis
(S. Kürten, M. Wunsch)

Our previous work documented, for the first time, that the enteric nervous system is a target of autoimmune processes in our animal model of MS. In this project, morphological and functional analyses are carried out to provide detailed insight into the degenerative processes in the gut in the course of MS. In addition, we are aiming at identifying target antigens of the immune response in the gut. We are also interested to find out whether degeneration of the enteric nervous system is initiated at the onset or in the chronic phase of the disease, allowing us to differentiate whether it may be a causative process or should be classified as an epiphenomenon. The results of the project could, in the long run, be of significant clinical relevance for MS therapy.

Anti-angiogenetic effector molecules and tumor matrisome-modulation in cancer therapy
(E. Henke, S. Ergün)

In addition to tumor cells, the tumor stroma consists of numerous cell types with various functions (Fig. 2A). The stroma cells support, via vascularization, the supply of oxygen and nutrients to the tumor. The composition of this tumor microenvironment influences the biological behavior of the tumor. Using transgenic mouse models, we investigate the influence of the tumor vessels and their permeability on the efficacy of anti-cancer therapy. Furthermore, matrix proteins form an essential part of the tumor microenvironment. Enzymes secreted by tumors influence the stiffness of the extracellular matrix (ECM), the tumor matrisome, via crosslinking of the molecules. An increased stiffness of the tumor matrisome is accompanied by decreased matrisome permeability for therapeutic drugs (Fig. 2B). Low permeability-ECM provides a physical barrier protecting the tumor cells from the action of the anti-cancer drugs. A further research focus is to study the interactions between the different constituents of the tumor microenvironment. Thus, the research interest is directed not only at the direct effects with which an ECM alteration changes tumor supply, but also at the secondary effects wrought upon the infiltration of the tumor tissue by stroma- and immune cells.

Teaching activities

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

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Institute of Anatomy and Cell Biology, Chair of Anatomy II

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Professor Dr. rer. nat. Frank Edenhofer (until 2/2016)

Professor Dr. Gabriela Krasteva-Christ (until 10/2016)

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, Prof. F. Edenhofer until November 2015) is focused on the generation of iPS (induced pluripotent stem cells) and the endogenous reprogramming mechanisms 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 monoaminergic and peptidergic system on processing of emotional stimuli in the amygdala. The AG Pulmonary neurobiology (head: Prof. G. Krasteva-Christ) studies the significance of innate immunity in the regulation of the respiratory tract and the effect of non-neuronal acetyl choline in the cardiopulmonary system.

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

Focus of research

Stem cells and regenerative medicine
(S. Ergün, F. Edenhofer, P. Wörsdorfer, S.R. Mekala, J. Bauer)

Recently developed techniques enable the generation of patient-derived induced pluripotent stem (iPS) cells, which provide a promising basis for modelling diseases and developing cell- and tissue replacement therapies. Our AG has succeeded, for the first time, to generate neural stem cells (iNS cells) from connective tissue cells of the mouse. Furthermore, our AG has identified a stem cell niche in the adventitia of adult human blood vessels, which harbours not only vascular, but also non-vascular stem- and progenitor cells and has been named "vasculogenic zone". Our research aims at reprogramming and endogenous recruitment of adult stem cells of the central nervous system and the cardiovascular system for cell replacement therapies (Fig. 1).

Endothelial barrier, vascular inflammation and atherosclerosis
(S. Ergün, N. Wagner, H. Bömmel, A. Hübner, J. Bauer)

Cardivascular diseases are leading in statistics of lethal diseases. The proverb: "one is as old as the own vessels" is still up-to-date. We are using various in vitro- (endothelial migration, proliferation and tube generation), ex vivo- and in vivo-models to find out how the endothelial barrier is protected and the neo-intima development blocked, and how the structural regeneration of lesioned blood vessels can be therapeutically influenced. In the course of these experiments, we study the contribution of vascular wall-resident progenitor or stem cells to the development of atherosclerosis, the mechanistic role of CEACAM1 and of the CEACAM1-isoprostan interaction in these processes in vitro and in vivo, using mouse models like Ceacam1-KO, Ceacam1-transgenic (endothelium) and Thromboxan-receptor-KO. Furthermore, the activation processes for vascular wall-resident stem cells from coronary vessels are studied (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. 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-cell-adhesion 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

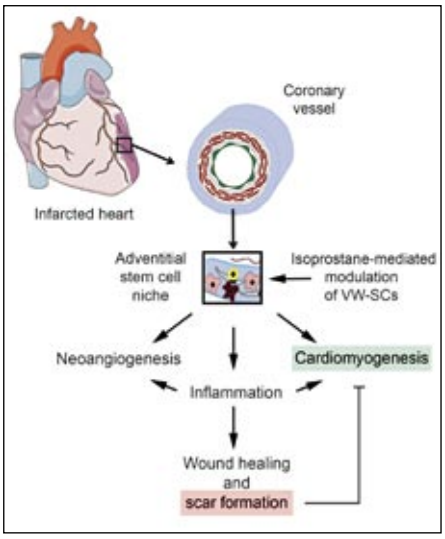

Fig. 1: Stem- and progenitor cells from the vascular adventitia, for instance from the adventitia of coronary vessels, are activated after myocardial infarction. They are presumably involved in neoangiogenesis, inflammation, wound healing and generation of cardiac muscle tissue (cardiomyogenesis). The regulatory mechanisms are not completely understood.

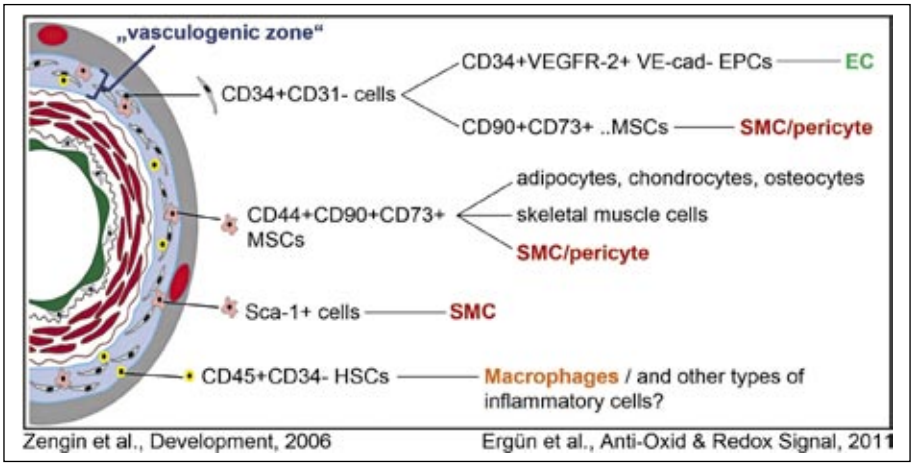

Fig. 2: Vascular wall-resident stem- and progenitor cells with their immune phenotypes known to date and with differentiation pathways into mature vascular and non-vascular cells.

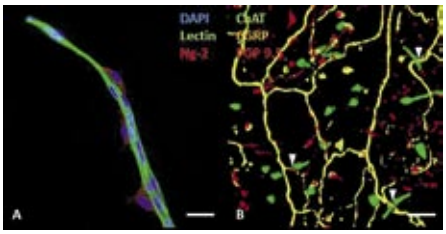

Fig. 3: Confocal fluorescence microscopy (A) Newly formed microvessel from an aortic ring. Blue=cellular nuclei, green = endothelial cells; red= pericytes. Bar = 10 µm. (B) Trachea, mouse. Whole-mount immunohistochemistry with 3D reconstruction. Intraepithelial nerve fibers (red) contain neuropeptides (yellow) and are in contact (arrowheads) with cholinergic epithelial cells (green = brush cells). Bar = 20µm.

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. Particularly, analyses are focused on the role of monoaminergic and peptidergic systems and of their interrelations for the processing of and reaction to emotional stimuli in the telencephalic amygdaloid complex (Amygdala). Additionally, light- and electron microscopic analyses of various regions in the central and peripheral nervous system and of different neural cell types in situ and in vitro are performed in cooperation with other research groups of the faculty. 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, and contribute to 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 in the adult nervous system.

Pulmonary neurobiology
(G. Krasteva-Christ)

In recent years we succeeded in identifying the function of a specific cell type of the respiratory epithelium, the so-called brush cell. Although this cell has long been known, its function has remained mysterious for decades. In the respiratory tract, brush cells, among other functions, serve as sensors for potentially hazardous substances and initiate alterations in respiration. Recently, we have identified brush cells in hitherto unknown localizations, such as, for instance, the urethra, the thymus, the conjunctiva and in the glands of the respiratory tract. These cells are cholinergic and use components of the classical taste transduction cascade to detect bacteria in the urethra. Our working hypothesis is that these chemosensory cells are guardians of the respiratory tract, protecting it from the intrusion of hazardous substances and bacteria. This constitutes a novel concept for pathogen recognition in the respiratory tract and lung. In two DFG-funded projects we are carrying out the characterization of this cell type. Our studies are particularly focused on elucidating the role of brush cells for innate immunity in the context of respiratory infections. Furthermore, we are interested in developing novel therapeutic strategies for treating hyperreagibility and inflammation of the respiratory tract and in analyzing the role of non-neuronal acetyl choline in the cardiopulmonary system.

Teaching activities

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 2017).

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Institute of Physiology, Chair of Vegetative Physiology

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Mission and Structure

The Institute of Physiology comprises chairs for Vegetative Physiology and for Neurophysiology (Prof. Heckmann). The building accomodates the research laboratories and offices, a lecture hall seating 200 students, course laboratories, seminar rooms, and a library. Facilities for animal husbandry, for work with radioactive isotopes and a repair shop are also available. 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. Miranda Laferte.

Major Research Interest

We investigate the regulation and function of guanylyl cyclase (GC) receptors and of their second messenger cyclic GMP. Some of these receptors are transmembrane proteins, such as GC-A, the receptor for atrial (ANP) and B-type natriuretic peptides (BNP), and GC-B, receptor for C-type NP (CNP). In contrast, the GC receptor for nitric oxide is intracellular (NO-GC). To dissect the regulation, pleiotropic functions and disease relevant alterations of these hormones and of cGMP, we generate and characterize genetic mouse models with conditional, cell-specific deletion of these receptors or of regulatory proteins involved in their signal transduction. Other projects focus on the function of cytoskeleton-associated proteins containing EVH1 domains, such as SPRED (Sprouty-related protein with an EVH1 domain), MENA and VASP as well as on the regulation of cardiac calcium (LTCC) channels. Our research is supported by the DFG (SFB 688, etc.), the IZKF und the CHFC Würzburg. Our teaching duties are financed by the University of Würzburg.

Cardiovascular functions and cellular signaling pathways of natriuretic peptides

(M. Kuhn, K. Völker, K. Spiranec, W. Chen, F. Werner, E. Prentki, L. Krebes, S. Tauscher, K. Michel, T. Naruke and coworkers)

Since many years our research focuses on the endocrine heart and the (patho)physiological roles of the cardiac hormone ANP (Kuhn, 2016). Our work showed that ANP not only exerts endocrine, blood pressure/volume regulating actions, but also local, auto/paracrine cardiac effects. These effects can counterregulate pathological cardiac remodelling and myocyte hypertrophy (Nakagawa et al., 2014). The cardiac effects of ANP are complemented by CNP, a little peptide participating in the crosstalk between endothelial cells and fibroblasts, exerting antifibrotic effects. These cell-specific protective actions of natriuretic peptides (NPs) are mediated by intracellular cGMP and cGMP-modulated third messengers such as specific protein kinases and phosphodiesterases (Kuhn, 2015 and 2016). In cardiac pathologies, i.e. in hypertensive heart disease, the secretion and action of these hormones are markedly altered: the cells release less active prohormones and the receptors and intracellular signaling pathways are downregulated (Kuhn, 2015). This ultimately leads to a functional imbalance between the vasodilating/antihypertrophic NPs and prohypertrophic, vasoconstrictory hormones such as Angiotensin II and aldosterone (Nakagawa et al., 2014). This imbalance possibly contributes to the progression of cardiac disease and heart failure. Therefore the improvement of this hormone-receptor system has become a target for novel heart therapies (Kuhn, 2016).
Other projects of our group aim to dissect the vascular and metabolic actions and action sides of NPs. In particular, the fine blood capillaries are surrounded by spider-like contractile cells, the pericytes, with poorly characterized and surely underestimated functions. These cells embrace endothelial cells. They control capillary diameter and thereby flow and release paracrine factors modulating the endothelial barrier and endothelial regeneration. Our ongoing studies reveal that pericyte functions are modulated by endocrine and locally formed NPs which participates in the resetting of arterial blood pressure homeostasis (see Figure).

The significance of NO/cGMP signaling in the cardiovascular and gastrointestinal system

(A. Friebe, D. Groneberg, B. Voußen, K. Beck, A. Aue, S. Dünnes, L. Kehrer)

NO-sensitive guanylyl cyclase (NO-GC) has a key function in the NO/cGMP cascade by catalyzing the synthesis of the intracellular signaling molecule cGMP. As the most important receptor for the signaling molecule nitric oxide (NO) 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. To characterize the

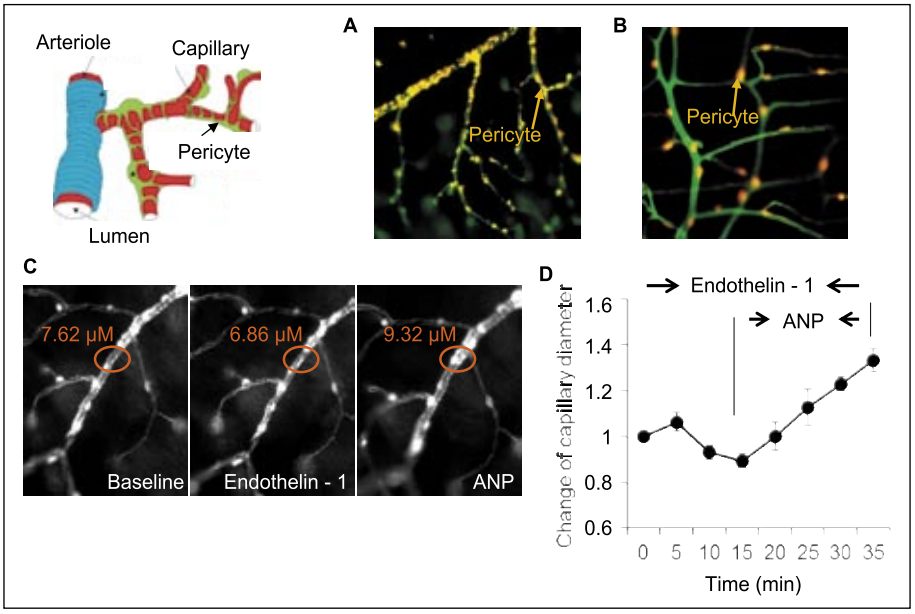

Fig. 1: Pericytes surround almost all capillaries of our bodies, with specially high density in the brain and retina (A) and less density for instance in the skeletal muscle (B). C) and D) The endothelial peptide endothelin induces a contraction of the pericyte´s body and arms which shrinks the capillary lumen. This contraction is reversed by ANP. Thereby ANP improves the capillary perfusion and lowers arterial blood pressure.

role of NO-GC in gastrointestinal motility and lower urinary tract function, we generated mouse KO lines in which NO-GC is specifically ablated in smooth muscle cells or interstitial cells of Cajal or both. Our observations in these mice showed that both smooth muscle cells and interstitial cells of Cajal mediate gastrointestinal nitrergic relaxation and motor activity in murine colon (Lies et al., 2015). In addition, a prominent role of NO-GC in angiogenesis and arteriogenesis was identified.

Physiological characterization of SPRED proteins
(K. Schuh, M. Ullrich, M. Abeßer, B. Aßmus)

Gene targeting is an elegant tool to combine the ablation of a specific gene with a parallel integration of a reporter gene to investigate gene expression. We used such techniques to characterize the relevance of various EVH1 domain-containing proteins *in vivo*. At present, we investigate the effects of SPRED2- and SPRED3-deficiency on the cardiovascular system and the nervous system. Of particular interest are the involved intracellular signaling pathways and intracellular transport. We could show that SPRED2 gene ablation leads to a disorganization of intracellular vesicle transport in the heart, resulting in severe consequences for the electrical conduction and contractile performance, finally resulting in cardiac failure (Bundschu & Schuh).

Cardiac roles of the beta-subunit of L-type calcium channels (LTCC)
(E. Miranda Laferte, C. Heindl, S. Pickel)

The cytosolic beta-subunit regulates the activity of LTCCs and thereby calcium homeostasis of cardiomyocytes. Interestingly, this protein is also located outside sarcolemmal LTCC protein complexes, even in the myocyte nucleus, with unknown functions. This project, which recently started at our institute, aims to dissect the specific functions of different splice variants of the beta 2 subunit. Modern proteomics and high-end microscopy will be combined to analyze the subcellular localization in micro-/nanodomains of the cardiomyocyte and functionally relevant protein interaction partners.

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 - 4th term). In winter 2013 Prof. Andreas Friebe received the Albert Kölliker-award for his outstanding seminars and courses.

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Professor Dr. med. Tobias Langenhan (from 5/2016 to 10/2016)

Professor Dr. rer. nat. Erhard Wischmeyer
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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

Presynaptic proteins and spatial working memory in Drosophila melanogaster
(K. Neuser, M. Heckmann)

Intelligent behaviour is based on learning and usage of memorized contents. Drosophila melanogaster flies show intelligent behaviour as well. For example, they possess a spatial working memory. That is, they are able to store the position of visual objects and to use that memory content to show goal-directed movement even if the object has disappeared. This project aims to test whether the neuronal correlate of working memory can be linked to the molecular organisation of presynaptic proteins. Furthermore, ultrastructural changes of synaptic organization in aging flies have been analysed using light- and electron microscopy.

Nanoscopy of Active Zones
(M. Paul, S. Proppert, M. Pauli, M. Heckmann)

At synapses information flow from a neuron to a downstream cell is mediated by chemical transmission. As action potentials arrive at a presynaptic terminal they initiate the fusion of synaptic vesicles with the presynaptic plasma membrane which leads to the release of the contained neurotransmitters. These fusion events don't occur randomly at the cell membrane but are restricted to specialized sites, so called Active Zones. Active Zones show a complex molecular architecture and although numerous molecular components like Bassoon, RIM, and calcium channels have yet been identified, we still lack a fundamental understanding of the ultrastructural arrangement and basic function. Presynaptic Active Zones are too small to be resolved by conventional light microscopy. We use super-resolution *d*STORM light microscopy together with the Sauer laboratory (Department of Biotechnology and Biophysics) to study the molecular architecture and dynamics of Active Zones in preparations of hippocampus, cerebellum and neuromuscular junctions.

Adhesion GPCRs – a class of metabotropic mechanosensors
(T. Langenhan)

Adhesion G protein-coupled receptors (Adhesion GPCRs) are evolutionarily highly conserved biosensors that are present on cell surfaces of all tissue types from earliest developmental stages onwards until adulthood. We have elucidated several physiological functions of Adhesion GPCRs that include their contribution to tissue polarity and cell fate induction, and we have recently defined them as a large class of putative metabotropic mechanosensors. We are currently investigating the molecular properties of Adhesion GPCRs, which underlie their large functional versatility. Specifically, we are interested in the processes involved in Adhesion GPCRs signal perception and transduction, and their relevance in physiology and pathophysiology.

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

Two-pore domain K^+ (K_{2P}) channels give rise to time- and voltage- independent background currents that substantially control cellular excitability and K^+ homeostasis. The activity of K_{2P} channels is modulated by various physical and chemical stimuli as well as by G-protein coupled receptors. As some members of the K_{2P} 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 signaling 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.

Molecular mechanisms of synaptic plasticity
(R. J. Kittel)

Our research studies molecular mechanisms of synaptic plasticity and sensory physiology by combining neurogenetics, electrophysiology, super-resolution microscopy and op-

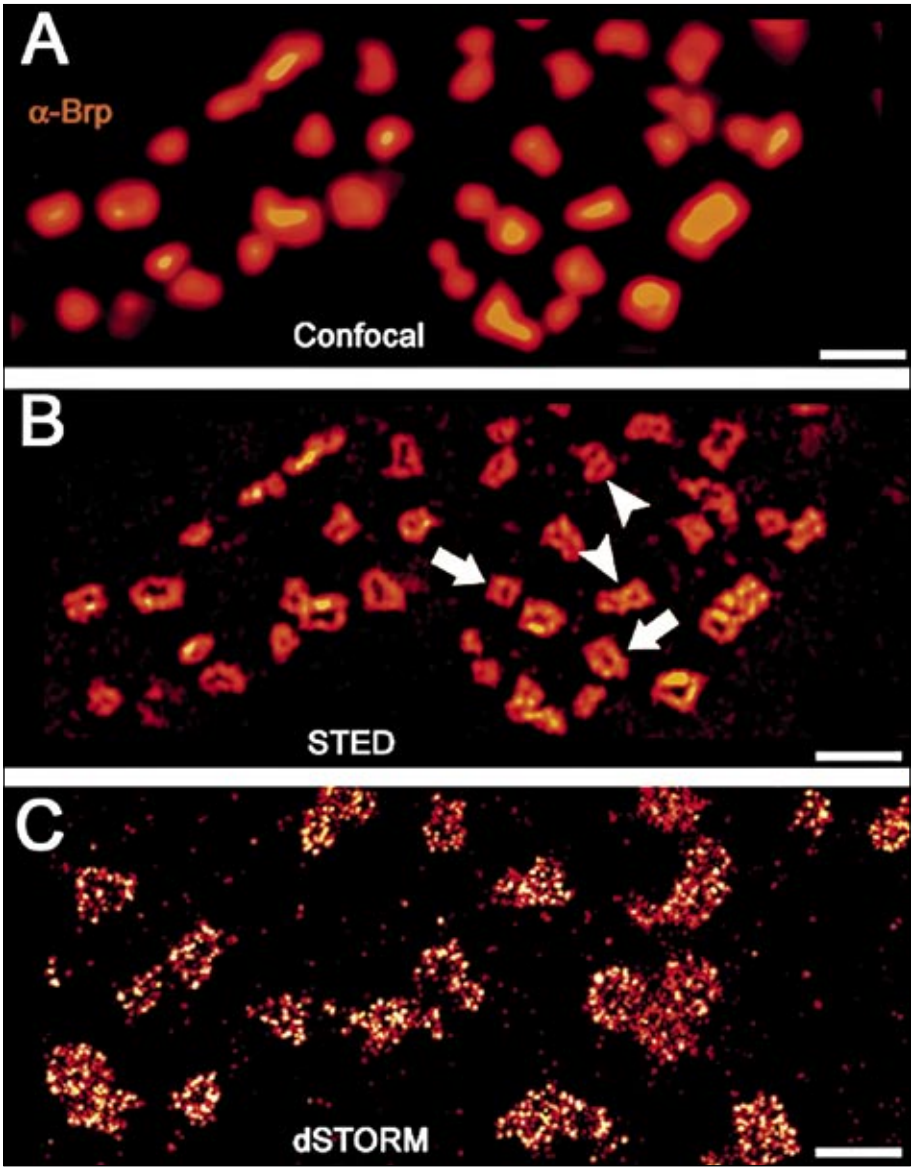

Fig. 1: Molecular Structure of Active Zones. Investigations by the Kittel Emmy-Noether group in collaboration with the Sauer laboratory (Department of Biotechnology and Biophysics) concerning the spatial distribution of the Bruchpilot (Brp) protein in active zones. Application of „Super-Resolution" light-microscopy (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).

togenetics. Specifically, we are pursuing the following projects: functional nanoscopy of the presynaptic active zone, activity-dependent glutamate receptor dynamics, circadian synaptic plasticity, and the physiological role of Adhesion-GPCR auto-proteolysis.

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.

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Biocenter Würzburg, Chair of Physiological Chemistry

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Mission and Structure

In accordance with the research perspectives 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 on 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 material. One focus is traditionally the studies on the 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 for melanoma development. These studies include besides the protein-coding mRNAs also the analysis of microRNA and other non-coding RNA classes because those molecules are expected to play a role in tumor development. However, their function for the oncogenic processes are so far not understood. 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. Our novel strategy is based on the hypothesis that therapeutic effects become recognizable on the gene expression level much earlier than any phenotypic changes in tumor growth will be visible. This should allow a most effective screening procedure and at the same time will reduce animal experiment load in the future.

Senescence escape and reactive oxygen stressin melanoma
(S. Meierjohann)

Premature senescence is a state which is caused by aberrant activation of oncogenes and which is thought to block the progression of premalignant lesions to cancer. Thus, the process of tumor transformation from premalignant lesions was inscrutable for a long time, and it was not known whether the tumors arise from premalignant oncogenic cells which have not entirely entered senescence, or whether they can indeed derive from senescent cells. We have now found that melanocytes expressing the melanoma oncogene $NRAS^{Q61K}$ enter a state of multinucleated senescence, which is characterized by

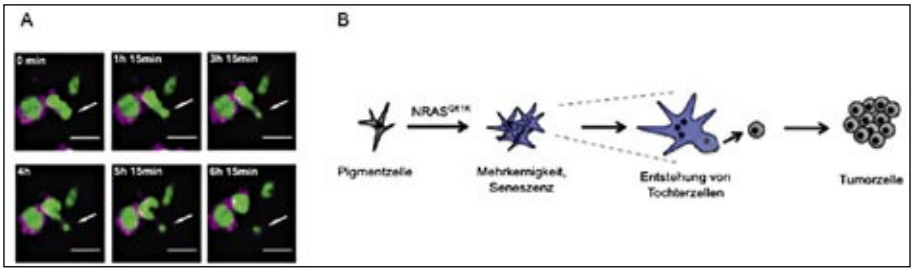

Fig. 1: Multinucleated senescent cells give rise to malignant daughter cells. A: Time lapse images of the generation of a daughter cell from a multinucleated cell. green: nucleus; purple: membrane. B: Schematic representation of the corresponding event

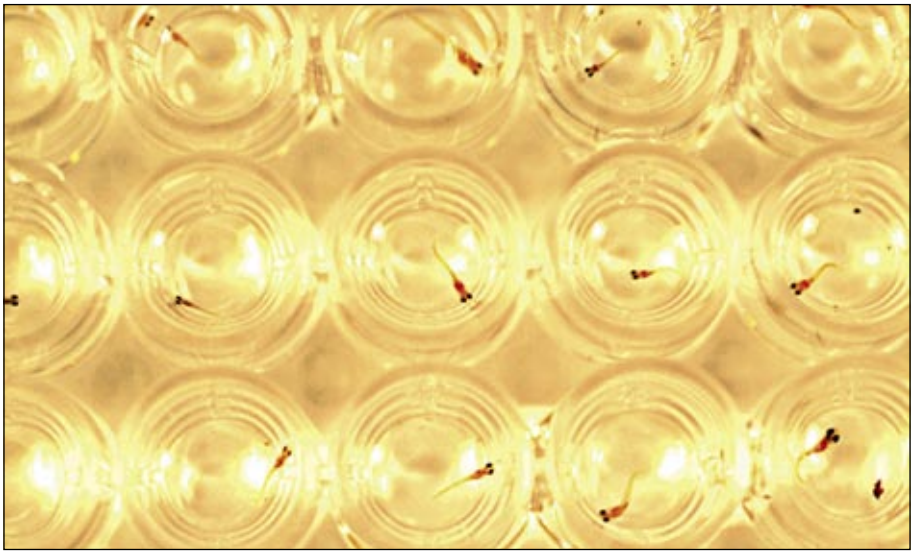

Fig. 2: Medaka larvae in a 48-well plate. Such plates can be used for high-throughput drug screens

high p53 activity, and which poses a strong risk factor for tumorigenesis. We could show that multinucleated senescent cells are able to undergo de-polyploidisation, thereby giving rise to highly dedifferentiated daughter cells with stem-like properties and full transformation potential.
In addition to these early events in melanoma development, our group is interested in essential signalling processes, which can be exploited for tumor therapy. As the classical pathways such as MAPK or PI3K pathways show a high degree of plasticity and compensation after pharmacological inhibition, we follow alternative strategies such as the targeting of antioxidant pathways. It is known that melanoma cells have multiple sources of reactive oxygen species, which renders them dependent on efficient anti-oxidant strategies. We have found that melanoma cells rely on the transsulfuration pathway, which is responsible for de novo synthesis of cysteine and thereby guarantees the supply with this cellular antioxidant. We are currently investigating components of the transsulfuration pathway as well as other antioxidant enzymes for their therapeutic use in different models for human melanoma.

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

Our research focuses on E2F transcription factors, the retinoblastoma protein and related pocket proteins. 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 E2F/ pocket protein complex in human cells that is related to similar complexes in invertebrates. The composition of this DREAM complex is dynamic and in quiescent cells it associates with p130 and E2F4 and contributes to the repression of E2F-regulated genes. In late S phase, the interaction of DREAM with p130/E2F4 is lost and DREAM now binds to the B-MYB transcription factor. Genome wide expression studies have shown that DREAM mediates the activation of a cluster of genes required for entry into mitosis, spindle assembly and cytokinesis. It has been proposed that overactivity of these mitotic proteins contributes to chromosomal instability and thus promotes tumorigenesis. We are currently investigating the role of DREAM and DREAM-target genes in an *in vivo* mouse model of lung cancer driven by oncogenic Ras and mutant p53. These studies could lead to the development of new therapeutic approaches for lung cancer.
We are also interested in the function of novel target genes of DREAM such as GAS2L3, an actin and microtubule-interacting protein that plays important roles in cytokinesis and genome stability.

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Biocenter Würzburg, Chair of Biochemistry and Molecular Biology

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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 Prof. Martin Eilers, Prof. Peter Gallant and Prof. Ernst Conzelmann, Prof. 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 focus of the work in my lab has been to understand how metabolic reprogramming contributes to cancer cell survival and to identify selective metabolic sensitivities in cancer cells. Our work has highlighted several important areas of crosstalk between oncogenic signalling and metabolic regulation in cancer cells.

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.

Metabolic Pathways in Peroxisomes: alpha-Methylacyl-CoA-Racemase
(E. Conzelmann, until 12/2015)

We analyse the structure and function of the alpha-Methylacyl-CoA-Racemase. Gene knockouts of this protein is investigated in mouse models, to understand the role of this enzyme in lipid metabolism. Furthermore, we are interested in the function of this enzyme as a marker protein in many tumours, in particular in prostate cancer.

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 sys-

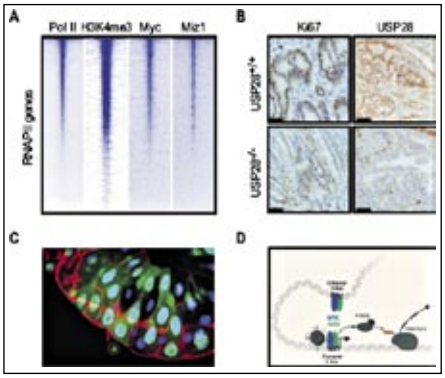

Fig. 1: MYC proteins are central regulators in the development and maintenance of normal tissue and in the process of tumorigenesis (A) Heatmap showing binding to all genes based on global analyses (ChIP-sequencing). Our experiments demonstrate, that MYC and the MYC interacting protein MIZ1 are global 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.

tem 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 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.

MYC-dependent co-ordination of RNA polymerase activities during ribosome biogenesis and cell growth
(E. Wolf)

Growth is a basic principle of life but deregulation of growth is also a hallmark of human cancers. Our group is interested in how cell growth is coordinated by the oncoprotein Myc. It is well established that Myc increases the production of all growth-relevant components on one hand and that uncoordinated cell growth influences the activity of Myc on the other hand. However the mechanistical details of this cross-talk are largely unknown. We use genome wide technology like next generation sequencing to investigate how Myc and cell growth are interconnected in the process of tumorigenesis.

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.

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Biocenter Würzburg, Chair of Developmental Biochemistry

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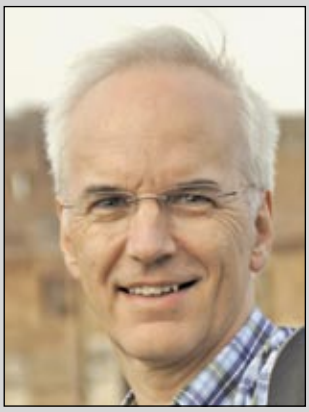

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Mission and Structure

The scientific interests within the Chair of Developmental Biochemistry range from the elucidation of the molecular control of development and differentiation processes to the uncovering of disease mechanisms that are brought about by deregulation of these pathways. The current focus is on the development of the cardiovascular system and the kidneys as well as on childhood kidney cancers, i.e. nephroblastomas (Wilms tumor) that are characterized by high throughput methods. These projects are funded by the DFG, the BMBF and the Wilhelm-Sander-Foundation. The Chair participates in the training of students of Medicine and Dentistry, Biology, Chemistry, Biomedicine and Biochemistry.

Major Research Interests

Analysis of Hey gene functions

In their function as central transducers of Delta/Notch signals, Hey genes control the embryonic development of the cardiovascular and other organ systems. In the developing heart Hey1, Hey2 and HeyL are critical for epithelial-mesenchymal transformation (EMT) within the endocardium. This is a prerequisite for the formation of precursor cells that are in turn needed to build the cardiac septum and valves. This could be demonstrated through *in vitro* and *in vivo* analysis of cardiac precursors from knockout mouse embryos. Combinatorial gene deletions revealed that Hey2 as well as Hey1/HeyL exert similar functions and they exhibit partial redundancy. Hey1 and Hey2 also appear to participate in the positioning of the atrioventricular canal as an organizing center.
Target genes of Hey factors in these processes have been identified through gene expression analyses and sequencing of genomic binding sites based on ChIPseq analyses. For this we employ various cell types including embryonic stem cells, which can be differentiated *in vitro* into cardiomyocytes or endothelial cells. In this way global as well as cell-type specific regulatory mechanisms of Hey proteins can be elucidated. These helped to gain novel insight into cardiac electrical activity and conduction, where Hey2 seems to play an important and previously unrecognized role.
Hey genes are also important for embryonal angiogenesis and remodeling and for arterialization of blood vessels. A lack of Hey1 and Hey2 results in a lethal angiogenesis defect. Both genes block expression of the venous regulator Coup-TFII (NR2F2) in the context of the hypoxia response. Again, *in vitro* differentiation systems were employed to recapitulate these processes and to identify or to modulate corresponding target genes. The antagonistic factors Coup-TFII and Hey1/2 are both active during lymphatic differentiation and we try to find out if their targets overlap. To better understand the molecular mode of action of Hey proteins we characterize their interaction partners and their role in the nucleus.
Besides these cardiovascular functions we could identify clear evidence for a role of Hey genes in the development of the inner ear, the activation of macrophages, bone homeostasis and adipocyte differentiation. This underscores that Hey genes can be activated by different stimuli in a variety of cell types and they likely regulate a multitude of physiological functions.

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

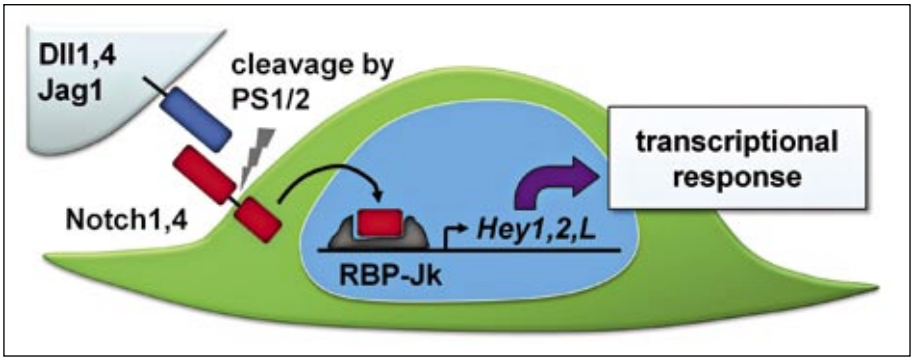

Fig. 1: The Delta/Notch signaling pathway activates transcription of Hey genes that in turn act as transcriptional repressors of target loci.

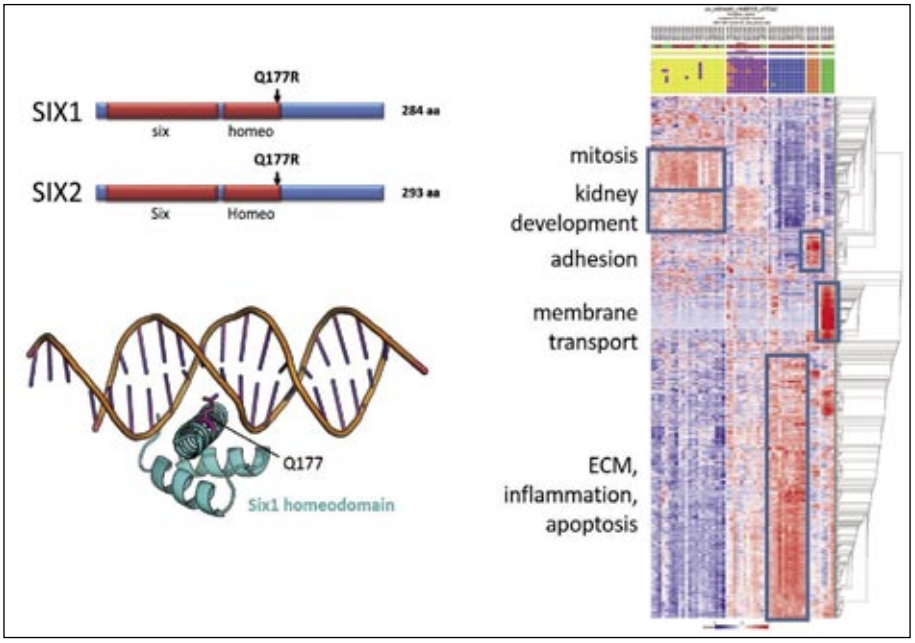

Fig. 2: Highly specific SIX1/2 mutations in Wilms tumors alter the DNA binding domains of these transcription factors (left). mRNA expression profiles define subgroups of Wilms tumors with response to chemotherapy or unaltered further growth (right).

established a tumor bank that by now includes more than 1200 tumors and corresponding control tissues. These are routinely screened for chromosomal alterations and mutations in known tumor genes like WT1, CTNNB1, DROSHA, DGCR8 or SIX1/2 and they are used to identify novel biomarkers and target structures for improved diagnosis and treatment.

All attempts to analyze the biology of Wilms tumors through *in vitro* experimentation have been hampered by the lack of suitable cell culture systems. We have now established and characterized a series of primary cultures that can be used for functional studies. These cultures recapitulate critical features of these tumors, namely the stromal and epithelial components, but blastemal cells cannot be detected under these conditions. Primary cultures have been immortalized through expression of telomerase to establish permanent and stable lines. Meanwhile we are also able to successfully propagate blastemal cells in spheroid cultures. This allows us for the first time to perform functional in vitro studies in standardized cell cultures that represent all components of typical Wilms tumors and are amenable to genetic manipulation.

Our microarray analyses revealed that tumors which poorly respond to chemotherapy are characterized by a decreased activity of the retinoic acid signaling pathway. Thus, activation of this pathway might in turn be beneficial for patients. This could be substantiated in experiments with primary tumor cell cultures. We could show in several primary and permanent cultures that retinoic acid derivatives slow down the growth of tumor cells and induce further differentiation. First clinical applications in patients with refractory relapses showed promising results.

In cooperation with the Heidelberg Initiative for Personalized Oncology (hipo) we employed high-throughput sequencing methods for mutation screening and expression analysis, focusing on the high-risk group of blastemal-type Wilms tumors. We were able to identify several novel candidate genes that currently undergo extensive validation. Impairment of miRNA processing by the DROSHA/DGCR8 microprocessor complex and deregulation or mutation of a network of growth promoting genes including SIX1/2, MYCN, and LIN28B among others appear to represent novel triggers of Wilms tumors. This revealed completely unexpected and novel insights into the biology of these tumors since some of these genes are uniquely affected in this tumor type only.

In the case of another pediatric kidney tumor, clear cell sarcoma of the kidney (CCSK), we could demonstrate that around 85% of cases carry a small duplication within the BCOR gene. We are currently trying to define the functional consequences of this alteration. The remaining CCSK cases present with somewhat different clinical parameters, suggesting that testing for this mutation may become relevant to define diagnostic and therapeutic subgroups.

Teaching

Together with the Chairs of Physiological Chemistry and Biochemistry and Molecular Biology we offer a broad spectrum of lectures, seminars and practical courses. A focus is on the theoretical and practical training of more than 400 students of Medicine and Dentistry in their curricular subjects of Biochemistry and Molecular Biology. In addition, students of Biomedicine (B.Sc./M.Sc.) are taught in Biochemistry, Molecular Biology and Developmental Biology. For Biology and Biochemistry students advanced modules with a focus on Biochemistry, Developmental Biology and Tumor Biology are offered. Additional training courses for PhD students are offered within the framework of the Graduate School of Life Sciences (GSLS).

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Institute for the History of Medicine

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Mission and Structure

The origins of the Institute for the History of Medicine date back to the 19th 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 for medical history in Germany under 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 ONT-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 important aspects of the more recent history of medicine and nursing such as the history of palliative care, medicine in the National-Socialist era and the representation of medicine, physicians and nurses in film. Various projects with third-party funding are run at the Institute.

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

Under the auspices of the Bayerische Akademie der Wissenschaften, a work group for the study of early modern physicians' correspondences has been established in early 2009 which is expected to run for a total of 15 years. The work group 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 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 which is freely accessible to the international research community via internet.

Medical Practice, 1500-1850
(M. Stolberg, K. Nolte, S. Schlegelmilch, S. Neuner)

In two projects which were originally part of a German-Swiss-Austrian research network funded by the Deutsche Forschungsgemeinschaft (coordinator M. Stolberg) a physician's medical practice around 1650 and domestic out-patient care provided by the policlinics in Würzburg and Göttingen around 1800 have been studied since 2009. Based, in particular, on manuscript sources such as practice journals and physicians' notebooks, this work has more recently expanded to include the history of medical paper tools, medical training and early modern medical practice in general.

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 from the Deutsche Forschungsgemeinschaft this project examines the development of medical ideas about the dangers of corpulence from the Renaissance to the early 20th century, looking for long-term continuities as well as major turning-points. Based on a wide range of non-medical writings, from letters, diaries and other ego-documents to advertisements and commercials it looks at the language and images which were used to express esthetic, moral and economic judgments about corpulence in the media and among the population at large. And it looks at the impact of these – largely negative – judgements on the perception and treatment of corpulence in medicine and health care.

Teaching

The Institute offers about 15 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 open to all Bavarian students of medicine and dental medicine via the "Virtuelle Hochschule Bayern". The Institute is also responsible for organizing the compulsory transdicisplinary course on the history, theory and

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

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. Furthermore, a wide variety of elective courses and seminars is offered, ranging from medical English and courses in bibliography and paleography to seminars dealing with specific topics of medico-historical interest. The Institute is also responsible for the teaching of medical history and medical theory at the University of Regensburg. Members of the Institute have also organized several series of events in a Würzburg cinema, for students and the general public, showing films of medico-historical or medico-ethical interest with an introduction by an invited specialist and a discussion afterwards.

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Institute for Medical Radiation and Cell Research (MSZ)

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Mission and Structure

The chair is provisionally headed by Prof. Dr. Müller and comprises a total of 18 staff. The Institute 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 (residing in building E4) is studying signal transduction within the progenitor compartment of the developing *Drosophila* brain. The MSZ is working together with several institutes of the faculties of medicine and biology and is part of several national research cooperations.

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. The possibility to reprogram cells into any type of adult stem cells for the purpose of cell replacement holds tremendous therapeutic promise and may circumvent ethical considerations concerning the derivation of new human embryonic stem cells. The molecular pathways controlling pluripotency and cellular reprogramming are now only beginning to unravel. In the course of a project within the national DFG priority program 1356 (*Pluripotency and cellular reprogramming)* we recently identified the polycomb group (PcG) protein Pcgf6 as a novel reprogramming factor. Expression of Pcgf6 together with the classical reprogramming factors Oct4, Klf4 and c-Myc induced reprogramming of somatic cells to induced pluripotent stem (iPS) cells (see Fig. 1). We also identified Pcgf6 as a crucial factor for the maintenance of embryonic stem cells (ESCs). Apart from ESCs and iPS cells the stem cell biology group focuses on hematopoietic stem cells. Of central importance to our studies is the question of how global chromatin states guide stem cell behavior. In this connection we were able to demonstrate that inhibition of the chromatin regulator EZH2 (another PcG protein) facilitates the *in vitro* expansion of functional human hematopoietic stem cells. These studies were performed as part of the BMBF-consortium: CB-HERMES (*Cord Blood-Hematopoietic Stem Cells: Reliable Methods for ex-vivo Expansion*). Further key aspects of our work comprise the developmental potential of mesenchymal and uniparental stem cells.

Molecular Genetics

(T. Raabe)

In our group we take advantage of the genetic model organism Drosophila in combination with molecular and cell biological approaches to elucidate mechanisms that control generation and differentiation of neuronal cells. Indeed, more than two-third of human disease-associated genes are conserved in Drosophila. We are investigating a number of mutations, which cause an altered proliferation pattern of neural progenitor cells leading to hypo- or hypertrophy of the adult nervous system. Our current research focuses on the control of cell growth as a critical parameter to maintain the proliferation potential of progenitor cells throughout development. In collaboration with Prof. Gallant (Biochemistry & Molecular Biology) we have characterized a new nucleolar protein, which is transcriptionally controlled by Myc and regulates growth of neural progenitor cells at the level of ribosome biogenesis. In addition, we have evaluated the effect of mutations in a certain class of small nucleolar RNAs using a Drosophila model of neural

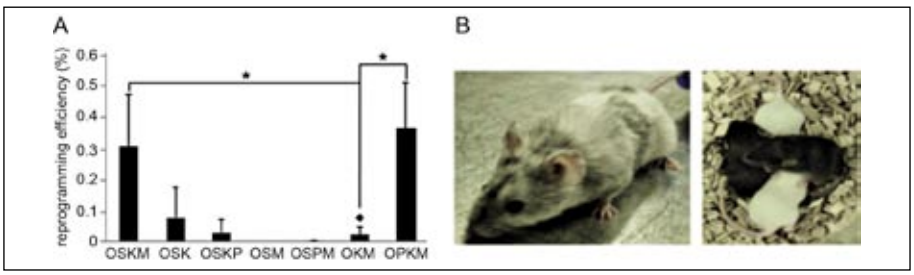

*Fig. 1: The PcG protein Pcgf6 can replace Sox2 but not Klf4 or c-Myc in the generation of germline-competent iPS cells. A) iPS reprogramming efficiencies using different factor combinations. O = Oct4, S = Sox2, K = Klf4, M = c-Myc, P = Pcgf6. *, p < .0.5. n = 3. Error bars = s.d.. B) Germline competent mouse (left) generated by blastocyst injection of a OPKM iPS cell line and corresponding F1 offspring generation (right). Data taken from Zdzieblo et al. 2014.*

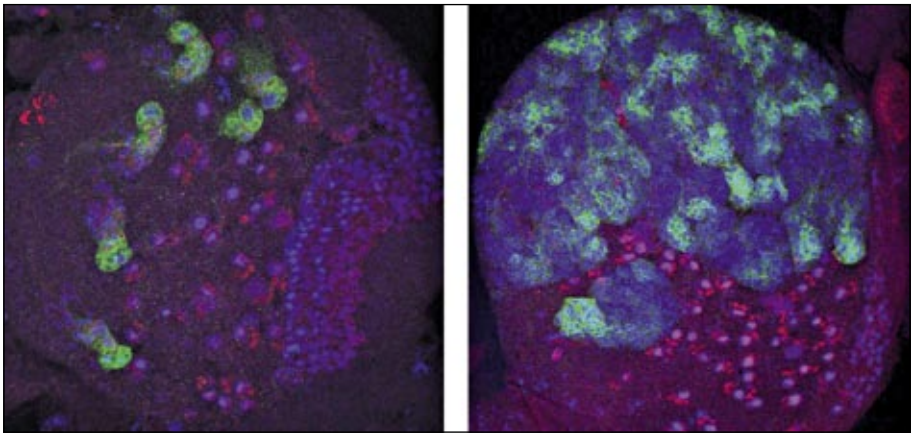

Fig. 2: Drosophila as a model for neural stem cell tumors. Left: Labeling of a subclass of neural stem cells and derived cells (green) in larval wild-type brains. Progenitor cells are marked in pink/blue. Right: Mutation of the TRIM32 orthologue Brain tumor (Brat) results in reversion of further differentiated cells into the stem cell fate.

stem cell tumors (see Fig. 2). A further focus of our research lies at the neurophysiological level. In collaboration with clinical groups (Dr. Fischer, Psychiatry; Dr. Kittel, Physiology II) the function of the kinase RSK in synaptic organisation, neurotransmission, axonal transport and regulation of the MAPK signalling pathway in motoneurons was analysed. These new findings might contribute to a better understanding of the molecular mechanisms of mental retardation caused by mutation of the human RSK2 gene. In a project within the Collaborative Research Centre SFB1047 ("Insect timing"), we analyse the involvement of the circadian clock in synaptic plasticity and cell metabolism. Finally, we use the developing Drosophila eye as a model to study the role of p21-activated kinases in regulation of cell morphogenesis through modulation of Cadherin-mediated cell adhesion.

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 to modern techniques in cell biology, biochemistry and microscopy. 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. Albrecht Müller is the Study Responsible for the Accompanying and Master Study programme "Experimental Medicine".

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Institute of Molecular Infection Biology

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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 Centre for Infectious Diseases (ZINF). It also accommodates the young investigator groups of the ZINF. The research at the institute aims to elucidate fundamental principles of infection processes. This is being achieved by studying 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 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 Clinics, ZINF and IZKF.

Main Research Interests

The main research interests at the institute are related to understanding the biology of the pathogens and their interaction with host cells and the immune response. This is primarily achieved by using molecular and cell biological methods and global high-throughput approaches, such as genomics (functional genome analysis), proteomics (protein expression analysis) and bioinformatics as well as RNA deep sequencing with the aimof understanding the infection process from a new global perspective.

RNA biology of bacterial infections
(J. Vogel)

Next generation sequencing technologies have enabled approaches such as RNA-seq to globaly identify non-coding RNAs in prokaryotes and eukaryotes. This has revealed that these molecules are much more diverse than previously thought. The Vogel group focuses on the identification and functional analysis of noncoding RNAs that play an important role in host-pathogen interactions and the immune response. This includes the characterisation of small regulatory RNAs in bacterial pathogens and long noncoding RNAs in eukaryotic host cells. In addition, they are using global approaches to study RNA binding proteins in bacteria and their role in virulence.

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.

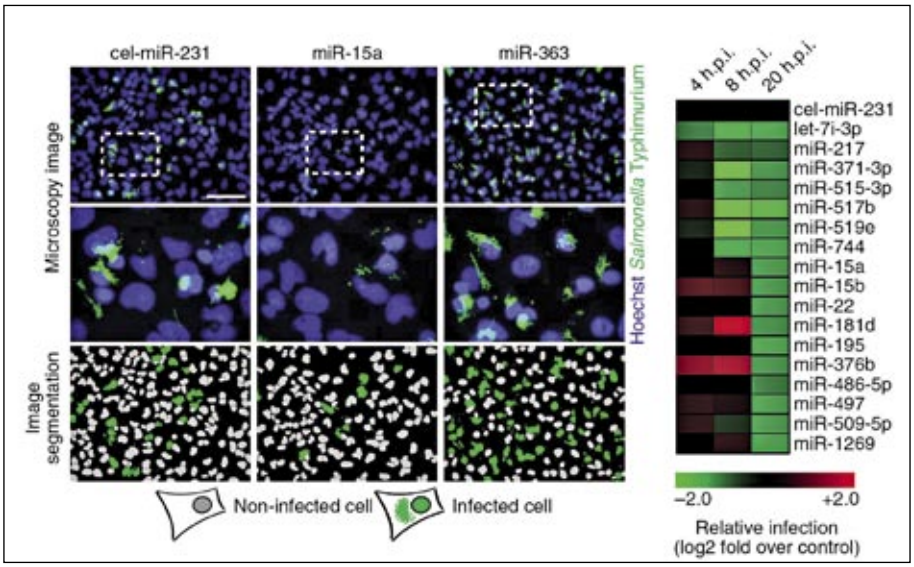

Fig. 1: A: Analysis of HeLa-cells infected with salmonella after treatment with microRNAs. B: microRNAs are able to influence the level of infection with salmonella (modified, Maudet et al. 2014, Nature Communications 22;5:4718).

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 to host cells. The Ölschlaeger group is focusing 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 they have shown that it interferes with the adhesion and invasion of pathogenic bacteria. Another research focus is 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 ist he elucidation of thefunction 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 which 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)

A proper 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 human and mouse microRNAs. To achieve this they are 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.

Teaching activity

The scientists at IMIB teach under graduateand master students from medicine, biology and food chemistry, which include bothlecture-based and practical courses. A considerable part of the teaching activities contribute to the training of biology students in the Department of Microbiology. These activities include lectures in general microbiology, pathogenicity and immunology, as well as seminars on current topics in Infection Biology. The institute also organizes lectures, courses, seminars and summer schools for the members of the Graduate College 'Infectiology' in association with the International Graduate School of Life Sciencesat the University of Würzburg. It also hosts several internships.

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Institute for Hygiene and Microbiology

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Mission and Structure

The tasks of the Institute for Hygiene and Microbiology comprise the laboratory diagnosis of infectious diseases caused by bacteria, fungi and parasites, the advice of clinicians with respect to diagnosis, therapy and prevention of infectious diseases, the research on 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 routinely used diagnostic tools the institute also provides special molecular and serological test systems. Our commitment to patient care also includes the development of strategies for the prevention of hospital infections and the monitoring of hospital hygiene. Annually approximately 80.000 microbiological analyses are performed. The research activity of the institute mainly focuses on the elucidation of the molecular mechanisms in the pathogenesis of infectious diseases. Using tools from molecular genetics, cell biology, immunology and genome research the pathogenicity of bacteria and parasites is investigated and novel strategies for the diagnosis, therapy and prevention of infectious diseases are developed. The Institute also hosts the infection control unit of the University Clinic.
At the institute, the Robert-Koch-Institute established the national reference centre for meningococci and *Haemophilus influenzae* (NRZMHi). 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 part of the pan-European network of reference centres, the European Meningococcal and Haemophilus Disease Society. In cooperation with the European Center for Disease Control (ECDC) the "Laboratory surveillance and external quality assurance of invasive bacterial diseases in EU" (IBD-labnet) project is coordinated by the Institute for Hygiene and Microbiology which focuses on the establishment of an 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.

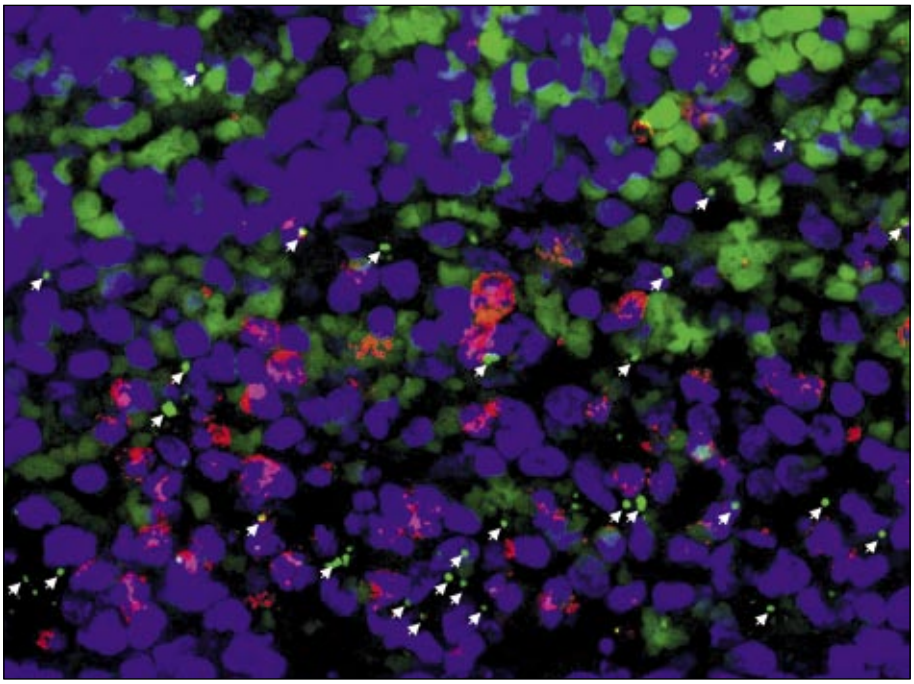

Fig. 1: N. meningitidis induces the formation of ceramide-enriched membrane platforms on brain endothelial cells (HBMEC). HBMEC were infected with a GFP-expressing wildtype strain MC58 for 2 h, fixed, left intact, stained with anti-ceramide antibodies and secondary Cy3-conjugated anti-mouse-IgM antibodies and analyzed by confocal microscopy. Ceramides accumulate in close association with attached bacteria (doi:10.1371/journal.ppat.1004160.g001).

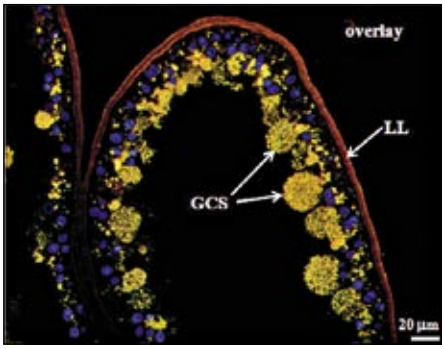

Fig. 2: Expression of an E. multilocularis insulin receptor, EmIR1, in glycogen storage cells of the metacestode. Immunohistochemistry against parasite vesicles using anti-Echinococcus surface antigen (red), an anti-EmIR1 serum (yellow), and Hoechst (nuclear staining; blue). LL = laminated layer, GSC = glycogen storage cells (Preparation: Andrew Hemphill).

Major Research Interests

Infection biology of meningococcal disease
(A. Schubert-Unkmeir)

Meningococci, an important cause of septicemia 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 the analyses of bacterial factors as well as host cell receptors, which determine the interaction, and the characterization of major signalling pathways resulting in cytoskeletal remodelling and bacterial engulfment.

Meningococcal host interaction during colonization 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, the factors which allow for *N. meningitidis* colonization of the nasopharyngeal mucosa are characterized. Of particular interest is whether and how the complement system affects mucosal colonization, 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 the systemic hyper-inflammation, their contribution to the pathophysiology of meningococcal sepsis is analysed using an experimental sepsis model.

Genome research on pathogenic bacteria
(C. Schoen, M. Frosch)

N. meningitidis is an important commensal, accidental pathogen and model organism with a small but hyperdynamic genome. Meningococcal fitness and genome evolution result from a fine-tuned balance between mechanisms for genome variability and maintenance where chromosomal alterations and polymorphisms provide the meningococcus with adaptability and ensure a lasting coexistence with their human host. The study of the genetic mechanisms shaping meningococcal genome diversity as well as causing differences in genome expression among different strains are thus another main research focus of the institute, ultimately aiming at a better understanding of the genetic factors that separate purely commensal from accidentally invasive strains.

Population biology invasive pathogens
(U. Vogel, H. Claus)

The molecular epidemiology of *N. meningitidis* and *Haemophilus influenzae* is analyzed by bacterial finetyping. Representative strain collections continuously assembled at the National Reference Laboratory are used. Laboratory surveillance also comprises monitoring of resistance to antibiotics Furthermore, the group studies capsule biosynthesis in meningococci.

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 metastases 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 have shown 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 long-term persistence of *Echinococcus* in the host.

Teaching

Student's 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.

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Institute of Clinical Epidemiology and Biometry (ICE-B)

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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 ICE-B is clinical epidemiology comprising studies on: causes of diseases and its respective risk factors; therapy and prevention; prognosis and outcome; diagnostics and screening; as well as adequacy and quality of medical care for defined diseases and syndromes. Hereby clinical relevant patient-oriented research questions will be answered by appropriate study designs. Furthermore, the ICE-B aims to improve education and training activities of medical students, scientists and physicians in epidemiology and biometry at different stages of their career at the University of Würzburg.

Research focus

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. These projects are conducted in close cooperation with various departments and institutes of the University Würzburg and the University Hospital Würzburg, e.g. the Comprehensive Heart Failure Center (CHFC) of the University of Würzburg or the Clinical Trial Center of the University Hospital Würzburg (CTC), as well as with external national and international cooperation partners.

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 cooperating with the Clinical Trial Center of the University Hospital Würzburg, especially in the area of biometry. The thematic focus in biometry is being 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 area "prognostic studies" includes to establish, perform and analyse cohort studies in high risk groups of the general population as well as in patients with specific disease conditions.
For example, prognostic studies in stroke patients are initiated for investigating factors influencing long-term outcome as well as for developing risk prediction models for the occurrence of relevant complications. Recently, the SICFAIL study was established as cooperative project between the ICE-B, the Department of Neurology (Prof. Dr. C. Kleinschnitz, PD Dr. P. Kraft) and the Comprehensive Heart Failure Center (Prof. S. Störk) for determining the natural course of heart failure in ischemic stroke patients.
In 2013, the STAAB cohort study is started as joint project between the Comprehensive Heart Failure Center (Prof. S. Störk) and the ICE-B. Within the STAAB study, frequency of early stages of heart failure (stages A and B) and its determinants within the general population will be identified. For this purpose, a representative sample of 5000 men and women between 30 and 79 years of age from the study region of Würzburg will be recruited. Participants will be randomly selected from the local registration office and will be interviewed comprehensively regarding life style, health related factors, and comorbidities. In addition, standardized vascular and cardiovascular diagnostic procedures (e.g. echocardiography, ECG) will be performed, as well as anthropometric investigation (e.g. bioimpedance), neuropsychological and laboratory testing (including biomaterial collection). The baseline examination takes place in the joint epidemiological survey unit of the ICE-B and the CHFC. It is planned to re-examine the participants three years after the baseline examination for potential changes in heart function. The STAAB study was positively re-evaluated in 2015 by an international review board and will be funded until 2020 by the BMBF within the CHFC.

Health services research

The thematic area "health services research" addresses research questions related to adequacy and quality of medical care within the population. These studies comprise for example the development of methods to eva-

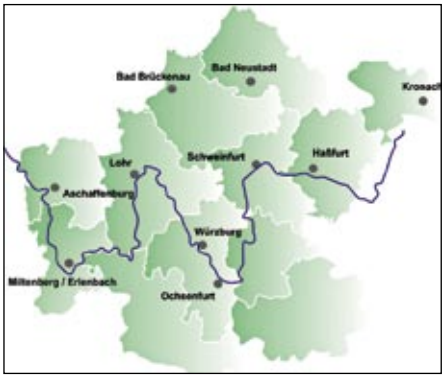

Fig. 1: TRANSIT-Stroke network (as at January 2016).

luate quality of patient care in routine clinical practice as well as to improve translation of research outputs from clinical trials into clinical care of the population.

Within this thematic field a number of register and cohort studies in the area of coronary heart disease (e.g. EUROASPIRE) as well as stroke (e.g. EIS Collaboration) were performed.

For example, recently the „Transregional Network for Stroke Intervention with Telemedicine“ (TRANSIT-Stroke; www.transit-stroke.de) was initiated. TRANSIT-Stroke is a collaborative telemedical stroke network comprising different hospitals in Northwest-Bavaria and is coordinated by the Department of Neurology of the University Hospital Würzburg (managing director TRANSIT-Stroke: PD Dr. Kraft). TRANSIT-Stroke aims to improve acute care and management of stroke patients in Northwest-Bavaria. The participating hospitals are organised in a three-stage system comprising the following stages: Stage I (hospitals without a certified Stroke Unit that can make use of tele-neurological consultation by network hospitals anytime for all stroke patients); Stage II (hospitals with a local Stroke Unit); as well as Stage III (hospitals with a regional Stroke Unit). Three of the participating hospitals with regional Stroke Units (University Hospital Würzburg, Leopoldina Hospital Schweinfurt, Neurological Hospital Bad Neustadt/Saale) ensure the continuous tele-neurological consultation service for the cooperation hospitals of Stage I and II and acting as network centre.

Within the TRANSIT-Stroke network also secondary prevention of stroke patients to reduce risk of subsequent stroke shall be optimised. The investment costs of the network were funded by the Bavarian Ministry of Health and Care and the running costs were covered by the Bavarian health insurance companies. The implementation of the network is scientifically evaluated by the ICE-B. For this purpose, the effect of the implementation of the telemedical network will be investigated by the ICE-B as methods centre by analysing the quality of acute stroke care as well as the situation of care of stroke patients three months after the stroke event. The network shall also be used as platform for implementing projects to improve stroke care in the region, TRANSIT-Stroke was honoured in 2014 by the award „fight against stroke“ of the Hentschel foundation.

Teaching

In teaching activities, the ICE-B gives specific emphasis to improve education and training of medical students, young scientists and physicians 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. Within these courses, the relevance of epidemiology and biometry in daily clinical practice were demonstrated by practical clinical examples. In addition, extended modules for medical students on epidemiological and biometrical topics were implemented, including for example critical appraisal skills or courses on statistical analyses for different levels of expertise.

Since October 2014 the ICE-B also offers a statistical consultancy service for medical students at the University of Würzburg performing their thesis. The statistical consultancy service serves as “help for self-help” to support the students regarding planning, performing, analysing and interpreting their thesis project. Within the first 12 months of this service more than 210 consultancies were performed.

The ICE-B contributes actively in establishing advanced education activities in the area of clinical research, clinical epidemiology and health services research in close collaboration with a number of established research facilities in Würzburg (e.g. the Comprehensive Heart Failure Center). These activities include for example the establishment of a program “clinical research and epidemiology” for medical students since the winter term 2012/2013 in which participants will gain basic skills in clinical research as well as in theory and praxis of epidemiological and biometrical methods in clinical research. Until the winter term 2015/2016 in total 23 students started this program; four of them already successfully passed the program. Based on the curriculum of the program also a Master course in “clinical research and epidemiology” was developed that is offered since 2015 by the medical faculty.

For qualifying young scientists to conduct independent patient-oriented research projects, the ICE-B contributes to the establishment of a new section Clinical Sciences within the „Graduate School of Life Sciences (GSLS)“ together with various other institutions of the University and the University Hospital. Within this new section for example a curriculum „Clinical Research“ was established for qualifying residents and fellows. In addition, a yearly “Winter School in Clinical Epidemiology” takes place since 2012 including practical exercises and theoretical lectures on recent patient-oriented research topics with participation of a national and international faculty of clinical epidemiologists and biostatisticians.

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Institute of Forensic Medicine

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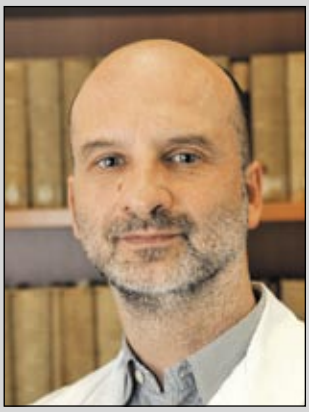

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Mission and Structure

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 2015 the academic staff of the University of Würzburg Institute of Legal Medicine consisted of 1 consultant (Oberarzt), 3 senior house officers (Assistenzärzte), 2 biologists and 1 toxicologist. 9 of the 19 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 the expression of glucose transporters in craniocerebral trauma, the determination of the post-mortem interval by means of bones as well as the detection and documentation of blood traces using infrared optical imaging techniques.

Expression of glucose transporters in the brain in the presence of craniocerebral trauma

(S. Oerter, M. Bohnert)

In a collaboration project between the Hospital and Polyclinic for Anaesthesiology (Prof. Förster), the Department of Neuropathology, and the Institute of Legal Medicine the issue is investigated whether it is possible to demonstrate the sodium-dependent glucose transporters SGLT1, SGLT2 as well as the uniporters GLUT1 and GLUT3 in human brain tissue of decedents undergoing forensic autopsy because of craniocerebral trauma or asphyxiation. Further issues to be investigated are the chronological course of the expression of the various forms of sodium-dependent glucose transporters after traumatisation and whether the volume and distribution of SGLT1, SGLT2, GLUT1 and GLUT3 as well as their relationship to each other provides information as to the vital or post-mortem origin of a trauma and its survival time. The results obtained from the human brain specimens are compared with the results from an in vitro trauma model with endothelial cells of human brain. The objective is to generate an expression pattern for glucose transporters depending on the time and cause of death.

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 (Fig. 1.), histology, molecular degradation, densitome-

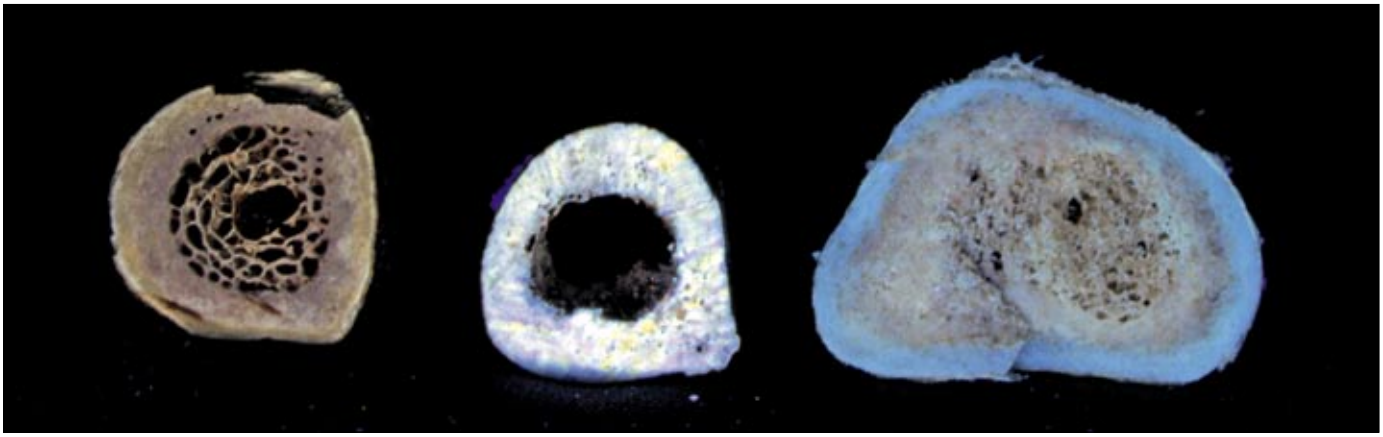

Fig. 1: UV-reflection of a cross cut bone sample (middle) with negative control (left) positive control (right).

try) 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, University of Tenneseee, Knoxville.

Infrared optical imaging of latent blood traces
(V. Sterzik, M. Bohnert)

In collaboration with the Institute of Legal Medicine of the University of Munich techniques for optical visualization and documentation of latent and small to very small blood traces on a dark background have been developed. Especially the small blood traces forming during dynamic courses of events are highly important for the reconstruction of a crime, especially if they can be demonstrated on the clothing of the persons involved in the event. By using lamps emitting light in the near infrared region in combination with filters it is possible to make such traces visible without destroying them, so that they are available for molecular biological analysis. With a modified single-lens reflex camera these traces can also be documented photographically (Fig. 1).

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.

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Institute of Pathology

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Mission and Structure

The Institute of Pathology is an academic center with more than 100 employees including 20 pathologists. The institute delivers clinical care for the university hospital and outside health care providers that includes histological and cytological diagnostic assessments of human biopsies and other tissues, 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 hematopathology and constitutes one of six German reference centers for hematological malignancies. 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-gradenon-Hodgkin lymphomas (DSHNHL)'. Prof.Rosenwald's and Prof.Geissinger's 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. In recent years, new biological risk factors could be determined in young high-risk patients with diffuse large B-cell lymphomas. The group plays a major role in several national and international research networks, such as in the International Cancer Genome Consortium (ICGC), the Leukemia and Lymphoma Molecular Profiling Project (National Cancer Institute, USA) and the local Clinical Research Unit 216 'Signalling in Multiple Myeloma'.

Molecular Pathogenesis of Hematological Malignancies
(E. Leich)

Within the context of the Clinical Research Unit 216 and the Sander-Therapy Unit "Multiple Myeloma" this research group works on the molecular characterization of multiple myeloma. With the help of next generation sequencing technologies a signaling network of receptor tyrosine kinases, adhesion molecules and their downstream effectors could be defined that are frequently affected by somatic mutations in multiple myeloma patients. Another research focus of this group in recent years is the molecular characterization of t(14;18)-negative follicular lymphomas. In contrast to their more frequent counterpart of t(14;18)-positive follicular lymphomas these lymphomas appear to be enriched for molecular features that suggest a late germinal center phenotype of B-cell differentiation. The aim of an ongoing effort is to decipher the molecular basis that underlies the pathogenesis of t(14;18)-negative follicular lymphomas in more detail.

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 experimentsare performed in cooperation with the reference center for hematological malignancies and funded by the Wilhelm Sander- and Thyssenstiftung.

Human cancer immunity by natural antibodies
(S. Brändlein)

The resarch in the last two years was focused on further developing tumor-specific human monoclonal antibodies into clinical products. In particular, the apoptosis-inducing IgM antibody PAT-SAM-6 targeting GRP78 (glucose regulated protein 78) turned out to be a promising agent for immunotherapy. The results from a clinical phase I/IIa study in patients with relapsed or refractory multiple myeloma were encouraging and stimulate additional investigations in the future. Furthermore, the treatment of a patient with drug refractory multiple myeloma with intra- and extrame-

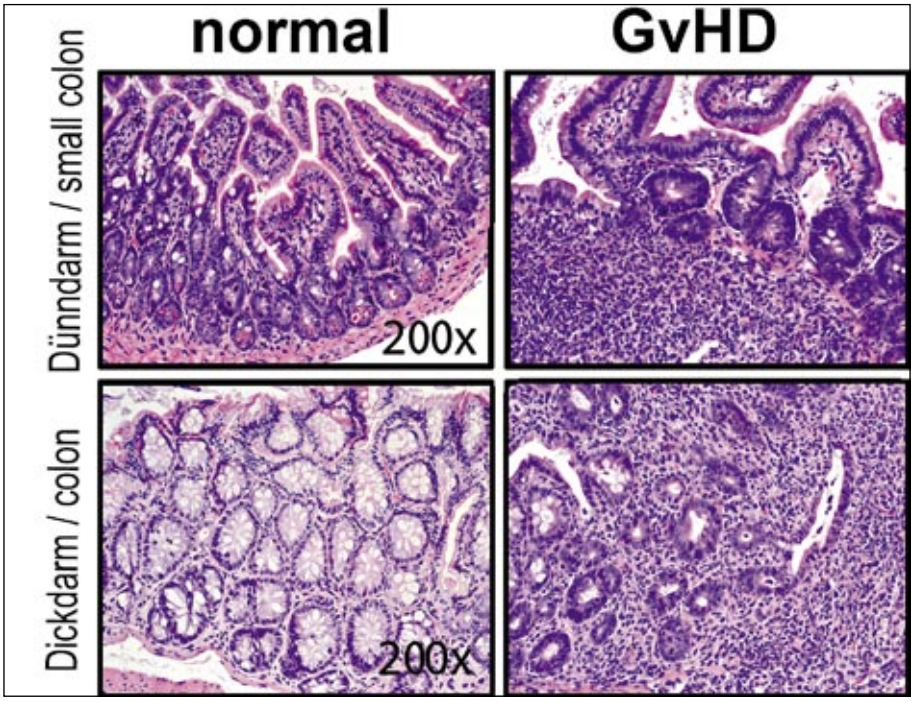

Fig. 1: Graft-versus-Host-Disease (GvHD) in a mouse model. Bone marrow was transplanted alone (normal) or in conjunction with T cells (GvHD). Shown are representative H&E-stained tissue sections from small bowel and colon. [Vaeth M et al., 2015].

dullary lesions with PAT-SM6 in combination with bortezomib and lenalidomide showed therapeutic efficacy.
Natural human antibodies are promising therapeutic agents and interesting combination partners for current cancer therapies due to their excellent tolerability, safety, efficacy and new mechanisms of action. Our future research will focus on extended clinical applications of these antibodies as well as on the analysis of the underlying targeted tumor toxic effects.

Neurooncology and Neurodegeneration
(C. Monoranu)

A research focus in the Department of Neuropathology is the gene expression analysis of human *post mortem* brain tissue from patients with Alzheimer's disease at different stages, based on the concept of selective vulnerability of different brain regions, which is not yet fully understood. Early affected regions such as the hippocampus show differences in gene expression compared to more resistant regions such as the cerebellum. Candidate genes responsible for the development of neurofibrillary changes were identified. Due to the increasing relevance of the neuroinflammation for the pathogenesis and progression of neurodegenerative diseases and malignant gliomas, a new research focus was recently developed in our department. We could provide evidence for changes in the expression of genes related to neuroinflammation (CX3CL1, TREM2) over the course of sporadic Alzheimer's disease progression, and additional studies on the role of M1 and M2 microglia are in progress. In the neurooncological field our work focused on the identification of prognostic markers for ependymomas, molecular features (RNAscope based gene expression analysis) in gliomas and on the role of the neuroinflammation mediated immunity for the clinical outcome of glioblastoma patients. Furthermore, we currentlyexplore the development of new theranostic markers (e.g. CXCR4) for glioblastoma and malignant meningeomas.

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 hematopathological 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.

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Institute of Pharmacology and Toxicology, Chair of Pharmacology

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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 and that is chaired by Prof. Lohse.
The chair employs ca. 75 staff members (about half of them grant-funded). All research groups focus on the molecular mechanisms of cellular communication, their role in physiological function and their potential to serve as targets for therapeutic drugs. In addition to standard biochemical and molecular biology equipment, the chair has a SPF unit for the generation of transgenic mouse models as well as equipment for rapid microscopic imaging, for confocal, 2-photon and TIRF microscopy, for electrophysiology and for cardiovascular phenotyping of transgenic mouse models.
The chair also provides a drug information service for the university hospital and medical faculty as well as 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 the mechanisms of cellular movement and its control by intracellular signaling processes. A third focus is on heart failure and the development of new therapeutic strategies. Our research is funded by grants from the DFG, the Rudolf Virchow Center for Experimental Biomedicine, the SFB688 and the TR166, the European Research Council, the BMBF (Federal Ministry of Education and Research), the Elitenetzwerk Bayern and others.

Mechanisms und Function of G-Protein-coupled Receptors

(M. Lohse, D. Calebiro, 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 sensors and fluorescence microscopy methods. This allows us to directly observe receptors and signaling mechanisms „at work“. This approach enables us to analyze the speed and localization of signals and receptor even at the level of single molecules in isolated cells and *in vivo*. We have recently succeeded in precisely characterizing the dynamics and localization of receptors and their signal. This has allowed us to discver a sequence of distinct receptor-triggered “signaling waves”.

Phosphatases and Cellular Motility

(A. Gohla; also Rudolf Virchow Center)

We have discovered a new class of human phosphatases that play major roles in regulating cellular metabolism and the cytoskeleton. These enzymes may represent novel targets for the development of drugs against cancer and cardiovascular diseases. Using biochemical and cell biological methods, we study their regulation and substrates. We further investigate their (patho)physiological functions in gene-deficient mouse models.

The Effects of Bacterial Toxins

(A. Iliev, Emmy-Noether group; also Rudolf Virchow Center)

Some bacterial toxins such as pneumolysin are able to induce the formation of pores in

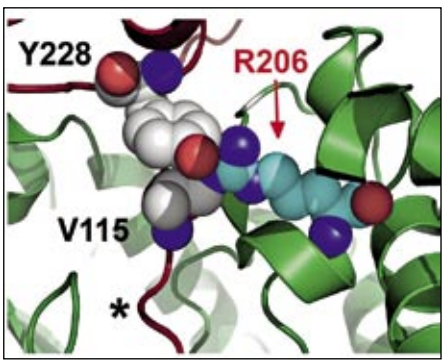

Fig. 1: A mutation in a signaling protein (protein kinase A) results in its two subunits not fitting to each other and, thus, its continuous activation. This causes a severe hormonal disease (Morbus Cushing). From: Calebiro et al., Nature Commun. 2014.

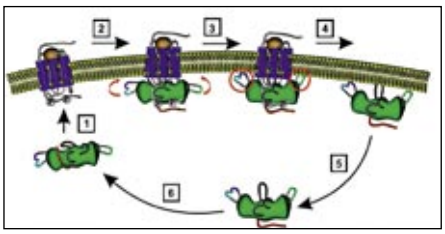

Fig. 2: The activation cycle of β-arrestin (green) by receptors (blue). From: Nuber et al., Nature (in press).

the membrane of other cells resulting in cell lysis or apoptosis. But also in concentrations lower than those needed for pore formation, they cause cell damage as, for example, in meningitis. The effects of bacterial toxins can be transmitted via the cytoskeleton. We investigate mechanisms of their toxicity and explore therapeutic strategies.

Adenosine Receptors and their Ligands
(K.-N. Klotz)

Adenosine is a ubiquitous mediator that acts on cells via four different G-protein-coupled receptors. In collaboration with chemists we develop selective ligands for these receptors and investigate the principles of their specific recognition.

Mechanisms of Heart Failure and Cardiac Signaling
(K. Lorenz, also Comprehensive Heart Failure Center, DZHI)

Chronic heart failure is one of the main health problems of old age. Based on patient samples, transgenic mouse models and freshly isolated primary cells, we investigate genes and mechanisms that contribute to heart failure and dilatation. A number of biochemical mechanisms that play an important role in heart failure, but also in vascular diseases such as atherosclerosis, have been identified over the last few years. Currently, we are exploring strategies to interfere with these signaling pathways in order to find new targets for heart failure therapy.

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. 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.

Bedeutung von microRNAs bei neuropsychiatrischen und kardiovaskulären Erkrankungen
(L. Hommers, also Department of Psychiatry and Interdisciplinary Center for Clinical Research)

Comorbidity of cardiovsacular 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.

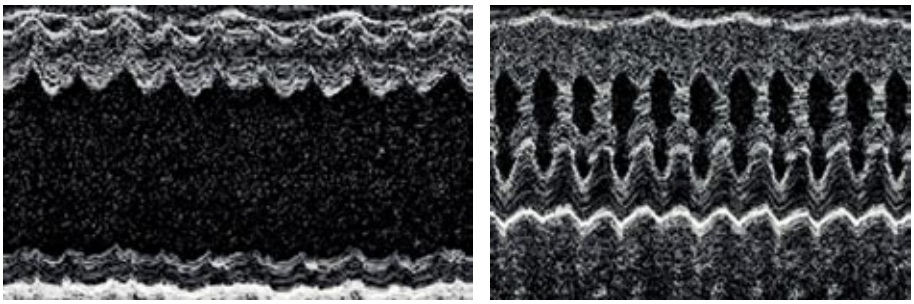

Fig. 3: Gene therapy with the protein RKIP can rescue chronic heart failure. Echocardiograms of mouse hearts with chronic heart failure (left) and after gene therapy (right). From: Schmid et al., Nature Medicine 2015.

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. We also offer the full curriculum for medical doctors specializing in pharmacology.

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Institute of Pharmacology and Toxicology, Chair of Toxicology

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Mission and Structure

The departments of Pharmacology (chaired by Prof.Dr. Martin J. Lohse), 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 50 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

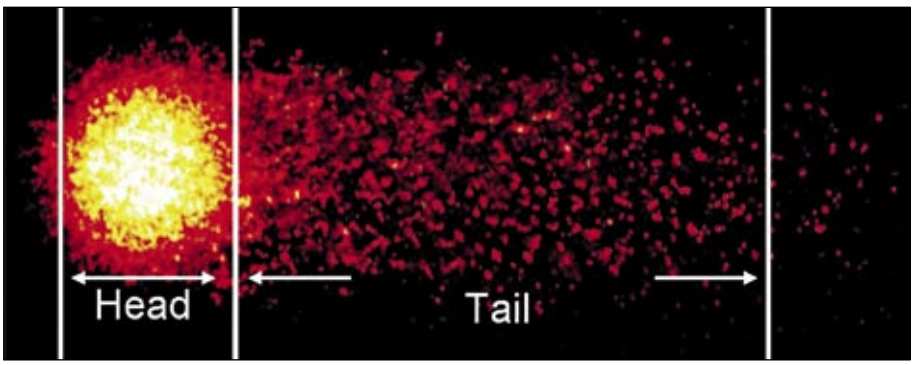

Fig. 1: "The Comet Assay": DNA fragments induced by a genotoxic agent migrate in an electric field out of the cell nucleus (Head) into a Tail.

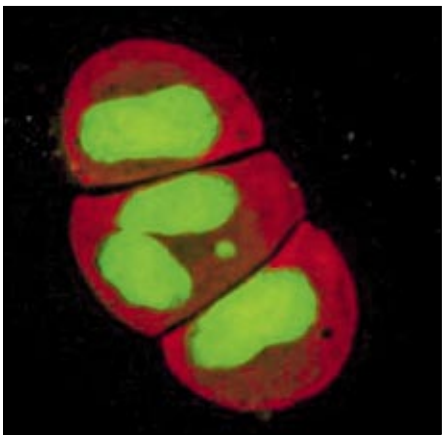

Fig. 2: "The Micronucleus Test": Chromosome damage is indicated by the presence of a DNA-containing fragment in the cytoplasm of the bi-nucleated cell in the middle of the three cells.

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.

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Institute of Virology and Immunobiology, Chair of Immunology

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Mission and Structure

The research groups at the Chair of Immunology study basic questions in immunology such as the mechanisms with which regulatory T-cells and myeloid 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 on tolerance induction by manipulated dendritic 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 Centre 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

Role of the costimulatory receptor CD28 in the control of T-cell responses
(T. Hünig)

CD28 is the key costimulator of T-cell responses: its ligation provides a second essential signal for T-cell activation in addition to antigen recognition by the TCR. Using inducibly CD28-deleting mice and blocking as well as stimulating CD28-specific mAb, we study the contribution of this receptor to the function of the immune system. Of specific interest is the role of CD28 for the homeostasis and function of regulatory T-cells, and its role in the generation and recall of CD8 T-cell memory.

Stimulation of human regulatory T-cells by the CD28 superagonist TGN1412/ TAB08
(T. Hünig)

In animal models, stimulatory CD28-specific mAb had shown therapeutic potential in multiple models of autoimmunity and inflammation. However, a FIH study of the human CD28 superagonist TGN1412 in 2006 resulted in a life-threatening release of proinflammatory cytokines. We have clarified the reasons for the failure of rodent models to predict this problem, and have developed a novel PBMC-based assay system, which will drastically improve the predictive capacity of preclinical tests. Based on these results, clinical development of TGN1412 has been resumed under the name of TAB08 by the company TheraMAB, and after a successful phase I study with healthy volunteers as well as a phase Ib/ IIa with RA patients, is currently being tested in a placebo-controlled phase II study.

Activation of non-conventional T cells: Molecular basis, evolution and therapeutic potential
(T. Herrmann)

Non-conventional T cells, such as iNKT cells or Vγ9Vδ2 T cells build a bridge between innate and adaptive immune system. Their antigen receptors (TCR) recognize often disease associated molecular patterns instead of pathogen-specific antigens. We are interested in the mechanisms underlying this recognition, and in evolution and activation of such cells. With the help of newly generated CD1d oligomers and mutagenesis studies iNKT cells and their TCR have been studied in rat and cotton rat. The analysis revealed a special role of amino acid position 93 and of the HV4 fourth region oft the TCR-α chain for antigen-recogntion. Furthermore parameters affecting in vitro loading of the CD1d molecules of mouse, human, rat and cotton rat were compared and for the first time the CD1d-iNKT cell system of the cotton rat was characterized which serves as model for human virus infections.
The TCR of Vγ9Vδ2 T cells recognize phosphoantigens (metabolites and modulators of isoprenoid synthesis) and so far have been considered as being restricted to primate species. We found now evidence for functional genes of the Vγ9Vδ2 TCR and its interaction partner BTN3A1 in a non-primate species (alpaca). Furthermore, we found that in addition to BTN3A1 other genes on human chromosome 6 were mandatory for phosphoantigen-mediated T-cell activation. Our analysis of the mechanism underlying BTN3A1 mediated Vγ9Vδ2 T cell activation and of the modulation of the mevalonate pathway as strategies of Vγ9Vδ2 T cell based tumor therapies will be continued.

Novel functional aspects of immature dendritic cells for their induction of regulatory T cells
(M. Lutz)

Dendritic cells (DCs) at their immature or resting differentiation state induce T cell anergy. Although T cell anergy is an accepted mechanism of T cell tolerance their long-term maintenance with otherwise passive lack of functions unclear. In another project we could identify that a second stimulation of anergic T cells leads to their conversion into Foxp3- IL-10+ regulatory Tr1 cells. This requires short-term restimulationin during a time-window where both CD28 and CTLA-4 signals can occur. These data indicate that anergic T cells represent a memory cell phenotype of Tr1 cells.

Signals for conversion of monocytes into myeloid-derived suppressor cells (MDSCs)
(M. Lutz)

MDSCs represent bulk immunosuppressive populations of early myeloid cell differentiation stages. Their direct progenitor cells are not known. MDSCs are induced by tumors or mycobacteria (Fig. 1). Our analyses demonstrate that murine and human monocytes can be differentiated into MDSCs in a two-step process. This requires transcriptional and translational modifications through the IRF-1 molecule and the PI3K/AKT/mTOR signaling pathway. These signals are induced by GM-CSF-

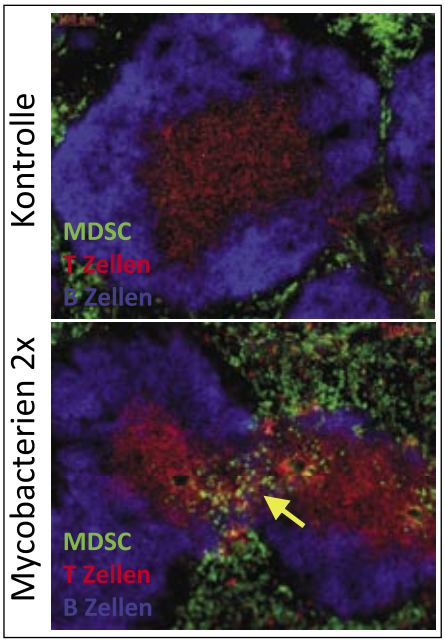

Fig. 1: Infiltration of myeloid-derived suppressor cells (MDSCs) into the splenic T cell areas after mycobacterial challenge of mice. Mice were immunized twice with mycobacteria-containingFreund's adjuvants (CFA) and then stained with markers for MDSCs, T cells and B cells. As compared to the control, MDSCs infiltrate through bridging channels into the T cell areas of the mouse spleen after repeated mycobacteria exposure (yellow arrow) to exert immunosuppression. Foto: Dr. E. Ribechini.

or M-CSF-"licensing", which occurs independent from their functions as growth factors.

B cell maturation
(I. Berberich)

B cells recognize microbes, viruses and foreign substances (antigens) with their B cell and Toll-like receptors (BCR and TLR). After contact with antigens, B cells proliferate and differentiate to antibody-producing "factories" (plasma cells). Proteins like Blimp-1 drive the differentiation. So-called Bcl-2 proteins allow the cells to survive during this process. Currently, we are trying to understand by *in vivo* and *in vitro* experiments how the Bcl-2 protein A1/Bfl1 impacts on the physiology of B cells.

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 Graft-versus-host-disease (GvHD), a major complication after allogeneic bone marrow transplantation. In the GvHD model we discovered that direct functional modulation of so-called conventional T cells efficiently protects mice from GvHD, thus curing them from leukemia.

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

In collaboration with Prof. Dr. S. Frantz and PD Dr. U. Hofmann, Internal Medicine I, the group has recently identified CD4+ regulatory T cells to improve wound healing after myocardial infarction. In 2015, Dr. Johannes Weirather received the Wollheim prize for his contribution to this project. The Wollheim prize is awarded annually for the best dissertation in the medical faculty dealing with cardiovascular medicine.

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

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 protein secreted by *C. albicans* directly to the surface of T cells, which reduced pro-inflammatory cytokine release from the T cells.

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 function of sphingolipids in conventional and Foxp3+regulatory T cells. Here we could show in a mouse model that sphingolipids have a great impact on persistent infection of the central nervous system (CNS) with the measles virus.

Teaching

Various theoretical and practical courses are provided to students. These include basic immunology lectures for medial, 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.

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Institute for Virology and Immunobiology, Chair of Virology

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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 immunevasion, 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.

Major Research Interests

Systems biology of herpes virus infections

(L. Dölken)

Herpesviruses cause a broad spectrum of diseases ranging from the common cold sores to cancer. Upon primary infection, all herpesviruses establish a life-long latent infection. Under certain conditions, such as immunosuppression, they can reactivate and cause life-threatening disease. We study how various human and murine herpesviruses reprogram their host cells and escape the immune system. We employ a broad spectrum of high-throughput technologies to identify new regulatory mechanisms and detail their complex interactions. In particular, we are interested in regulation at RNA level, e.g. by small and large non-coding RNAs, uORFs and alterations in RNA processing, which provide interesting targets for new antiviral drugs. We reported that Herpes Simplex Virus 1 (HSV-1) disrupts transcription termination of most, but not all cellular genes (Fig. 1). This results in continuous transcriptional activity for tens-of-thousands of nucleotides beyond poly(A)-sites and into downstream genes. This explains why hundreds of cellular genes, seemingly induced transcriptionally, are not translated. In contrast to textbook knowledge, we show that HSV-1 does not globally inhibit mRNA splicing but triggers unusual splicing events particularly in genes, which suffer from poly(A) read-through. Recently, similar processes have also been observed in cellular stress responses and cancer. We are working on the underlying molecular mechanisms.

Viral T cell suppression

(S. Schneider-Schaulies)

Suppression of T cell activation is a highly potent viral strategy to avoid immune control. The research group focuses on viral interference with the ability of dendritic cells (DCs) to activate T cells. We found that interaction with glycoproteins of human endogenous retroviruses or measles virus (MV) infection prevented the recruitment of T cells into activatory conjugates by DCs. Secondly, T cell activation may be prevented upon acquisition of infectious MV, which is enhanced by formation of transmission structures. So far only investigated in 2D co-cultures, a novel research focus within the group addresses dynamics and efficiency of MV transmission 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. Alterations of membrane lipids by sphingomyelin converting enzymes play an important role in this process. As part of a research unit (‚Sphingolipid dynamics in infection control' FOR2123) the group focusses on the role of sphingomyelinases in both physiological T cell activation and effectors of MV-induced T cell suppression. We found that genetic ablation of the neutral sphingomyelinase (NSM) conferred hyper-responsiveness to T cells. Enforced and sustained NSM activation induced by MV was required for sustained T cell suppression. Molecular targets of NSM-catalysed membrane restructuring are currently being identified using functionalized sphingolipids in bio-orthogonal click reactions (collaboration with J. Seibel, Organic Chemistry, Z01 FOR2123).

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. We established a model of the persistent CNS infection using recombinant measles virus in mice. In cooperation with Dr. Niklas Beyersdorf (Institute of Immunobiology), we employ this model within the research group FOR 2123 to study the role of the sphingolipid metabolism in the immune response. Genetic ablation or pharmacological inhibition of the acid sphingomyelinase (ASM) increases the frequency and activity of regulatory T cells. 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. The sphingolipid metabolism may also be a promising target enabling a directed manipulation of viral replication. 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. Neither antiviral drugs nor a vaccine are available. We combine model systems for RSV with the surrogate in vivo model of the RSV-mouse homolog, the

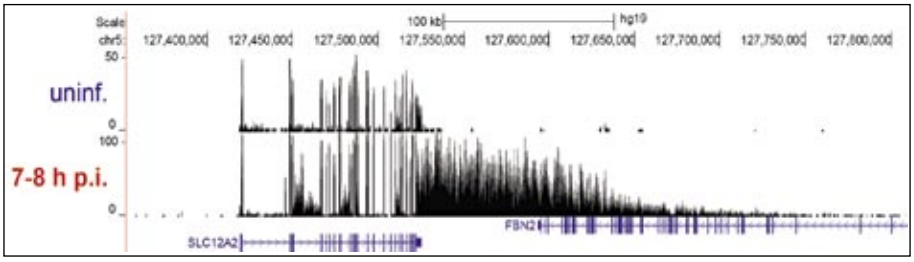

Fig. 1: Herpes simplex virus 1 (HSV-1) disrupts transcription termination of cellular genes. Example of poly(A) read-through arising during HSV-1 infection revealed by RNA-seq analysis of nascent RNA (Rutkowski et al, Nat. Commun. 2015).

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-Sahara 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 prevalence of neuropsychiatric complications is increasing. These so called "HIV-associated neurocognitive disorders" (HAND) occur in various forms in HIV-infected individuals and affect both their quality of life and compliance. We study the role of the neurotransmitter dopamine and the influence of genetic polymorphisms at the dopaminergic synapse on disease progression in patient cohorts in Germany, South Africa and Tanzania. In a randomized controlled trial, we analyse efficacy, safety and tolerability of lithium in the treatment of HAND in HIV-infected patients on antiviral treatment. A particular focus is on the influence of lithium on central and peripheral dopaminergic neurotransmission.

Novel Dengue virus NS2B/NS3 protease inhibitors
(J. Bodem)

Dengue viruses (DENV) are enveloped positive-strand RNA viruses. The number of countries with DENV epidemics has risen from 9 in 1970 to more than 100 in 2015. No specific therapy or vaccine is still available. The DENV NS2B/NS3 protease is a promising target molecule for antiviral drugs. In cooperation with the group of Prof. Tanja Schirmeister (University of Mainz), we identified and optimized diaryl (thio)ethers as novel antiviral agents. The identified substances inhibit viral replication at sub-micromolar concentrations and serve as lead-substances for further drug development.

Determination of the foamy virus protease cleavage site repertoire
(J. Bodem)

In contrast to orthoretroviruses, the foamy virus protease is only active as a protease-reverse transcriptase fusion protein and requires viral RNA for activation. In addition, maturation of foamy viral proteins seems to be restricted to a single cleavage site in Gag and Pol. We provide evidence that unprocessed Gag is required for optimal infectivity. The RNase H domain of the reverse transcriptase appears to be involved in the stabilization of the protease dimer, while the reverse transcriptase domain is essential for RNA dependent protease activation.

Clinical Virology
(B. Weißbrich, J. Schubert, C. Prifert)

The clinical diagnostic unit of the Institute provides the virological diagnostics for the University Hospital of Würzburg. Every year, approximately 40,000 samples are processed and analysed. A variety of clinical-virological research topics are studied on a collaborative basis, in particular with the Department of Paediatrics focussing on respiratory viruses.

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.

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Institute of Human Genetics

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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 counseling 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 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

(C. R. Müller-Reible)

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 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. Clemens Müller-Reible serves as a member of several European committees on quality assurance in genetic diagnostics.

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 CNVs affect coding regions (genes) as well as non-coding sequences with regulatory function. 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 next generation sequencing 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).

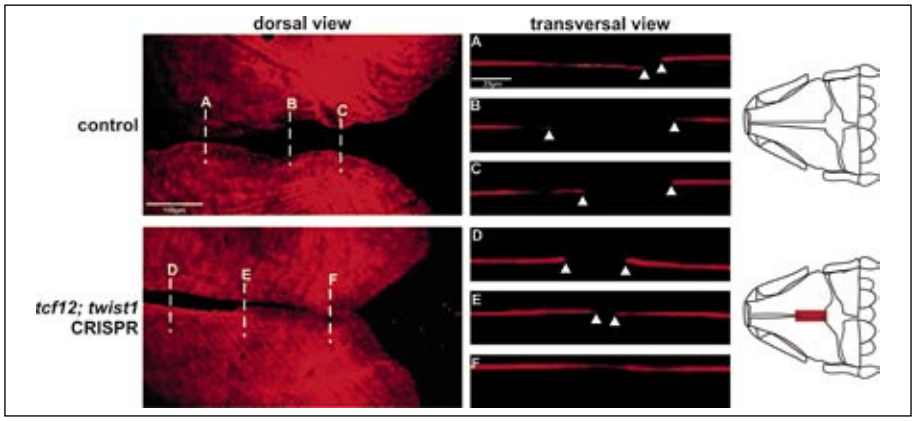

Fig. 1: Combined mutations in tcf12 and twist1a/b genes result in suture fusion and craniosynostosis in zebrafish (right panel: sketch of zebrafish skull). Alizarin red staining of calcified skull tissue.

Somatic cell genetics
(D. Schindler)

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. They include, among others, the Fanconi anemia (FA) family of genes. Recently, the group participated in the identification and characterization of seven novel of these FA genes (*FANCI, FANCJ*, *FANCN*, *FANCO*, *FANCP, FANCQ* and *FANCT*). As a partner of *BRCA2*, one of the high-penetrance breast and ovarian cancer genes, biallelic mutations in *FANCN/PALB2* play a significant role in the emergence of embryonic or developmental types of tumors. Monoallelic mutations of *FANCN*, but also of *FANCJ* or *FANCO* predispose for breast and ovarian cancer. Collaborating with groups from Germany and abroad, the Schindler laboratory has made major contributions to cell genetic and cellular aspects of FA and other caretaker gene syndromes. The group investigates protein complexes (MRN complex, FA core complex, and histone-fold complex) and pathways (FA/BRC pathway for genomic maintenance, non-homologous end joining and homologous recombination repair) in which caretaker genes exert their roles. Current efforts are directed at identifying new members of the genomic maintenance gene networks, elucidating their function, and studying their phenotypic effects.

Cytogenetics
(M. Schmid)

Using classical and molecular cytogenetic methods, this group studies the structure, evolution and pathology of chromosomes. Comparative cytogenetic analyses of fish, amphibians, reptiles, birds and mammals (including the human species) disclose the understanding of the chromosomal mechanisms of vertebrate evolution. Prof. Schmid serves as Editor of the journals *Cytogenetic and Genome Research*, *Sexual Development* and *Molecular Syndromology*, and the book series *Genome Dynamics* and *Monographs in Human Genetics*).

Epigenetics
(T. Haaf)

Epigenetic information is not encoded by the DNA sequence itself but by reversible modifications of DNA (methylation of CpG dinucleotides) and/or histones. In mammals, the paternal and maternal genomes undergo parent-specific methylation reprogramming in the germ line and early embryogenesis (Fig. 2). Stochastic and/or environmentally induced errors (epimutations) in this highly coordinated process may contribute to human disease. The group analyze 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 diseases later in life. In addition, we analyse the effects of paternal factor, in particular age and body mass index on the sperm epigenome and the resultant 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.

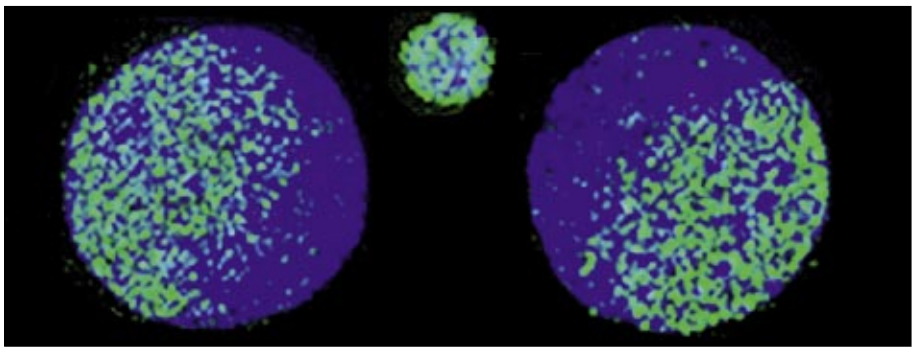

Fig. 2: Methylcytosine staining of mouse two-cell embryo. The already demethylated maternal genome (blue DAPI staining) and the not yet demethylated maternal genome (green anti-MeC immunofluoresescence) are spatially separated, occupying opposing nuclear territories. The second polar body which is still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

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.

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Department of Anaesthesia and Critical Care

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Mission and Structure

The Department of Anaesthesiology annually performs anaesthesia for approximately 31.000 surgery (König-Ludwig-Haus). The outpatient and daycare pain centre of the outpatient department of Anaesthesiology have each more than 9.000 patient contacts per year of patients suffering from acute and chronic pain.
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 all state of the art support for various 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
a
b
c
The department further consists of a section for trauma and emergency medicine which is responsible for clinical education as well as research in this field of medicine. Doctors of the department staff the Intensiv-Transport-Wagen (ITW) and the Verlegungseinsatzfahrzeug (VEF) for the interhospital transfer of intensive care patients.
The department further provides a modern simulation centre 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 which might occur quickly and be life-threatening during anaesthesia. 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)

The major aim of the research is the improvement of care for patients with acute and chronic pain. One approach aims to enhance drug transport across the perineural barrier of peripheral nerves. This involves the elucidation of the molecular mechanisms regulating the permeability of the barrier. Novel therapeutic strategies for the selective and temporary opening of the barrier are being developed (e.g. molecules interfering with barrier forming tight junction molecules and agonsists for regulatory receptors [LRP-1]). In a further approach novel pronociceptive mediators (e.g. oxydized phospholipids) are being characterized. Novel strategies aim to selectively target these mediators and thereby decrease pain at the site of inflammation. As part of a research grant of the European Union individual risk factors (e.g. miRNAs) for the development of neuropathic pain syndromes are being evaluated in clinical and animal studies.

Clinical Trials & Evidence Based 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 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.

Organ protection
(C. Lotz, J. Stumpner)

Ischemia-reperfusion injury occurs in multiple patients and scenarios. Clinicians face this issue during emergencies like cardiac arrest and surgical procedures. Perioperative protective strategies, e.g. ischemic and volatile anesthetic-induced pre- and postconditioning are powerful strategies and of enormous interest to facilitate best medical care for our patients. Eliciting the underlying mechanisms of protection and its interaction of concomitant diseases and medical therapy are the focus of our research.

Acute respiratory distress syndrome
(R. Muellenbach)

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

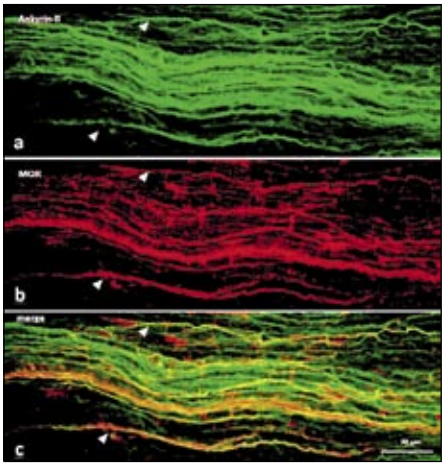

Fig. 1: Opioid receptors in peripheral nerves (longitudinal section): (A) ankyrin B (green): a marker for sensory nerves (B) μ-opioid receptors (MOR, red) as a target for pain therapy in regional anesthesia (C) Arrow: MOR-expressing nociceptive fibers (cooperation with the Institute of Anatomy).

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.

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.

Microcirculation
(C. Wunder)

The term microcirculation denotes the blood-flow in the smallest vessels and capillaries. The perpetuation of the microcirculation in the different organs is fundamental for the function and metabolism of the different cell populations. The patho-physiological coherences of the microcirculatory disturbances and the underlying changes in the vascular endothelial cells in the liver and the intestine during systemic inflammatory states and shock are the aim of the investigated projects. The organ failure of the liver and / or the intestine is associated with a high mortality. By means of small animal models, in-vitro cell culture experiments and clinical studies, the underlying mechanisms of microcirculatory failure in the liver and intestine and the potential therapeutic interference are investigated.

Emergency Medicine
(T. Wurmb)

Emergency Medicine research focuses on the development and evaluation of cognitive aids to facilitate emergency management. Other important research projects are the impact of automated external defibrillators on cardio-pulmonary resuscitation (CPR), the simulation and training of CPR and the development of algorithms and standard operating procedures to provide optimal treatment for multiple trauma paients.

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.

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

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Mission and Structure

The Department of General, Visceral, Vascular and Pediatric Surgery offers excellent services for the whole spectrum of general and visceral surgery, as well as liver transplantation. There are three special units for vascular, pediatric, and transplantation and hepatobiliary surgery. The department has 132 beds, including a surgical Intensive Care Unit and an Intermediate Care-Station. Six thousand surgical procedures are performed every year. The department provides consultations for many specialties of surgery.
Surgery I is an intrinsic part of the Comprehensive Cancer Center Mainfranken, supported by German Cancer Aid (Deutsche Krebshilfe e.V.). The department is also the main treatment partner of this leading oncological center, which is certified by the German Cancer Society (DKG). The Competence Center for Peritoneal Carcinosis is 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 standard therapy for 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 findings of science and research.
The Thyroid Center Wuerzburg is especially skilled in the surgical treatment of endocrine diseases. It is a certified reference center for endocrine surgery.
The Center for Obesity Medicine offers different surgical solutions for permanent 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 in a flourishing research network. Successful third party funding (DFG, BMBF), patents, prizes, awards, and scholarships complement the project achievements. Further information is available on our website (www.zom-wuerzburg.de).

Clinical Studies

(U. Dietz, M. Gasser, J. Lock, T. Meyer, A.M. Waaga-Gasser)

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 studies (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). Currently a study is being done on the downregulation of inflammation parameters in chronic pain patients (Frau Prof. A.M. Waaga-Gasser).

Inflammation and Sepsis

(N. Schlegel, N. Burkhard, S. Flemming, M. Meir)

The pathophysiology of the microcirculation and microvascular endothelium barrier is being investigated in acute and chronic inflammation such as sepsis and inflammatory bowel diseases. The DFG is currently funding two projects that examine the clinical value of a potential early marker for disturbances of the microvascular endothelium barrier and the role of desmosome adhesions in damaged bowel barriers in patients with M. Crohn.

Molecular Aneurysm Pathology

(A. Busch, C. Otto, R. Kellersmann, U. Lorenz)

The most important aneurysm entities in the arterial vascular system are the abdominal

aorta aneurysm and the popliteal venous aneurysm. The operating material receives a "molecular fingerprint" to help investigate the pathogenesis. Cell and molecular changes in the vascular walls are being examined in established animal models for aneurysm formation. The focus is on the role of microRNAs in the disease process and the possibilities of influencing them directly. (supported by the IZKF and DFG).

Oncology
(A. Wiegering, C. Otto, N. Matthes, A.M. Waaga-Gasser)

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 the microbiota, the intestinal glucose transporter SGLT1 (in cooperation with Prof. Dr. H. Koepsell), metabolomic changes and their effects on oxidative stress and tumor development. Another main interest is examining neuroendocrine mechanisms of appetite regulation. The DFG is currently funding a research network of national and international cooperations.

Tissue Engineering
(U. Dietz, T. Meyer)

Biocompatible materials are being tested to determine their suitability for treating large congenital defects of the abdominal wall. The degradation and biocompatibility of explanted hernia nets is being examined. Close cooperations exist with the Chair for Tissue Engineering and Regenerative Medicine (Prof. Dr. H. Walles) and the Department of Functional Materials in Medicine and Dentistry (Prof. Dr. J. Groll), both University of Würzburg.

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 Centre (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.

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Department of Trauma, Hand, Plastic and Reconstructive Surgery

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Mission and Structure

In the Department of Trauma, Hand, Plastic and Reconstructive Surgery, 22 medical doctors are employed. For the treatment of patients, 52 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 modern shock room 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 centre, 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.
The experimental research was further intensified over the last two years.

Bone Fracture Healing and Muscle Regeneration

(R. Meffert, S. Frey)

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 well-established factors, such as $VEGF_{165}$. Furthermore, in collaboration with N. Schütze, Orthopedics, applying CYR61 also resulted in distinct improvement of bone regeneration. Currently, the set-up of the rabbit model for investigating the restoration of muscle force is transferred to a mouse model.

Biomechanics in Traumatology

(S. Doht, M. Jordan, R. Meffert)

Different fracture models (tibial plateau, ankle joint, hand a.o.) were established for biomechanical studies of locking plates and bone substitutes. Furthermore, different suture techniques for tendon repair were evaluated. In an IZKF-funded project, a new fracture model was established in synthetic bones for tibial head depression fractures. With this model, different stabilization techniques for these fractures were analyzed biomechanically. Conclusions from the results could be drawn with regard to clinical practice and the best operative technique, respectively. On the one hand, different osteosyntheses, screws, and a plate in combination with screws, were compared with each other. On the other hand, established bone substitutes (calcium phosphate cements) were analyzed concerning their handling for filling a bone defect and their bonding with the spongiosa, which had a relevant influence on the stability under loading.

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.

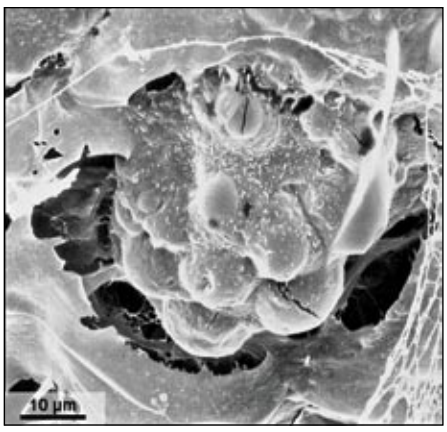

Fig. 1: Differentiating adipocyte in 3D cell culture (scanning electron microscopy).

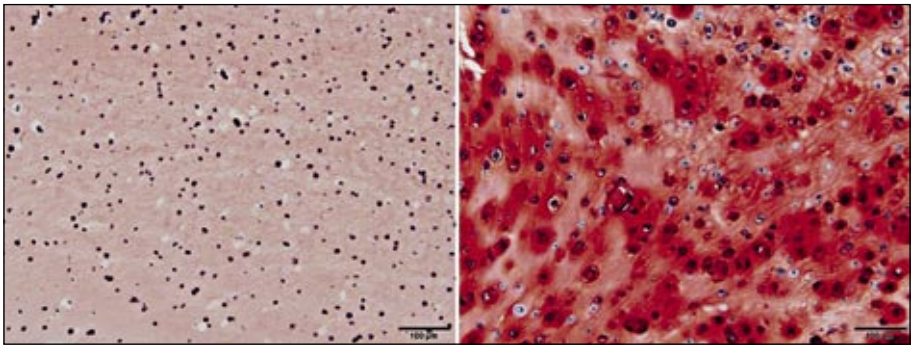

Fig. 2: Chondrogenic differentiation of bone marrow-derived mesenchymal stem cells in newly developed 3D hyaluronic acid- and polyglycidol-based hydrogels. Left: without TGF-β1, right: with covalently bound TGF-β1 within the hydrogels. Safranin-O staining (red) for glycosaminoglycans after 3 weeks in culture shows chondrogenic differentiation only in TGF-β1-loaded hydrogels. (Collaboration with J. Groll, Department for Functional Materials in Medicine and Dentistry).

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. A main focus is the development of vascularization strategies for adipose tissue constructs, which was investigated within a research consortium funded by the Bavarian Research Foundation (Speaker: T. Blunk). For the first time, it was demonstrated that the stromal-vascular fraction (SVF) from adipose tissue can be successfully employed for adipose engineering. In a further project within the consortium FORMOsA (Bavarian Research Foundation), a 3D adipose tissue construct, partially made from genetically modified stem cells, is under development that can serve as a biodelivery device (collaboration with H. Walles and F. Jakob). Moreover, 2D and 3D adipose tissue models for basic research were 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.

Cartilage Regeneration
(T. Blunk)

Another focus is the tissue engineering of cartilage. Bone marrow-derived stem cells and chondrocytes 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. Novel hydrogel systems are explored, e.g., providing the possibility of covalently binding chondrogenic peptides and growth factors. Within the EU-funded consortium HydroZONES, integration of cartilage is investigated biomechanically and in cell culture. Besides fundamental studies, innovative materials (collaboration with J. Groll) to improve cartilage integration are examined.

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.

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Department of Thoracic and Cardiovascular Surgery

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Professor Dr. med. Thorsten Walles
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Mission and Structure

The department of Thoracic and Cardiovascular Surgery is a 58-bed department with 3 operating theaters and its own 12 bed intensive care unit. A new 8-bed intermediate care unit will go into operation in the summer. At present 26 physicians are employed.
Approximately 2100 procedures are performed annually covering the entire field of adult heart and thoracic surgery. 1170 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 transplant and VAD patients and for patients requiring aortic surgery. In addition there is a tumour outpatient clinic for thoracic tumours.
Within a radius of 100 kms we represent 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 new techniques for the treatment of sternal deformities like pectus excatavum. We regularly perform extended thoracic procedures like tracheal resections utilizing the heart-lung-machine.
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.

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).

Secondary sclerosing cholangitis (SSC) in cardiac surgical patients

Incidence and outcome of SSC in cardiac surgical patients are not characterized. All patients affected are evaluated (Dr. Schade, Prof. Aleksic). The manuscript is under review.

COMT study

The catechol-O-methyltransferase (COMT) represents the key enzyme in catecholamine degradation. Recent studies indicate that a Val108/158Met polymorphism of COMT is common, resulting in three phenotypes of different enzyme activity: There is growing evidence, that in particular in the COMT-LL phenotype, the risk of vasodilatory shock, acute kidney injury and ICU- and in-hospital stay are dramatically increased. The aim is to investigate the prevalence of the described phenotypes of COMT activity and their impact on cardiac and renal endpoints in patients undergoing cardiac surgery. The study is conducted in close cooperation with the Institute for Clinical Epidemiology and Biometrics and the Comprehensive Heart Failure Center (Dr. Oezkur, Dr. Wagner, Prof. Heuschmann, Prof. Störk).

IROCS

Studies describing surgical determinants for rehospitalisation for patients undergoing cardiac surgery are lacking. The proposed cohort study aims to investigate the cumulative rate of rehospitalisation and mortality one year after cardiac surgery focusing on surgical determinants in three different hospitals (University Hospital Würzburg, University Hospital Nürnberg, University Hospital München). As a major secondary study aim, changes in cardiac function early in-hospital and one-year after surgery will be described in patients undergoing cardiac surgery at the University Hospital Würzburg.
The main area of interest are surgical factors of cardiopulmonary bypass (temperature of cardioplegia, body perfusion temperature and cardiopulmonary bypass time). Their association with outcome will be analysed considering patient-related factors and structural factors of the treating hospitals
At all study time-points, standardized CRFs will be used as well as study procedures according to SOPs. Furthermore, during the in-hospital stay, parameters of clinical routine will be used for study specific purposes according to standards developed within the CHFC (Data Warehouse)

Skinned fibers

The use of skinned human fibers from the right or left auricle is an established experimental approach to investigate contractility and calciumsensitivity of myofilaments in human tissue. Direct investigation of the contractile apparatus is possible by withdrawal of all membrane-dependent processes and receptors due to the skinning process. Important insights have been gained concerning changes of calciumsensitivity in different diseases, like volume overload in mitral regurgitation or pressure overload in aortic valve stenosis (Cummins 1982, Wankerl 1990).
The tissue can be harvested in the operation room before implementation of extracorporal circulation by resecting the right auricle for venous cannulation. This offers the possibility to examine the impact of gender or diabetes on human contractile capacity and many other research questions (Schwertz 1999).
Currently we investigate::
1. gender specific differences in cardiac contractility (pCa/Force curve)
2. activity and localisation of enzymes, associated with diabetic cardiomyopathy (SERCA 2++, ROCK, OGT, OGA)
3. gender specific differences in the appearance/ distribution of estrogen receptors α and β
4. correlation of estrogen receptors and cardiac contractility
5. correlation of estrogen receptors, cardiac contractlity and clinical characteristics of pts

Tissue engineering

Left ventricular contractile function can be severely impaired by non-contractile scar tissue formation after myocardial infarction. Tissue engineering offers a promising therapeutic alternative by in vitro generation of autologous replacement tissue. To this end, the Leistner/Walles group ("myocardial tissue engineering", group leaders Dr. M. Leistner, Prof. Dr. H. Walles) drafted a fully vascularized whole wall patch for immediate surgical host integration. Based on a collagen I hydrogel a compressed patch with an imprinted central channel was generated. The latter was seeded with endothelial cells and subjected to a minimum of 7 days of continuous medium perfusion within an individually designed bioreactor system yielding a macroscopic primitive vessel. In addition, the capillarization potential of different cellularizing regimens within the surrounding collagen matrix was evaluated. All cells applied were isolated from human atrial appendages which had been excised during open heart surgery for postoperative thromboembolic prevention after obtaining patients` informed consent.
After sufficient repetition of the above mentioned experiments, a switch to "iPSC (=induced pluripotent stem cells) – derived cells" with near-term integration of parenchymal cells - cardiomyocyte progenitors - shall be evaluated (cooperation: Prof. F. Edenhofer, Institute of Physiology). Experimental data and results have been presented at numerous national and international conferences, 2 major publications are currently in preparation.

Prevention and therapy of deep sternal wound infections (DSWI)

Dr. 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" to be published by the end of 2016. 12 different specialties are involved. The second consensus meeting took place in 2015.
In addition, Dr. Schimmer focusses on clinical studies in the ICU setting and has achieved a significant reduction of perioperative empiric antibiotic therapy.

Thoracic surgery

On January 1st, 2012 Prof. T. Walles took over the newly created W2-position as chairman of the division of thoracic surgery. His research interest is the application of tissue engineering techniques for tracheal replacement and the establishment of VATS-lobectomy. The division is the leading investigational site for the WOPP-study regarding the best management of pneumothorax.

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.

This department is the only one in the state of Bavaria which offers German board certified training in cardiac surgery, cardiac surgical intensive care medicine and thoracic surgery within one department.

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Department of Urology and Paediatric Urology

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Mission and structure

The Department of Urology and Paediatric Urology is a tertiary referral centre 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 surgical roboter 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 perineal, retropubic and robot-assisted prostatectomy (nerve-sparing techniques); 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 and renal transplantationen (cadaver and living related transplantation).

Major Research Interests

Translational Prostate Cancer Research
Treatment of patients with high risk prostate cancer
(B. Kneitz, C. Kalogirou, M. Krebs)

The percentage of patients with high risk prostate cancer (PCa) (≥T2c or PSA >20 ng/ml or Gleason score ≥8) is still significant (2003: 22%). In this group of patients the risk of biochemical progression after radical prostatectomy within a 5-year period is approximately 40%.We evaluate the outcome of surgical techniques in high risk PCa in an European multicenter study.

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 (Figure 1). 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*.

Impact of mismatch repair defects on pathogenesis and prognosis of prostate cancer
(B. Kneitz)

To answer the question which impact mismatch repair (MMR) defects play a role for PCa development we generated novel mouse models based on a prostate specific inactivation of the MMR system using the Cre-LoxP. This model will provide the opportunity to study the molecular and genetic mechanisms of the early development, progression and eventually metastasis of PCa and will allow to functionally explore different therapies *in vivo*.

Identification and description of tumor-suppressor- 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.

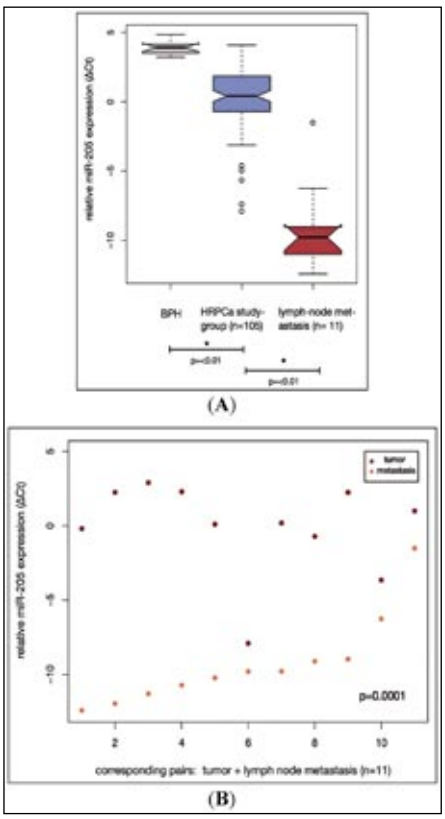

Fig.1: Progressive down-regulation of miR-205 in high-risk-PCa-lymph node metastasis.

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 tumor-suppressor- und onco- microRNAs in progressive non-muscle-invasive urothelial carinomas (NMIBCs)
(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 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.

T-cell mediated therapy in invasive bladder cancer
(M. Wölfl, A. Kocot, C. Kalogirou)

Cancer-testis (CT) antigens, which are expressed in various cancer cells but not in normal cells except germline cells of the testis, have been used as targets for cancer therapy. The aim of our study is to identify and characterize specific CT antigens on invasive urothelial cancer cells. Specific T-cells against these epitopes are isolated from peripheral blood cells of healthy donors and mixed with urothelial (tumor-) stem cells ("killing-assay"). A further aim is a targeted and individualized tumor therapy.

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), emergency medicine, 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.

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Department of Internal Medicine I

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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, Endocrinology has become the international reference centre for adrenal carcinoma and treats more than 150 patients per year.The interdisciplinary team of the integrated obesity centre 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 in arrhythmias and hypertension. 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 ZIM 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 M. Fabry and kidney transplantation in cooperation with the transplantation centre 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.

Pneumology 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 like the Collaborative Research CenterSFB 688 “Mechanisms and imaging of cardiovascular cell-cell interactions”, the Comprehensive Heart Failure Center (CHFC), the Cardiovascular Center, the Interdisciplinary Center for Clinical Research, the Comprehensive Cancer Center, Center for Infectious Research, and the Interdisciplinary Training and Simulation Center (INTUS).

Endocrinology
(M. Fassnacht, S. Hahner)

A major research focus are translational and clinical studies in adrenocortical carcinoma. Since 2003, the German Adrenocortical Carcinoma Registry has been headed by Würzburg and was developed into a European registry. The international first published phase III studies as well as the ADIUVO trial in adrenocortical carcinoma werecoordinated in Würzburg. Together with the Early Clinical Trial Unit we are currently working on the international first phase I trial on adrenal tumours.
A second focus, initiated by Endocrinology together with the Department of Nucle-

Fig. 1: Professor Dr. med. Martin Fassnacht, Head of the Division of Endocrinology.

ar 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 Council (DFG) and the European Union.
Due to our participation in the interdisciplinary obesity centre Würzburg the treatment of massive obesity is another important focus of our daily work and several clinical and preclinical studies are in full swing.
Moreover, several phase II and IIIstudies on adrenocortical insufficiency, thyroid carcinoma, obesity, and on Cushing syndromhyponatremiaas well asother endocrinopathies are in progress.

Cardiology/Angiology
(Coordination: G. Ertl, W. Bauer)

Cardiovascular research is involvedin several research consortia. In 2010, the Comprehensive Heart Failure Center (CHFC) was founded on the basis of the intensive efforts of DIM I. The CHFC initiated a faculty-wide biobank concept supported by the BMBF. Furthermore, cardiology is actively involved in the National Competence Network Heart Failure and the Collaborative Research Center688. In general, research iscentredonmolecular mechanisms, imaging, and treatment of heart failure with *in vitro* and *in vivo* methods.

Basic science projects:
(W. Bauer, T. Pelzer)

The focus is onMRI-Imaging of the heart and cardiac biophysics in rodents and humans. New methods and technologies for blood flow/supply measurements were developed with the purpose of detecting microcirculation failures. By the application of molecular imaging using MR and nuclear medicine procedures, early changes in arteriosclerosis can be identified, resp. in rodents the immune response after myocardial infarction was studied.

Translational projects
(R. Jahns, P. Nordbeck, O. Ritter, S. Störk)

Currently clinically applicable, diagnostic detection methods for activating, cardial receptor antibodies are under construction (BMBF, MolDiag). Long-term goal is the indication for application of therapeutic cyclopeptidesin autoimmune mediated heart failure (BMBF, GoBio, R. Jahns).The first clinical phase IIa trial was prematurely terminated by the enrolled pharmaceutical company. The cyclopeptides impact was neutral in this pilot study, the number of cases too small. Currently a new edition of a phase IIa trial is in preparation. Furthermore, the preclinical lead substance (Calportin) for the treatment of heart failure is in clinical development (VIP, m4 award, BMBF, O. Ritter).
Research focus of the department for rare diseases is presented in translational projects by the investigation of myocardial changes in M. Fabry (P. Nordbeck) and Sarcoidosis (T. Pelzer).

Clinical projects
(Coordination: S. Störk, G. Ertl)

Clinical cohorts exist for rare diseases like M. Fabry and M. Friedreich (P. Nordbeck, C. Wanner). Clinical trialsdeal with MR compatible pace maker leads and electrophysiology catheters (W. Bauer/O. Ritter, first in man application), as well as innovative echocardiographic methods (S. Herrmann).At the Comprehensive Heart Failure Center several studies on diagnoses and prognosis of heart failure are performed, f. ex. the long-term trials of chronic and acute heart insufficiency in theInterdisciplinary Network Heart Failure (INH Study, Acute Heart Failure Registry, C. Angermann/ S. Störk; INH), the role of beta1-autoantibodies in heart failure (ETiCSR. Jahns), the role of FXIII for remodeling after myocard infarct (FXIII Studies, G. Ertl), diagnosis and prognosis of heart failure patients followed by general practicioners(RECODE, S. Störk), prognostic effect of the serotonin reuptake inhibitor escitalopram in patients with heart failure (MOOD-HF,C. Angermann/ G. Ertl), impact of a bariatric treatment in obesity (WAS Trial, M. Fassnacht), role of structural and morphological changes in cerebral structures and cognitive function (COGNITION.MATTERS-HF, G. Stoll, S. Störk).Würzburgmanages the national lead offices of 2 mega-trials: Randomized Evaluation of Anacetrapib through Lipid-modification Study (REVEAL, C. Angermann, G. Ertl, C. Wanner, 30.000 subjects);Cardiovascular OutcoMes for People using AnticoagualtionStrategieS-Studie (COMPASS, G. Ertl/ S. Störk, 21,000 subjects), Recombinant human RELAXin-2 for treatment of acute Heart Failure – European Union Study (RELAX-AHF-EU, C. Angermann, G. Ertl, 2700 patients). Und die International Registry to assess medical Practice with lOngitudinal observation for Treatment of Heart Failure (REPORT-HF, C. Angermann, G. Ertl, 20.000 patients). The STAAB trial (P. Heuschmann, S. Störk) is a prospective study with 5.000 Würzburg citizens investigating initial and progression factors of heart failure.
In cooperation with the institute of diagnostic radiology (Prof. Dr. T. Bley) clinical and experimental studies on cardio-CTs are performed. Another clinical focus is on the development and validation of virtual-reality si-

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Weirather J, Hofmann U, Beyersdorf N, Ramos GC, Vogel B, Frey A, Ertl G, Kerkau T, Frantz S. (2014) Foxp3+CD4+ T Cells Improve Healing after Myocardial Infarction by Mod-ulating Monocyte/Macrophage Differentiation. Circ Res 115:55-67.

mulations for the training of interventional procedures. Furthermore, the virtual-reality simulation is used to evaluate new imaging techniques in the interventional cardiology (W. Voelker).

Nephrology
(C. Drechsler, V. Krane, D. Kraus, R. Schneider, 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). 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. 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, f.ex. 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 pneumonologyunit 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)

In the area of internal intensive medicine we study in a monocentric, randomized pilot trial the effects of a special combination of dialysis filters in sepsis patients, treated with continousveno-venous hemodiafiltration. Another registry study recruits patients with symptomatic hyponatremia with the purpose to create an improved data basis for developing new treatment strategies for patients.
In the area of internal emergency care we cooperate with the CHFC in recruiting patients for the “Acute Heart Failure Registry (S. Stoerk, C. Angermann) and for two pharmaceutical studies, which evaluate the effects of Serelaxin in acute decompensated heart failure. Another registry study collects data on the effectiveness of Vernakalant in emerging atrial fibrillation. Smaller research projects focus the measurment of haemodynamic parameters in patients with ventricular assist systems.

Fig. 2: Professor Dr. med. Christopf Wanner, Head of the Division of Nephrology.

Teaching

About 650 undergraduate clinical students participate in courses ofthe 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 Medicineis 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).

Department of Internal Medicine II

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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 Centre for Internal Medicine (Zentrum Innere Medizin, ZIM) and provide state-of-the-art infrastructure and environment 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.

A completely new **Stem Cell Transplantation Unit (PD Dr. G. Grigoleit, Prof. Dr. S. Mielke)** 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 11.000 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, PNET center and gastric and pancreatic carcinoma). Since 2007 a "Darmzentrum" is established including an unit for pancreatic carcinoma.

In 2012 the **Division of Hepatology (Prof. Dr. A. Geier)** has been newly established to strengthen the treatment of liver disorders including a liver transplant program (15 transplants in 2015 - specialized inpatient and outpatient facilities). The clinical focuses are metabolic liver disorders, viral hepatitis B and C as well as malignant tumors of the liver including. For non-alcoholic fatty liver disease a national clinical research network program is coordinated by our center. A functional liver testing unit has been established.

In the **Division of Clinical Immunology/ Rheumatology (Prof. Dr. H.-P. Tony, Dr. M. Schmalzing)**, patients with vasculitis and specific forms of rheumatoid arthritis, scleroderma and sjögren's syndrome are cared for. In the specific ward of the division and its outpatient clinics more than 3.000 patients per year are cared for. Specific expertise of the division are the diagnosis and treatment of autoimmune disorders including novel therapeutic interventions in the frame of phase I-III studies, diagnostic and treatment of arthritis and tissue disease.

A **Division of Infectiology (Prof. Dr. A. Ullmann, Prof. Dr. H. Klinker)** was certified 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. The clinical focuses of the division are HIV-infections and chronic virus hepatitis, opportunistic infections in immunocompromised, esp hematological patients.

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 are the care of patients undergoing stem cell transplantation.

Interdisciplinary projects

The co-chair of the TR/CRC124 FungiNet (H.Einsele) and the speaker and the chair of the Clinical Research Unit 216 "Oncogenic

Signalling in Multiple Myeloma" are members of the department of Internal Medicine II (H. Einsele, R. Bargou). H. Einsele is also the speaker of the EU-funded network FP7 T-Control and AspBioMICS. 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
(H. Einsele, R. Bargou, M. Topp, S. Knop, T. Bumm, M. Hudecek, U. Grigoleit, S. Mielke, V. Kunzmann)

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. H. Einsele is the speaker, R. Bargou the chair of the clinical research group (CRU) 216 "Oncogeneic signaling in multiple myeloma". 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. In addition a large EU-sponsored FP7 consortium (Optatio) has been initiated in which novel animal models and biomarkers are developed for MM (H. Einsele, co-chair). 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 (U. Grigoleit) and José Carreras and Sander Foundation (S. Mielke, 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 (R. Bargou, A. Beilhack, T. Bumm, M. L. Rasche, 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.

Research in Gastroenterology
(M. Scheurlen, W. Burghardt, S. Reimer)

With the support of the IZKF and BMBF a tumor 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 consortium FOR 2314 Würzburg-Tübingen novel strategies in cancer therapy are pursued, particularly for pancreatic cancer (A. Beilhack).

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

Clinical research projects in Hepatology (A. Geier, T. Kudlich, O. Götze, J. Schmitt, M. Rau, D. Jahn), address the pathophysiology and treatment of chronic liver disorders, specifically metabolic liver disorders, viral hepatitis B and C as well as liver cancer including prospective cohort studies for non-alcoholic fatty liver disease, hepatitis C and liver cancer. A translational research project on intratumoral drug-uptake has been established within the international *TRANSFER* study group. A clinical RCT phase II trial on vitamin D treatment for steatohepatitis is ongoing. Additional research projects address: role of the microbiome, enterohepatic signalling and hepatic micro-RNAs in the pathophysiology of human fatty liver disease, therapeutic anti-cytokine strategies in murine models. Projects in the field of viral hepatitis C address genetic markers and metabolic host factors of disease progression and therapy response, especially the role of bile acids. Funding is received from the Swiss National Foundation (SNF), the Center for Integrative Human Physiology (ZIHP) of Zürich University, the Velux Foundation, and the Wilhelm Sander Foundation.

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, cardiovascular comorbidity in patients with rheumatoid arthritis, the development of biomarkers for monitoring of treatment of autoimmune disorders and the pathological immunological regulation in systemic sclerosis.

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 performedin 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 (A. Ullmann, W. Heinz). 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, EU NANOII, EraNet PathoGenoMICs – AspBioMICS and the new established SFB/TR124. 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 497 users and > 15.000 included cases is extremely accepted.

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Division of Molecular Internal Medicine

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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 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 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 Pro-

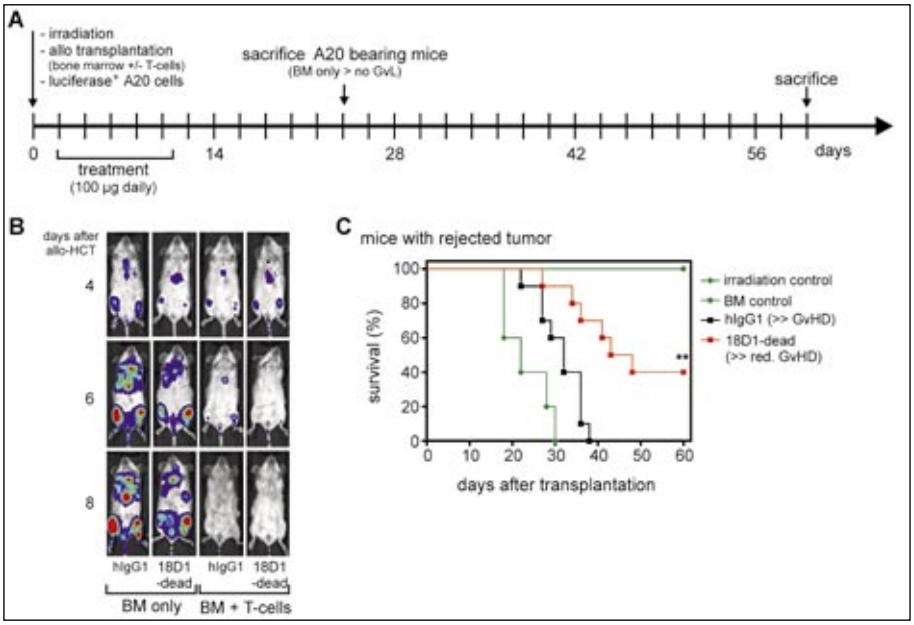

Fig. 1: The blocking, ADCC-defective Fn14-specific antibody variant 18D1 inhibits graft versus host disease (GvHD) without interference with the graft versus leukemia (GvL)-effect. (A) Mice were lethally irradiated and reconstituted with allogeneic bone marrow cells with (GvHD and GvL) or without (control; 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).

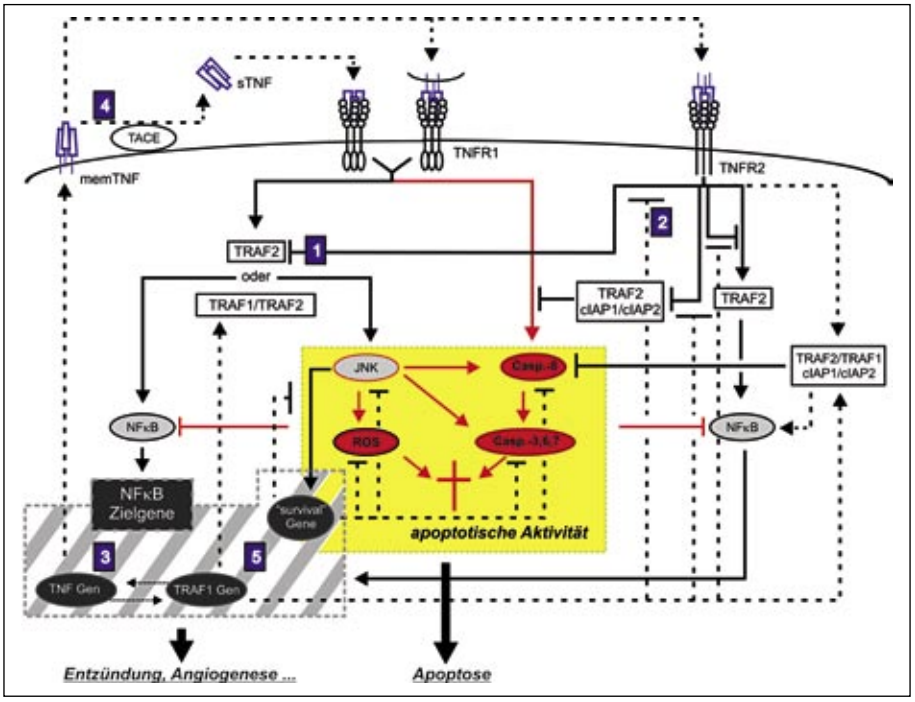

Fig. 2: TNFR1 and TNFR2 are functionally linked in a highly complex manner. Activation of TNFR2 by transmembrane TNF leads to degradation of the adapter protein TRAF2 (1). Because this protein is important for TNFR1-induced activation of the pro-inflammatory transcription factor NF-kappaB and recruitment of anti-apoptotic cIAP proteins into the TNFR1 signaling complex, cells are sensitized toward TNFR1-mediated cell death. Stimulation of TNFR1 by soluble TNF can induce NF-kappaB-dependent expression of endogenous TNF (3,4). In its membrane-bound form, it activates TNFR2 and sensitizes cells again for TNFR1-induced apoptosis, as described above. Another NF-kappaB target gene is TRAF1 (5). TRAF1 forms heteromeric complexes with TRAF2 and prevents its degradation by TNFR2 (2). TRAF1 antagonizes therefore TNFR2-mediated enhancement of TNFR1-induced apoptosis. Further, TRAF1 does also enhance TNFR2-induced non-apoptotic signal transduction, which contributes both to induction of TRAF1 and transmembrane TNF.

teins 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. In tumor cells which are resistant to apoptosis due to mechanisms acting downstream of caspase-8 activation, this group identified various substrates of caspase-8 that become cleaved under these non-apoptotic conditions. The main activities of this group are therefore currently focused on the evauation of the relevance of processing of caspase-8 substrates for the pro-tumoral activities of death receptors.

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 (Fig. 2). 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 these crosstalk mechanisms for tumor metastasis.

Teaching

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

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Institute of Transfusion Medicine and Haemotherapy

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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
- a department for therapeutical apheresis
- 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 or 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.

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 difficult patients”
- Lecture “Production of blood components”
- Lecture “Biology and function of red cells”
- Lecture “Transfusion therapy with and without red cells”
- 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”

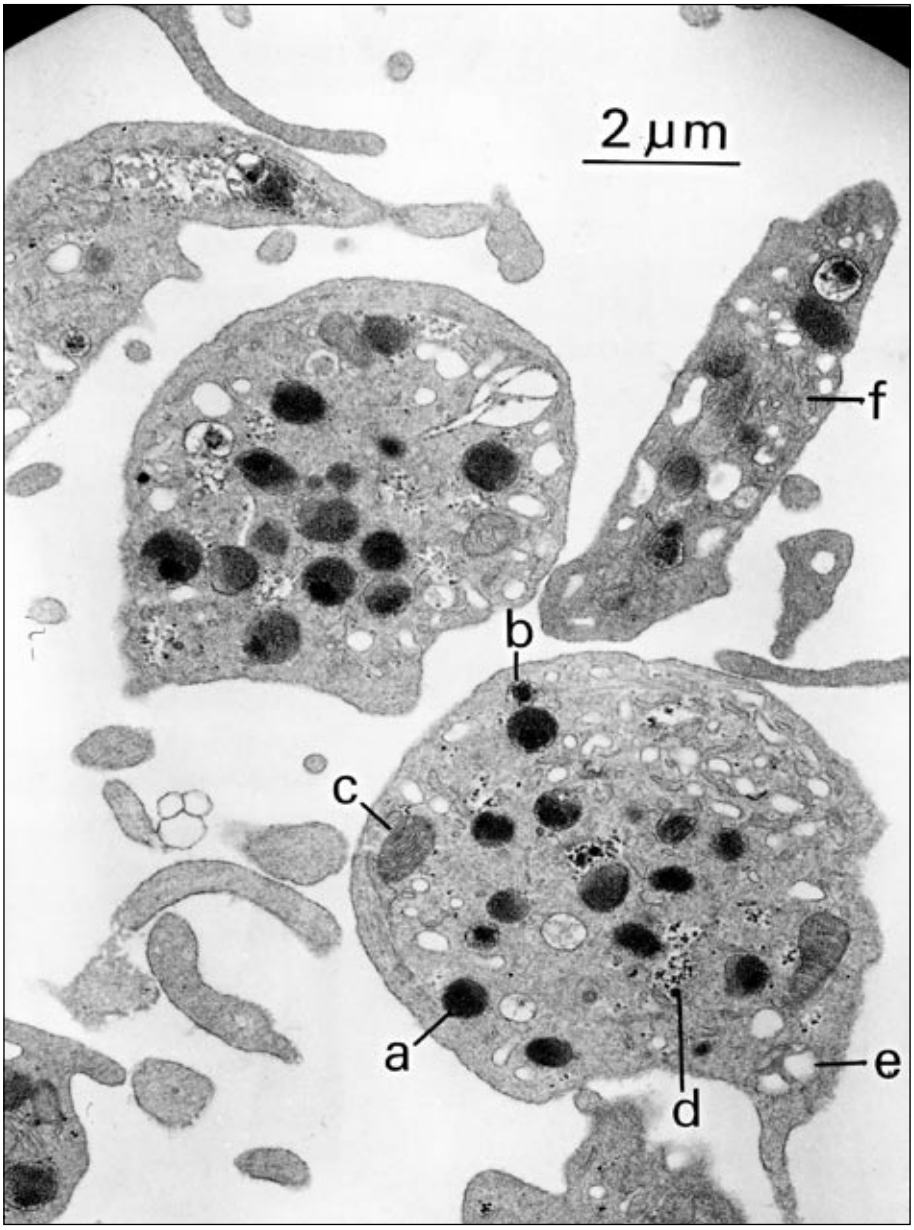

Fig. 1: Electron-microscopic image of platelets from a stored platelet concentrate.

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Department of Diagnostic and Interventional Radiology

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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. 34 physicians and eight scientists as well as 45 technicians work together to ensure state-of-the-art diagnostics and interventional radiology.
Four MRI systems (2 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 25.800 patients annually. Sonography is performed on roughly 12.300 patients per year with five machines. To rule out breast cancer 6000 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

Interventional Radiology
(R. Kickuth, A. Dierks, N. Hassold, A. Sauer)

The effectiveness and clinical outcome of covered stent implantation for bleeding complications after pancreatic surgery are being evaluated. A further main topic of research is the periprocedural measurement of blood flows after percutaneous aortic fenestration of aortic dissection membranes for patients showing malperfusion syndromes. In order to optimize postinterventional hemostasis after utilization of large caliber introducer systems (6 – 8 French) effectiveness and clinical outcome of patches with bioactive surfaces are evaluated.

Novel MR Methods
(H. Köstler, A. Dierks, H. Neubauer, T. Klink, A. Sauer, S. Veldhoen, F. Hilbert, F. Ratz, A. Slawig, J. Tran-Gia, T. Wech, A. Weng)

New methods are being developed to accelerate MRI for real time imaging of the human lungs, of the human heart and of dynamic defecation. Fast mapping of relaxation parameters and artifact reduction for balanced steady state free precession imaging are additional topics. For these projects we apply techniques with non-Cartesian data acquisition and reconstructions with parallel imaging and compressed sensing.

Cardiovascular Imaging
(Th. Bley, H. Köstler, J. Donhauser, N. Hassold, S. Herz, Gassenmaier, J. Kunz, B. Petritsch, T. Wech, A. Weng, A. Kosmala, N. Konasin, A. Kunz, I. Distelmaier, T. Klink)

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. Techniques for displaying myocardial hemorrhage and for quantifying myocardial perfusion are specifically investigated. Furthermore, sodium content of skeletal muscle and myocardium is quantified in patients suffering from hyperaldosteronism using high-field sodium MR imaging. 1H-spectroscopies are performed for detecting fatty infiltration within the myocardium and the liver as negative prognostic parameters. Diffuse myocardial fibrosis is assessed and quantified in patients with different cardiomyopathies using T1-mapping. Another research project aims to improve the MR diagnosis of giant cell arteritis. 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. Furthermore, the value of computed tomography for planning Transarterial Aortic Valve Implantation (TAVI) and surgical techniques are investigated. Hemodynamic changes within the aorta after aortic valve replacement are assessed using 4D flow MR imaging. Physiologic and pathophysiologic flow within the heart is investigated before and after cardiac surgery and in patients with congenital heart disease.

Pediatric Radiology
(Th. Bley, H. Köstler, A. Kunz, H. Neubauer, T. Pabst, A. Sauer, S. Veldhoen, A. Weng, C. Wirth)

Interdisciplinary projects study whole body MR techniques including diffusion weighted imaging in inflammatory and oncological diseases. Ultrasound-based tissue elastography is employed and studied with diseases of the thyroid gland and liver. A clinical main topic are MRI-techniques with expedited data acquisition for contrast-enhanced T1-imaging (TWIST-angiography, CAIPIRINHA [Fig.

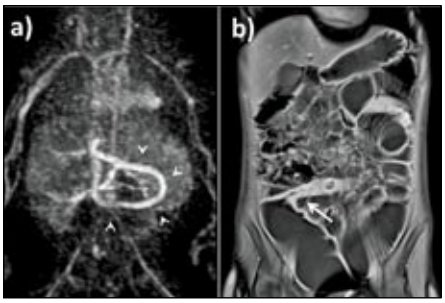

Fig.1: a) Contrast enhanced MR-angiography with high spatial and temporal resolution (TWIST) in a premature infant with portosystemic shunt Abernethy Type II (short arrows), measured in a free breathing, sleeping child („feed-and-wrap"). b) CAIPIRINHA-accelerated T1w 3D-FLASH-imaging after i.v. contrast application (total acquisition time 15s) in a pediatric patient with Crohn's disease. The arrow marks a long inflammatory intestinal stenosis causing intestinal obstruction.

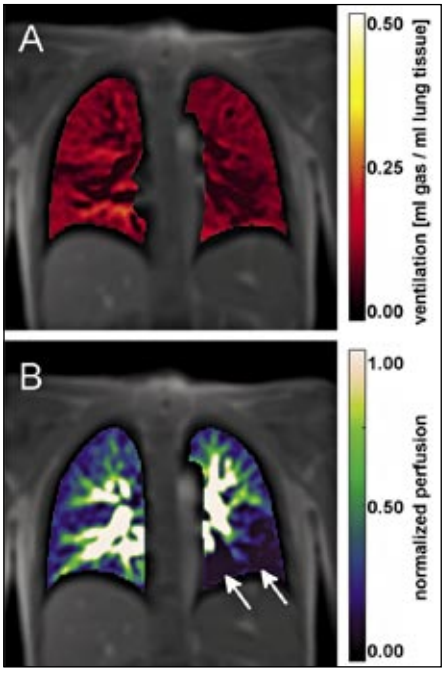

Fig.2: Ventilation-weighted maps (A) acquired by SENCEFUL-MRI show the ventilation in ml air per ml lung tissue. This example shows a homogeneous ventilation in a 30 year old patient. The corresponding semiquantitative perfusion-weighted map (B) shows a reduced perfusion of the left lower lung caused by regional pulmonary embolism, which was previously diagnosed by lung scintigraphy.

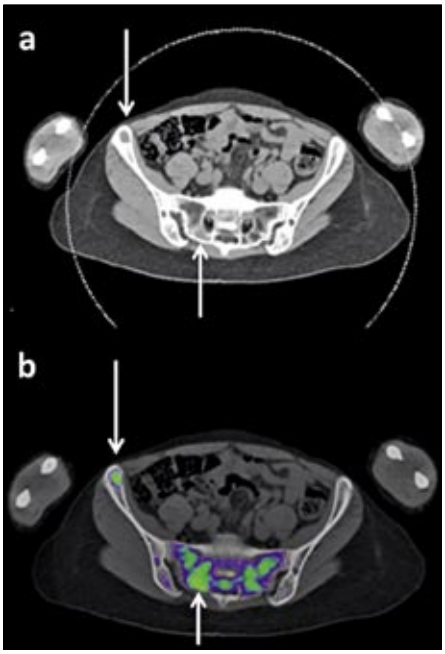

Fig. 3: Focal bone marrow infiltration (arrows) in a patient with multiple myeloma. Visualization of bone marrow in Standard-CT (a) is hampered by the dense trabecular structure of the cancellous bone. Dual Energy CT (b) clearly depicts focal infiltration in the sacral bone and the iliac crest.

1]) and highly resolved diffusion imaging with few artefacts (RESOLVE) for patient-friendly MRI imaging especially for children. Other interdisciplinary research areas include long-term studies on safety of ultrasound contrast media and on morphological changes in hypophosphatasia with enzyme replacement therapy.

MR mammography of pathologies of the female breast
(J. Wiederer, S. Sauer, T. Pabst)

Aiming to improve specificity of MR-mammography, high temporal resolution 3T-MRI techniques for visualization and quantification of contrast agent enhancement, a fat saturation method (DIXON) and diffusion weighted imaging of the breast are performed.

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 Interdisciplinary Center for Clinical Research Würzburg.

Computed Tomography / Dual Energy CT
(B. Petritsch, A. Kosmala, T. Gassenmaier, S. Veldhoen, A. Heidemeier, H. Köstler, A. Weng, Th. Bley)

Dual energy computed tomography (CT) is used for assessment of bone marrow edema in occult fractures. In cooperation with the Department of Internal Medicine II, the potential of dual energy CT to improve the detection of multifocal and diffuse bone marrow infiltration in multiple myeloma is evaluated. The purpose of this study is to assess medullary infiltration, which is not detectable in regular CT images even without obvious bone destruction (Fig. 3). 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. A phantom (QRM-phantom) and ex-vivo (explanted human hearts) study is performed. In addition, the impact of new iterative reconstruction algorithms is investigated.

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.

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Department of Diagnostic and Interventional Neuroradiology

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Professor Dr. med. László Solymosi
(Head of the Division until 9/2016)

Mission and Structure

The Department of Neuroradiology was founded in 1977 and since has been an integral part of interdisciplinary patient care within the Kopfklinikum (Head-Clinic). In 2016, Prof. Dr. Solymosi retired as the Department head. Under his guidance the spectrum of diagnostic and therapeutic neuroradiological procedures has evolved and entered the modern era of diagnostic and interventional Neuroradiology. Prof. Dr. Solymosi was succeeded by Prof. Dr. M. Pham in October 2016. With the appointment of Prof. Dr. M. Pham 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 (Figure 1). 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, 7 Physiciancs with fellow-status, 12 Radiology-Technicians,
2 Physician-Scientists, 4 student research assistants, 2 MR physicists,

Equipment:

2 MRI, 1 Multislice CT
1 MRI operated jointly in the Pediatric Clinic with the Department of Radiology
2 Fluoroscopy/Angiography-Units for Neuro-endovascular Interventions
2 CR Units for conventional X-ray studies

Major Research Interests

Neuroimaging
(B. Alkonyi, G. Homola, E. Schmid)

As part of the Comprehensive Heart Failure Centre (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.1). Third-party funded by the German Research Foundation (DeutschenForschungsgemeinschaft, DFG).

Neurooncology
(M. Warmuth-Metz, 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 criterion for most of the pediatric brain tumor studies. New methods and treatment con-

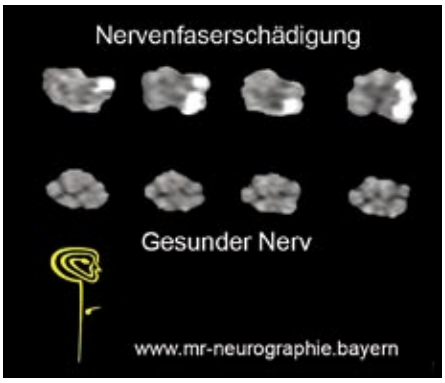

Fig. 1: One of the research topics to which the Department of Neuroradiology is dedicated deals with high-resolution nerve imaging. On this representative image fine details of nerve-fiber-bundle lesions are visualized which so far have remained elusive by any other diagnostic method including clinical-neurophysiological testing.

cepts 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
(M. Warmuth-Metz)

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)

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
(L. Solymosi)

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
(L. Solymosi)

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.

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Department of Nuclear Medicine

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Mission and Structure

The Department of Nuclear Medicine employs unsealed radioactive tracers for research purposes, education, diagnosis and therapy of a multitude of diseases. Most frequent examinations are performed in patients with oncological, cardiac and neurological diseases. Using 2 PET or 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 800 in-patients and 200 out-patients are treated with radioactive isotopes. Full nuclear medicine specialist training is available.

Major Research Interests

Radiochemistry/Radiopharmacy
(S. Samnick, A. 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. The following interdisciplinary research projects could be initiated or supported: SFB688 "Mechanisms and imaging of cell-cell interactions in the cardiovascular system" (DFG), "FDG-PET and iodometomidate imaging for adrenocortical tumors (FAMIAN)" (DFG), IFB "Prevention of heart failure and its complications" (BMBF), "Integrated therapy unit multiple myeloma" (Wilhelm Sander-Stiftung), "Novel recombinant vaccinia viruses and radiotracers for molecular PET imaging and tumor treatment (MoBiVir)" (BMBF), „Imaging dyskinesia in people with Parkinson's disease" (The Michael J. Fox Foundation for Parkinson's Research) and „Imaging of molecular biomarkers for clinical heterogeneity and disease progression in Parkinson´s disease" (IZKF Würzburg).

Cardiology/pre-clinical imaging
(T. Higuchi)

A high number of imaging biomarkers are utilized in translational research projects based on PET and SPECT. A particular focus is cardiac imaging which is headed by Prof. Higuchi. 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 type2-diabetes, studies on the cardiac remodeling after myocardial infarction and imaging of hypertrophic cardiomyopathy in an autoimmune rat model are further projects addressed by the working group. In cooperation with neurology, experiments in animal models of stroke and neurotrauma are performed. The working group of Prof. Higuchi is supported by the DFG, the BMBF and the European Union.

Medical Physics/Radiation Safety/Biodosimetry
(M. Lassmann)

The main scientific research areas comprise radiation protection, internal dosimetry in nuclear medicine and the combination of biodosimetric methods and physical dosimetry as well as improvement of dosimetric methods for radionuclide therapies. In collaboration with a Norwegian company all necessary licenses for a clinical phase I dosimetry trial in patients with Non-Hodgkin's lymphoma were obtained in 2015. The study will focus on the use of a ^{177}Lu-labelled CD37-specific antibody. Patient recruitment will start in early 2016. Participation in an international European project led by the UK-based "National physics Lab (NPL)" further enhanced standardization efforts for improving quantitative imaging and Monte-Carlo-simulations for dosimetry in target radionuclide therapies. The DFG-sponsored project "Comparison of physical and biologic DNA dosimetry after treatment with radionuclides", initiated in 2012, will continue until 2017.

Experimental Oncology
(K. Lückerath)

The group is interested in identifying and characterizing biomarkers for molecular imaging of cancer. In translational studies the value of promising PET biomarkers for sensitive detection of cancers, early response monitoring, prediction of individual prognosis as well as depiction of tumor heterogeneity and biology will be evaluated. Retention of various biomarkers will be correlated with the underlying biology and metabolic processes. The ultimate goal is to use non-invasive imaging for selecting the most effective treatment strategy, resulting in superior out-

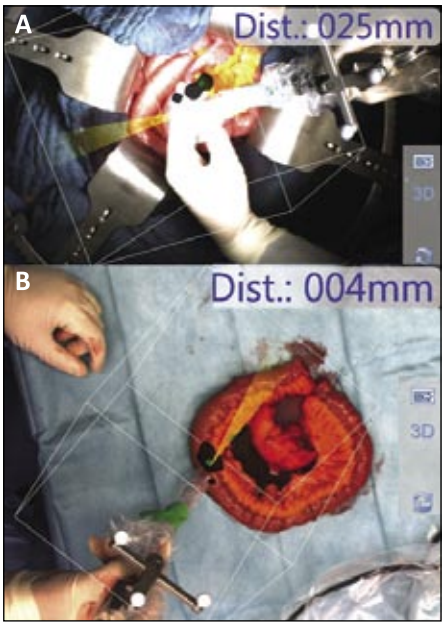

Fig. 1: Intraoperative probe-guided 3D navigation for targeted tumor resection. (A) Radiolabelling of a neuroendocrine tumor using ^{111}In-octreotide and subsequent visualization using infrared cameras and freehand-SPECT technology. Due to the specific retention of the radiotracer in the tumor, the latter can be identified during the procedure. After resection (B), complete removal of tumor tissue can be verified by another probe assessment.

come and reduced side effects. A second focus is on the establishment of theranostic concepts. In these, a ligand coupled to a diagnostic radionuclide is used for non-invasive quantification of target expression on tumors and thus, patient selection for subsequent peptide-receptor-radio-therapy (PRRT) with the same ligand coupled to a therapeutic isotope.

Clinical Oncology
(A.K. Buck, K. Herrmann, C. Lapa, C. Blümel)

In addition to the clinically established imaging biomarkers for glucose metabolism (^{18}F-FDG), lipid metabolism (^{11}C-choline) and protein biosynthesis / amino acid transport (^{18}F-FET, ^{11}C-MET) we have successfully translated two peptide ligands into the clinical routine for imaging expression of the prostate specific membrane antigen (PSMA) and the chemokine receptor 4 (CXCR4) investigating the biodistribution of the corresponding PET tracers ^{68}Ga-PSMA and ^{68}Ga-Pentixafor. Moreover, we extended the use of these peptide ligands to therapeutic applications performing the first in human CXCR4-directed endoradiotherapy using ^{177}Lu-/90Y-Pentixather as well as conducting PSMA targeted receptor therapy with ^{177}Lu-PSMA. Recently, Deutsche Krebshilfe granted financial support of the COLPRIT study, a prospective multi-center study investigating ^{177}Lu-Pentixather as myeloablative treatment prior to conventional high-dose chemotherapy followed by autologous stem cell transplantation in patients with CXCR4-positive Non-Hodgkin`s lymphoma and multiple myeloma. Würzburg is not only a key site for this trial but also in charge of the central review of involved ^{68}Ga-Pentixafor studies.
Together with clinical partners (Dept. of Oromaxillofacial Surgery, Gynecology, General Surgery), a novel in-vivo imaging modality for targeted resection of small lymph nodes and tumors is evaluated (e.g., NET3D study, Fig. 1). In a translational research project funded by the Wilhelm Sander-Foundation (integrated therapy unit multiple myeloma), innovative and established radiotracers addressing tumor heterogeneity are compared with each other. In a translational approach, suitable imaging biomarkers have been selected in-vitro and are currently assessed in preclinical models. Permission for a clinical trial has already been granted by the relevant authorities. A close collaboration exists with members of the Comprehensive Cancer Center Mainfranken. This cooperation allows us to outreach also to regional hospitals and local practitioners.

Neurology/Psychiatry
(I. Isaias, S. Samnick, J. Brumberg, E. Al-Momani)

The research area "functional neuroimaging" is coordinated in close collaboration with the Dept. of Neurology. Prof. Isaias chairs the research program "Imaging of molecular biomarkers for clinical heterogeneity and disease progression in Parkinson's disease" which is funded by the IZKF (project F-255). The aim of this project is to replace clinical-pathological correlations in Parkinson's disease by a novel in-vivo multi-imaging approach, including multiple compounds for SPECT and PET and to compare functional imaging with other imaging techniques, such as MRI and high-density EEG. Innovative radiotracers such as ^{123}I-5IA, ^{11}C-methylreboxetin or ^{18}F-fallypride are utilized in translational studies. Active collaborations have been established with, e.g., Prof. D. Brooks (Imperial College, London), Prof. Y. Ding (New York University School of Medicine) and Prof. D. Eidelberg (Feinstein Center for Neurosciences, New York).

Thyroid/Endocrinology
(AG J. Biko, A. Schirbel, C. Blümel, A.K. Buck)

Thyroid cancer is a major focus of clinical research. An incidence registry is carried out in cooperation with the CCC Mainfranken. The Dept. of Nuclear Medicine actively participates in clinical phase III/IV-studies evaluating novel drugs for thyroid cancer (e.g., E7080). A joint research project of nuclear medicine and endocrinology for the clinical evaluation in patients with newly diagnosed adrenocortical tumors is funded by the DFG since 2013 ("FDG-PET and Iodo-Metomidate Imaging for Adrenocortical Tumors", FAMIAN). Based on the high specificity of this tracer and rapid metabolism, the therapeutic analog ^{131}I-iodometomidate has been used for treatment of patients with metastatic adrenocortical cancer and has shown remarkable response rates with only few side effects.

WHO REMPAN-Center
(C. Reiners, R. Schneider)

The major research interest of the 2013 newly accredited WHO REMPAN collaboration center (Radiation Emergency Medical Preparedness and Assistance Network) includes protection of inhabitants in case of radiation emergencies. In cooperation with the Belarus partner institution ARNICA, the WHO REMPAM Center (www.rempan.ukw.de) evaluates the incidence of breast cancer with radiation induced thyroid carcinoma in adolescents and young females in Belarus.

Teaching

Teaching of students is coordinated together with the Institute for Diagnostic and Interventional Radiology and the Department of Radiooncology. In addition to lectures performed within the program "imaging techniques, radiation treatment and radiation protection", the Department of Nuclear Medicine participates in interdisciplinary lectures (e.g. "Interdisciplinary Oncology", "Communication in Oncology"). Lectures at a local technical school are performed as well as dedicated programs for assistant medical doctors (workshop "thyroid ultrasound"). Since 2012, the scientific program "Forum Nuklearmedizin Würzburg" is offered to medical doctors and scientists in the field. Since 2013, the lecture series "Dialogue between Radiology and Nuclear Medicine" exists.

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Department of Radiation Oncology

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General Information

The Dept. of Radiation Oncology (staff: 18.5 physicians, 112 medical physicists, 19 radiographers, 16 nurses) uses 5 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 careunit 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 psychooncolgist). 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. Image guidance is of increasing imprtance (Fig. 2).
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, image registration, - tracking of moving targets, - calculation of the accumulated dose in the presence of tumour movements, - development of recipes for optimisation and adapta-

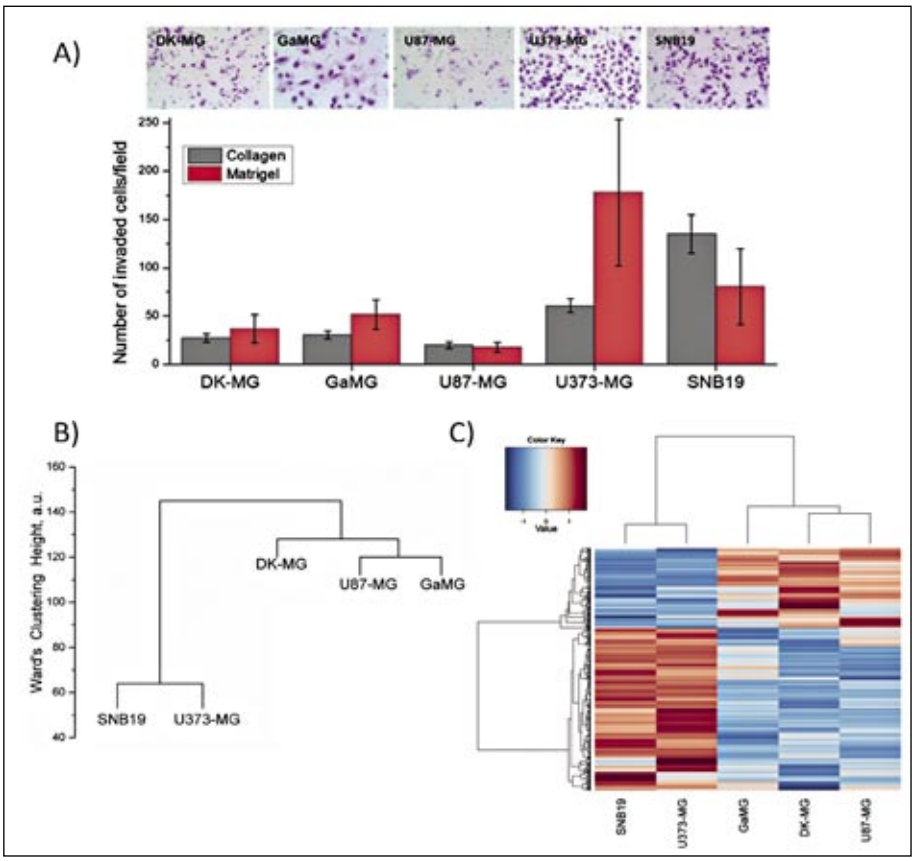

Fig. 1. GBM cell lines differing in p53 and PTEN status showed striking differences in the invasion rates (A). In addition, gene expression analysis reveals two clusters including highly invasive SNB19 and U373-MG and less invasive GaMG, DK-MG and U87-MG cell lines (B). Heat map (C) shows differentially expressed genes between highly and less invasive cells (reproduced from Djuzenova et al., 2015).

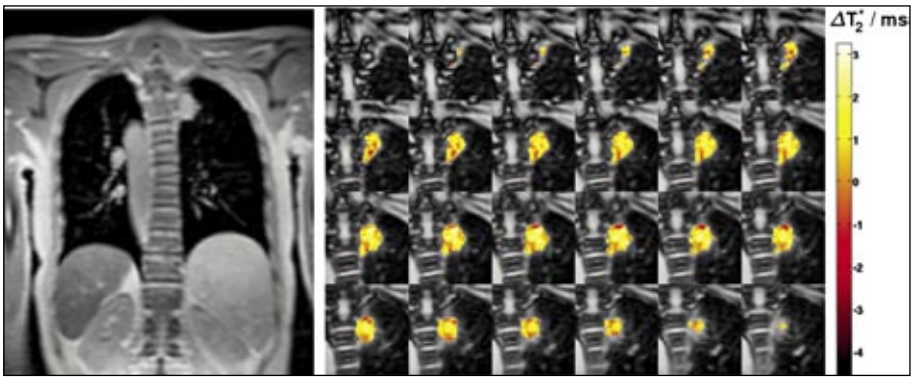

Fig. 2 Repräsentative anatomische Schicht einer navigierten 3D Patientenmessung aufgenommen mit einer mGRE Sequenz. Ein scharfer Diaphragmaübergang und ein Tumor in der linken Lunge sind deutlich zu erkennen. Rechts: T2 Differenzkarte (Oxygenierungsänderung) des gesamten segmentierten Tumorvolumens. Auflösung: 2.9 x 2.9 x 5 mm3*

tion of intensity modulated radiotherapy and of fast application methods like volumetric arc therapy (VMAT), - development of non-coplanar techniques for the body region, - dose measurement and dose calculation under non-equilibrium conditions, especially for small fields and online dosimetry and integration of MRI.

Radiation Biology
(T. Djuzenova, N. Popov)

Two groups focus on cellular (T. Djuzenova) and molecular (N. Popov) predictors of radiation outcome and modulation of radiation response in malignant tumour patients. During the last 2 years we completed a prospective study (funded by the Deutsche Krebshilfe) on blood lymphocytes derived from patients with rectal carcinoma (Djuzenova et al., 2015). The study revealed significantly higher degree of DNA damage in the group of rectal carcinoma patients compared to the control group.
In addition, we studied the migration and invasion of five human Glioblastoma multiforme (GBM) cell lines. There are striking differences not only in the organization of F-actin cytoskeleton among the cell lines but also in their migrational and invasional behaviour (Fig. 1A) Gene profiling analysis revealed two clusters of cell lines corresponding to the most (i.e. p53 and PTEN mutated) and less invasive cells (Fig. 1B) which were differing in the expression of distinct genes including p53, MAPK, adhesion family, and F-actin. (Fig. 1C).
Osteopontin is upregulated in many tumor entities has prognostic impact in head&neck and colorectal cancer. Elevated plasma levels correlate with endogeous tumor hypoxia (Wohlleben et al. 2015). The research focus on oncogenic signal transduktion (especially c-myc/ ubiquitinilation) of N. Popov was integrated into the department of radiation oncology.

Palliative Care
(B. van Oorschot)

The early inclusion of palliative care is an import aspect of providing quality care for severely and terminally-ill patients. Therefore criteria are required that are sensitive to which patients with palliative care needs can be identified. One research focus at the Interdisciplinary Center for Palliative Care is the evaluation and validation of a screening procedure to assess psychosocial and palliative care needs (BUKA project). Funded by the German Cancer Aid, the study investigates the extent to which palliative care can be appropriately and effectively improved by utilizing a tablet-based symptom and burden screening that covers key areas of symptom relief, patient satisfaction, and quality of end of life care.

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 and is visible in national and international consortia on dose escalation studies through precision radiation therapy (Spine, Synergy Consortium, WG stereotaxis of DEGRO). 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

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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 Centre 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. Centres of the clinic are: The interdisciplinary treatment of gynecological cancers, including breast (certified breast centre), the centre 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. Häusler, S. Milak)

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. The scientific project has just started in collaboration with the department of obstetrics and gynecology of the University of Ulm.

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)

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.

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. Since 4/2015, this project is funded by the IZKF after the 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, 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.
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, and 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 were 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, S. Häusler, J. Diessner, R.G. Stein, M. Haake, T. Schäfer, B. Bergmann, S. Ebert, L. Schlahsa, T. Kluge, A. Kuzkina, B. Fischer, 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 will be derived and analyzed from the preclinical understanding of the mechanisms. Translational implementation of the strategies is especially promoted in the GO-Bio project for „antagonizing GDF-15 in solid tumors" followed, at which a broad portfolio of patents was generated.
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 founded by the BMBF (GO-Bio program), the IZKF, the DFG (through the Graduate School of Life Sciences), the Else-Kröner-Fresenius-Foundation, the TaNeDS program of Daiichi Sankyo, and others.

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 centre.

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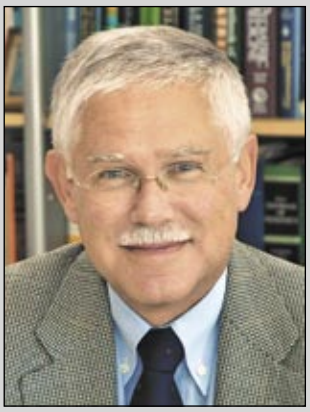
Department of Pediatrics

CONTACT DETAILS



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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 centre (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. There are many close collaborations to the other institutions of the university hospital.

Major Research Interests

Neonatology
Characterization of airway remodeling in acute and chronic lung disease of premature infants and newborns

Surfactant replacement has become a milestone in the treatment of neonatal respiratory distress syndrome (RDS) and has significantly decreased acute pulmonary morbidity and mortality of preterm infants worldwide. Besides improving lung function, surfactant acts as a key modulator of pulmonary innate and acquired immunity thereby regulating acute but also chronic inflammatory processes of the lung. In different studies the effect of new synthetic surfactant preparations on RDS and their immunomodulatory role is characterized. In addition, the role of caffeine on the surfactant system and on airway remodelling processes is analysed. Furthermore, translational research involving various in vitro and animal models is pursued to analyse the effects of coffein citrate for the pulmonary surfactant-system.

Pathophysiology of Ureaplasma-infection in neonates

The role and pathomechanism of inflammation due to ureaplasma infection with regard to neonatal morbidity is still not fully elucidated. Prevalence and morbidity may in fact be much higher in pre-term infants than commonly suspected. Current data point towards an Ureaplasma-mediated trigger leading to a pathological inflammatory reaction especially in the lungs and CNS. Using in vitro models, we examine the proinflammatory capacity of U. urealyticum and U. parvum. A prospective clinical study is focused on perinatal colonization and infection and its correlation with outcome for pre-term children <30 weeks gestational age (close cooperation with the University Children's Hospital, Poznán, Poland).

Pediatric Oncology, Hematology and Stem cell transplantation: Cellular immunity and immunmodulation in patients with malignant diseases

The immune system is capable of destroying residual tumor cells after chemotherapy or stem cell transplantation. We analyzed the T-cell function in patients with leukemia or brain tumors and were able to correlate the findings with disease outcome.
Moreover requirements for efficient T-cell priming are analyzed in a robust, antigen-specific in vitro model and the influence of immune response modifiers is studied. Furthermore we strive to develop new immunotherapies for patients with malignant diseases (dendritic cell vaccination, antigen-specific T-cells), and – in collaboration with the Comprehensive Cancer Center Mainfranken – aim to implement these techniques in clinical studies. A clinical study on tumor-lysate loaded autologous dendritic cells is set to recruit glioblastoma patients in 2016. We also explore new treatment options using a new murine model of medulloblastoma, focusing on the molecular subgroup 3, - an entity with an extremely poor prognosis. Within the area of hematopoeitic stem cell transplantation, several multi-center studies are performed, focusing on engraftment after haploidentical stem cell transplantation using new methods for graft manipulation. These studies are part of our translational approach to get novel treatment strategies into the clinic.

Hypophosphatasia – pathophysiology and new treatment options

Hypophosphatasia is a rare bone disease characterized by reduced tissue nonspecific alkaline phosphatase. Bone mineralisa-

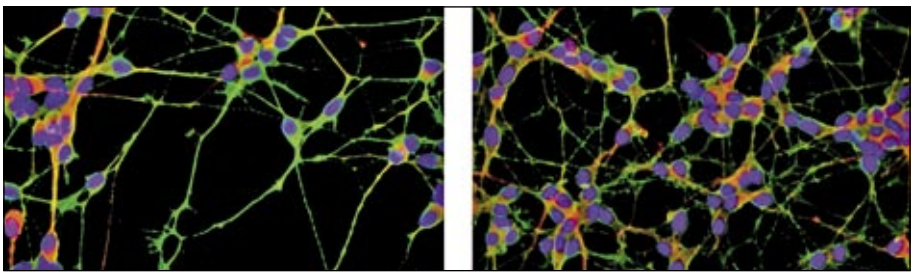

Fig. 1: The tissue-nonspecific alkaline phosphatase promotes the expression of neurogenic differentiation markers. Shown are neuroblastoma cells (SH-SYS5) after 6 (left) and 8 (right) days; red: tau, green: AP (2). (From: Graser, Hofmann).

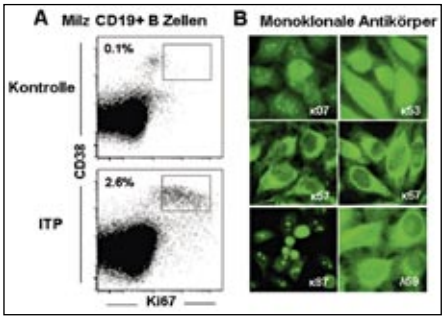

Fig. 2: A: Expansion of activated plasma cells in the spleen. B: Patient-specific produced antibodies show enhanced autoreactivity against Hep2 cells. (From: Morbach).

tion, 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. An international phase II study for enzyme replacement is still ongoing (Fig. 1).

Pediatric Infectious Diseases: Epidemiology and prevention of infectious diseases

The burden of pediatric infectious diseases and the effects of vaccination programs on their epidemiology in children and adolescents are evaluated in prospective and retrospective studies (main research projects 2014/2015: varicella, pneumococcal disease, influenza, RSV, and other viral respiratory infections). Laboratory samples and clinical data on patient characteristics and severity of disease are collected from a network of hospital and practice pediatricians. Viral and bacterial pathogens (types and subtypes) are identified, using various molecular-biological methods in collaboration with the Institutes of Virology (Würzburg, Jena) and Hygiene and Microbiology (Würzburg), as well as the National Reference Center for streptococci (Aachen). Adaptations of pathogens, e.g. serotype replacement of pneumococci in pleural empyema under current vaccination programs are investigated.

Pediatric rheumatology: Pathogenesis of rheumatoid and chronic-inflammatory 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.

Clinical Immunology

Autoantibody secreting B-cells play an essential role in the pathogenesis of many autoimmune diseases. We aim to elucidate the molecular and cellular mechanisms, which are involved in defective immune tolerance and the production auf autoantibodies. For this we produce monoclonal antibodies from single sorted B cells isolated from patients with autoimmune diseases and primary immunodeficiencies and assess the reactivity of these recombinant antibodies. Our special focus lies on the analysis of anti-platelet antibodies, which cause immune thombocytopenia (ITP) (Fig. 2).

Pediatric Pulmonology / Cystic Fibrosis / Sports Medicine: Physical activity and conditioning in healthy children and those with chronic lung diseases

Regular physical activity and exercise have become a major component in the care for people with cystic fibrosis (CF). The main research activities over the last years focused on the question how people with CF might be motivated to engage in regular intense activities and which effects such an intervention might have on many outcomes. Initiated and coordinated by the CF team in Würzburg, a physical activity intervention package including a web-based activity diary has been developed which is now available in four languages. A multi-center randomized controlled trial has now started in six European and North American countries to test the effects of the intervention. Furthermore, an international data base on exercise testing results in CF was coordinated from Würzburg which is now used to determine the prognostic value of exercise testing in this condition. Finally, a study assesses physical activity levels and exercise capacity in patients with chronic recurrent multifocal osteomyelitis.

Teaching

The Children's Hospital of the University of Würzburg offers several courses for medical students. Students have repeatedly evaluated the main lecture in pediatrics regularly as one of the best courses in the faculty of medicine. 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.

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Braun M, Ress ML, Yoo YE, Scholz CJ, Eyrich M, Schlegel PG, Wölfl M. (2016) IL12-mediated sensitizing of T-cell receptor-dependent and -independent tumor cell killing. Oncoimmunology 5:e1188245.

Department of Dermatology, Venereology and Allergology

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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 4 associate professors have been working in research and education during the period under report. Ten attendings, 5 further specialists in dermatology and 17 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, autoimmune disorders, 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)
- 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 (A. Gesierich, M. Goebeler, A. Kerstan, M. Wobser)
- Allergology (A. Trautmann, A. Kerstan, J. Stoevesandt)
- Autoimmune and inflammatory skin diseases (M. Goebeler, S. Benoit, J. Stoevesandt)
- Hair diseases (H. Hamm, A. Kerstan)
- Dermatologic surgery (G. Weyandt, D. Presser, A. Gesierich)
- Phlebology (D. Presser) and proctology (G. Weyandt)
- 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.

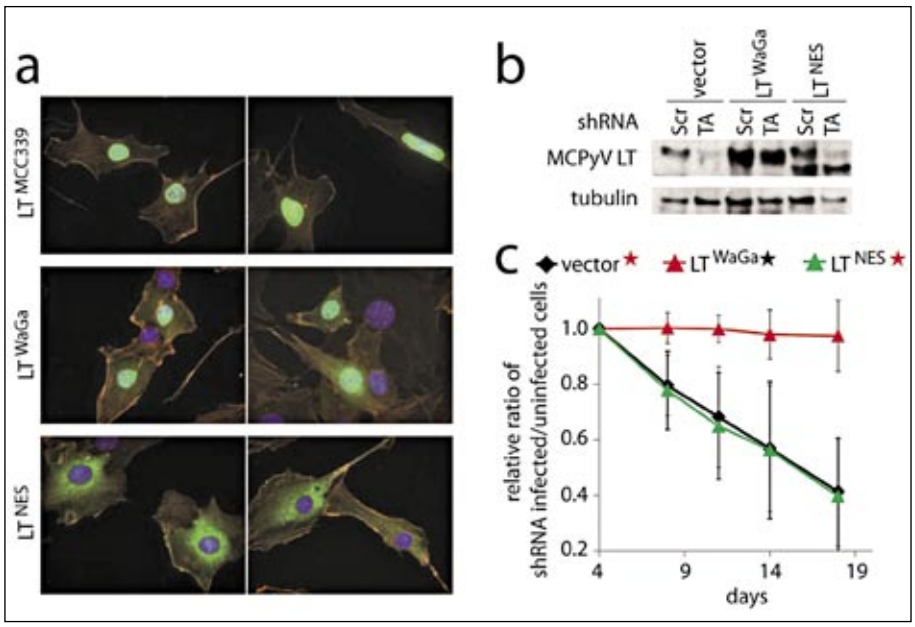

Fig.1. Merkel cell carcinoma (MCC) is an aggressive skin cancer often associated with the Merkel cell polyomavirus (MCPyV). Survival of such tumour cells is dependent on the expression of the viral protein MCPyV-LT. The functionality of LT is dependent on nuclear localization but not on a nuclear-localization-signal (NLS). A) Immunofluorescence stainings demonstrate nuclear localization of MCPyV-LT even in the absence of an intact NLS (LTWaGa). Upon addition of a nuclear export signal, however, cytosolic localization is observed (LTNES). B) Functionality of these LT variants can be tested by specific reduction of the endogenous LT expression (TA). Upon knockdown, LT detection is restricted to cells with ectopic LT expression (LTWaGa und LTNES). C) The ratio of a mixture of normal cells with cells with downregulated endogenous LT expression stays only balanced when functional LT is ectopically expressed. This experiment demonstrates that the lack of a NLS does not impact LT functionality, but that a nuclear localization is mandatory for its function.

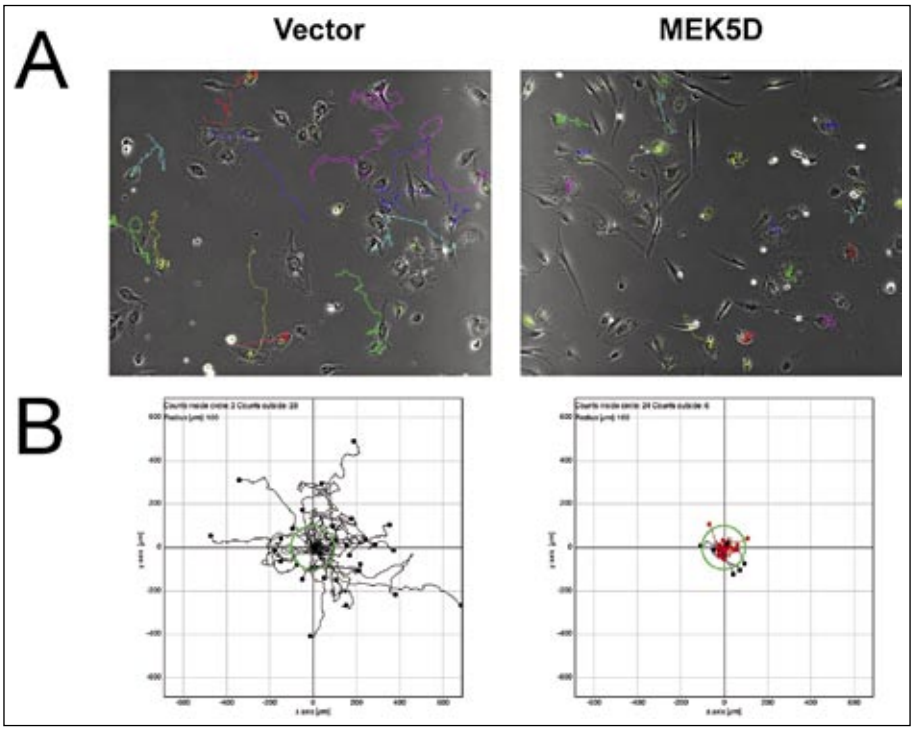

Fig. 2. A laminar blood flow in vessels activates the endothelial MEK5/ERK5 signal transduction pathway, which protects against inflammation at the vessel wall and suppresses neoangiogenesis. Activation of MEK5/ERK5 furthermore blocks migration of endothelial cells. The Figure shows results of a single-cell tracking experiment of human primary umbilical vein endothelilal cells (HUVEC) infected with either an empty retrovirus (vector) or a retrovirus encoding a constitutively active mutant of MEK5 (MEK5D). A) Phase contrast images showing endpoint frames of a representative single cell tracking experiment performed with vector- or MEK5D-infected HUVEC, respectively. Individual paths of 15 different cells followed for 16 h by timelapse microscopy are shown by overlay. Dots represent the migration endpoints of the indicated cells. Green colour overlays indicate positively infected cells as identified by green GFP fluorescent marker expression from the viral backbone. B) XY diagram, showing cell movements in X-Y direction (in µm) with reference to their starting position (0) over a period of 16 h. Each dot marks one of 30 individually tracked cells as in (A). The green circles indicate a migrated Euclidean distance of 100 µm. Trajectories of cells migrating < 15 µm/h are represented in red. Data illustrate an impaired directional motility (as indicated by overall smaller migrated Euclidean distances) and slower average migration velocity of MEK5D-expressing cells relative to vector-infected HUVEC.

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
- small molecule inhibitors of the MAP kinase pathway in melanoma
- tumour suppressor proteins in skin cancer
- melanoma immunology
- melanoma genetics and mutation analysis
- apoptotic signalling pathways in epithelial cutaneous tumours
- 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

Genodermatoses

- clinical and genetic characterization of genodermatoses in cooperation with the German Network for Ichthyoses and Related Cornification Disorders, the German Network Epidermolysis Bullosa and with national and international laboratories for research in molecular genetics

Teaching and further education

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 doctoral theses derive from the research projects listed above.

SELECTED PUBLICATIONS

Alrefai H, Muhammad K, Rudolf R, Pham DA, Klein-Hessling S, Patra AK, Avots A, Bukur V, Sahin U, Tenzer S, Goebeler M, Kerstan A, Serfling E. (2016) NFATc1 supports imiquimod-induced skin inflammation by suppressing IL-10 synthesis in B cells. Nat Commun 7:11724.

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Houben R, Angermeyer S, Haferkamp S, Aue A, Goebeler M, Schrama D, Hesbacher S. (2015) Characterization of functional domains in the Merkel cell polyoma virus Large T antigen. Int J Cancer 136,E290-300.

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Komaravolu RK, Adam C, Moonen JR, Harmsen MC, Goebeler M, Schmidt M. (2015) Erk5 inhibits endothelial migration via KLF2-dependent down-regulation of PAK1. Cardiovasc Res 105:86-95.

Department of Oto-Rhino-Laryngology, Plastic, Aesthetic and Reconstructive Head and Neck Surgery

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Mission and Structure

The clinic of Otorhinolaryngology, plastic and aesthetic 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 centre), 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 centre for surgical treatment of pediatric sarcomas, 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

Middle ear implants
(R. Hagen, A. Radeloff, K. Rak, S. Schraven, S. Kaulitz)

Development of new middle ear implants including implantable active middle ear amplifiers in cooperation with medical technology industry

Biophysics of middle ear
(S. Schraven, A. Bahmer, F. Kraus, 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, L.Jürgens, S. Frenz, 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 post-natal 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
(A. Radeloff, 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.

Pedaudiological tests, newborn hearing screening, hearing development, genetics of hearing disorders
(W. Shehata-Dieler, W. Grossmann, 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, B. Vona)

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
(A. Radeloff, W. Shehata-Dieler, K. Rak, S. Schraven, 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, R. Keim, W. Grossmann)

Further development of diagnostic tools for objective frequency specific measurement of the absolute threshold of hearing. Stan-

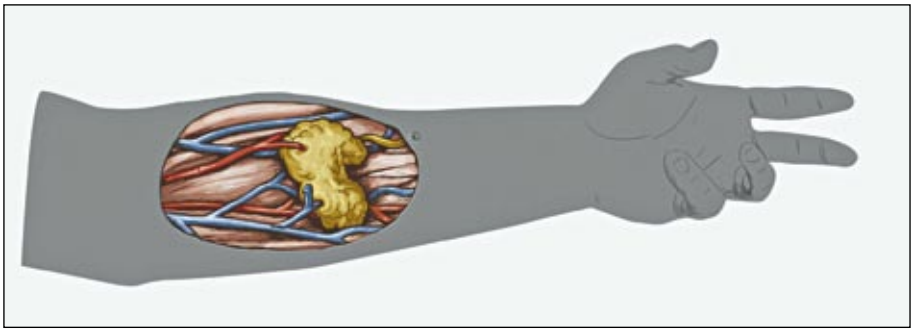

Fig.1: Schematic drawing of a transplanted submandibular gland in a patient´s forearm.

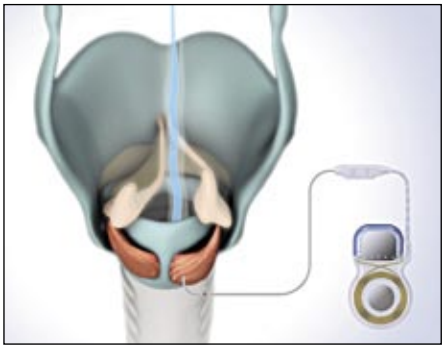

Fig. 2: Schematic drawing of the new Medel laryngeal pacemaker.

dardisation 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.

Electrophysiological hearing research
(M. Vollmer, A. Wiegner, in cooperation with the University of California, R. Beitel, and the Ludwig-Maximilians University Munic, B. Grothe)

Animal experiments in gerbils for investigation of central neuronal interactions in electric acoustical stimulation of the cochlea, central neuronal processing of interaural time differences (ITDs) in acoustical and electrical stimulation of the cochlea, effects of long term deafening to temporal and spatial discrimination of intracochlear electrical stimulation in the colliculus inferior and the primary auditory cortex, psychophysical and neuronal models for temporal integration of electrical stimuli, neurotrophic effects of GM1 gangliosides and electrical stimulation to spiral ganglion cells following neonatal deafening

Tumour biology and functional rehabilitation following tumour surgery
(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)
(N. Kleinsasser, A.Scherzad, S. Hackenberg, G. Steussloff, P. Ickrath)

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.

Tissue engineering in laryngology
(K. Frölich, A. Scherzad, N. Kleinsasser, in cooperation with the department of surgery, T. Blunk)

Establishment of stabile cartilaginous structures with different scaffold materials. Functionality of stem cell engineered tissue in an animal model.

Functional electrostimulation of the larynx
(R. Hagen, W. Grossmann, M. Bernhardt in cooperation with the university department of ORL Jena, Germany and 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, H. Walles, 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".

Compensatory saliva production following radiotherapy
(R. Hagen, N. Kleinsasser, M. Scheich, T. Gehrke)

Development of a new transplantation technique for a two staged autotransplantation of submandibular gland in humans.

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

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 (actually doctors from Saudi Arabia, Afghanistan, Peru, Spain). Full-time hospitations for consultants.

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Mission and Structure

A staff of 34 physicians and about 90 nurses, technicians and scientists care for approximately 20.000 outpatients and about 5.700 inpatients annually. In 2015, about 6.900 surgical procedures and more than 2200 laser treatments were performed. As one of the largest eye hospitals in Germany, 68 beds for inpatients and und 4 operation theatres are provided, offering the full range of medical and surgical eye care and diagnostics.
The eye hospital is a center for diagnosis and treatment of adults and children with vitreoretinal diseases providing all modern diagnostic and microsurgical techniques including treatment of major ocular injuries. The Glaucoma Unit offers all modern methods for diagnosis and treatment of glaucoma. Conjunctival and corneal diseases as well as eyelid and orbital disorders are treated by specialized teams within the eye hospital. There is a special Unit for the diagnosis and treatment of pediatric eye diseases as well as strabismus and neuro-ophthalmology. The Ophthalmic Imaging Unit comprises all modern devices for imaging of the anterior and posterior segment of the eye.
Besides inpatient care of patients with multiple ophthalmologic and general health problems, the eye clinic also offers outpatient surgery.

Major Research Interests

Clinical Research
Anterior Segment
The team for anterior segment diseases 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. Also, the eye clinic has a major role in the development of novel methods for monitoring intraocular pressure.
Especially the advent of new imaging techniques such as imaging of the peripapillary nerve fiber layer using spectral-domain OCT augmented morphological follow-up examinations for glaucoma patients.

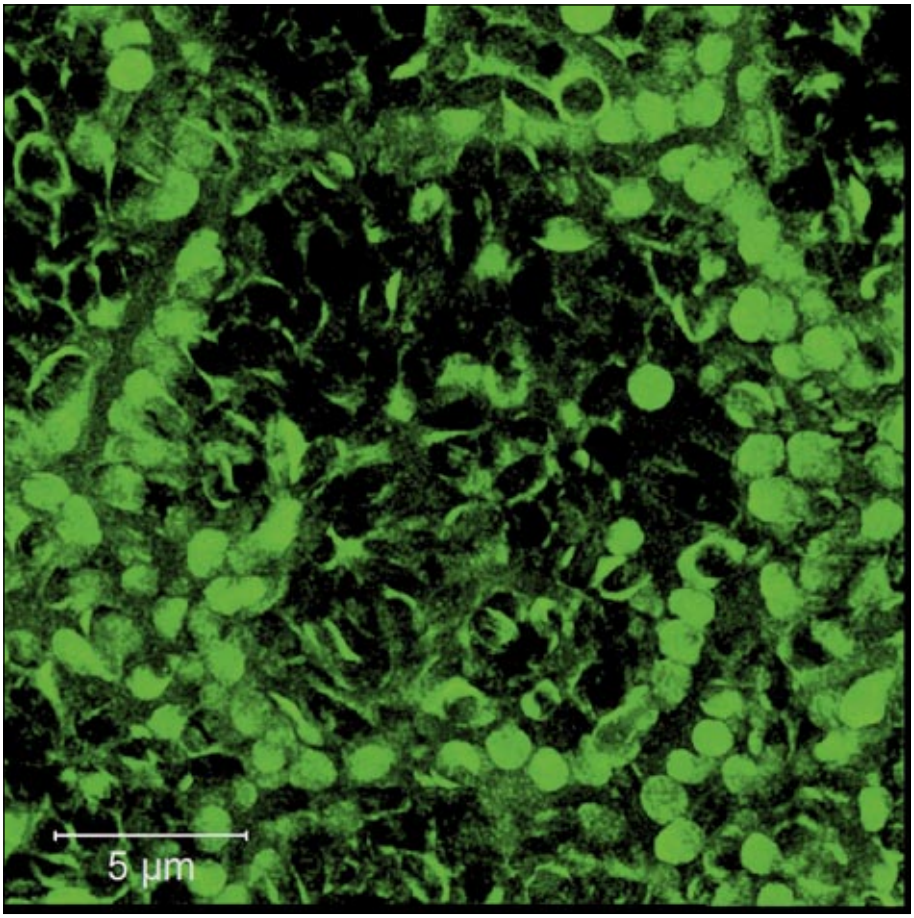

Fig. 1: High-definition imaging of autofluorescent granules within one RPE-cell (Dr. T. Ach).

Retina and Imaging of the Posterior Segment

OCT allows non-invasive analysis of single retinal layers and ultrastructure of the retinal pigment epithelium and offers important information in the diagnosis of retinal disorders, vitreo-retinal tractions syndromes and age-related macular degeneration.
Peripapillary nerve fiber layer alterations are found in numerous neurologic diseases. According to recent publications also the retinal ganglion cell layer is reduced in degenerative CNS diseases. In cooperation with the Department of Neurology (Prof. Dr. J. Volkmann) these retinal changes are evaluated by spectral-domain OCT and correlated to different disease stages.

Basic Research
Anterior Segment

In-situ regeneration of amitotic ocular tissues, especially of corneal endothelium and retinal pigment epithelium, by means of gene-transfer (Dr. D. Kampik).

Development of a 3-dimensional artificial cornea-tissue model as a replacement for animal experiments in cooperation with the Chair for Tissue Engineering and Regenerative Medicine of Würzburg University Hospital (Dr. D. Kampik, Prof. Dr. H. Walles).

Posterior Segment
Ciliary neutrotrohic factor (CNTF) within the human retina in Age-related Macular Degeneration (AMD)

CNTF is a neurotrophic and myotrophic factor supporting survival of motoneurons and neurons as well as of retinal cells. In animal studies, degeneration of photoreceptors could be reduced by intravitreal application of CNTF. Similar effects were seen in humans. However, there is lack of data on the exact mechanism of action of CNTF in murine and human retinas.
A project in cooperation with the Institute for Clinical Neurobiology (Dr. T. Ach; Prof. Dr. M. Sendtner) supported by the IZKF Würzburg characterizes CNTF-expression and distribution of CNTF-receptors within normal aging retina and in AMD patients. Additional studies on murine models will be performed to evaluate CNTF signaling cascades and to describe phenotypic changes of the retinal pigment epithelium and photoreceptors with the goal of developing possible concepts for novel AMD therapies.

Spectral studies of cells and autofluorescent granules of normal aging retinal pigment epithelium and the retinal pigment epithelium of AMD patients

Autofluorescent granules accumulate within the retinal pigment epithelium throughout life. However the function of these granules and their possible role in the development of AMD has not been established, yet. This project (Dr. T. Ach, supported by Dr. Werner Jackstädt Foundation, Essen) aims at visualizing and analyzing these granules (lipofuscine, melanolipofuscine) using high-resolution microscopy with a special focus on age-dependent accumulation intracellular distribution and spectral characteristics. This data will help to better understand physiology and pathophysiology of RPE-cells and to better discriminate normal senescence from early AMD.

Teaching

Lectures, practical training and special interest seminars are offered to undergraduate medical students. The residency program comprises daily morning rounds with case presentations and CME-seminars. Another series of four extensive seminars per year is dedicated to update colleagues in private practice on the most recent developments in the field. In addition, lecturers from the University Eye Hospital teach at regional and international ophthalmology conferences.

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Department of Neurosurgery

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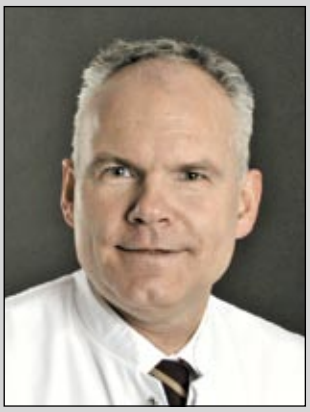

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Clinical Focus and Structure

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 (2014-2015), 3,705 patients were treated surgically and 13,520 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 Focus

Neurooncology
(M. Löhr, C. Hagemann, C. Matthies, R.-I. Ernestus)

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 dedifferentiation, 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. In cooperation with the Department for Tissue Engineering (Prof. Dr. Walles, Dr. Nietzer) culture models are developed to study tumour growth and invasion and for testing of pharmacological agents for future individualized adjuvant therapies.

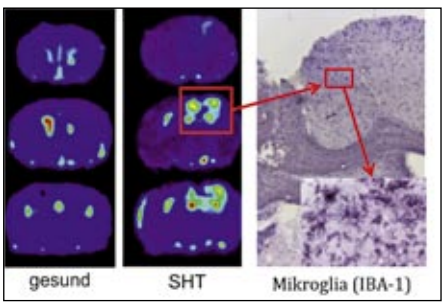

Fig.1: In-vivo-PET imaging of inflammation after traumatic brain injury (TBI) in mice. Left panels depict autoradiographic images of activated microglia cells using labelling with the translocator proteing (TSPO) ligand [18F]DPA-714. Immunohistochemical labelling of the same tissue section with the microglia specific marker IBA-1 reveals strong expression of activated microglia (right panel).

Functional Microsurgery & Neurostimulation
(C. Matthies, 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 centre 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. A developing topic is the combination of neuroprotective and regenerative factors.

Neurovascular Disease
(E. Kunze, S. Köhler, C. Stetter, N. Willner, 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 Projects F199 and Z3/50.

Translational Neurotrauma Research
(A.-L. Sirén, C. Stetter)

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 trauma. On-going 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. We aim to elucidate regeneration and synaptic plasticity after trauma at the level of individual synapses by using cell culture, transgenic and experimental brain injury models, behavioural testing and super resolution light- and electron microscopy. Funding: DFG/TRR-SFB-166-TP6, BMBF-EU-ERANET-NEURON-CNSAflame-01EW1502B, IZKF Projects A226, N229 und E313.

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.

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Department of Neurology

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Professor Dr. med. Guido Stoll
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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 2015 we treated 3.400 inpatients including 532 cases on the ICU. On our emergency service we took care of 4.950 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. In 2015 a neurogeriatric-neurorehabilitation ward was opened. 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-geronto-psychiatric 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 43 full time academic members, 76 nursing staff members, 23 technicians and 10 staff members in administration and special services. Additional 13 academic positions are supported by extramural grants. The Department of Neurology contributes to the Sonderforschungsbereich (Cooperative Project Center Grant) #688, joint projects within the FP7 Programme of the European Community, and the Chronic Heart Failure Center Würzburg funded by the Federal Ministry of Education and Research (BMBF).

Major Research Interests

Parkinson´s Disease and Neurodegenerative Disorders
(J. Volkmann, F. Steigerwald, S. Klebe (until 8/2015), C.W. Ip, I.U. Isaias, 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; 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.

Stroke
(C. Kleinschnitz, P. Kraft, W. Müllges, G. Stoll)

Assessment of molecular mechanisms of thrombus formation in experimental cerebral ischemia and the contribution of innate immunity to stroke development (“thrombo-inflammation”); development of novel anti-platelet strategies and anticoagulants not affecting hemostasis (cooperation with Prof. B. Nieswandt; Rudolf Virchow Center and SFB 688); mechanisms and prevention of brain edema formation in stroke and traumatic brain injury (cooperation with Department of Neurosurgery); studies on cognitive decline and interactions between heart and brain function during heart failure and stroke (Chronic Heart Failure Center, Würzburg); supraregional stroke telemedicine network TRANSIT-Stroke; 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-im-

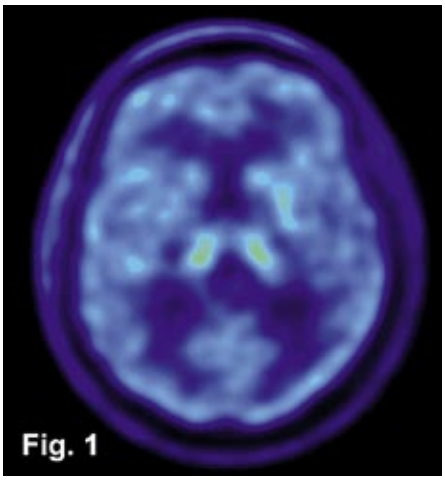

Fig. 1: Positron emission tomography (PET) of the noradrenergic system with the newly developed PET- ligand methylreboxetine. This method for the first time allows visualization of noradrenergic defects in Parkinson patients.

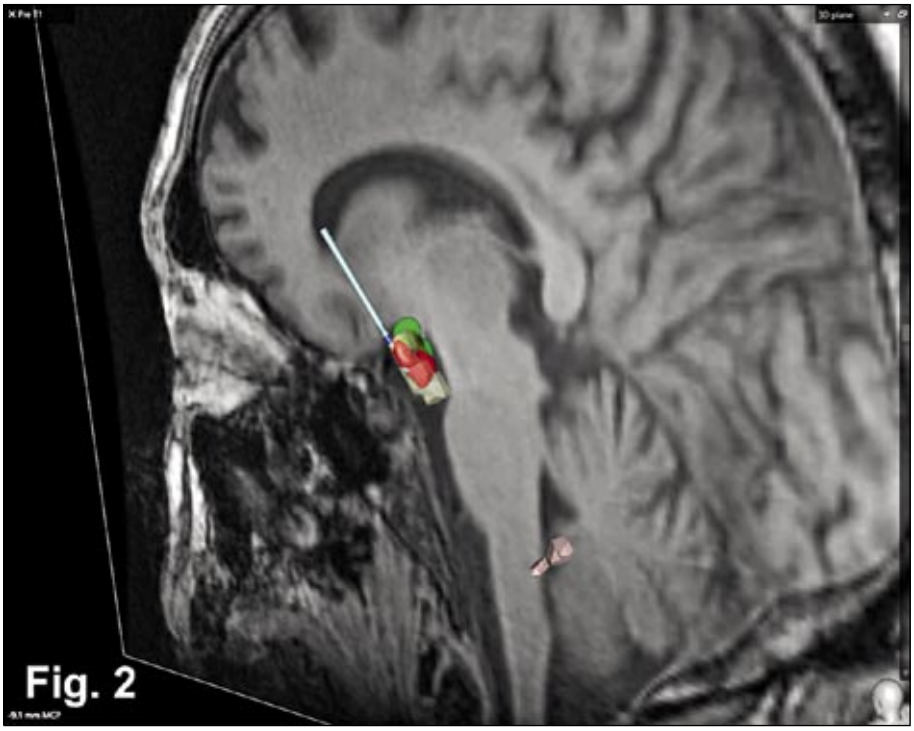

Fig. 2: Deep brain stimulation may induce ataxia in patients with tremor as a side effect. We could demonstrate that stimulation sites for tremor suppression (green) and those inducing ataxia (red) are closely related, but non-overlapping. Stimulation of ataxia-inducing areas leads to antidromic activation of the cerebellar vermis as shown by FDG-PET. These findings may help to define optimized target areas for deep brain stimulation.

mune interactions and their molecular regulation; 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; pathophysiology of antibody-associated disorders of the CNS and PNS; international trials on treatment of pain and neuropathies.

Multiple Sclerosis and Neuroimmunology (Clinical Research Group) including Neuroimaging and CSF-Laboratory
(G. Stoll, M. Buttmann, C. Kleinschnitz, A. Weishaupt in cooperation with Division Developmental Neurobiology)

Neuroimaging: Development and evaluation of new methods for in-vivo imaging of neuroinflammation by magnetic resonance imaging and PET (cooperation with Prof. P. Jakob, Department of Physics V, and Prof. S. Samnick, Nuclear Medicine). Pathogenesis of multiple sclerosis and polyneuritis (experimental autoimmune encephalomyelitis and neuritis); molecular mechanisms of disturbances of the blood brain barrier; molecular biomarkers in multiple sclerosis; international treatment trials; role of autoreactive antibodies in neurological disorders.

Experimental Developmental Neurobiology
(R. Martini, J. Groh, D. Klein)

Research is focussed on pathogenic mechanisms underlying genetically-mediated demyelination and neurodegenerative disorders 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", and consequently, immunomodulation emerges as treatment strategy in the respective mouse models. Morphological methods, such as confocal and electron microscopy, combined with the assessment of molecular alterations are used for the analysis of glial damage, impaired axonal transport and synaptic alterations. Particular focus is on analytical techniques related to clinical translation, such as OCT.

Clinical Neurophysiology und Neuromuscular Disease Center; Motor Neuron Disorders
(K. Reiners, D. Zeller, C.W. Ip, M. Buttmann)

Neurophysiological examinations in patients with neuromuscular and CNS disorders (> 25,000 examinations per year); coordination of the Interdisciplinary Neuromuscular Center and participation in the Musculoskelettal Center of the University of Würzburg; establishment of neurophysiological parameters for the assessment of disease severity and progression in MS and ALS; molecular assessment of disease-modifiers in sporadic and familial ALS (in collaboration with Prof. Sendtner, Institute of Clinical Neurobiology); genetics of neuromuscular disorders.

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 in differential diagnosis of neurological disorders, neuromuscular diseases and nerve/muscle pathology and participates in numerous interdisciplinary seminars (Anatomy, Physiology, Oncology Center, Pain-Curriculum, Psychology, Neurobiology, Biomedicine and all classes of the Würzburg International Graduate School of Life Sciences). Teaching languages are German and English.

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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 and autism. Specialized out-patient services as part of the outpatient clinic as well as 51 day-care therapy slots for psychiatric, psychosomatic and neurogerontopsychiatric disorders complement the 144 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, Turkey, Cile, Columbia, Nigeria, Tanzania, Japan and China. Close ooperations at the level of the UKW exist in the context of the GK 1253, the GSLS, the IZKF, 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, Schizophrenic Psychoses and Frontotemporal Lobe Dementia, as core laboratory of BfARM-networks on Therapeutic Drug Monitoring and the TRR SFB 58 on Fear, Anxiety and Anxiety Disorders. At the international level, the PPP participates in cooperations with the NIMH and takes part in DAAD programs and EU programs, but also international research collaborations such as IMpACT, IMAGE2, the ADHD Molecular Genetics Network, PANIC, ANGST, ConLiGen, the SSRI Pharmacogenomics Consortium and the Psychiatric GWAS Consortium as well as EU networks on anxiety disorders, affective disorders, suicidality and impulsivity. Funding agencies include the DFG, the BMBF and the EU. 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).

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-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

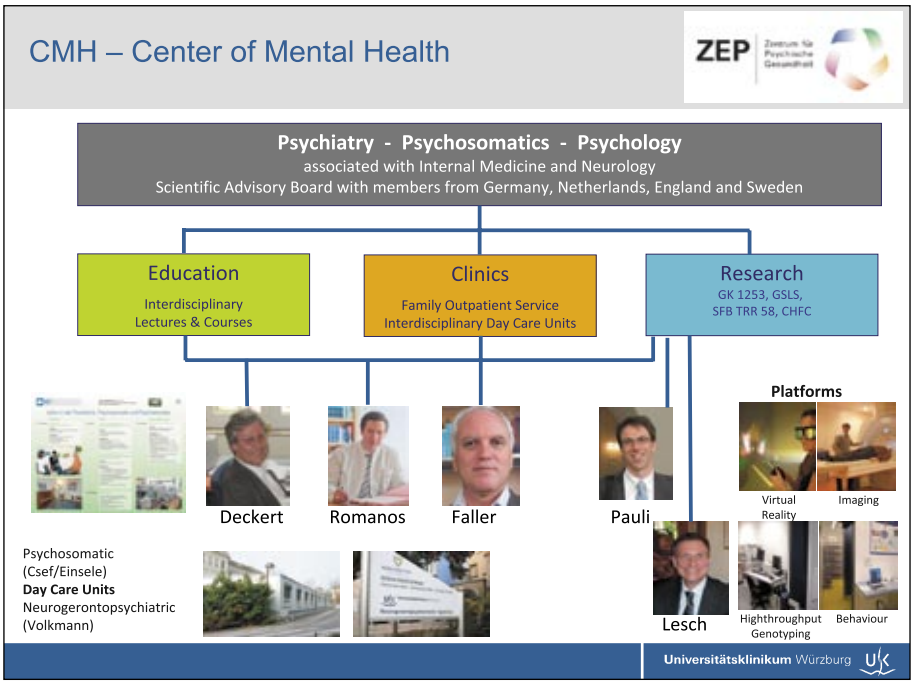

Fig. 1: Center of Mental ofthe University Hospital and University of Würzburg.

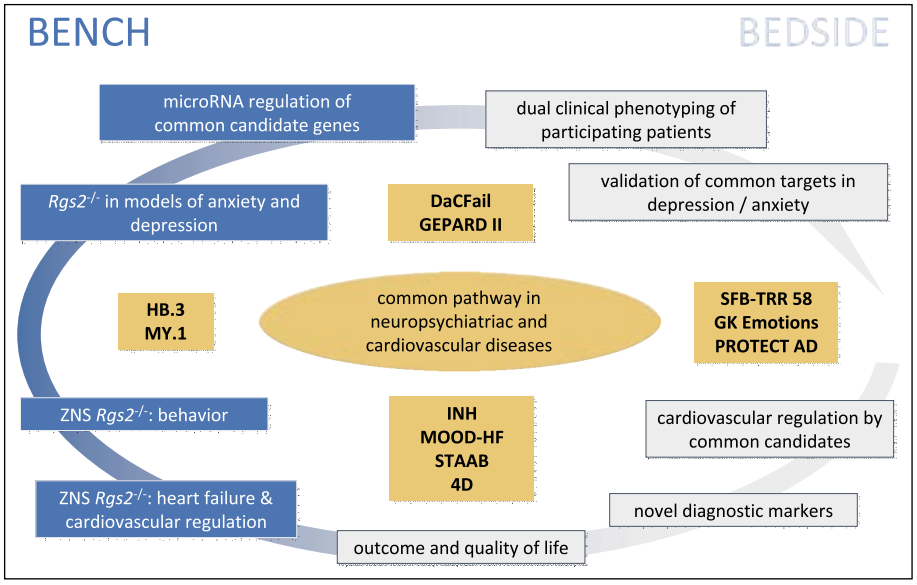

Fig.2: IZKF/DZHI junior group on common molecular mechanisms of neuropsychiatric and cardiovascular disorders

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 Pschiatry, 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 K.P. Lesch as W3 chair of molecular psychiatry, K. Domschke as W2 professor and L. Hommers as head of the IZKF/DZHI junior group (figure 2) in the context of the SFB TR 58, the GK1253 and the DZHI was supported after the departure of A. Reif to Frankfurt (W3 chair of psychiatry) by the recruitment of U. Lüken as W2 professor for experimental and clinical psychotherapy research.

The main research topics thus are:

- Markers for early diagnosis and innovative preventive and therapeutic as well as personalized approaches in affective disorders, anxiety disorders,adult ADHD,psychoses of the schizophrenia spectrum and dementias (J. Deckert, A. Menke, K. Domschke, U. Lüken, B. Warrings, A. Reif, S. Unterecker, M. Gawlik, G. Stöber, B. Warrings, S. Unterecker, M. Lauer , T. Polak).
- Identification of (epi)genetic factors in affective disorders, psychoses of the schizophrenia spectrum, anxiety disorders and ADHD, dementia disorders and rare syndromes (K. Domschke, J. Deckert, K.-P. Lesch, A. Reif, G. Stöber, M. Gawlik, L. Hommers, M. Fischer).
- Imaging of emotional and cognitive processes in adults, adolescents and children (U.Lüken, M.J. Herrmann, K.-P. Lesch, A. Reif, K.Domschke, J. Deckert) in close cooperation with the department of child and adolescent psychiatry, psychosomatics and psychotherapy.
- Gene-environment-interactions, neuronal plasticity, adult neurogenesis and induced pluripotent stem cells in humans and in rodent models (K.-P. Lesch, J. Deckert, A. Reif, K. Domschke, L. Hommers, M. Fischer, A. Schmitt, S. Kittel-Schneider).

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, psychology and logopedics. Extracurricular seminars are offered to graduate students of medicine, experimental medicine, clinical research, 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 Master in Translational Neuroscience is offered in English.

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Division of Molecular Psychiatry

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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 (schizophrenia spectrum) 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 behavioural level using a validated set of paradigms and at molecular, cellular and systemslevels 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 investigatingmutual 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:

- Identification of common and rare variation in risk genes using genome-wide approaches (GWAS, CNV screening, whole-exome/genome sequencing) (e.g. O'Dushlaine et al. 2015). A database for selected multiplex families with high density of ADHD, psychotic and bipolar disorder (30-40 members per family) has been set up. 24 of these extended pedigrees have already been collected and subjected to genome-wide screening approaches, including whole-exome/genome sequencing and the assembly of another 20-25 families is planned.

- 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 (e.g. Gutknecht et al. 2015).

- 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 and other stressors (GxE mouse models) that simulate neurobehavioural characteristics of psychiatric disorders (e.g. 5-Htt, Tph2, Cdh13 and Lphn3 knockout mouse models) (e.g. Schraut et al. 2014).

- 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 excitatory-inhibitory dysbalance reflecting the pertinent concept of synaptopathy in neurodevelopmental and psychiatric disorders: Our contri-

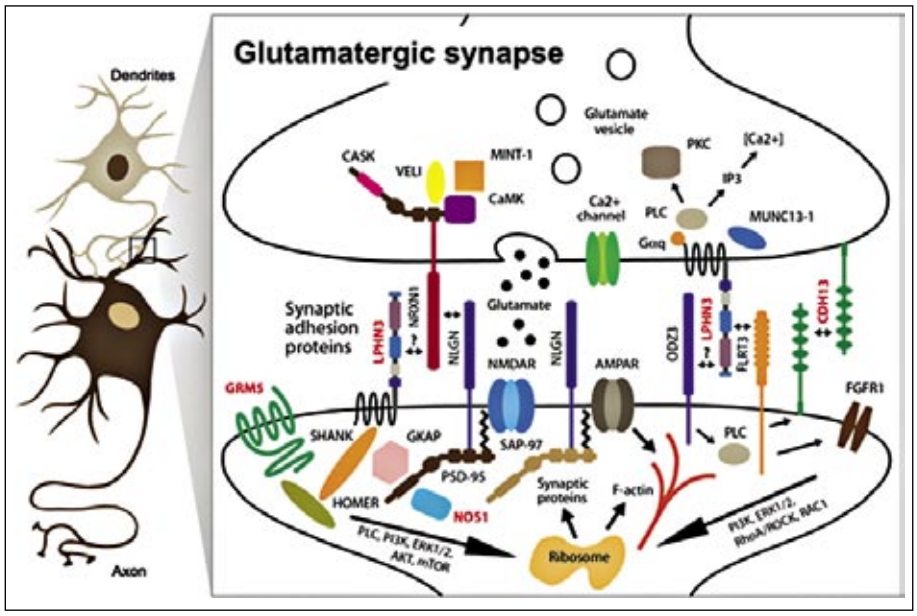

Fig. 1: Schematic diagram of a glutamatergic synapse displaying involvement of synaptic proteins in attention-deficit/hyperactivity disorder (ADHD). The genes and respective proteins identified as associated with ADHD risk are indicated in red: CDH13, cadherin-13; GRM5, metabotropic glutamate receptor-5, LPHN3, latrophilin-3; NOS1, nitric oxide synthase-1.

bution to the discovery of variation affecting genes encoding glutamate receptors (e.g. metabotropic glutamate receptor-5, GRM5) and mediators of their intracellular signaling pathways (e.g. nitric oxide synthase-1, NOS1) as well as molecules interacting in the formation and plasticity of glutamatergic (e.g. latrophilin-3, LPHN3) and GABAergic (e.g. CDH13) synapses as relevant causative factors point to compromised monoamine-glutamate-GABA system interaction in neurodevelopmental/psychiatric disorders. Synaptic adhesion molecules, receptors and mediators of intracellular signaling pathways are principal components of the molecular machinery that connect pre- and postsynaptic neurons, facilitate transmission, control synaptic plasticity and empower intersecting neural circuits to process and refine information. These mechanisms require meticulous dissection at several levels of complexity to pinpoint dysfunction related to disease mechanisms, using cellular, in vivo animal models and neural systems using neuroimaging (e.g. Rivero et al. 2015).

- Exploring alternative disease definitions based on the discovery of molecular, cellular and systems-related disease mechanisms for various neurodevelopmental/psychiatric disorders, which 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 (e.g. Transregio 58, ERA-NET/BMBF consortia) and international collaborations (e.g. IMpACT, MiND, NIMH, NICHD, NHGRI, NIDA, NIAAA, Stony Brook, EMBL, Karolinska Institute, Universities of Maastricht, Nijmegen, Paris, Oxford, Shanghai, Bergen, Rome, Florence, Barcelona, Lisbon, Budapest and Tartu, to name only a few). For example, IMpACT (http://impactadhd-genomics.com), is a consortium of clinical and basic researchers from several European countries (The Netherlands, Spain, Norway, UK, Sweden, Denmark) as well as from the USA and Brazil focussing on all aspects of ADHD across the lifespan. This consortium boasts to have collected a cohort of 18,000+ patients with ADHD.

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.

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Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy

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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 mental disorders across the whole range of psychiatry and psychosomatics. 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“ (15 beds), and a day clinic (14 beds). In addition, there is a „parent pavilion“ and 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-behavioral 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 department´s capacity is above 100 %.

Research Projects

Anxiety Disorders

(M. Romanos, J. Reinhard, A. Bürger, S. Neufang)

Within the SFB TRR 58 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 have assessed 500 healthy children between 8 and 12 years undergoing a differential fear-conditioning and generalization paradigm revealing stronger generalization in children compared to adults. Furthermore, generalization is correlated with dimensional anxious traits. We have tapped an interesting and highly relevant mechanism in early developmental stages of anxiety disorders that will be pursued in further studies.
Furthermore we are part in a multicentre trial funded by the BMBF on anxiety disorders in children in cooperation with the Universities of Bochum and Dresden.

Autism Spectrum Disorders

(R. Taurines, T. Jans, J. Geissler)

Autism spectrum disorders are accompanied by complex neurobiological maldevelopment; however, no markers have been identified with diagnostic or therapeutic value so far. In our studies, we have determined the mRNA expression of candidate genes in full blood. On the protein level, we have assessed e.g. oxytocin by radioimmunoassay in blood plasma. We have applied proteomics to identify potential novel pathophysiological candidates. Furthermore, the impact of gene variants on peripheral mRNA and protein concentrations of candidates have been determined. Our projects were realized in cooperation with the Department of Psychiatry and Psychotherapy, University of Rostock, the Department of Child and Adolescent Psychiatry, University of Zurich, the Institute of Life Science, Swansea, and the Department of Functional Proteomics, MedizinischesProteom-Center, Ruhr-Universität Bochum.

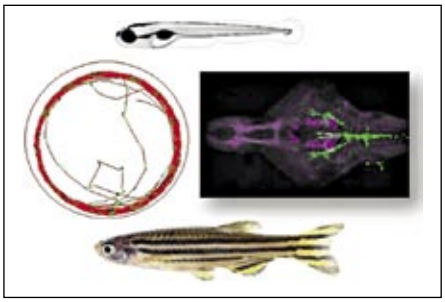

Fig. 1: The effects of genetic manipulation of zebrafish by morpholino-injection or CRISPER/Cas allows for the assessment of behavioural changes (e.g. motoric acitivity patterns) as well as central nervous alterations (e.g. by CLARITY or immunostaining).

Attention-Deficit /Hyperactivity Disorder (ADHD)

(M. Romanos, J. Geissler, M. Gerlach, T. Jans)

In our past clinical research unit on ADHD (KFO 125) numerous scientific studies on the neurobiology and moleculargenetics of ADHD have been conducted. Alongside our neurobiological focus on ADHD, our department is committed to translational psychotherapy research. The BMBF-funded ADHD-Net multicentre initiative was conducted from our department. We have currently acquired funding by the BMBF within the ESCAlife consortium carrying out multicentre RCTs in 1200 patients with ADHD in different age groups applying a demanding stepped care-design approach.

Biomarkers

(M. Romanos, C. Drepper, J. Geissler, R. Taurines, 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, 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.-Y. Dang, S. Fekete, S. Reichert, R. Taurines, M. Romanos, M. Gerlach)

Increasing prescription numbers of psychotropic drugs in children and adolescents are contrasting with the uncertainties of safety and efficacy issues due to the lack of clinical (authorization) trials. A multicentre clinical trial on pharmacovigilance in children and adolescents (“TDM-VIGIL”) under the guidance of our department and funded by the German Federal Institute for Drugs and Medical Devices (BfArM) collects epidemiological prescription and safety data of psy-

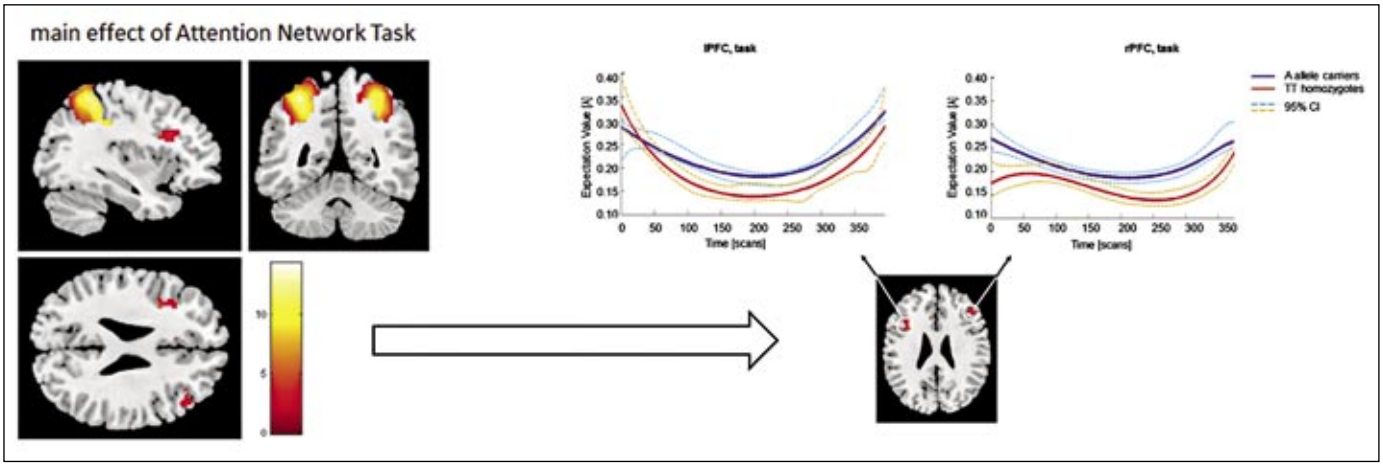

Fig. 2: In this project we examine attention functions in the context of anxiety disorders using functionalmagnetresonance imaging. First results in healthy volunteers show that predominantly frontal activation patterns were modulated by the Neuropeptid S receptor 1 gene (NPSR1), which is associated with panic disorder.

chotropic drugs to evaluate the benefit-risk-ratio as well as minimize and prevent adverse effects by therapeutic drug monitoring.

Developmental Neuroimaging
(S. Neufang, J. Geissler, A. Akrif)

The Developmental Neuroimaging Lab focuses on the examination of brain maturation processes in combination with the development of cognitive skills. We use mr-based functional imaging techniques, e.g. fMRI (task- and resting-state fMRI), and structural MRI (morphometry, DTI). In one study we investigate the pathophysiological role of iron in dopamine-associated movement disorders.
In the IZKF-funded collaboration project *"Neurobiology of Attention Networks in Anxiety and Anxiety disorders" (IZKF N262)* of PD S. Neufang with the Department of Psychiatry, Psychosomatics and Psychotherapy (Prof. K. Domschke) and the Department of Neuroradiology (Dr.G.Homola) the efficiency of the attention network and its neurotransmitter-related neuronal correlates is examined using the attention network test via a combination of neuropsychological and neuroimaging techniques in patients with panic disorder and healthy controls. Furthermore, in an imaging (epi)genetic approach, genetic/epigenetic variants will be examined for their potential as biomarkers of a dysfunctional attention network and/or predictors or even neurobiological correlates of therapy response.

Developmental Psychiatric Neurobiology
(C. Drepper, M. Romanos)

The working group promotes the development of biological models of neuropsychiatric disorders. Due to the increasing identification of disease-associated gene variants in humans, the functional characterization of these variants in model organisms will be essential for the understanding of the involved pathomechanisms.
Within the IZKF-funded project *„Anatomical and functional investigation of the CNS of zebrafish models – for attention deficit/hyperactivity disorder (ADHD) (IZKF N-320)"* we have established a larval zebrafish-model, that will be extended to adult stages, thus providing a model of investigate the functional characteristics of human candidate genes. Amongst other we will apply the CRISPR/CAS technology and CLARITY to assess structural characteristics of the CNS.

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 internal medicine. 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".

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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 mortality risk. In a randomized controlled multicenter study, the efficacy of pharmacotherapy in heart failure patients suffering from major depression was examined in reference to reducing depression and mortality (MOOD-HF Study).

Psycho-Oncology
(H. Faller)

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 addition, patients' need for information as well as their need for psychosocial support were assessed. Furthermore, the impact of response shift, i.e. change of patients' internal judging standards, on the assessment of quality of life among prostate cancer patients was examined in a project involving two university centers (Würzburg, Hamburg), which was performed in collaboration with the Departments of Radiotherapy (Prof. Flentje) and Urology (Prof. Riedmiller).

Patient Education
(H. Faller, K. Meng, A. Reusch, H. Vogel)

Innovative educational concepts 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. They also implement specific strategies to increase the sustainability of education effects and to transfer newly learned skills into everyday life. In other projects, a generic self-management program and different methods used to disseminate innovative educational programs into routine health care were evaluated.

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 (Health Education Impact Questionnaire). Using complex statistical approaches such as structural equation modeling, we evaluated the measuring properties of these instruments including measurement invariance across different assessment occasions and stable vs. variable components of constructs over time.

Psychotherapy Research
(H. Vogel, S. Neuderth)

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 counseling, screening and supervision, are being developed, implemented, and evaluated.

Occupational Rehabilitation
(S. Neuderth, H. Vogel)

In medical rehabilitation, patients with vocational impediments are provided special treat-

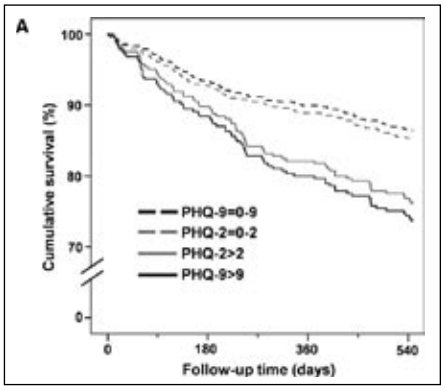

Fig. 1: Survival by level of depressive symptoms in chronic heart failure, comparing the two-item and the nine-item versions of the Patient Health Questionnaire. (from: Piepenburg, SM, Faller H*, Gelbrich G, Störk S, Warrings B, Ertl G, Angermann CE (2015) Comparative potential of the two- versus the nine-item Patient Health Questionnaire to predict death or re-hospitalization in heart failure. Circulation Heart Failure 8:464-472.)*

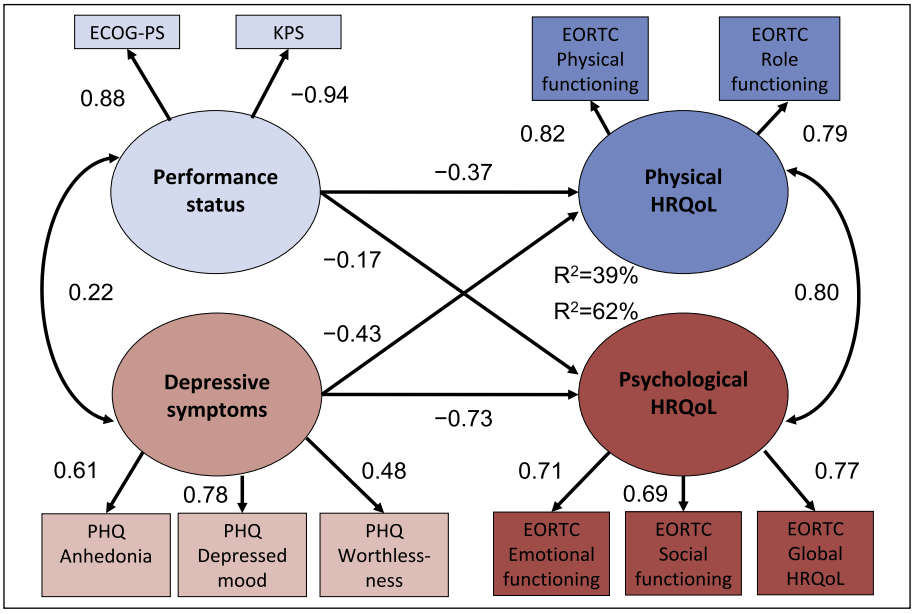

Fig. 2: Structural equation modeling of the simultaneous effects of performance status and depressive symptoms on the physical and psychological dimensions of health-related quality of life in cancer patients. (adapted from: Faller H, Brähler E, Härter M, Keller M, Schulz H, Wegscheider K, Weis J, Boehncke A, Richard R, Sehner S, Koch U, Mehnert A (2015) Performance status and depressive symptoms as predictors of quality of life in cancer patients. A structural equation modeling analysis. Psycho-Oncology 24:1456–1462.)

ments addressing work (so-called work-related interventions). Members of our team participated as experts in the development and revision of standards for medical work-related rehabilitation issued by the German Statutory Pension Insurance as well as the formative evaluation of the implementation of these standards in rehabilitation centers. Current projects deal with the evaluation of such work-related interventions in comparison to regular medical rehabilitation in routine healthcare (effectiveness), 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.

Quality Assurance and Quality Management
(H. Vogel, S. Neuderth)

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 has for several years 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, S. Neuderth)

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. In another project, teachers are educated on how to identify and manage psychological distress in their students.

Teaching

As part of the subjects "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

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Institute of Experimental Biomedicine, Chair of Experimental Biomedicine I

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Mission and Structure

The Chair of Experimental Biomedicine I was established in 2008 as part of the Rudolf Virchow Center for Experimental Biomedicine (RVZ, see page 136) and is co-funded by the University Clinic 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. Large parts of the research projects are integrated into the Collaborative Research Center 688 (SFB 688, page 142) at the University of Würzburg. With the appointments of Prof. Dr. Harald Schulze in 2014 and the DFG-Emmy-Noether group of Dr. Markus Bender in 2015, research at the institute now also covers the fields of hematopoiesis and inherited platelet disorders.

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* (MKs) 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 adhesion, activation and aggregation. These experiments serve as a basis for the development of novel anti-thrombotic therapeutic strategies which are subsequently tested using *in vivo* models of ischemic and inflammatory diseases.

The adapters SLAP/SLAP2 negatively regulate platelet activation in thrombosis and thrombo-inflammation

GPVI and CLEC-2 are essential platelet activating receptors in hemostasis and thrombo-inflammatory disease which signal through a (hem)*immunoreceptor tyrosine-based activation motif* (ITAM)-dependent pathway. The adapter molecules *Src-like adapter protein* (SLAP) and SLAP2 are involved in the regulation of immune cell receptor surface expression and signaling, but their function in platelets was unknown. We could demonstrate that SLAP and SLAP2 play largely redundant roles in platelet biology and single deficiency of SLAP or SLAP2 in mice had only moderate effects on platelet function. By contrast, SLAP/SLAP2 double deficiency resulted in markedly increased signal transduction, integrin activation, granule release, aggregation, procoagulant activity and thrombin generation following (hem)ITAM-coupled, but not G protein-coupled receptor activation. *Slap*$^{-/-}$/*Slap2*$^{-/-}$ mice displayed accelerated occlusive arterial thrombus formation and a dramati-

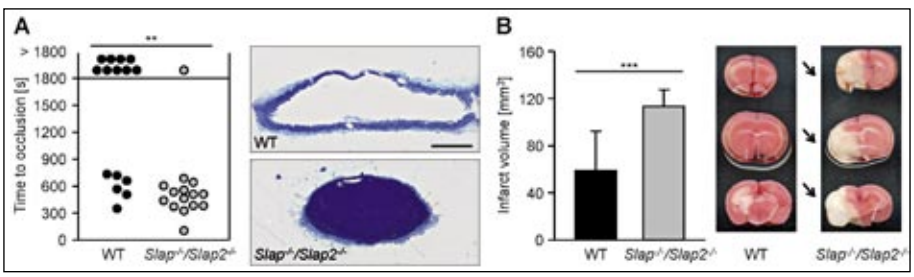

Fig. 1: SLAP/SLAP2 limit thrombus formation and infarct growth after focal cerebral ischemia. (A) (Left panel) The left carotid artery of wild-type (WT) and Slap$^{-/-}$*/Slap2*$^{-/-}$ *mice was injured by a topical application of 2.5% $FeCl_3$ and blood flow was monitored with a Doppler flow probe until complete vessel occlusion, or for a maximum period of 30 min. Each symbol represents one animal. (Right panel) $FeCl_3$-injured carotid arteries were excised and stained in toluidine blue. Bar: 1.1 µm. (B) (Left panel) Infarct volume. (Right panel) Representative images of 3 coronal brain sections 24 h after 30 min of transient middle cerebral artery occlusion. Arrows indicate infarcted areas in the brains of Slap*$^{-/-}$*/Slap2*$^{-/-}$*mice. WT, wild-type.**, P < 0.01; ***, P < 0.001.*

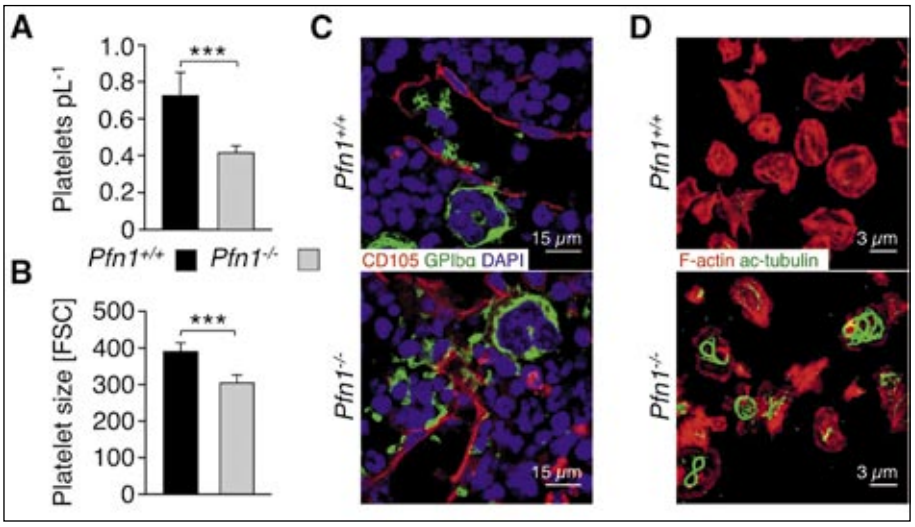

Fig. 2: MK-/platelet-specific Pfn1 deficiency (Pfn1-/-) results in microthrombocytopenia. (A, B) MK-/platelet-specific Pfn1 deficiency results in a reduced platelet number (A) and size (B). (C) Confocal images of immunostained bone marrow. MK, proplatelets and platelets are shown by GPIbα staining in green color. Endoglin staining (red) labels vessels. DAPI nuclear stain, blue.(D) Spread platelets were stained for acetylated-tubulin (green), a marker for stable microtubules and filamentous actin (red) and visualized by confocal microscopy.

cally worsened outcome after focal cerebral ischemia (Figure 1). These results establish SLAP and SLAP2 as critical naturally occurring inhibitors of platelet (hem)ITAM signaling in the setting of arterial thrombosis and ischemic stroke.

Profilin1 regulates microtubule-driven proplatelet formation in the bone marrow

Platelets are continuously produced from MKs in the bone marrow by a cytoskeleton-driven process. Although *Profilin1* (Pfn1) is a key molecule that regulates dynamic rearrangements of the actin cytoskeleton, its function in thrombopoiesis was ill-defined. We could show that MK-/platelet-specific Pfn1 deficiency results in microthrombocytopenia, a hallmark of the *Wiskott-Aldrich syndrome* (WAS) in humans (Figure 2). Both Pfn1-deficient mouse platelets and platelets isolated from WAS patients contained abnormally organized and hyper-stable microtubules that most likely account for the decreased platelet size and revealed for the first time an unexpected role of Pfn1 in the regulation of the microtubule cytoskeleton. In marked contrast to *Wiskott-Aldrich syndrome protein* (Wasp)-deficient mice, conditional Pfn1-deficient mice recapitulate the MK/platelet phenotype of WAS patients. Therefore, we speculate that WASp may act as a modulator of Pfn1 function in MKs and that this process is disturbed in WAS patients, leading to the known platelet formation defect.

Light sheet fluorescence microscopy (LSFM) of the bone marrow challenges the concept of MK-migration

In mammals, anucleate blood platelets are produced by giant *bone marrow* (BM) precursor cells, the *megakaryocytes* (MKs), which originate from hematopoietic stem cells and are thought to migrate from the endosteal niche towards the vascular sinusoids during their maturation. However, the concept of migrating MKs is mostly based on evaluation of cell populations present at distinct spatiotemporal niches, using BM sections which are intrinsically limited to 2D information.To assess the MK distribution in the intact 3D environment, we utilized *light-sheet fluorescence microscopy* (LSFM) and established a clearing protocol for intact entire bones, leading to optically transparent samples. 3D reconstructions of LSFM data revealed a surprisingly dense bone marrow vasculature, leaving no space for such vessel-distant niches. Moreover, MKs are distributed homogeneously throughout the entire BM and the majority of the MKs is in direct contact with blood vessels. Thus, these data – in combination with data originating from *in vivo* multi-photon microscopy and computational simulations – reveal surprisingly slow MK migration, limited intravascular space and a vessel-biased MK pool. These observations demonstrate that MKs do not need to migrate to reach the vessel and thereby contradict the current concept of directed MK migration during thrombopoiesis.

Mechanisms of integrin activation

Inside-out activation of integrin adhesion receptors is the "final common pathway" of platelet activation. A long-standing model of platelet integrin activation proposed a key role for the adapter RIAM in this process. We could now show in RIAM-deficient mice that the protein is dispensable for integrin activation in platelets *in vitro* and *in vivo* (Stritt et al., Blood 2015 – PLENARY PAPER). This finding led to a revised model of platelet integrin activation.

Teaching

The Chair of Experimental Biomedicine - Vascular Medicine 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.

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Institute of Experimental Biomedicine, Chair of Experimental Biomedicine II

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Mission and Structure

The Institute of Experimental Biomedicine was newly founded on 01.03.2016 by the Institute of Clinical Biochemistry and Pathobiochemistry (Prof. Dr. Alma Zernecke-Madsen) and the chair of Experimental Biomedicine – Vascular Biology (Prof. Dr. Bernhard Nieswandt). The Institute of Clinical Biochemistry and Pathobiochemistry was initially founded in 1995 at the conclusion of a DFG-funded Clinical Research Group (1989–1995) by Prof. Dr. Ulrich Walter. In 2001 the Institute merged with the Central Diagnostic Laboratory to provide an institutional platform for patient-oriented and basic research. In 2012, the Institute was newly structured and demerged with the Central Diagnostic Laboratory. After Prof. Dr. Elke Butt provisionally headed the Institute, Prof. Dr. Alma Zernecke was appointed new director of the Institute of Clinical Biochemistry and Pathobiochemistry in 2014.

Major Research Interests

Research activities focus on pathophysiological aspects of cardiovascular diseases (atherosclerosis, myocardial infarction) by using murine and human model systems. Research projects are supported by the DFG/SFB 688 (www.sfb688.de), foundations, and industry.

Cardiovascular Diseases

(A. Zernecke)

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. Elucidating the pathways and a better understanding of the mechanisms underlying cardiovascular diseases is thus perquisite for the development of novel therapeutic approaches.

Inflammation has emerged as a crucial force driving the initiation and progression of atherosclerotic lesion formation and myocardial remodeling. 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 or heart. We are investigating the generation and differentiation of immune cells and their recruitment to the inflamed tissue, and the role of different effector molecules herein. In particular, the systemic interplay of these mechanisms is of interest. For instance, monocyte generation is enhanced in the bone marrow during atherogenesis, and controlled by $CD8^+$ T cells. Increased circulating levels of monocytes subsequently trigger their enhanced accumulation in the vessel wall, leading to an exaggerated atherosclerotic lesion growth (Fig. 1). In a different study, we could show that extracellular RNA that accumulates within atherosclerotic lesions and was found to be increased in blood after arterial injury provoked an increased leukocyte recruitment and neointimal hyperplasia after injury (Fig. 2). We are also interested in the interaction of immune cells, the ensuing immune responses and their modulation, which determine disease progression; in these processes, a special focus lies on transcription factors and cytokines. Finally, we address epigenetics and the role of microRNAs in atherosclerosis and myocardial infarction, which regulate key functions of immune cells and thereby control disease development.

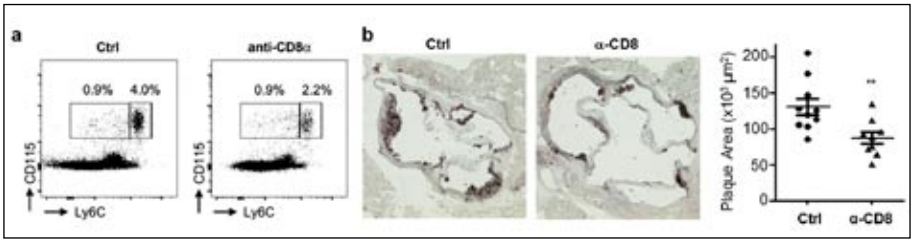

*Fig. 1: (a) Representative fluorescence activated cell sorting (FACS) plots of CD115 vs Ly6C expression on total blood cells of low density lipoprotein receptor deficient mice treated or not with depleting anti-CD8α antibody after 6 weeks of high-fat diet feeding. (b) Representative oil-red-O-stained aortic root sections and quantification of aortic root lesion area are shown. **P<0.01.*

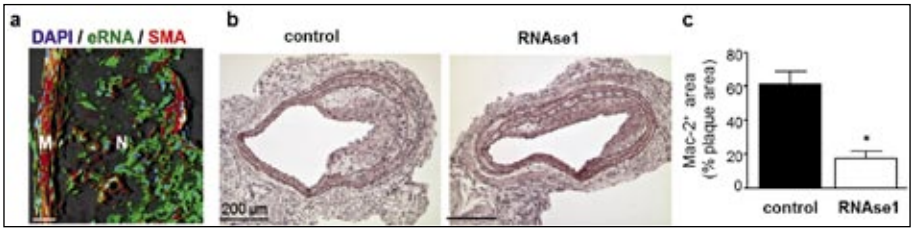

*Fig. 2: (a) Distribution of extracellular RNA (eRNA) in atherosclerotic lesions. The presence of eRNA in aortic root tissue from low density lipoprotein receptor deficient mice fed a high-fat diet for 12 weeks was demonstrated by confocal microscopy with the use of an RNA-binding fluorescence dye (RNA Select) together with cell nuclei staining (4',6-diamidino-2-phenylindole [DAPI]). Confocal images with merged immunostaining for eRNA (green), cell nuclei (DAPI, blue), and smooth muscle actin (SMA, red) are sown. M indicates media; and N, neointima. (b) Apolipoprotein E-deficient mice fed a high-fat diet and treated with vehicle or RNase1 were subjected to wire-induced injury of the common carotid artery. Neointimal areas were assessed 3 weeks after injury. Representative images of pentachrome-stained sections and (c) quantification of the relative content of Mac-2–positive neointimal macrophages are documented. *P<0.05.*

Protein Biochemistry and LASP1
(E. Butt)

The group of Prof. Butt investigates the biological role of the protein LASP1 in vascular inflammation and atherosclerosis. For this purpose, knockout models are used to elucidate LASP1-driven signalling pathways that control adhesion and migration of immune cells.
In addition, the pathophysiological function of LASP1 for tumor progression and metastasis is investigated. A second research area focuses on the characterization of cyclic nucleotides and their effector proteins. At www.cyclic-nucleotides.org side effects of customary used cGMP-and cAMP- analogues are predicted.

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).

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Institute of Clinical Neurobiology

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Mission and Structure

The Institute of Clinical Neurobiology was founded in 2000 as an independent research institute at the University Hospital. The scientific focus are the cellular and molecular mechanisms of neurodegenerative disorders, but it 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. Since 2010, the institute is situated in building E4.

Major Research Interests

Central research focus are studies on the mechanisms of neuronal cell death, the establishment and analysis of animal models for motoneuron diseases, and the development of new therapies for the treatment of amyotrophic laterals sclerosis and spinal muscular atrophy, the most common forms of motoneuron disease in children and adults.

Further lines of research focus on the mechanisms how neural stem cells differentiate into neurons and functional neural circuits. Investigation of the signal transduction pathways by which neurotrophic factors influence differentiation, survival and axonal growth of neurons are of central interest. The generation and analysis of gene knockout mouse models allows investigating which signal molecules are involved in mediating the cellular effects of neurotrophic factors.

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 in motoneurons. On the basis of these experiments, new therapeutic strategies for this disease can now be developed.

In 2012, a new research group headed by Prof. Carmen Villmann was founded at the Institute. This group is interested in the molecular pathomechanisms of motor dysfunction caused by defects in glycinergic neurotransmission. Mutations in genes that code for glycine receptor subunits or adjacent proteins (glycine transporter 2, gephyrin, collybistin) at glycinergic inhibitory synapses are responsible for hyperekplexia (Startle Disease, Stiff-Baby Syndrome, OMIM #149400). Tactile or acoustic stimuli cause a typical startle reaction that leads to loss of control on muscle tone and posture. Mouse models with corresponding mutations in the glycine receptor subunits and similar symptoms have been established (spastic, spasmodic and oscillator). These mouse lines can be used to study these diseases and the underlying mechanisms of altered motor control.

Central technologies, besides modern cell culture methods for primary motoneurons and the generation and analysis of mouse models, are modern microscopic techniques, including confocal microscopy, 2-photon microscopy and life imaging, in order to study dynamics and defects in structure and function in neurons from models of neurodegenerative diseases.

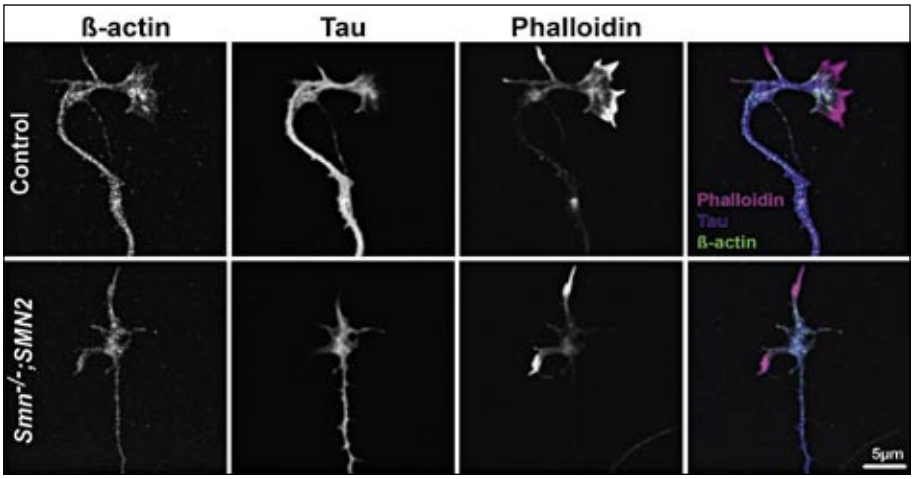

Fig.1. Misdistribution of cytoskeletal proteins in isolated spinal motoneurons from a mouse model of spinal muscular atrophy. In comparison to wildtype motoneuron (upper lane), Smn deficient motoneurons show reduced levels of globular ß-actin and Phalloidin stained F-actin in axon terminals (reproduced from Jablonka et al., J. Anat. 224, 3-14, 2014).

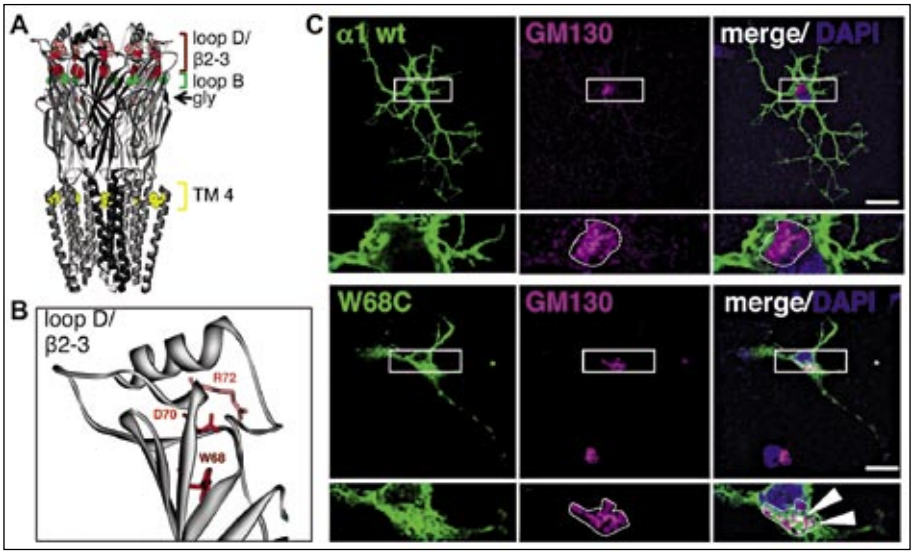

Fig. 2: Human hyperekplexia variants in loop D disturb neuronal ER-Golgi sorting. (A) Pentameric glycine receptor with loop D at the protein surface (red). (B) Magnification of loop D with human variants (red, light red, pink). (C) Glycine receptor variant W68C with cis-Golgi and cytoplasmic accumulation in contrast to wild-type receptor (wt) with mainly dendritic localization. (taken from Schaefer et al., J. Neurosci. 2015).

Teaching

The Institute for Clinical Neurobiology is involved in the training of students in the Master program for Translational Neuroscience which has been established in 2015 at the Faculty for Medicine. Furthermore, students of Human Medicine and from the Faculty of Biology (Bachelor and MSc Courses) are trained in clinical neurobiology. Another focus is the training of students in biomedicine and biochemistry and participation in training programs for the class Neuroscience of the Graduate School Life Science at the University of Würzburg. Further courses are offered for students of the course experimental medicine within the training program for MD students.

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Chair of Tissue Engineering and Regenerative Medicine (TERM)

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Structure and general data

The focus of TERM is on three scientific areas: Technologies for tissue engineering (TE) – 3D tissue models – Implants for regenerative medicine (RegMed). In order to manufacture innovative and biologized implants and to examine human vascularized tissue models interactions of cells and materials, tissues and substances or tissues and microorganisms, the TE was continuously developed further in the past two years. These new developments are the basis for the successful acquisition of various projects which serve as fundamental basis for the strategic focus of TERM. Since 2014, the junior group ETface, funded by BMBF and lead by Dr. Jan Hansmann can already publish its first innovative results. In cooperation with the team of the Biocentre the group could successfully present the first Proof of Principle experiments, in 2014, which showed that human 3D tissue models can also be applied to study the mechanisms of certain infections. As a result of this since April 2016, the DFG supports the graduate program 3D Infect. Within this framework, diverse 3D in vitro test systems based on the BioVaSc-TERM are being used and further developed. The field of transplant development using endogenous cells was strengthened in 2015 by the EU Project HemAcure. For the first time, genetic repair is combined with tissue engineering in order to develop an autologous cell therapy to cure haemophilia A patients. The funding by the EU is 5.5 million euros and the project is coordinated by the UKW.

Focus of research

Junior group ETFace: Development of seamless tissue-technique-interfaces

The junior group ETFace is part of the BMBF program NanoMatFutur and has its focus on the interactions of cells and implant materials. Basis for the scientific questioning is that only one percent of the energy of a cardiac pacemaker is applied for the stimulation of cardiomyocytes. The remaining energy is lost in form of leakage currents at the interface between cardiac pacemaker and the tissue. By means of nanostructured surfaces, the efficacy of the implants is thought to be increased and the rejection and encapsulation reactions induced by implants are expected to be reduced or minimized. Therefor, complex 3D in vitro tissue models are established to examine of **Cell-Implant reactions** at an early stage. The induction of the fibrous encapsulation of the implant materials is examined during early development of the nanostructure surface modification and simultaneously analyzed to increase pacemaker efficiency.

Bioreactors

(J. Reboredo, J. Hansmann, T. Schwarz)

The bioreactor systems established at the TERM enable the reconstruction of the physiological environment of cultivated tissue, such as blood vessels, intestinal- and lung tissue. During the continuous development of these technologies, a modular scalable platform of the system has been realized. Furthermore, the systems are developed to manufacture implants under GMP-conditions. Another focus is on the automation: by applying state-of-the-art robot technology, processes like 3D tissue culture and various test can be carried out human independent and automatically.

Vascularized human tissue and disease models

(A. Appelt, Dr. D. Zdzieblo– iPS technology for the establishment of test systems, Dr. F. Ehlicke, Dr. J. Nickel tissue models for musculoskeletal issues, Dr. G. Dandekar, Dr. S. Nietzer–tumor tissue models, Dr. M. Steinke, A. Rossi, Dr. M. Metzger, M. Schweinlin – human barrier models)

Fig. 1: Incubator for special bioreactorsystems to cultivate 3-dimensional tissues.

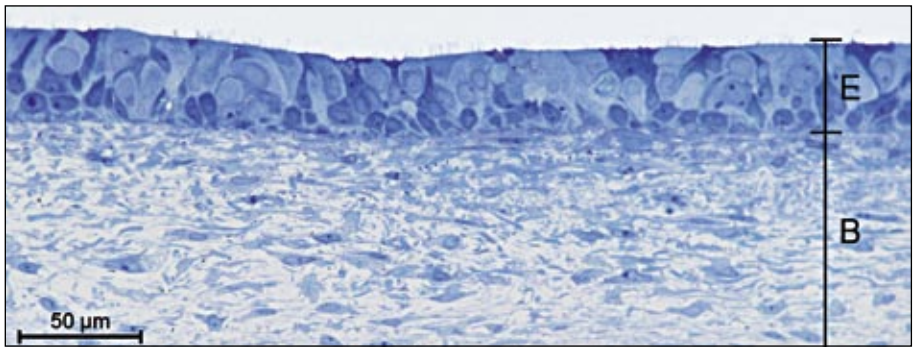

Fig. 2: 3D in-vitro-model of human respiratory mucosa (stained with methylene blue). E: epitheliallayer, B: connectivetissue.

iPS technology

For the importance of standardization and due to the high need, human tissue models based on iPS cells are established. Therefore, the iPS cell culture methods and their efficient differentiation into different cell types such as endothelial cells, astrocytes, pericytes or cariomyocytes was established. The blood-brain-barrier (BBB) displays the tightest and most important barrier between the blood circulation and the central nerve system. At TERM, a BBB models based on iPSC was established.For this, human iPS cells are differentiated in vitro into endothelial cells and astrocytes, the two most important cell types of the BBB. These are then used to establish 3D BBB tissue models. A further objective is to use human iPS cells from diseased donors to rebuild in vitro disease models allowing the use of such diseased tissue models for drug screening and efficacy testing.

Infection models

For the development of novel preventive and therapeutic strategy to battle infection diseases, understanding the natural way of infections is essential.
We have developed 3D in vitro test systems tostudy such infection mechanisms. The bacteria Bordetella pertussis causing whooping cough is located and thus attacks the human airway. In our test system which has functional cilia, we could reconstruct an infection with B. pertussis and verify the destruction of epithelial airway cells for the first time. In addition, at TERM we have developed an intestinal tissue model by using the proprietary BioVaSc-TERM®-technology and dynamic tissue culture systems. In cooperation with the group of Prof. Dr. Jörg Vogel from IMIB, and based on our technology a human triple culture model was established which representsthe human intestinal tissue, build from intestinal epithelial cells, the intestine endothelial barrier to the blood stream and the immune system (PBMCs). By using marked salmonella bacteria, the transmigration of bacteria through the intestinal epithelial barrier could be examined and verified. A time-depending increase of infected epithelial cells could be seen while the endothelia layer was not affected. Interestingly, the infection, lead to a release of interleukin and an activation of monocytes and NK-cells.

Transplants
(J. Braspenning, M.Haddad-Weber, O.I. Pullig, H. Walles)

For the anufacturing of transplants, (autologous) cell-matrix-products based on the BioVaSc®-technology or CellPouch™ are developed. Thus, complex tissues with vascular structure and improved integration ability can be established in vitro. Moreover, projects in different (pre-)clinical stages of development can be processed. Within the EU project HemAcure, autologous cells are genetically modified in the laboratory with the aim of producing the missing clotting factor VIII. Afterwards, these cells are then implanted within a medical device into the abdominal wall of the patient. Once the tissue is ingrown, the medical device is then filled with the genetically modified cells. Asthe medical device (BioVaSc or CellPouch) is connected to the blood circulation, the cells cancontinuously produce the clotting factor VIII to cure heamophiliaA patients.

Lectures/Science

Our lecturers are actively involved in lectures and internships in the following fields: Master Biomedicine, Bachelor and Master in "Technology of Functional Materials", Bachelor and Master "Biology". Medical students can participate in the integrative seminar "Biochemistry – Blood and bone diseases"

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Department of Orthopedics

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Professor Dr. med. Franz Jakob
Phone: 0931/803-1580

Professor Dr. med. Andre Steinert
(until 12/2016)

Mission and Structure

The Orthopedic Hospital König-Ludwig-Haus is a top level hospital for the treatment of musculoskeletal diseases and injuries. The hospital is operated by the District of Unterfranken. Integrated are the Chair of Orthopedics and the Outpatient Department for Orthopedics of the University Hospital, as well as the Orthopedic Center for Musculoskeletal Research. The Chairman of the Department, one full Professor for Osteology, 6 Associated Professors and 15 Residents are taking care of the patients and teaching. The hospital has 123 beds and in 5 operating theatres more than 4.175 surgical procedures are performed each year. The University Outpatient Department provides care for about 18.300 patients a year. The König-Ludwig-Haus also runs its own x-ray department and physiotherapy.
The Orthopedic Center for Musculoskeletal Research is an interactive platform between basic science, translational research and clinical implementation of innovative therapeutic strategies. The main 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 facilities 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 representation of 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 Würzburg MCW, which plays an important role in the development of a growing research branch at the university.

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
- SpineSurgery
- 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)

Orthopedic consulting is offered for several other hospitals and centers for disabled.

Major Research Interests

The OrthopedicCenter for Musculoskeletal Research is located in a 600 sq. m laboratory space (S1, S2, radioactivity) with one location at Brettreichstrasse 11 and another at Röntgenring 11 and a third one at Friedrich-Bergius-Ring 15 in the “Gründerzentrum” of Wuerzburg University. The Center is supported by the District of Unterfranken. It is funded by the German Research Society (DFG Research

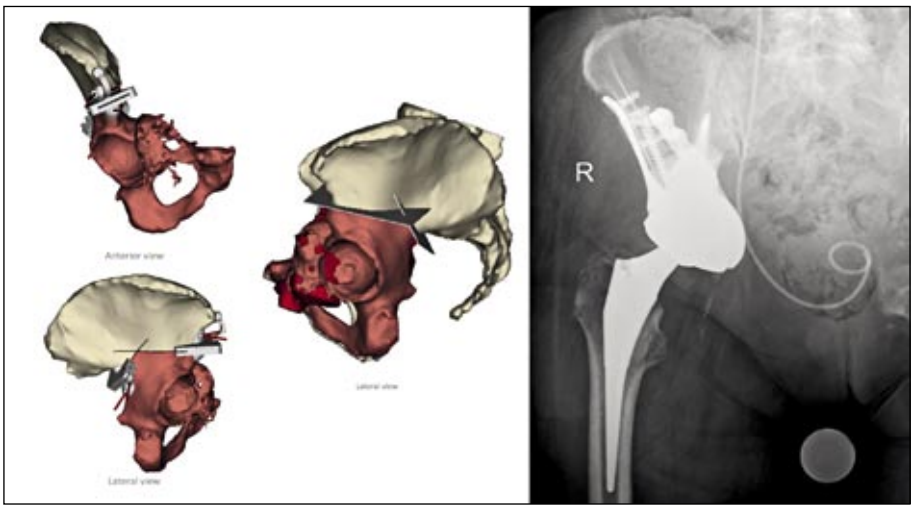

Fig. 1: Partial reconstruction of the pelvis after resection of a chondrosarcoma. Preoperative 3D design and clinical results after resection type II/III.

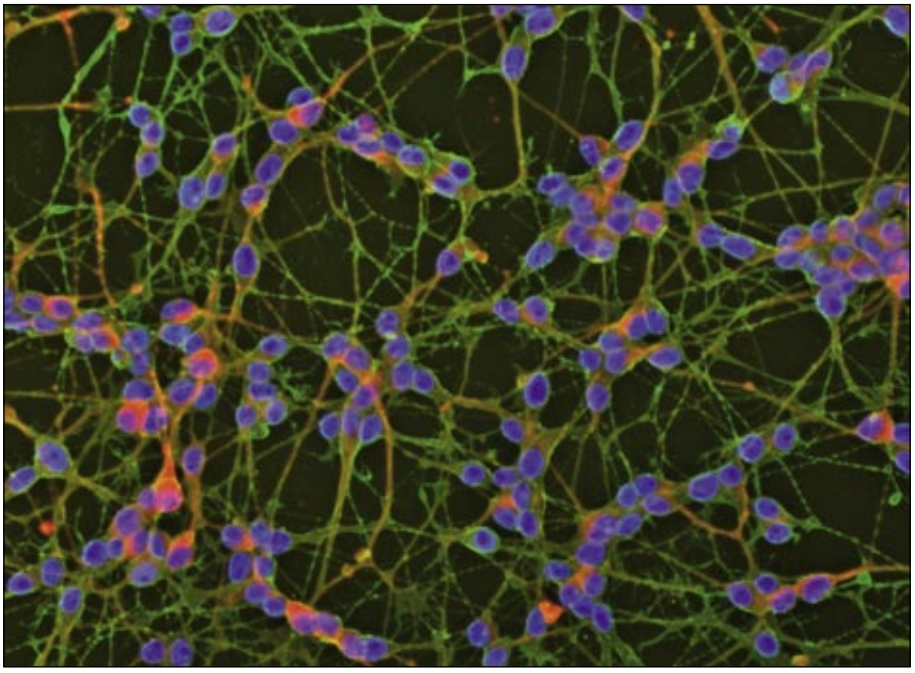

Abb. 2) Effects of Alkaline Phosphatase on the differentiation on neuronal cells SH-SY5Y^{TNAPhigh} after 8 days of neurogenic differentiation (double staining TNAP (green)+ tau (red)), (adopted from the work of Graser et al., Bone 2015).

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 Würzburg, 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). The clinic provides a clinical study Unit (Head Dr. L. Seefried) which runs Phase II/II -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)
- 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 (A. Steinert, M. Rudert)
- Gene Therapy and Regenerative Medicine in Musculoskeletal Diseases (A. Steinert, B. Holzapfel, M. Weissenberger, B. Geyer)
- Biomechanics and Mechanobiology (F. Jakob, L. Seefried, S. Müller-Deubert, A. Steinert, M. Hoberg, R. Ebert)
- Tissue Engineering of the Meniscus (M. Rudert, M. Hoberg, A. Steinert)
- 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 (A. Steinert, 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, M. Hoberg)
- Patient individual joint supply of knee, hip and pelvis (M. Rudert, A. Steinert, M. Hoberg, B. Holzapfel, J. Arnholdt)
- Special Orthopaedic Pediatric Surgery, Spine and Foot Surgery (P. Raab, M. Walcher)
- 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

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Institute of Medical Teaching and Medical Education Research

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Activities and Structure

The Institute of Medical Teaching and Medical Education Research was founded on 01.10.2016. The activities of the interdisciplinary team 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

Evaluation of the Educational Environment and Knowledge Gain during the Practical Year
(C. Rabe)

Evaluation results make an important contribution to quality control. Furthermore, reasonable measures may be derived from them that serve to improve classes (all modes) as well as curriculum conception. Prerequisite is a valid and reliable measurement tool that is currently in development for workplace-based teaching of medical students during their Practical Year. For the first time, data pertaining to the educational environment and self-assessed knowledge gain in students on their compulsory trimester rotations in surgery and internal medicine will be collected in the form of an online survey. In addition to the psychometric testing of the questionnaire, a number of calculations lie in the foreground to determine the gain in knowledge. In future, this student assessment will be made available to all of the participating clinics of University Hospital Würzburg and its associated teaching hospitals using comparative scores and mappings.

Scientific Competence in Training and Continuing Professional Development
(C. Rabe)

Scientific competence constitutes an important basis to practising as a doctor. Within the framework of an interview-based study on participants of a research training programme, young researchers in medicine (so-called clinician scientists) as well as their supervisors are questioned on their assessment of their needs, the content form, as well as structures conducive to scientific competence (retrospective view). In addition, study participants assess the general programme framework as well as courses offered to acquire and develop personal skills. The results of this qualitative study may be implemented as an aid to embedding a longitudinal module on “scientific work” into the degree of medicine and integrating structured postgraduate programmes.

The Competence-based Assessment of Clinical Practical Skills
(J. Backhaus)

Clinical-practical competence is assessed on a regular basis during the study of medici-

Fig. 1: Interprofessional cooperation of a team with different health care professionals. At the university hospital, students and nursing staff in the training phase are teached together. Photograph: Andrew Entwistle.

ne in the form of objective structured clinical examinations (OSCEs). The evaluation by means of item-response theory (IRT) contributes to quality assurance and enables us to inspect the data psychometrically. We need to clarify to what extent the items (assessment criteria) on the respective assessment lists for each of the OSCE stations encompass the construct of clinical competence, as well as to what extent the construct remains stable throughout the course of subsequent semesters. A particular syntax was adopted as the basis of this new assessment method, which includes among other things the calculation of personal competences and differential item functioning.

The Creation of Stereotypes in the Interprofessional Working Environment
(S. Sippel)

The creation of stereotypes and reciprocal expectations of role is an important aspect of interprofessional teamwork in the healthcare professions. The analysis of development processes as well as training a willingness to change with doctors, nurses/carers, and therapists are elements essential to improving teamwork and mutual perception and esteem. The attitudes of both medical students and trainees towards their own and the other professional group is determined with the aid of quantitative and qualitative methods. Subsequently, fitting interventions can be developed from the signs pointing to individual mechanisms of action to counteract the prejudice.

Teaching

Teacher Training (Certificate in Medical Didactics)

The Institute has implemented an interprofessional training programme as a basic qualification in medical didactics for educators in medicine. The qualification programme is recognized throughout the State of Bavaria and comprises 60 hours of teaching. It is aimed at all educators in the field of medicine (physicians, carers/nurses, therapists) who wish to expand their competence in didactic methods. 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.

Novel E-Learning Module: "Informed Consent prior to Surgery"

In cooperation with the Clinic for General, Visceral, Vascular, and Paediatric Surgery, the Institute has integrated a new online module on the subject of "Informed Consent prior to Surgery" into the one-week practical course in surgery. The so-called flipped-classroom concept is based on a podcast preparation including a guide to self-directed study. Students work through the course content independently and carry out interviews with simulated patients as a practical application. This enables patient-centred training for students.

Judge the Situation

A new compulsory seminar affords students of medicine and dentistry in their first semester their first contact with the subject of science. The aim of the interactive seminar is to sensitize participants to science and to reflect on good scientific practice, the handling of data, and copyright. Here the situational judgement test is employed, in which students analyse and assess a situation according to five predetermined courses of action in the conflict between legal basis and social acceptability. In addition, students are given an insight into research structures and offers available to working scientifically in and around Würzburg.

Interprofessional Communication and Teamwork

The Robert Bosch Foundation is funding a new teaching concept at the Institute, in which medical students and trainees in healthcare professions alike are taught together as a team. The aim is to achieve greater harmony and improve efficiency in teamwork in the workplace later in life. Participants complete a three-part workshop. They reflect on typical "critical incidents" taken from their interprofessional career experience and collate reciprocal expectations and specific preconceptions. Participants practice the cooperative management of occupational situations in theatre or on ward in mutual roleplays and with simulated patients. Here they analyse feedback strategies, dimensions of communication, rules of collaboration, as well as hierarchical structures.

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Department for Functional Materials in Medicine and Dentistry

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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 work with clinicians to realize the departments´ mission statement "higher quality of life through innovative materials". The Department is divided into five competence platforms: hierarchical structures, biofabrication, bioactive inorganic scaffolds, nano-biotechnology and microbiological testing. The research of the department was financially supported during the past two years by the Interdisciplinary Centre for Clinical Research of the University Hospital Würzburg, the German Research Foundation (DFG), the Federal Ministry for Education and Research (BMBF) and the European Union.

Main Research Focus

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. Figure 1 shows a cartilage mimetic, layered construct with aligned micropores, which run orthogonal to the layers and accordingly will enable cell invasion in the different layers of the construct.

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. Figure 2 shows the example of a computer model of a human ear, which is printed from a hydrogel using a 3D dispense printer. Yet another method, which is established at FMZ, is an emerging 3D printing technology that fabricates with micrometer thin fibres that form highly ordered scaffolds for cell culture. This precision is achieved by combining electrostatic drawing of polymer melts together with automatized collection of the formed fibres.

Bioactive inorganic scaffolds

The development of inorganic scaffold materials for bone regeneration at FMZ is based on reactive calcium- and magnesium phos-

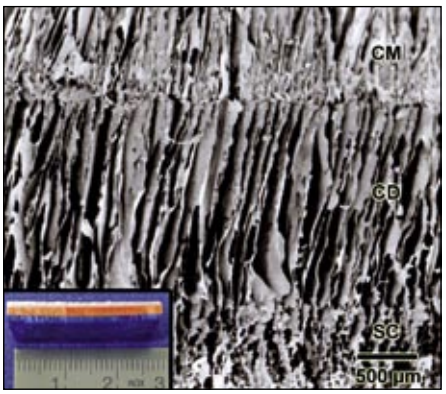

Fig. 1: Scanning electron microscopy of a layered, cryostructured construct with three different layers, with a composition mimicking the composition of osteochondral tissue. The insert depicts the construct with added colour to further demonstrate the hierarchical structure of the scaffold.

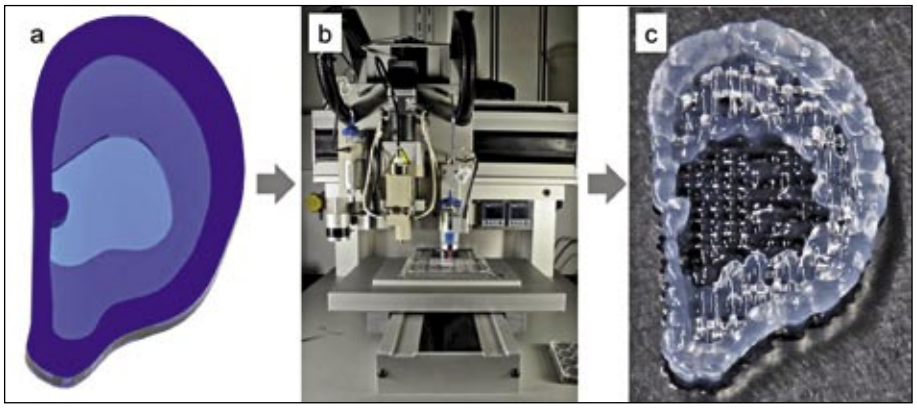

Fig. 2: (a) CAD-model of the shape of a human ear. (b) 3D printer for the biofabrication using hydrogels. (c) Printed hydrogel ear.

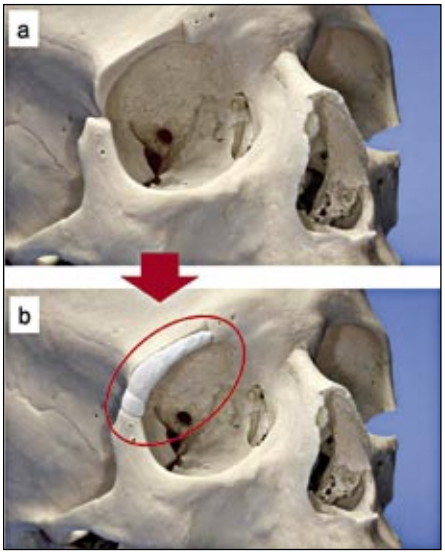

Fig. 3: (a) Skull with defect in the orbita region. (d) Customized printed and inserted calcium phosphate implant.

phates that set after addition of water under ambient conditions to form a stable implant without the need for sintering. Depending on the application site, the biodegradable bone replacement materials are applied either as pastes, preformed monoliths or granules. The transfer of the cement systems to 3D powder printing enables the fabrication of patient specific implants (Figure 3). All application forms are microporous and hence bioactive cement morphologies. The fabrication at room temperature additionally offers the possibility to modify the material with organic bioactives such as antibiotics or proteins. The local release of such drugs from the cement matrix into bone enables the controlled release of pharmaceutical active doses without systemic side-effects. Besides protein based growth factors the ceramics are also modified with bioactive ions such as Sr^{2+} or Cu^{2+}. In the past years, research on hybrid systems came to the fore, e.g. by using fibres during 3D printing or by developing dual-setting cement systems by combining cements with cross-linkable hydrogels.

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. For this purpose, human cell types and prokaryotic cells of different strains are used. 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. 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, graduate students of Biomedicine and, together with the faculty of Physics and Astronomy for students of “Nanostrukturtechnik”. 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 master course Biofabrication together with the University of Utrecht (NL) and the Queensland University of Technology (QUT, AUS).

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Department of Orthodontics

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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 me-

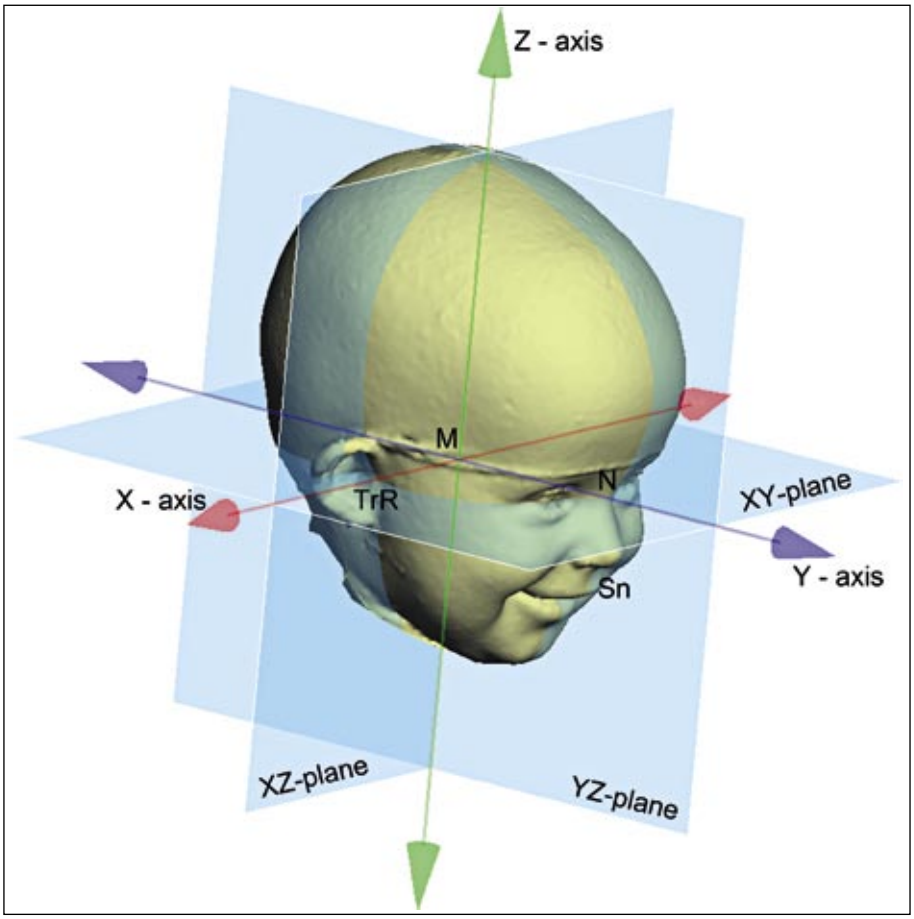

Fig. 1: Three-dimensional analysis of baby's heads.

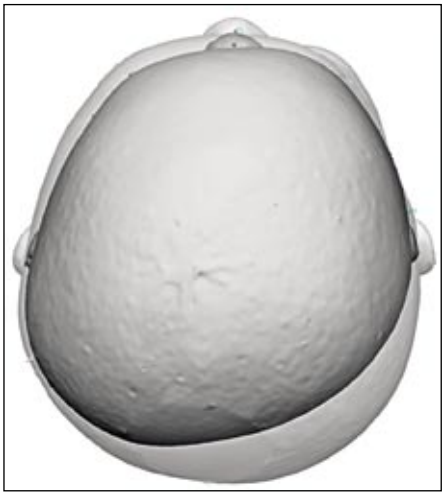

Fig. 2: Superimposition of three-dimensional data of a patient with positional plagiocephaly before- and after successful head orthesis therapy.

thod 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 a further externally funded research projekt (German Society of Orthodontics) the longitudinally growth of the infants' skull has been analysed. The objective is to build up a database of three-dimensional, morphometric, longitudinally recorded data from baby and infant skulls. Therefore with morphometric 3D-data standardised physiological data can be etsablished.

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 the oral health related quality of life of orthodontic patients.

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 PTHR1 gene in diseased patients were first described in an interdisciplinary clinical and molecular genetic study. A part of these results were honored with the prize of the best publication in the „Journal of Orofacial Orthopedics" in 2011.
In a proposed future study in collaboration with the Physiology Institute and the Department of Oral, Maxillary and Plastic Facial Surgery, it is planned to analyze the underlying pathogenesis of failure of eruption. 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.

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Department of Oral and Maxillofacial Surgery

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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 the in-patient care (about 1.650 patients each year), approximately 19.000 patients are treated in the outpatient clinic. Furthermore the clinic provides a comprehensive consultant support, particularly for the paediatric clinic (craniofacial dysplasia and cleft-lip-palate patients) and within the interdisciplinary emergency treatment and intensive care of traumatised patients. Together with the adjacent specialities, especially 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 tumors as well. Furthermore the department belongs to the *Musculoskeletal Center Würzburg*, the *Craniofacial Center Würzburg*and the *Center for rare Diseases Würzburg*.

Within the in-patient treatment as well as the consultation hours for outpatients, we treat patients with:

- tumors of the head and neck
- trauma of jaws and face
- craniofacial deformities
- plastic-aesthetic reconstruction
- dental implants including bone augmentation
- oral surgery (e.g. cysts, abscesses, osteomyelitis)
- diseases of salivary glands
- TMJ disorders

Major Research Interests

Tumor 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 tumor development and –progression. Here special attention is paid on signal transduction pathways and their intracellular switching points. Furthermore modern therapy strategies in treatment of oral squamous cell carcinoma and its precursor lesions are investigated. In this, additional points of attack like tumor antigens play an outstanding role. In cooperation with CCC Mainfranken, at protein- and genetic level research is performed to discover mutations in proteins of the tumor metabolism in order to utilize them for tumor therapy. This research lays the foundation for the participation to pharmaceutical drug trials, which are provided to our patients in cooperation with our ambulatory care for solid tumors.

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 retrospectivemonitoring, risk factors and a strategy for the prevention of BION are to be outlined. These molecular biological, bone metabolism-affecting therapy approaches are promoted by the “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 is the development of a melt-electrospun membrane for the intraoral rehabilitation of hard- and soft-tissue defects. Melt-electrospinning allows the predictable fabrication of fibres in a micro- or even nanometre scale out of molten polymers, which can be spun to a membrane. This membrane consists completely of medical-grade polycaprolactone and should provide the following properties: ideal growth conditions for oral mucosa, a bacteria-tight core layer and best regeneration conditions for a bony graft site.

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 premature closure of the cranial sutures or positional plagiocephaly. The aim of this project is: First, to establish a 3D-stereophotogrammetry as a non-invasive imaging technique in diagnostics and follow up of infantile skull deformities; second, comparing different therapeutical strategies (surgical or conservative

approach in children with a sagittal craniosynostosis, and molding therapy in positional plagiocephaly (with an individual CAD/CAM manufactured orthesis) versus positioning and physiotherapy alone) in regard to morphologic skull changes and neuropsychological development. Documentation and analysis of early language skills as well as individual evolution of neuropsychology parameters are monitored. Predictive parameters for counseling and disease progress under different therapeutical strategies will be defined.

Bone regeneration and bone substitution
(C. Linz, A. Fuchs, 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 implantation in orthotopical, potentially load-bearing defect situations. The behavior of these materials in direct contact with a bony transplant site should be evaluated. Especially degradation of the pastes/granules and their remodeling into functional, local bone are to be observed.

Modern Imaging
(C. Linz, R. Brands, U. Müller-Richter, A. Buck (Nuclear Medicine), A. Kübler)

For 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 specifity 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.

Investigation of resistances of targeted therapy 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. The reason for that is on the one hand a high genetic heterogeneity of tumors and on the other hand an activation of alternate signalling pathways. The aim of the project is to investigate the main causes of these resistances to EGFR- antibodies and PI3K-inhibitors. In this context, amongst others, current investigations focus on receptor tyrosine kinases (RTK). Furthermore the influence of human papilloma virus on expression levels of the aforementioned RTKs is observed.

Basic research on induction of apoptosis in oral squamous cell carcinoma
(Clinician Scientist Program/CCC Mainfranken, R. Brands)

Within a targeted therapy of tumors of the head and neck region tyrosine kinase inhibitors (TKI), which inhibit intracellular signaling pathways selectively, play an important role. So called SMAC mimetics are pro-apoptotic molecules which have 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 tumor 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) shows 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 therapeutically approach in treatment of MM is evaluated. By 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 educational engagements within both the medicine and the dentistry course.
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 the local dental anaesthetic techniques. These various fields are communicated theoretical as well as in practical courses and clinical traineeships.
Furthermore the clinic is involved in the advanced education for already approbated colleagues due to the organisation of certified meetings and courses, e.g. an annual international course on orthognathic surgery.

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Department of Prosthodontics

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Professor Dr. med. dent. Dipl.-Ing.
Ernst-Jürgen Richter
(Head of the Department until 9/2016)

Mission and Structure

The Department of Prosthodontics currently has 51 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.

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 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.

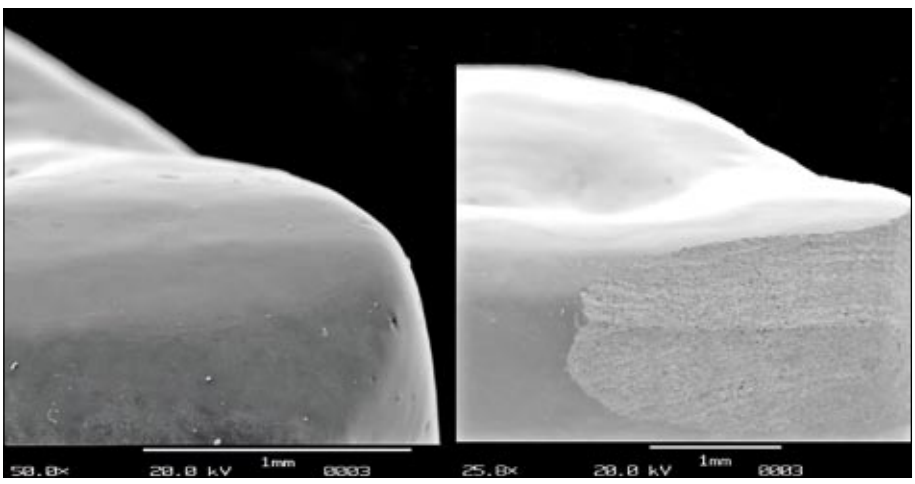

Fig. 1: Surface of a ceramic restoration. Left hand side: untreated. Right hand side: after occlusal adjustment.

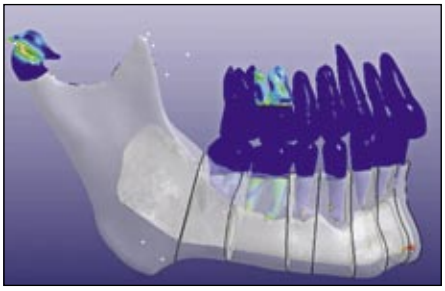

Fig. 2: FEA during clenching on the molars. The colors represent different levels of strain in the periodontal region and the temporomandibular joint.

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. 2015, close to 370 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 on prosthodontics (Prof. Dr. Dipl.-Ing. E.-J. Richter) 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 2015 this equated to almost 600 prosthetic restorations which were made per class, as well as about 400 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.

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Department of Conservative Dentistry and Periodontology

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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 centres 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 Centre of Dental Traumatology in Würzburg was founded as the first interdisciplinary centre 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. M. Jahreis, Dr. R. Krug and Dr. S. Soliman).

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 morpho-

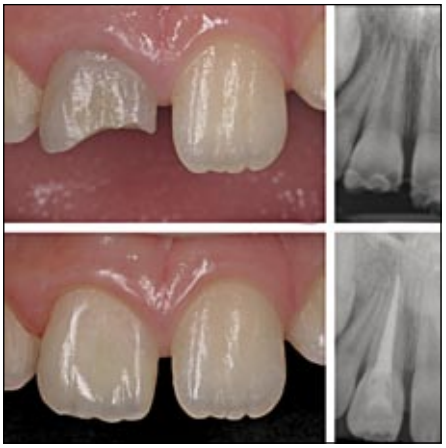

Fig. 1: Esthetic, minimal invasive treatment of a traumatized incisor.

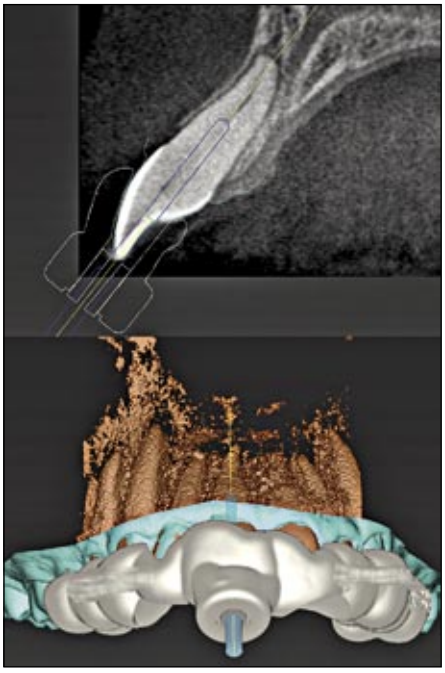

Fig. 2: "Guided Endodontics" a new treatment approach for teeth with pulp canal obliteration.

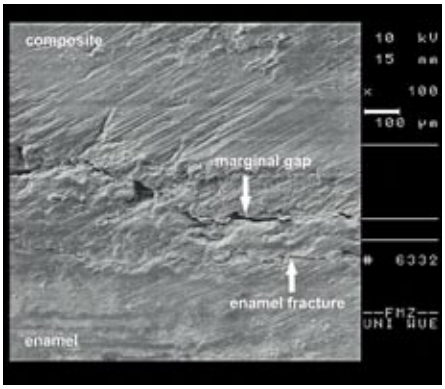

Fig. 3: Marginal analysis of a composite restoration using a scanning electron microscope.

logically 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 in the years 2016 and 2017.

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.

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Division of Periodontology

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Mission and Structure

Besides Prof. Schlagenhauf the staff of the division comprises further four dentists and 3 dental assistents. 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 Unterfranken and beyond. In collaboration with 7 other periodontal competence centers in Germany the efficacy of antiinfectious strategies for the therapy of aggressive periodontitis and perimplantitis has been evaluated in a major clinical multicenter study. According to established knowdlege the onset of periodontal disease is favoured by a proinflammatory dysbiosis of the oropharyngeal microbiome, which in itself is decisively modulated by malnutrition, stress, smoking as well as hereditary risk factors. Thus a variety of research collaborations has been established with other medical specialties amongst others internal medicine, medical microbiology, pediatrics, osteology as well as gynecology. Results for example in the field of nutritional modifications and guidance have already entered clinical practice.
Also surgical interventions for the minimally invasive correction or regeneration of periodontal lesion are part of the clinical standard procedures provided by the division.

Focus of Research

The main research projects of the Division. of Periodontology are listed below. Some of them are joint efforts in collaboration with other institutes and clinics in Würzburg and other national or international institutions.

Adjunctive use of systemic antibiotics in the therapy of chronic and aggressive periodontal disease
(Y. Jockel-Schneider, U. Schlagenhauf)

The evaluation of the usefulness of adjunctive systemic antibiosis in the course of antiinfective periodontal therapie has been a research focus of the divison since several yeras. Next to preceding clinical trials realized in collaboration with the Institute of Hygiene and Microbiology the Division of Periodontology was a major contributor a multicenter intervention study sponsored by the German Research Foundation on this topic, whose results are presently published .

Modulation of gingival inflammation by consumption of nitrate-rich foods
(Y. Jockel-Schneider, U. Schlagenhauf)

In a randomized clinical trial in collaboration with the Institute of Food Technology and Biotechnology of the University of Hohenheim,

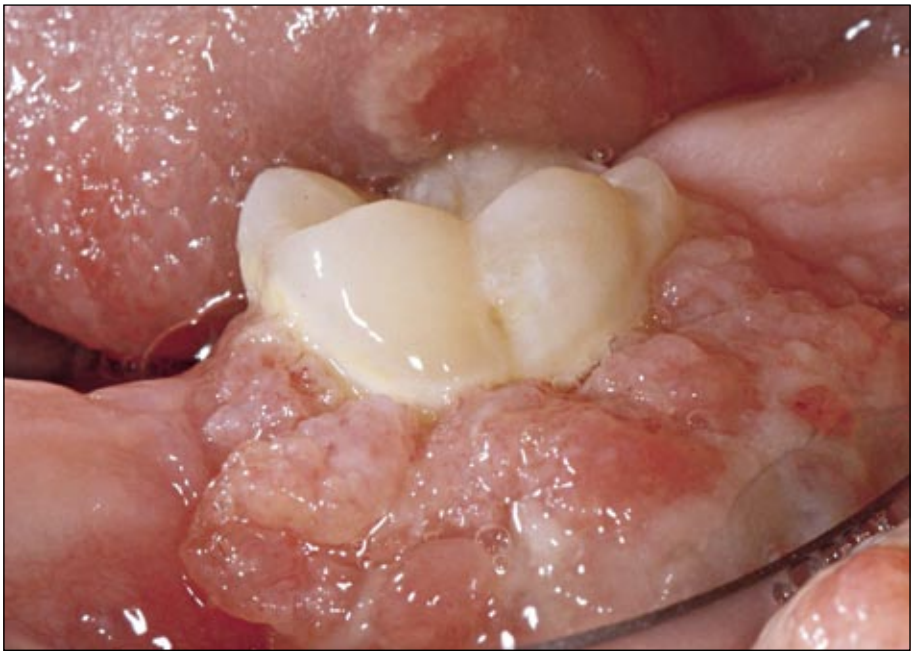

Fig. 1: Periodontal inflammation in a patient suffering from hereditary plasminogen deficiency.

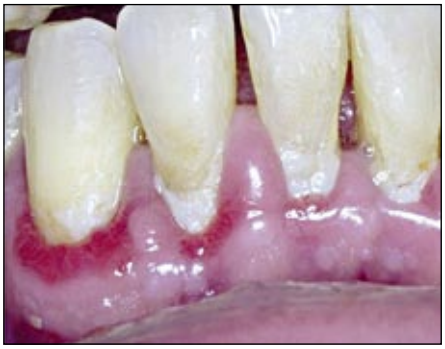

Fig. 2: Pronounced plaque-induced gingival inflammation in a patient with insufficently controlled diabetes type II.

the Divison of Periodontology evaluated the modulatory effect of nitrate-rich foods on inflammation. The data revealed a pronounced inhibitory effect of the consumption of nitrate-rich lettuce on chronic gingival inflammation, irrespective of the quality of personal plaque control.

Periodontal diseases and cardiovascular health
(Y. Jockel-Schneider, S. Störk, U. Schlagenhauf)

Investigations performed in collaboration with the Clinic for Internal Medicine I revealed, that patientes suffering from periodontal disease frequently display a significantly elevated vascular augmentation when compared to age-matched periodontally healthy controls. Whether successful periodontal therapy has a significant impact on the status of cardivovascular health is subject to an ongoing clinical trial which also is realized in collaboration with the Clinic for Internal Medicine I and supported by the DFG.

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 exent of aveolar bone resorption. The identification of further co-factors is subject of current investigations.

Teaching

Dental undergraduate training comprises the clinically most relevant aspects of periodontal diagnosis and therapy. Subsequent to the intensive teaching of the basic principles of periodontology firstly in dummy heads and subsequently in real patients nonsurgical minimally invasive periodontal therapy procedures are instructed and trained under the close supervision of experienced clinicians. The basic facts of periodontal surgergy are also demonstrated and practically instructed in a pig jaw model. Junior staff members of the Division of Periodontology are given the opportunity to acquire a formal postgraduate specialization in periodontology by following a formal 3 year postgraduate training program according to the guidelines of the German Society of Periodontology.

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Research Centers and Research Areas

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Research Center for Infectious Diseases (ZINF)

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General tasks and organisation

The Research Center for Infectious Diseases (ZINF) isa cross-faculty and interdisciplinary institution at the University of Würzburg that is dedicated to research of several infectious diseases that severely impact human health. The Center is structured in a manner that facilitates interdisciplinary cross-faculty communication, initiation of joint research activities and recruitment of extramural funding, as well as the joint organisation of international conferences and meetings. It includes researchers from four institutes within the medical faculty, the department of internal medicine II of the university hospital as well as five departments from the faculties of biology, chemistry, and pharmacy. An important element of the center is the four independent young investigator groups, whose work focuses on current emerging topics in microbiology and infectious diseases. These Young Investigator groups are associated with and physically located within the Institute of Molecular Infection Biology (IMIB). Notably, this Young Investigator programme has been identified as a means to successfully promote the research and careers of junior scientists throughout Germany and on the international level. Based on the high scientific output and international reputation of the ZINF, in 2009 it became a central and permanent institution of the University.

Research focus

Regulatory RNAs in Helicobacter pylori and Campylobacter jejuni
(C. M. Sharma, since 2010)

The Gram-negative Epsilonproteobacterium *Helicobacter* pylori colonizes the stomach of about 50% of the world's population leading to gastritis, ulcers, and even gastric cancer. The related pathogen, *Campylobacter jejuni*, is currently the most common cause of bacterial gastroenteritis in humans and it is also associated with several secondary autoimmune disorders. Using deep-sequencing technology we have analyzed the transcriptomes of these prevalent human pathogens on a global scale and identified many small regulatory RNA (sRNAs) candidates, an emerging class of post-transcriptional gene expression regulators in bacteria. Using genomics, biochemical, molecular biology and genetics approaches we are elucidating the functions and physiological roles of RNAs along with their underlying molecular mechanisms instress responses and virulence. For example, the abundant RepG sRNA from *Helicobacter*, directly targets a homopolymeric G-repeat in the 5'UTR of a chemotaxis receptor mRNA and thereby repress the expression of the pH-sensing chemotaxis receptor TlpB. While the sRNA sequence is conserved, the G-repeat varies in length in different *Helicobacter*-strains and leads to strain-specific regulation. Infection studies of human pathogens are often impeded by the use of artificial *in vitro* cell culture or an imal models, which are limited in their ability to comprehensively mimic the infection situation and disease development. In a collaborative project with Prof. Heike Walles (Dept. of Tissue Engineering and Regenerative Medicine) we are developing new three-dimensional (3D) infection models using tissue engineering to mimic the microenvironment of human tissue. Analysis of mutant strains has revealed different infection outcomes in 3D tissue models compared to standard 2D cell cultures, indicating that the 3D models can reveal infection phenotypes that are not evident in standard infection assays.

Bacterial cell differentiation
(D. Lopez, 2010-2015)

Biofilms are surface-associated microbial communities that play an important role in many chronic infections. They are composed of multiple subpopulations of cells with specialized roles in the community, for example, the bacteria are encased in an extracellular matrix that is produced by a subpopulation of specialized cells, while other subpopulations remain motile and others even benefit from the community by secreting proteases or antibiotics. The same situation also occurs during infections, where subpopulations of cells differentiate into specific states that express the distinct virulence factors required to trigger an infective process. We are using pathogenic bacterial models to study the molecular mechanisms involved in the differentiation process of distinct subpopulations of specialized cells, which are required to establish successful infection. Specifically, we have identified that specific receptor proteins are spatially organized into lipid microdomains within bacterial membranes, in an analagous manner to the lipid rafts found in eukaryotic cells. Importantly, we have found that disruption of these microdomains leads to the deregulation of several bacterial-signalling pathways involved in pathogenesis such as biofilm formation. We are also interested in identifying the selection pressures that drive the enormous genomic and phenotypic diversity of S. aureus clinical isolates. Using an *in vitro* biofilm assay to perform in time evolution experiments we have revealed that a single clone can evolve in a step-wise manner into phenotypically distinct clones with clinically relevant attributes. For example, an early arising strain produced toxins and antibiotics that led to the evolution of a subsequent strain that is resistant to the presence of these antibiotics. Importantly, interactions between these different evolving clones drives the evolution of strains that

Fig. 1: Scanning electron microscopy image of Campylobacter jejuni.

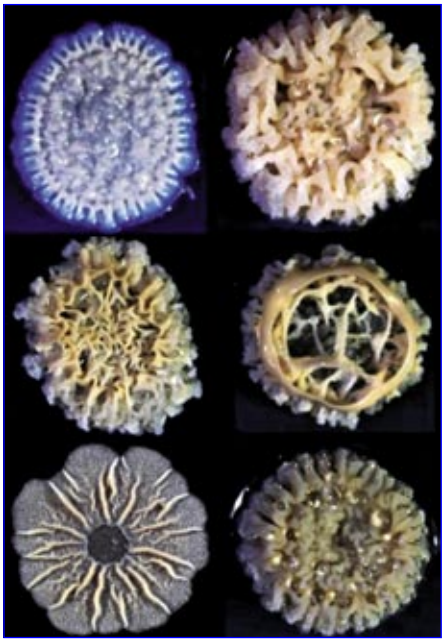

Fig. 2: Localization of lipid rafts in S. aureus cells using GFP-tagged flotilllin (green). Membranes stained in red. Scale bar is 1μm.

are genetically and phenotypically similar to the Vancomycin-intermediate *S. aureus* (VISA) strains found in the clinic.

Epigenetic gene regulation in Trypanosmabrucei
(N. Siegel, since 2012)

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 in Central and South America. Yet, many aspects of trypanosome biology are still not well understood, including the regulation of gene expression – which is the research interest of our group. Using the protazoan parasite *T. brucei*, we are studying the 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 post-translational histone modifications, histone variants and ncRNA 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
(Christian Perez, since 2014, joint ZINF-IZKF group)

The human body is inhabited by trillions of microorganisms comprising of bacteria, archaea and eukaryotes. While these microbes are, for the most part, harmless or beneficial to the host, occasionally some can cross the mucosal barriers and cause systemic, potentially fatal infections. In fact, many life-threatening infections in humans are caused by the very same bacterial or fungal species that comprise our microbiota. Despite their obvious medical importance, little is known about the mechanisms where by commensal microbes turn in to deadly pathogens and cause disease. *Candida albicans* is the most prominent fungal species residing in multiple human niches but most commonly in the gut. 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 fastidious mucosal disease in healthy people, particularly females. It is also the major cause of life-threatening fungal infections. The group studies the regulatory circuitry that enables the *C. albicans to* colonize different niches in the human body. Microorganisms in the gut typically not only compete with one another for nutrients but also establish mutually beneficial relationships. We are elucidating the genetic circuitry that allows *C. albicans* to colonize the gut and also which is dedicated to cope with cohabiting microbes. We are analyzing the role of various genes in gut colonisation in both conventional and germ-free mice, which lack an indigenous flora. These findings hint, for the first time, that C. albicans harbours gene circuits that operate exclusively in the context of the surrounding microbiota to enable colonisation of the mammalian gut. Therefore, we are using *C. albicans* as a model system to gain insights into the general strategies employed by members of the microbiota to proliferate as harmless commensals and how some of these microbes become life-threatening pathogens.

Teaching

ZINF members participate in practical courses and lectures for undergraduate students of biology, medicine and biomedicine and supervise Bachelor and Masters students' theses projects. In addition, members of the center are also members of the Graduate School of Life Sciences (GSLS) and involved in graduate student supervision and training. The center also regularly organises seminars, workshops and conferences covering current topics in medicine and microbiology.

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Comprehensive Heart Failure Center (CHFC)

Comprehensive
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General Information

The Comprehensive Heart Failure Center (CHFC, DZHI) investigates strictly interdisciplinary the systemic disease heart failure with all its comorbidities and accompanying illnesses with the purpose to develop innovative concepts for prevention and therapy. Since 2010 the center has been funded as one of eight integrated research and treatment centers in the field of widespread diseases. In January 2015 the CHFC was successfully peer-reviewed by an international committee.

Heart failure is a rapidly growing health care problem. The syndrome affects approximately one of ten subjects above the age of 70 years, currently accounting for 2-3 million patients in Germany and 28 million worldwide. Today, heart failure is recognized as common final, yet incurable stage of many cardiovascular diseases, which lead the illness-conditioned death statistics. The prognosis is as severe as in many malignancies. Repeated hospitalizations are frequent and costly. Heart failure severely compromises physical performance, metabolism, endocrine and cognitive function, and the quality of life. Yet, the various factors, which lead to the complex syndrome of heart failure are not fully understood. Hypertension, coronary artery disease, cardiomyopathies, valvular disease, and other illnesses can cause heart failure and stroke, renal failure, anemia, cerebral dysfunction, depression and the sudden cardiac death are frequent consequences. Therefore adequate and effectual strategies are of utmost medical importance. By its multidisciplinary approach the CHFC has already achieved important results for this demand. Hence, heart failure and its complications still constitute an interdisciplinary multi-faceted problem mandating an expanded interdisciplinary approach in research, teaching, and patient care.

The CHFC enhances and coordinates existing top-level basic, translational and clinical research activities in the field of heart failure, what is worldwide incredibly. Theoretical institutes (e.g. Physics, Chemistry, Pharmacology, Physiology, Tissue Engineering, Anatomy, Epidemiology) cooperate with clinical departments (e.g. Cardiology, Cardiothoracic Surgery, Endocrinology, Nephrology, Pulmology, Psychiatry, Psychology, Radiology, Hematology, Surgery) to develop innovative concepts in diagnostics and clinical management as well as new therapeutic strategies, which intervene early in the healing and remodeling processes of the heart. The interdisciplinary teams are supported by well-equipped core facilities (laboratory analyses, genetic analyses, animal housing, tissue engineering, documentation of patient data and

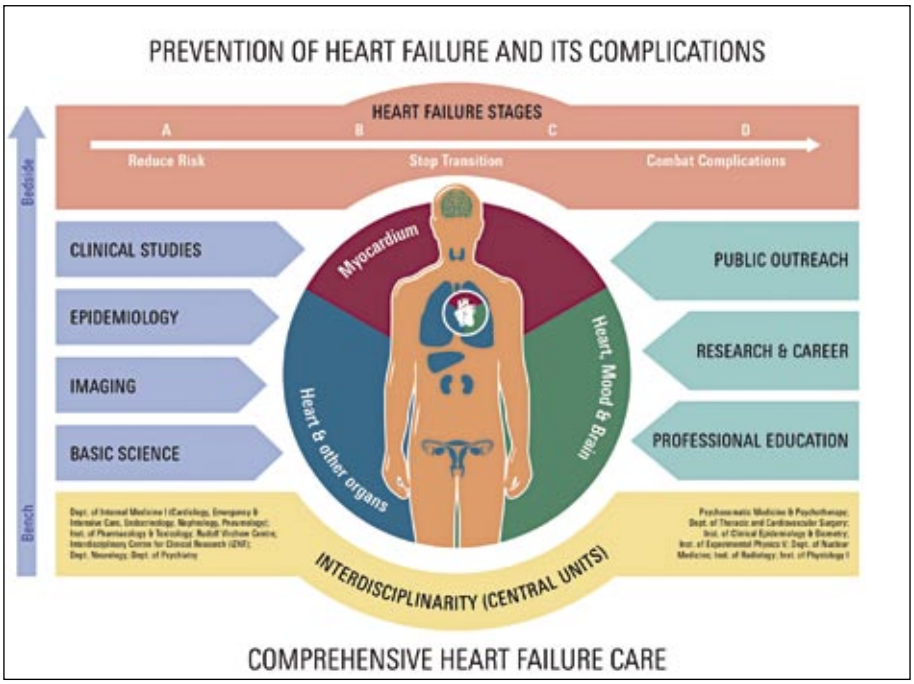

Fig.1: Research strategy of the CHFC from 2016 onwards.

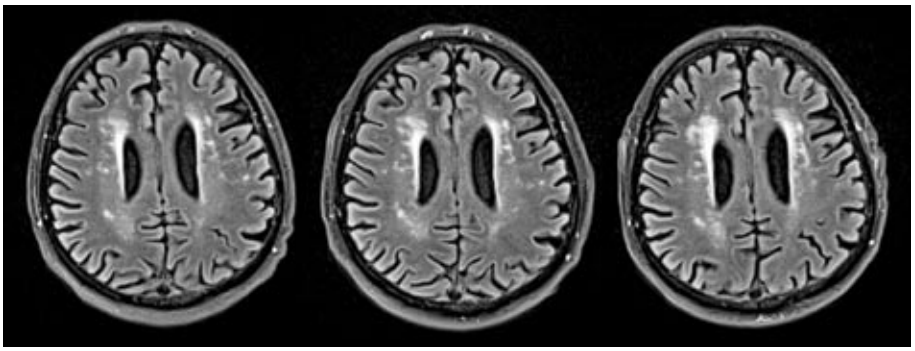

Fig. 2: The complex interactions between heart and brain are focused in one research area of the CHFC.

data mining) in order to succeed their ambitious endeavors. Since 2015 research at the CHFC was organized in eight Project Areas, which are now transformed into three Areas. They represent the most important structural subunits of CHFC's research.

The pre-existing clinical study unit in the University Hospital's department of cardiology was transformed into the central clinical research center of the CHFC with the aim of performing large clinical trials. Today, the CHFC is represented with four research departments (Imaging, Epidemiology, Translational Research and Genetics) lead by research professorships. Long-standing and very successful collaborations exist with the Collaborative Research Centers (SFBs) of the University, the Rudolf Virchow Center, the Interdisciplinary Center for Clinical Research, the Institute for Clinical Epidemiology and Biometry, and the International Graduate School of Life Science (Excellence Initiative) as well as with the national Competence Network Heart Failure (CNHF) whose main office was moved to Würzburg in 2012.

The CHFC supports excellent researchers of all career stages with ample opportunities to establish their independent scientific track, e.g. by supporting research projects, offering protected research time while working in the hospital, junior research groups, and research professorships. In cooperation with the Graduate School for Life Sciences the study course "Clinical Sciences" that may be extended into a masters degree shortly after finishing medical studies, a curriculum in clinical research for physicians, and a PhD track "Clinical Sciences" which started first in 2013, have been established. The master course "Clinical Sciences and Epidemiology" started 2015. In the summer of 2013 a new CHFC's research building was granted by the German Research Foundation with support of the Bavarian State Ministry of Education, Science and the Arts. In January 2017 the CHFC will be fully moved into its new facilities.

Major Research Interests

Research at the CHFC was re-organized into three Main Project Areas with the purpose to further improve interdisciplinary collaborations. The Areas represent the most important structural subunits of the CHFC for the implementation, coordination, performance and advancement of treatment and therapy strategies. The three Main Project Areas are **Myocardium, Heart & Brain** and **Heart, Metabolism and other organs**. Until Autumn 2015 the projects of the first funding period were organized into eight Project Areas:

Project Area A: Advancement of Diagnosis and Management

(Coordinators: S. Störk, A. Reif, H. Faller)

Using large established and new cohorts Project Area A is investigating the individual and combined clinical utility of diagnostic and therapeutic options for heart failure. Project Area A aims to establish new guidelines for diagnosis and therapy and works on complex multi-disciplinary interventions for heart failure patients ("management"), which were successfully tested in real world settings. On the basis of Project A1 (Characteristics and course of heart failure (stage A-D), and determinants of progression the STAAB Cohort Study investigates frequency and factors influencing the early course of heart failure (A and B) in a population of Würzburg. Biomaterials and standardized data sets are contributed by the prospect cohort study "Rheuma und Herz" (Associated Project A3) and the "Handheld BNP Studie" (Associated Project A4). The associated INH-study investigates heart failure patients after hospitalization in a long-term. Another topic is on effector kinases as target proteins of cardiac hypertrophy (Project A2). The three rotational positions do research in the field of aortic valve replacement and cardiac surgery. Additionally, Project Area A runs trials in regional health care organizations, like the cardiologist's network HeartFailureBavaria. Diagnosis and prognosis of patients in practitioner's care are observed in the RECODE study.

Project Area B: Healing, Remodeling, Protection

(Coordinators: O. Ritter, R. Leyh, B. Nieswandt)

Coronary heart disease is one of the most frequent causes for heart failure, e.g. the loss of tissue after myocardial infarct followed by chronic remodeling of heart tissue. Objectives of Project Area B are the identification of disease-specific mechanisms underlying those processes and identification of new therapeutic targets. This includes the crucial role of clotting factor XIII for infarct healing, the importance of the local, cardiac actions of C-type natriuretic peptide as well as the correlation between oxidative stress and the development and progression of chronic heart failure.

Project Area C: Rare Heart Diseases and Genetic Principles

(Coordinators: R. Bargou, R. Jahns, M. Gessler)

Project Area C addresses basic pathophysiological principles, clinical progression, and new approaches for prevention and therapy of orphan cardiac diseases. New cardiotoxic cancer drugs are investigated in clinical studies. Furthermore, the kinetics of myocardial inflammatory and autoimmune processes in the development of heart failure in animal studies and in a first human pilot study were investigated.

Project Area D: Endocrine System and Metabolism

(Coordinators: B. Allolio, H.-T. Pelzer)

Obesity is linked with diastolic and systolic heart failure. Clinical researchers investigated in the completed project parts the effect of a bariatric operation on cardiac function and quality of life in an interdisciplinary randomized clinical trial. For this purpose the biochemical, molecular and hemodynamic parameters of this intervention were investigated in animal models. In a prospective cohort study a registry of obesity and heart failure was established in order to identify prognostic factors which can predict cardiac symptoms and function in obese patients.

Project Area E: Cardio-Renal Crosstalk
(Coordinators: C. Wanner, V. Krane, F. Weidemann, P. Heuschmann)

Renal failure is a commonly observed complication of heart failure. Auto-antibodies that activate β1-adrenergic receptors may cause renal failure in heart failure patients (Project E1).
Patients with chronic kidney disease reveal a disproportionally high risk due to a high incidence and prevalence of cardiovascular disease. To identify new risk factors concerning heart failure and cardiovascular complications in patients with kidney disease are investigated by genome-wide association analyses in patients of the German Diabetes Dialysis Study (4 D Study, project E 5).
The rotational position in this project area also deals with the chronic cardiac and renal insufficiency by analysis of prevalence and risk factors of these diseases with data from the EUROASPIRE IV study. In the start-up project (E6) the correlation between COMT enzyme activity and clinical endpoints after cardiac surgery will be investigated in a pilot study

Project Area F: Emotion, Cognition, Cerebral Dysfunction
(Coordinators: S. Frantz, G. Stoll, K.-P. Lesch, M. Heckmann)

Interactions between heart failure and depression, cognitive and neurological dysfunction, and changes in brain structure are subject of Project Area F. In a murine model, Project F1 studies whether heart failure leads to anxiety or depression-like behaviour, and if behavioural changes adversely affect left ventricular remodeling. The consequence of heart failure on function of the brain is topic of ongoing projects and besides the human studies there are animal studies in mice and rats testing the influence of chronic heart failure on the brain morphology. The interdependency between cardiac diseases and stroke in human and animal studies are another important topic.

Project Area G: Advanced/ Terminal Heart Failure: Tissue Engineering and Regenerative Medicine
(Coordinators: C. Angermann, I. Aleksic, H. Walles, A. Müller)

Project Area G aims at a systematic prospective collection of data and biomaterials of patients with advanced or terminal heart failure. The psychological effect of an internet-based platform for ICD-patients is investigated in Project G2 (ICD Forum). The project will provide empiric data on the effect of a prevention program and affects also the treatments of Non-ICD-patients with heart diseases. Project G6 plans the development of new methods and technologies for the induction of neoangiogenesis in three-dimensional collagen scaffolds as well as the generation of functional vascular, autologous myocardial patches.

Core Facility Imaging
(Coordinators: W. Bauer, T. Bley, A. Buck, J. Deckert, G. Ertl, P. Jakob, H. Köstler, M. Lohse, S. Samnick, L. Solymosi, F. Weidemann)

The Core Facility Imaging develops advanced morphologic, functional and metabolic imaging techniques to support the Project Areas. Further, researchers of the Core Facility develop in start-up projects model-based magnetization transfer contrast imaging for cardiac MRI (CF 1.8), investigate myocardial sodium content in patients with hyperaldosteronism (MyStIC Study CF 1.9), and develop a new approach for coronary magnetic resonance angiography.

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Comprehensive Cancer Center Mainfranken (CCC MF)

Comprehensive Cancer Center Mainfranken

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General Information

The CCC Mainfranken (CCC MF) has evolved from the "Interdisziplläres Tumorzentrum der Universität Würzburg", which was founded in 1983. In 2008 the "Tumorzentrum" was transformed into the Comprehensive Cancer CenterMainfranken. In 2011, and reconfirmed in 2014, the German Cancer Aid awarded the CCC Mainfranken 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 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 November 2013. In addition eight organ cancer centers as well as the center for stem cell transplantation have been established and successfully certified under the roof of the CCC 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)

Multi-disciplinary Care

Medical care of patients suffering from cancer is provided at the UniversityHospital and its affiliates on an interdisciplinary basis. The CCC Mainfranken offers the structural framework for an efficient cooperation. All cancer patients entering the CCC MF are discussed in 15 weekly interdisciplinary tumor conferences and are treated by multidisciplinary teams. 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 (C16) houses the central quality assurance team, the central cancer registry, the CCC trial office and the interdisciplinary outpatient facility for clinical trials, the interdisciplinary outpatient chemotherapy ward, and provides a counselling ward for psycho-oncological and palliative care.

Additional multi-disciplinary offers for patients, health care professionals, and the community:

- Social service
- Information about self-helpgroups, meetings of self-help groups
- Sport courses and nutrition counselling hours for cancer patients
- Information seminars for patients, their relatives and the public about topics in the fields of cancer therapy and cancer prevention.
- Counselling of patients and their families with hereditary cancer
- Numerous training and education programs for physicians, clinician scientists, nurses and other health care professionals

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. Since 2014 a patient guidance system has been implemented to help patients navigate the different aspects of interdisciplinary treatment and follow-up care. The "pilots" act as trusted contacts for the patients, their relatives and also for physicians involved in the treatment.

Outreach/Regional Cancer Care Network

Cooperating partners of the CCC Mainfranken are the academic teaching hospitals (Julius-Spital and Medical Mission Hospital in Würzburg and the hospitals in Aschaffenburg and Schweinfurt) and other hospitals and specialists in private practices of the region Mainfranken e.g.in Coburg, Lohr, Bad

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Mergentheim, Bad Neustadt, Aschaffenburg and Kronach.

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: 3centers for oncology, 27 organ cancer centers). The CCC MF assures a high standard of medical care in the region by organizing joint tumor board activities, a regional trial network, central quality assurance, training and education programs, and the cancer registry services. In 2014 more than 10,000 cancer patients of the region of Lower Franconia were discussed in tumorboards of the regional cancer care network, 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, experts from the University Hospital work part-time in the respective local partner institutions (Main-SpessartKliniken, Kitzingen, Ansbach). In addition to the well-established network for hereditary gynecological tumors the CCC MF has in 2015 begun to establish a regional care and counseling network for hereditary gastro-intestinal tumors.

Translational Research

Clinicians work closely together with biologists and other scientists to perform cancer research on an international and competitive level. The University Hospital Würzburg, the clinical-theoretical and the theoretical institutes of the medical faculty are part of the CCC Mainfranken.

The main 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, theCCC MF has therefore developed translational research programs focusing on (A) the identification of critical regulators of tumor cell metabolism, (B) tumor immunology and immunotherapy and (C) targeted radiotherapy and molecular imaging. In addition, because tumor genome sequencing and personalized cancer treatment have grown in importance they have now been developed into a fourth research 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 of the CCC MF has demonstrated the first clinical proof-of-concept that T cell-based immunotherapy has the potential to eradicate bulk tumor masses and to cure patients with chemo-resistant disease (program B, Figure 1). Recently, CCC MF scientists have overcome a major obstacle for the clinical application of effective T cell-based immunotherapies by significantly shortening the time that is required to generate antigen-specific T cells in in vitro culture.

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) led to the identification new pathogenetic pathways and might lay the foundation for the development of personalized and targeted therapies in a series of different cancer entities. Potential new targets have been found in lymphomas, multiple myeloma, Wilm´stumor, melanoma, brain and endocrine tumors and lung cancer. Program D will in the future be extended to include gynecological tumors and head & neck cancer. For some cancer entities the results from tumor genome diagnostics are already beginning to have an impact on the therapy decisions for specific patients.

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. New developments in this area focus on the combination of radiotherapy with targeted treatments and immunotherapies.

Clinical Research

In addition to the translational research programs, the CCC MF has initiated a series of clinical research projects aimed at the improvement and further development of health care standards. The program includes studies on supportive care, psycho-social and palliative care, health care and outcome research, and investigator-initiated studies on therapy-improvements.

Outcomes research and the clinical cancer registry

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. The cancer registry is therefore also entrusted with the epidemiological cancer registration for the region of Lower Franconia within the frame of the Population Based Cancer Registry Bavaria (www.krebsregister-bayern.de). This registry 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 cancer treated at the CCC MF has markedly improved over the past decade (Fig. 2). Other projects aim to identify risk factors, prognostic markers and biomarkers in a number of different cancer entities. Recently, this has led to the discovery of novel markers for gastrointestinal tumors, bladder cancer and high-risk prostate cancer. Additional research programs at the CCC MF that focus on patient care are established in the areas of palliative medicine, psycho-oncology and breast cancer.

Clinical Trials

The central trial office of the CCC MF provides the complete infrastructure for planning and conducting phase-I, II, and III studies in all departments of Wuerzburg 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 Mainfranken is the Early Clinical Trial Unit (ECTU, Phase-I Unit). The ECTU is a highly specialized and fully staffed interdisciplinary clinical unit fo-

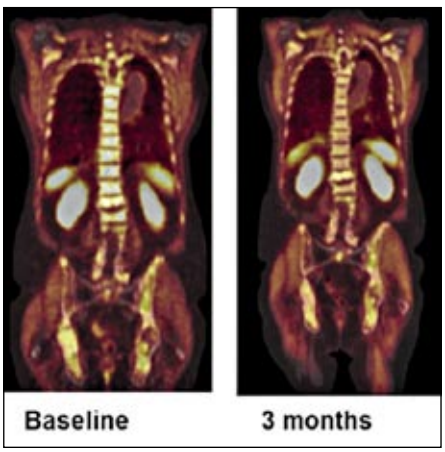

Fig. 1: PET-CT images of a patient with metastasized prostate cancer who was enrolled in a phase I trial at the Early Clinical Trial Unit of the CCC MF.

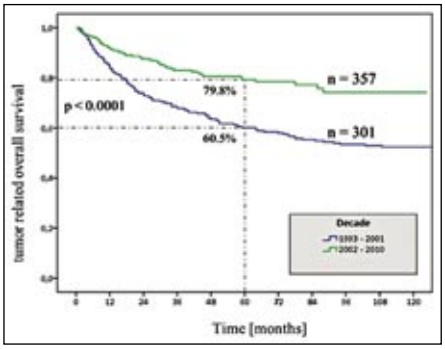

Fig. 2: Tumor related overall survival of patients treated for rectal cancer 1993–2001 (blue, n= 301) and 2002–2010 (green, n=357). (Wiegering et al. BMC, Cancer, 2014).

cussing 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 continually increased and for the years 2014/15 comprised 15-20 actively recruiting studies per year. A focus of these trials is the development of personalized treatments and immunotherapies with novel antibodies, radionuclides, tyrosine kinase inhibitors, heat shock protein inhibitors, HDAC inhibitors and other small molecules. Thus, the ECTU is an important structural element for the translation of basic research into the clinic(Fig.2). Recently, the ECTU has also been instrumental in the clinical testing of bispecific antibodies (which had primarily been developed for adults) in pediatric patients.

In addition, in 2013 the CCC MF has established a central interdisciplinary outpatient unit for clinical trial activities in solid tumors (ISAST). The new trial unit focuses on large multi-disciplinary phase II and phase III trials, thus complementing the activities of the well-established Early Clinical Trial Unit. The new trial unit has established multi-disciplinary trial program with a multi-institutional investigator teams comprising gyneco-oncology, uro-oncology, lung cancer, gastro-intestinal cancer and head & neck cancer.

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 Mainfranken and to establish a regional trial network. This has strongly enhanced accrual of patients from the regional area into clinical trials. In 2014 more than 1800 cancer patients of the region Lower Franconia were in clinical trials. Additionally, study programs in the fields of follow-up care and rehabilitation for cancer patients have been established in collaboration with a number of specialist institutions from the local area.

Based on this infrastructure the CCC MF has initiated a comprehensive program of investigator-initiated studies aiming at the improvement and further development of health care standards. Studies are currently running in various fields of clinical oncology. Key trials, chaired and initiated by Würzburg PIs, have led to results with practice changing impact in psycho-oncological and supportive care, endocrine tumors, hemato-oncology, non-small cell lung cancer, and gastro-intestinal cancer.

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Focus Area Regenerative Medicine and Biofabrication

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In recent years a number of large national and international research projects have emerged from the Musculoskeletal Center Würzburg (MCW) in the area of regenerative medicine and biomaterials research. This has made Würzburg an internationally visible and recognized center in this field of research. Most recently these research activities have been complemented with structural means. The first professorship for biofabrication in Germany was installed at the University of Würzburg. Moreover, the Fraunhofer Translational Center for Cancer and Musculoskeletal Diseases was established as joint institution of the Fraunhofer Society and the university hospital Würzburg in order to support and catalyze the translation of research results into the clinic. Latest development in this context is the installation of the so called Key Laboratory Polymers for Medicine within the Bavarian Polymer Institute (BPI). The Key Laboratory focuses on research for polymer based biomaterials with a special attention to biofabrication. Both the translational center and the Key Laboratory have been established through financial support by the state of Bavaria.

Musculoskeletal Center Würzburg (MCW)

(Professor Dr. med. Franz Jakob, Speaker)

Mission and Structure

The Musculoskeletal Center Würzburg MCW is an association of 20 clinics and departments in order **to treat musculoskeletal diseases and injuries and to propagate research within this field**. Musculoskeletal diseases are becoming increasingly important with rising life expectancy and the ongoing aging of society. Currently musculoskeletal disorders and injuries consume 16% of our total expenditure on health. They are the most common causes of disability and early retirement and at a later age often result in a hospitalization or long-term care. Disorders of bone, muscle and joints include common diseases like osteoporosis, osteoarthritis and the developing widespread disease of muscular dystrophy in old age (sarcopenia). The core facilities for the interdisciplinary clinical care of patients are the Department of Orthopedics with the Orthopedic Clinic König-Ludwig-Haus, the Department of Trauma, Hand, Plastic and Reconstructive Surgery and the Department of Oral and Facial Plastic Surgery. Based on the specific problem there is an intense collaboration with other hospitals and institutions of the Medical Faculty, in particular Internal Medicine, Nuclear Medicine, Pediatrics, Surgery, Neurology and the institutes of Radiology, Pathology and Genetics.

The **interdisciplinary basic research as well as the translational research** is conducted by the chairs of Tissue Engineering and Regenerative Medicine and the Fraunhofer Translational Center Würzburg, the Department for Functional Materials in Medicine and Dentistry, the Department for the Technology of Materials Synthesis and Fraunhofer ISC, the Chair of Pharmaceutical Technology and Biopharmaceutics, and by the respective research units of the core hospitals.

The network research is further supported by the collaboration with the IZKF, the ZEMM, the departments of biology, biophysics, bioinformatics, and with the faculties of theology and law for legal and ethical issues respectively. The central objectives of the collaborations in the MCW are interdisciplinary and across-faculty basic research with strong translational background, the interdisciplinary patient care is at the highest current level, as well as the education and training in medicine and medical technology.

The rapid translation of results from basic research into new clinical applications is now additionally supported by the recently established Fraunhofer Translation Centre, funded by the Bavarian government. The purpose of this institution is the actual link between basic research and clinical medicine, the training and promotion of "Clinician Scientists" and the education of personnel for the conduction of clinical trials with respect to Good Clinical Practice (GCP) in close collaboration with the Department of Clinical Epidemiology and Biometry. Intensive research at the interface between research, development and industrial production further results in a close cooperation with the Fraunhofer-Gesellschaft and the initial support of spin-offs.

Clinical research in the core hospitals of MCW is engaged with tissue replacements, implants and the care for trauma and inju-

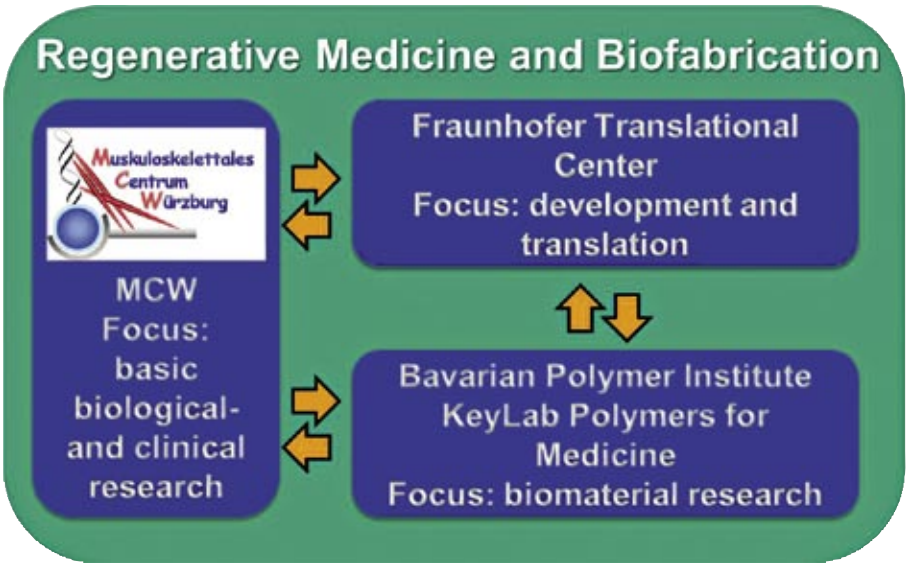

Fig. 1: Scheme of the interconnecting research- and translational structures within the field of regenerative medicine and biofabrication.

ries. Increasing effort is invested in the education of "Clinician Scientists" in cooperation with the Institute for Clinical Epidemiology and Biometry. Closely linked to this is again the translation and implementation of clinical trials in phases II-IV, together with the Translation Centre. A special focus of clinical research also lies on rare diseases, their investigation takes place within the framework of the newly established Centre for Rare Diseases ZESE. A working group on rare diseases of the skeleton in cooperation between Orthopedics and the University Children's Hospital and the Institute of Human Genetics was developed into a center for hypophosphatasia with worldwide visibility.

In **teaching**, special emphasis is placed on the participation of the chairs and associated professors and lecturers in a modern interdisciplinary education program in addition to the teaching of the core curricula within the medical and dental studies. Especially the study course "Functional Materials" is supported to a great extent by the members of the MCW. Also the participation in the study courses such as "Biomedicine" and "Life Sciences" as part of Würzburg Graduate School of Life Sciences GSLS is of great importance for the center. The intensive supervision of students during their internships, their bachelor or master theses as well as during their subsequent doctoral programs is standard practice in the different research facilities within the MCW.

Main Research Projects

The current research interests are focused on the needs of clinic-related research, current research questions arise from patient care and are then investigated in basic research and later returned to translational and clinical studies. An important area of research is the elucidation of the principles of tissue regeneration with a focus on musculoskeletal diseases and injuries. One main focus for regeneration research studies the molecular and cellular mechanisms of the early stages of tissue regeneration. This knowledge has a special meaning for the development of new materials and for *in situ* and *ex vivo* tissue engineering strategies. Within this research area, a junior research group is supported by funding from the IZKF. Special competences of the collaborating partners are in cell biology, epigenetics and aging of mesenchymal stem cells, in the development and translation of cell-based therapies, Tissue Engineering, the development of new materials, the application of pharmaceutical principles and the development of pharmaceutical drug delivery systems, as well as the modification and creation of new surfaces. Major work areas include the regeneration of bone, cartilage, muscle, adipose tissue, tendons and ligaments, the translation of new therapeutic strategies to treat injuries and degenerative diseases of the musculoskeletal system, including the oral and maxillofacial region. At the Department of Orthopaedics and in the Orthopaedic Clinic "König-Ludwig-Haus" a center for locomotion research is built with funds from the European Union Regional fond EFRE. The research program is focused on the technology transfer into research-based industrial companies with a special focus on small and medium enterprises. Main aspects include application of regeneration mechanisms in the context of locomotion during training and rehabilitation, as well as technical supports for prevention and rehabilitation. Also these studies are carried out in close cooperation with the Fraunhofer Translation Center.

Scientists of the MCW organize and / or participate in several local, national and international research networks: Therapy Unit Multiple Myeloma of the Sander Foundation, DFG research group FOR 1586, SFB630, BMBF consortium DIMEOs, German-French consortium OBELICS, EU consortia ADIPOA, VascuBone, HydroZONES, STEP (EU FP7), BioChip and HemAcure (EU H2020), and the consortium of Bavarian Research Foundation FORMOsA. Prof. Jürgen Groll furthermore received in 2013 an ERC Consolidator Grant from the European Research Council.

Fraunhofer Translational Center for Regenerative Therapies in Cancer and Musculoskeletal Diseases

(Prof. Dr. human. biol. Heike Walles, Head)

Mission and structure

Regenerative medicine and the development of medical products and therapies based on innovative drugs and cell-based strategies are core activities of the Fraunhofer translational center. An ageing society together with a growing awareness for well-being and rising costs in the healthcare system are reasons for increasing importance of personalized or individualized medical products and therapies. Regenerative medicine and the development of innovative drugs are key components of this process that are covered by the competence fields of the translational center. These competence fields are focused on the rapid transfer of new materials and/or cell based regenerative therapies for individualized patient care into clinical application. In order to catalyze this transfer, the Bavarian ministry for economy and media, energy and technology supports the installation of the translational center with 10 million euro for 5 years.

The establishment of a large interdisciplinary network enables the translational center to cover the complete developmental chain from biomaterials development and the generation and optimization of bioreactors over in-vitro test systems as alternatives to animal testing to therapy-accompanying diagnostics (theranostics) and the authorization of cell-based implants and medical products. Additionally, the translational center includes a pronounced expertise for relevant animal models and the accomplishment of (pre-)clinical studies.

Focus areas

Innovative products for therapeutic application in humans underly complex regulatory demands. The translational center consults and supports the planning and execution of preclinical and clinical studies. Together with the center for clinical studies (ZKS) Würzburg the translational center elaborates strategies that ensure the accomplishment of preclinical and

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clinical studies according to internationally accepted quality standards (GLP, GCP).
A unique selling point of the Fraunhofer-IGB team is the vascularized BioVaSc scaffold for the generation of implants that can be connected with the blood circulation during implantation. A number of complex tissue models based on this matrix, including a model of human skin (SkinVaSc-TERM®), intestine (GutVaSc-TERM®), trachea (TraVaSc-TERM®), and lung (LunVaSc-TERM®), have been registered as trademark in 2014. The technology has been transferred to the decellularization of other organs such as lung or heart for the isolation of tissue specific proteins. These proteins can directly be mixed with polymers for the generation of scaffolds or be used for the surface modification of implants.
Based on tissue engineering strategies, the translational center also develops human in-vitro test systems as alternatives for animal models, since data from animal testing often do not correctly represent the situation in the human body. Barriers in the human body, such as the skin, the digestive tract and the respiratory system are the main focus and systems of healthy and diseased tissues are being developed. These systems are used for risk assessment of biological substances and synthetic materials, for infection studies, especially with human obligatory pathogens, and in oncology. The tissue models are also used for the simulation of the interaction between medical products such as stents and the human organism in order to optimize the implant surface.
Activities in the competence field theranostics focus on the development of products that allow efficient and personalized therapy accompanying in-vitro diagnostic or the in situ combination of diagnosis with therapy. The platform bioreactor develops different bioreactors for application in Tissue Engineering, regenerative medicine and the extracorporal sustainment of organs and tissues. An underlying feature of our systems is the applicability for a broad number of users from research and development to industry. In addition, special and generic incubators are developed in which the different bioreactor systems can be operated (Figure 2).

Fig. 2: Incubator for the operation of special bioreactor systems for the cultivation of 3-dimensional tissue culture.

Bavarian Polymer Institute – KeyLab Polymers for Medicine

(Professor Dr. rer. nat. Jürgen Groll, Head)

Mission and structure

Within the Bavarian Polymer Institute (BPI), the universities Bayreuth, Erlangen-Nürnberg and Würzburg are joining and connecting their competences in polymer science and technology. Thereby a homogeneous research and know-how chain is created that is necessary for cutting-edge research projects and excellence in science in this interdisciplinary field. An important strategic element of the BPI is a complementary research infrastructure in form of Key Laboratories (KeyLabs) that will be build up and established at the three universities. These KeyLabs complement and connect the competences of the individual chairs and workgroups. In this context, the KeyLab Polymers for Medicine possesses a bridging function between the material- and fabrication oriented KeyLabs of the BPI, the polymer oriented basic research at the participating universities and the Fraunhofer-Translational Center for Regenerative Therapies in Cancer and Musculoskeletal Diseases.

Main research focus

Polymers are of increasing importance in medicine. Non degradable (PE, PP, PVDF, PTFE, PMMA, PEO) as well as degradable (most prominently polyesters) polymers are approved for the use in humans and routinely used in the clinic for various medical indications.
In many cases however, the medically approved polymers and products are not ideal, so that for example the mechanical properties, processability, the biocompatibility

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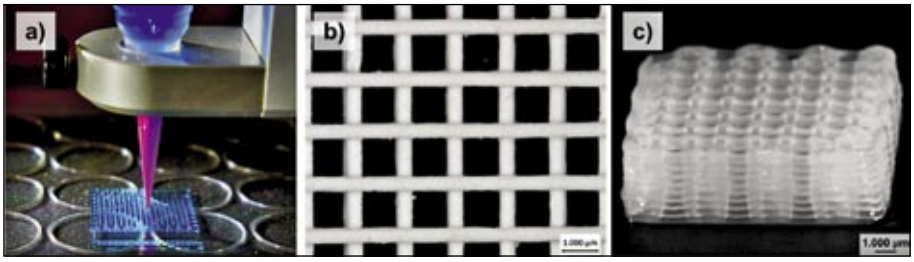

Fig. 3: 3-dimensional printing of a hydrogel via dispense plotting (a) and examples for a printed biodegradable thermoplastic polymer (b) and a printed hydrogel construct (c).

or the degradation behavior have to be improved. One example is the development and preparation of tailored medical textiles. In this context especially the control over the surface properties is crucial. Protein adsorption is the first and decisive step for the subsequent adhesion of cells and the overall response of the body, so that structuring, coating, functionalization and characterization of polymer interfaces represents a very important aspect of the research activities.

Most importantly, polymers play a central role in modern biomaterials research. Aside of bulk materials, especially hydrophilic polymers and their (reversible) formation of three dimensional networks are of interest. Tailored syntheses for polymers with specific reactivity (number, kind and distribution of reactive groups), amphiphilicity (introduction of hydrophobic or charged groups for the induction of self-assembly and direction of interaction with biologicals or drugs) and degradation open new applications for drug delivery and regenerative medicine. In this context also the processing and formulation of polymers is important, so that nanoparticulate systems for drug delivery as well as scaffolds and cell-material constructs for regenerative medicine can be generated with appropriate size and morphology. Central material components for these strategies are thermoplastic polymers as stable scaffolds and soft hydrogels as biomimetic culture environment for cells. Recently, the generation of tissue analogue structures through additive manufacturing technologies (so called Biofabrication) has turned into a central aspect of polymer based biomaterials research (Figure 3). Led by researchers from Würzburg, the international society for Biofabrication has most recently published a consensus article that updated the definition of this dynamic and evolving field of research (siehe Groll et al. Biofabrication 8, 013001, 2016).

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General Information

In 2001, the University of Würzburg won approval in the context of the first nationwide competition of the German Research Foundation (DFG) for Research Centers. The concept of the Rudolf Virchow Center was chosen among 80 submitted concepts. After reconstruction of the 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 are now open for research, teaching and training, as well as events for the public. The Center received funding as the DFG Research Center for Experimental Biomedicine for 12 years until June 2013; it is now being continued as a Central Research Institution of the University of Würzburg with funds of the State of Bavaria, the University and the Medical Faculty.

The center spans multiple faculties and was therefore established as a central institution of the University. Group leaders, if they are professors, belong to the Medical Faculty or have a dual membership in another faculty. The Rudolf Virchow Center is composed of different elements in research and teaching. Its interdisciplinary research focuses on „target proteins“, which are analyzed at several levels from molecules to diseases.

Right from the beginning the Rudolf Virchow Center´s intention was to create innovative structures within a University. An Institute for Junior Research Groups was established, providing junior scientists the possibility to work independently with the option of extension into temporary research professorships (tenure track) for excellent group leaders. The Core Center comprises groups that develop and utilize innovative and special research methods. Excellent established scientists have the possibility to concentrate on a five-year, high-risk project as Research Professors on the model of American Howard Hughes professorships. The Rudolf Virchow Center also offers Senior Professorships to scientists who want to continue their research programs after their retirement to emeritus status. Research programs of these scientists are in the general field of the center, but they are largely funded by external grants. The Bio-Imaging Center comprises research groups supported by the State of Bavaria and the University of Würzburg as basic funding, who study biological problems with optical methods. In order to strengthen collaborations with researchers in Würzburg the RVZ Network program was added. In addition to research, the Rudolf Virchow Center was also involved in conceiving and establishing the new Bachelor and Masters Program in Biomedicine, initiated in the winter term 2001/02 at the University of Würzburg. It is also involved in the more recently established programs in Biochemistry (BSc/MSc), the MSc program in Experimental Medicine, and the FOKUS Program “Life Sciences”. A “Graduate School” for Biomedicine was developed that has become the nucleus for a large-scale reform of graduate training at the University and culminated in the foundation of the “Graduate School of Life Sciences“. This school won approval in the context of the national “Excellence Initiative” in the fall of 2006. The Public Science Center of the Rudolf Virchow Center stays in contact with the press 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.

Major Research Interests

At the time of reporting 13 research groups are established at the Rudolf Virchow Center. Research groups work on “target proteins“. The research pursued at the Center can therefore be grouped into four Research Fields: (1) Protein Structure and Function, (2) Proteins in Cellular Signaling, (3) Nucleic Acid Binding Proteins, and (4) Proteins in Cell-Cell Interactions and Motility. The main projects reflect the focus on cell surface proteins and their signaling proteins, and on nucleic acid binding proteins.

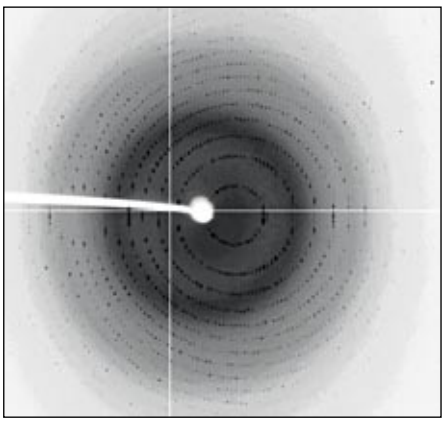

Fig. 1: Diffraction: If an X-ray beam impinges on a crystal of a particular protein, the beam is scattered. A detector provides a picture like the one shown here. Based on these patterns, the structure of a protein can be calculated. Picture: Group Schindelin /RVZ.

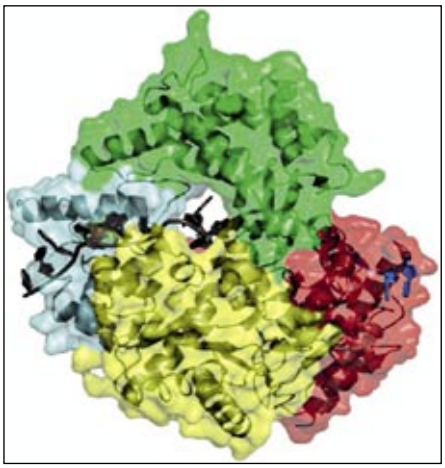

Fig. 2: The important RNA repair protein XPD. Individual domains of the protein are shown in different colors. In order to determine a possible repair need, the DNA (here in black) is drawn through the hole in the middle. Picture: Group Kisker / RVZ

HAD Phosphatases
(A. Gohla)
HAD-type phosphatases are an emerging class of enzymes with essential functions for transcription, cellular metabolism and cytoskeletal dynamics. We aim to understand the regulation as well as the physiological and pathological roles of Chronophin and AUM, two novel mammalian HAD phosphatases that we have discovered. Building on the important role of Chronophin for cofilin-dependent actin remodeling, our research has a strong focus on signaling to the cytoskeleton. Altered cytoskeletal dynamics play crucial roles in the pathogenesis of cardiovascular diseases and malignant tumors, and we now know that Chronophin and AUM are deregulated in some of these diseases.

Biophotonics
(K. Heinze)
In an interdisciplinary approach we combine high-resolution concepts of fluorescence microscopy with tricks from material sciences. Our approach involves designing and nanofabricating so-called metamaterials with negative refractive properties that can serve as modified microscope substrates for fast imaging of biological surfaces with superresolution. Suitable for live cell applications this low-invasive approach offers a fascinating prospect of observing individual biomolecules in their native environment and understanding how they act in concert.

Brain and Behaviour
(M. Heisenberg)
We study the fly *Drosophila melanogaster* trying to understand how the brain organizes behaviour. No other organism offers similar tools to manipulate the brain in the living, behaving organism and to relate behaviour to its underlying substrate. We analyse operant behaviour and in particular operant learning, selective attention, and endogenously changing perceptual hypotheses. We pay special attention 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)
In order 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 our research is to investigate such conformational changes during GPCR activation and deactivation. Therefore we develop FRET-based probes for GPCRs to image the conformational change in living cells and millisecond time resolution. The use of such FRET-based sensors allows us to study receptor ligand interaction directly at the level of the receptor itself. Thus we are able monitor the effects of potential future drugs at the protein level and can correlate the observed data with effects on different signalling pathways triggered by receptor activation.

Structural Biology: DNA-Repair and Structure-Based Drug-Design
(C. Kisker)
Maintenance of the genetic information is crucial for all living organisms. Thus different DNA repair mechanisms exist to protect our genome from endogenous and exogenous attacks. Defects in these repair mechanisms have serious consequences leading to a dramatically increased predisposition to cancer and accelerated ageing as well as many other diseases. Among the various DNA repair mechanisms available to the cell, nucleotide excision repair (NER) stands out because of its broad substrate specificity. The group aims to understand the fundamental mechanisms of the the pro- and eukaryotoc NER machinery to gain insight into the process of damage recognition/verification, incision and repair. A second focus is structure-based drug design against human pathogens to identify new therapeutics against infectious diseases.

Signaling Processes of Receptors
(M. Lohse)
Cyclic nucleotides – cyclic AMP (cAMP) and cyclic GMP (cGMP) – belong to the most ubiquitous intracellular messengers. Both are produced in response to multiple stimuli, act on several intracellular targets, and regulate a vast array of biological functions. However, in spite of the fundamental importance of these signaling systems, very little is known about the temporal and spatial patterns of their production and action. To gain an insight into these dimensions, the group develops methods to create images of these second messengers in intact cells, and to resolve these intracellular signals in space and in time.

Molecular mechanisms of ubiquitination and phosphorylation
(S. Lorenz)
Cells need to regulate the abundance, the localization, and the activity of proteins in response to a myriad of stimuli. A major way to accomplish this challenging task is through posttranslational modifications. Research in our lab is directed at understanding the structural basis and functional consequences of posttranslational modifications. In particular, we focus on enzymes of the ubiquitination cascade and protein tyrosine kinases. We follow an interdisciplinary approach by combining X-ray crystallography and NMR spectroscopy with various other biophysical, biochemical and cell biological techniques.

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 patho-

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Professor Dr. Alma Zernecke (2009 - 2013)
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logical thrombus formation, causing diseases such as myocardial infarction or stroke. 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 the cells, while preserving their hemostatic function.

Structural Biology: Protein Folding, Function and Degradation

(H. Schindelin)

The group focuses on protein folding in the endoplasmic reticulum (ER) and the degradation of mis-folded proteins via the ubiquitin-dependent protein degradation pathway. In a second topic the anchoring of inhibitory neurotransmitter receptors and their transport is investigated. Therefore the group uses a combination of complementary techniques for the biochemical and biophysical characterization in addition to X-ray crystallography. Mis-folding and aggregation due to, for example, defects in the endoplasmic reticulum associated degradation (ERAD) pathway, lead to a variety of pathophysiological states, such as the neurodegenerative disorders Alzheimer and Parkinson.

Mass Spectrometric Analysis of Posttranslational Protein Modifications

(A. Schlosser)

The main focus of our research is analyzing posttranslational modifications (PTMs) by mass spectrometry (MS). MS is an excellent technique for analyzing protein modifications and many advances in this area have been made over the last few years. However, the enormous potential of this technique for analyzing of PTMs is still far from being tapped. We develop new methods for the qualitative and quantitative analysis of protein modifications, such as phosphorylation, ubiquitination, deamidation, ADP-ribosylation, hydroxylation, methylation, acetylation, etc. This involves developing new methods for protein cleavage, peptide separation, fractionation and enrichment, chemical modification, optimizing peptide fragmentation (CDI and ETD), as well as developing new software tools for data analysis.

Hormonal Regulation of Metabolism

(G. Sumara)

Adaption to changes in nutrient availability is pivotal for survival of living organisms. Specific responses to fasting and feeding in different organs are regulated by a complex array of hormonal cues. Deregulation of nutrient sensing leads to development of metabolic diseases including type 2 diabetes. We combine genetic and biochemical approaches to understand the complex signaling events occurring in different organs (e.g. liver and adipose tissue) during fasting, feeding and other physiological conditions.

Single Molecule Studies of DNA Repair

(I. Tessmer)

We are using atomic force microscopy (AFM) in combination with other biophysical and biochemical techniques to study protein-DNA complexes involved in DNA repair. AFM enables us to directly visualize molecular assemblies at the level of the individual molecules. We are particularly interested in understanding the different DNA damage recognition strategies developed by the various DNA repair mechanisms as well their pathological disturbances.

Membrane Biology

(A. Wehman)

Throughout life, cells communicate to coordinate the organism's response to stimuli. Cells release extracellular vesicles that can carry signals to alter fate decisions or the immune response. The goal of our research is to discover how vesicles bud from the surface of cells and to determine how similar it is to viral budding. Defining how vesicles form is an essential first step to designing strategies to induce or suppress their formation and thereby monitor or influence disease severity.

Teaching

All groups offer internships and lectures for students of the Bachelor and Masters Program in Biomedicine as well as other programs. Annual symposia and conferences are held for scientists from medicine and natural sciences. Graduate students at the Center are members in the graduate program "Virchow Graduate Program" that belongs to the Section Biomedicine of the "Graduate School of Life Sciences".

SELECTED PUBLICATIONS

Group Kisker:
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WÜRZBURG

Collaborative Research Centers and Transregios

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Collaborative Research Center 688, Mechanisms and Imaging of Cell-Cell Interactions in the Cardiovascular System

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General Information

Cardio- and cerebrovascular diseases account for the most fatalities worldwide. The SFB 688 collaborative research centre, founded in 2006 and recently extended until 2017, creates a unique research network involving scientists and clinicians from four faculties and eleven institutes and clinics of the University of Würzburg. Its aim is to understand the central pathophysiological processes in vascular disorders with a clear focus on the identification of new signaling molecules and cell-cell interactions to create innovative concepts for the prevention and treatment of cardio- and cerebrovascular diseases.
Of special importance is 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 unites complementary areas of research including molecular biology, physiology, biophysics, proteomics and bioinformatics, with clinical medicine. Molecular and pharmacological murine disease models are generated in the SFB that allow clinically orientated groups to gain new insights into the development of thrombosis, myocardial infarction and stroke. Additional emphasis is put on secondary complications such as oedema and scar formation that strongly influence heart and brain function. The use of new MR contrast agents and high field MR imaging (up to 17.6 Tesla), novel fluor-based MRT contrast agents and PET tracers as well as advanced fluorescence microscopy imaging in animal models of thrombosis, myocardial infarction and stroke allow the better surveillance of heart, brain and vascular function in the living organism and provide a further link to clinical medicine.

Project Area A (Fundamentals and mechanisms of vascular cell-cell interactions)

This project area investigates 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 haemostasis and immune defence, but also in vascular thrombosis and inflammation often leading to organ dysfunction. During the last two years the following important new insights have been obtained:
Thrombosis and inflammation are central characteristics of stroke pathophysiology. We can now show that the serine protease plasma kallikrein (PK), an essential constitu-

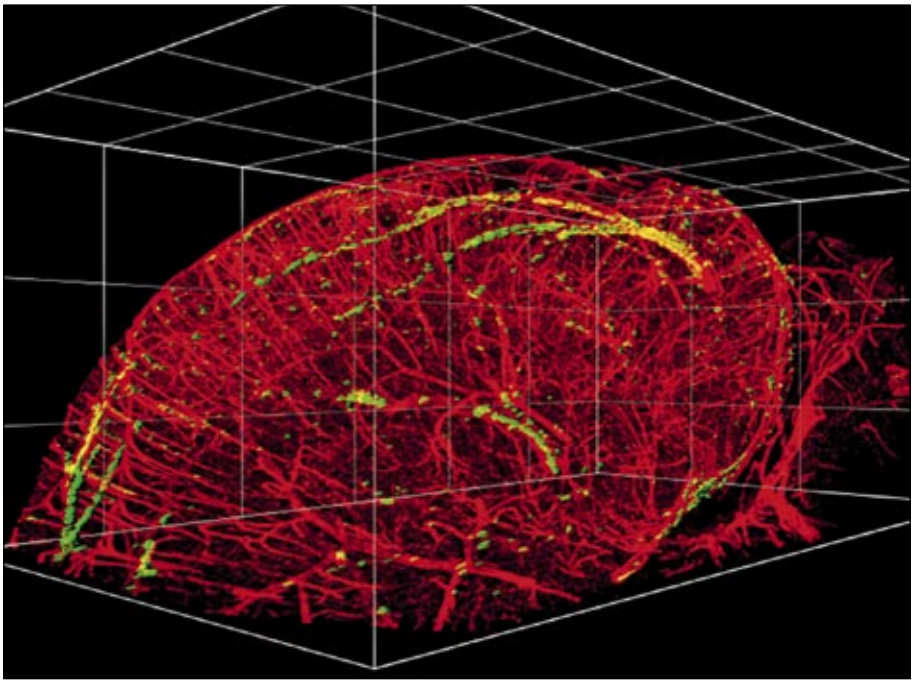

Fig. 1: Light sheet microscopy of thrombotic activity in the ischemic brain. Thrombi (green) and blood vessels (red) in the ischemic hemisphere of a murine brain 24 h after experimental stroke (Stegner et al., unpublished).

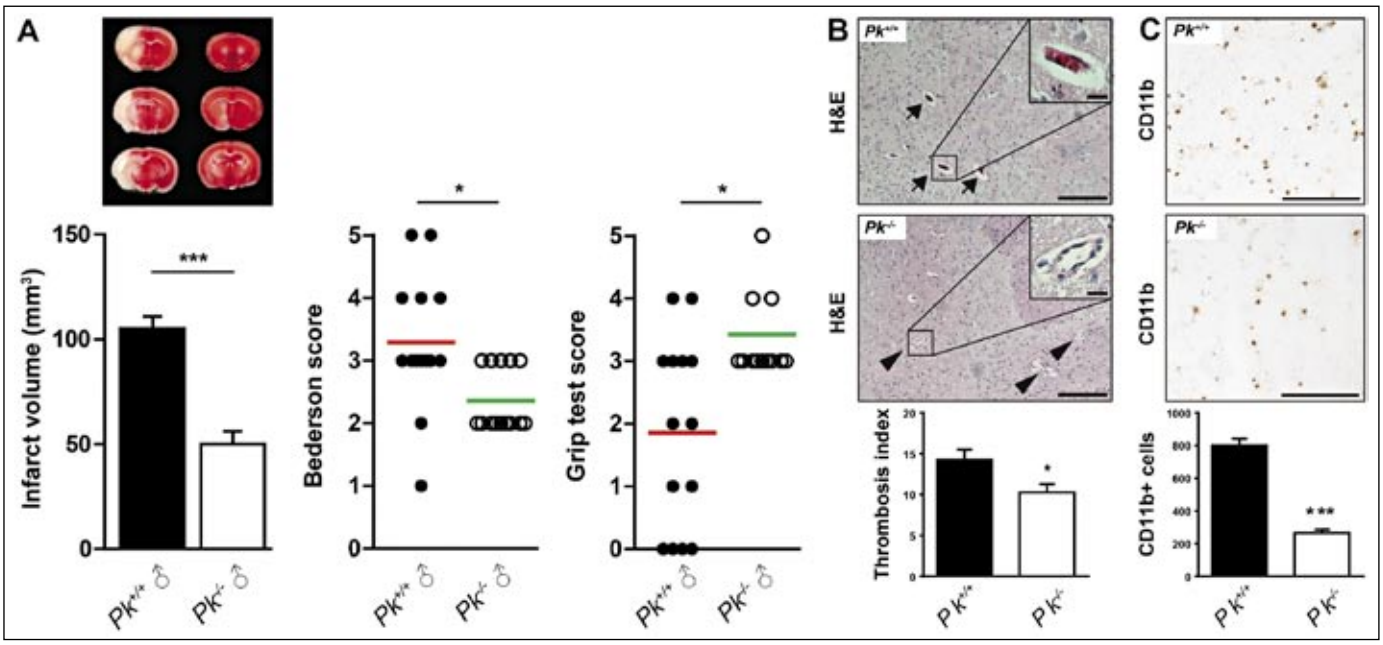

Fig. 2: Genetic depletion of plasma kallikrein reduces thrombotic and inflammatory reactions after cerebral ischemia in mice. (A) Pk-/- mice develop significantly smaller brain infarctions and less neurological deficits on day 1 after experimental stroke. (B) Deficiency in PK resulted in reduced thrombus formation within the ischemic microvasculature as well as (C) in an amelioration of post-stroke inflammation.

ent of the contact-kinin system plays a key role in ischemic stroke (see figure 2). Mice deficient for PK are strongly protected from ischemic brain damage and stroke-induced functional deficits without being prone to intracerebral bleeding complications (Göb *et al*., Ann Neurol 2015). Importantly, the pharmacological inhibition of PK with a specific blocking antibody achieved the same the stroke-protective effect.

In another project we could demonstrate a beneficial role for regulatory T cells in the process of cardiac remodelling after experimental myocardial infarction in mice and further show that this can be therapeutically modulated to improve outcomes (Mathes et al., J Mol Cell Cardiol 2016).

It is well recognized that atherosclerosis is a chronic inflammatory disease in which both innate and adaptive immune responses cooperate to fuel the inflammatory process within the vascular wall. Besides monocytes, macrophages and dendritic cells, the balance between pro-inflammatory and anti-inflammatory T cell responses and their modulation by regulatory mechanisms is also a critical determinant of atherosclerosis. We could reveal that CD8+ T cells play a key role in atherosclerosis by controlling monopoiesis and circulating monocyte levels, which contribute to plaque macrophage burden and atherogenesis (Cochain et al., Circ Res 2015).

The long-term objective of these combined research efforts are better therapeutic options for patients with atherosclerosis, myocardial infarction and stroke and more effective and safe prevention of thromboembolic events.

Project Area B and Z02 (Molecular and functional imaging of the cardiovascular system and its cell-cell interactions)

Imaging techniques play a pivotal role in the SFB 688, allowing the investigation of cardiovascular diseases in rodents and humans. In the funding period 2014-2016 several novel MRI-methods and radioactive tracers were developed, which are now available for our users. In the field of Magnetic Resonance Imaging a model-based perfusion method with retrospective cardiac triggering was established, that allows spatially resolved quantification of cardiac perfusion in the mouse at any given time point. In another project a sophisticated model for the quantification of cardiac perfusion (including several correction mechanisms) was developed (Kampf *et al*., Magn Res Med 2014). In the area of nuclear imaging a novel PET tracer (^{68}Ga-Fucoidan) was developed with the potential to detect vulnerable plaques in animal models.In addition a somatostatin receptor based PET/CT-imaging platform was established that identifies inflamed cardiac tissue as a new biomarker for cardiac remodeling (Lapa *et al*., Int J Cardiol 2015). We have also developed novel fluorescence microscopy techniques to visualize cell-cell interactions *ex vivo* and *in vivo*. While 4-color light sheet fluorescence microscopy (LSFM) is used to scan whole organs such as the ischemic brain (see figure 1) at subcellular resolution, multi-color two-photon microscopy is used to study dynamic processes deep in the tissue of living mice.

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Transregio-Collaborative Research Center 34, Pathophysiology of Staphylococci in the Post-genomic Era

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General Information

The aim of this SFB/Transregional collaborative research center (TR34) is 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 is 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 are grouped in four parts: in part A (4 projects), the general physiology of *S. aureus* is 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 in the past. The regulation of cell-surface-bound and extracellular virulence factors is the focus of part B (3 projects). Project area C (11 projects) deals with the behaviour of the pathogen in the host and will provide new information on the host-pathogen interaction. Part Z (4 projects) offers state of the art technologies to all projects to discover and analyze *S. aureus* metabolism and pathogenicity. The projects of the groups in Würzburg deal especially with different aspects of host-pathogen interactions. Project part A2 studies 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 will be 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 is being studied. Project part C6 is interested in the cellular response of host cells after internalization of *S. aureus* by using proteomics and RNAseq technology. The aim of project C11 is 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) are implemented to visualize the dynamics of *S. aureus* infections and corresponding morphological and physiological changes in host tissues.

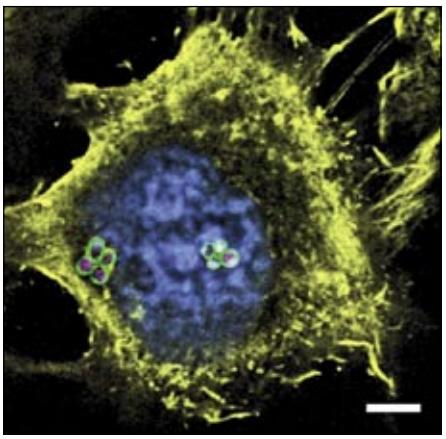

Fig. 1: Staphylococcus aureus (cyan) after invasion into host cell (actin=yellow; nucleus blue). Phagosomal escape of S. aureus is indicated by green fluorescence, scale 5 µm.

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Transregio-Collaborative Research Center 58, Fear, Anxiety, Anxiety Disorders

Fear, Anxiety, Anxiety Disorders
Furcht, Angst, Angsterkrankungen
SFB / TRR 58

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Mission and Structure

The Transregio-SFB 58 was initiated in 2008 and after the end of the first funding period and review in 2012 was extended until 2016. It comprises work groups of the Universities of Hamburg, Münster and Würzburg. The speakers are C. Büchel (Hamburg, deputy speaker), H.-C. Pape (Münster, speaker) and J. Deckert 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 second funding period 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 by innovative experimental approaches (*imaging genomics, epigenomics). Ge*netic 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 9 of the 18 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 and the role of epigenetic programming (A01 and A05; Lesch, Schmitt) are complemented by studies on the role of hippocampal BDNF and NOS1-dependent 5HT1A-transmission in the context regulation of fear and anxiety (A09 and B06; Blum, Sendtner, Reif).As one significant result of hypothesis-free genome-wide expression and methylation analyses a role of myelin basic protein as stress mediator was identified (Schraut et al., 2014).

In research area B – **behavioural 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 cue versus context fear conditioning and generalisation in virtual reality (B01; Pauli) are applied as well as studies on anticipation and perception of somatic symptoms employing neurophysiological and functional magnetic resonance imaging (B05; Wieser). Using this approach, the modulation of fear generalization by a functional BDNF polymorphism could be demonstrated (Mühlberger et al. 2014).

Research area C – **translational science** - focuses on the investigation of pathomechanisms which are differentially relevant for phasic/specific and sustained/generalized anxiety disorders and their treatment. Epigenetic experimental designs (C02; Domschke,

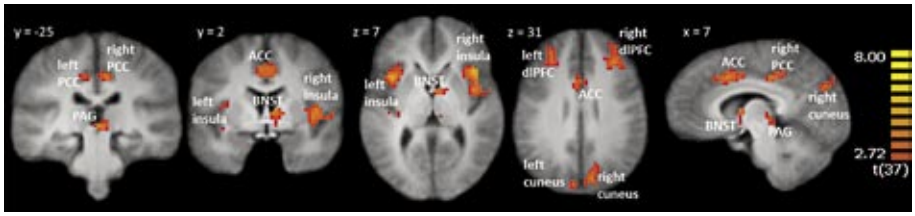

Fig. 1: Differential activation of fear and anxiety related networks (sustained fear) (Image from M. Herrmann, C06).

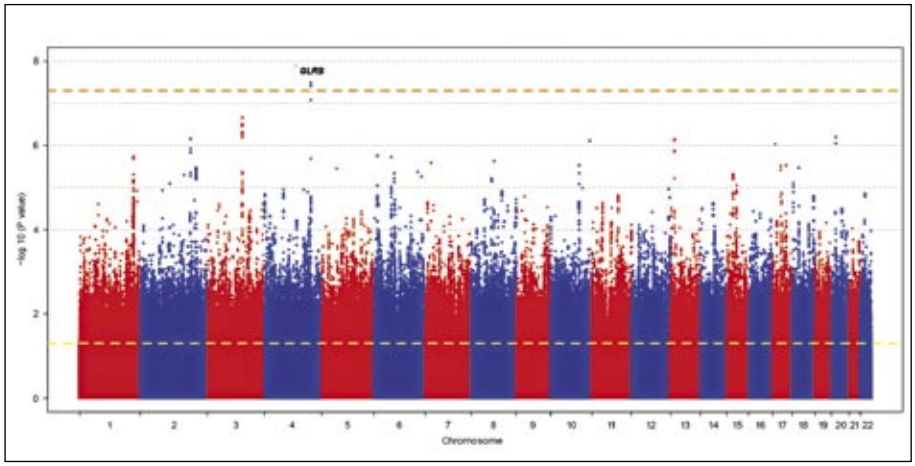

Fig. 2: Genome wide association study of dimensional anxiety phenotypes in 1372 healthy probands of the Z02 cohort of the 1st funding period (Image from H. Weber, Z02).

Lesch, Deckert) as well as electrophysiological and functional magnetic resonance imaging experimental designs (C06; Herrmann) are employed. For the first time reversibility of methylation by psychotherapeutic intervention was shown (Domschke et al., in press) and differential brain activation by phasic versus sustained fear was observed (Herrmann et al., in press; figure 1).

The large (n=1643) cohort with ex ante phenotypically and genetically well defined control subjects for the studies of areas B and C made available by the **central project Z02** (Deckert, Reif, Pauli) is extended in the 2nd funding period by a cohort of probands (n=1500) which in addition are experimentally characterized for fear generalization.As in the 1st funding period a genome-wide association study is performed as basis for the definition of polygenic risk scores. To allow for the investigation of developmental and preventive aspects the adult cohort is complemented by a cohort (n=500) of children and adolescents (Romanos).As in the 1st funding period, the cohort has provided probands for subprojects of areas B and C and by the analysis of the complex genetics of fear-and anxiety-relevant behaviours in genome-wide association studies (figure 2) it has delivered several new candidate molecules for research area A in the 3rd funding period.

A paradigmatic example for the interdisciplinary and synergistic research of the 1stand 2ndfunding 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.

At the University of Würzburg, the following institutions currently are involved:
Medical Faculty, Center of Mental Health, Department of Psychiatry, Psychosomatics and Psychotherapy (project leaders: J. Deckert, K. Domschke, K. P. Lesch, M. J. Herrmann, A. Schmitt), Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (M.Romanos), Institute of Clinical Neurobiology (R. Blum, M. Sendtner) and Institute of Phyiology (associated member: E. Wischmeyer).
Faculty of Human Sciences, Institute of Psychology I (project leaders: P. Pauli, M. Wieser).
A. Fallgatter, A. Reif, B. Gerber and A. Mühlberger left for W3 chairs at Tübingen and Frankfurt resp. (Departments of Psychiatry and Psychotherapy), Leipzig (Institute of Biology, Genetics) and Regensburg (Institute of Psychology) respectively, but are still associated with the SFB.

Symposia

- 1st International Symposium on Fear, Anxiety, Anxiety Disorders; Münster, 10.-12.12.2009
- 2nd International Symposium on Fear, Anxiety, Anxiety Disorders; Würzburg, 15.-17.9.2011
- 3rd International Symposium on Fear, Anxiety, Anxiety Disorders; Hamburg, 11.-13.10.2013
- 4th International Symposium on Fear, Anxiety, Anxiety Disorders; Münster, 25.-27. 9. 2015

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Ziegler C, Richter J, Mahr M, Gajewska A, Schiele MA, Gehrmann A, Schmidt B, Lesch KP, Lang T, Helbig-Lang S, Pauli P, Kircher T, Rief W, Vossbeck-Elsebusch AN, Arolt V, Wittchen HU, Hamm AO, Deckert J, Domschke K (2016) MAO-A hypomethylation in panic disorder –Reversibility of an epigenetic risk pattern by psychotherapy. Translational Psychiatry, in press.

Transregio-Collaborative Research Center 124, Pathogenic Fungi and their Human Host: Networks of Interaction

– FungiNet –

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General information

The Transregio CRC124 Jena-Würzburg was initiated and established in 2013 by the Deutsche Forschungsgemeinschaft (DFG) and began his work on October 1st, 2013.
The CRC/Transregio aims to combine state-of-the-art research in mycology and immunology to gain novel insights into the pathophysiology of invasive mycoses, a clinical entity of growing importance. In the long-term perspective, it is the explicit aim of this initiative to use modern sophisticated high-throughput tools in basic research to generate knowledge, which can be used to improve diagnosis and treatment of these infections. As this requires large-scale and project overarching data interpretation, project area B integrates systems biology and structured bioinformatical approaches to data processing, management and interpretation to connect the experimental project areas A and C and foster the translational approach. Furthermore, translational research is strongly supported by existing infrastructure at both sites, so in Jena, the Center for Sepsis Control and Care, and the Early Clinical Trial Unit and the interdisciplinary GMP facility in Würzburg.

Major research interests

Project Area A – *Aspergillus fumigatus*: From environmental microorganism to pathogen

Project area A aims at the characterization of the infection-relevant networks of *A. fumigates* (biology of the pathogen) and host cells upon confrontation with *A. fumigatus* (host response). Methods of functional genome analysis such as proteome and transcriptome analyses both of the pathogen and the host, *e.g.* different morphotypes of the pathogen, various host cell types, directly from tissue *etc*., will be employed. Both technologies were established by PIs involved in the proposed project area.
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.
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 interlinks the project areas A and C and is essential for the comparative approach of this CRC/Transregio. 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 Standard Operating Procedures until now, access only *via* password by the members from Würzburg and Jena).
The standardization 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 de-

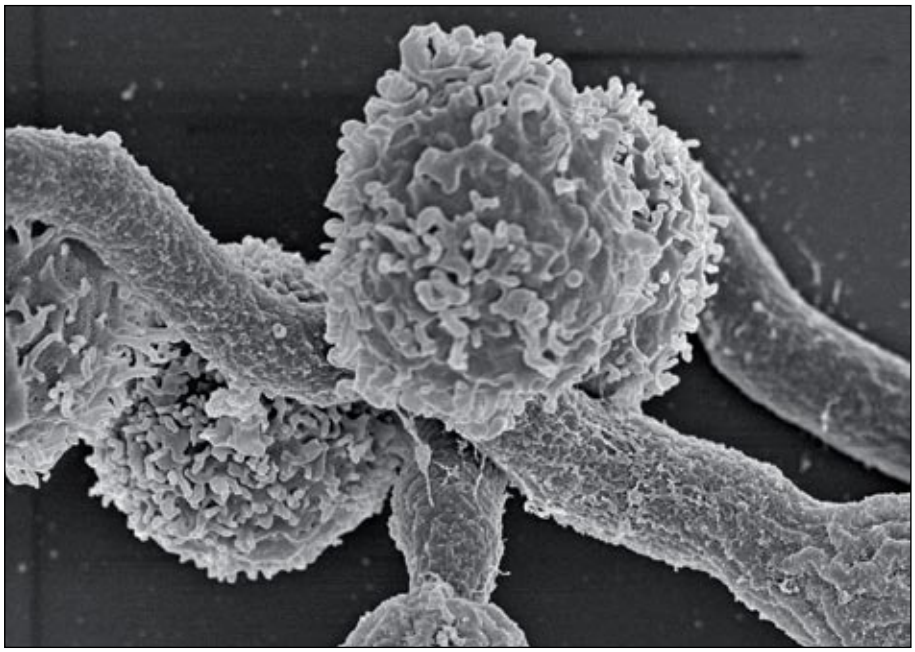

Fig. 1: Aspergillus fumigatus hyphae and activated human natural killer cells.

sign of further experiments 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) Besides the aforementioned genome-wide data, also genetic, microbiological and biochemical data as well as data from clinical investigations will be received and analyzed. (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), timelapse fluorescence microscopy, *in vivo* imaging and also MALDI-imaging.
Complementary bioinformatic methods to understand host-pathogen interactions are the metabolic reconstruction, game theory, Bottom-up: signaling molecules, knowledge-based networks, Boolean, Top-down: reconstruction of dynamic gene regulatory networks and Image data analysis and agent-based spatial modeling.

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 analyze 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 analyzing the stepwise processes preceding dissemination of the fungal pathogen, (2) to use high-throughput methods and advanced imaging tools to elucidate and functionally analyze 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.

The following projects of Würzburg are included in the CRC/TR124:

A2 Prof. Dr. Hermann Einsele und Prof. Dr. Jürgen Löffler, Internal Medicine II, University Hospital Würzburg
A3 Prof. Dr. Dr. Andreas Beilhack, Internal Medicine II, University Hospital Würzburg, und Dr. Katrin Heinze, Rudolf-Virchow-Center, University Würzburg
A4 Prof. Dr. Max Topp, Internal Medicine II, University Hospital Würzburg
B1 Prof. Dr. Thomas Dandekar, Center for Infectious Diseases, Dept. of Bioinformatics, University Würzburg
B2 Prof. Dr. Thomas Dandekar, Dr. Dr. Marcus Dittrich, both Center for Infectious Diseases, Dept. of Bioinformatics, University Würzburg
C2 Prof. Dr. Joachim Morschhäuser, Center for Infectious Diseases, Institute for Molecular Infection Biology, University Würzburg
C6 Prof. Dr. Thomas Hünig, Dr. Niklas Beyersdorf, both Center for Infectious Diseases, Institute for Virology and Immunobiology

SELECTED PUBLICATIONS

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Transregio-Collaborative Research Center 166, High-end light microscopy elucidates membrane receptor function – ReceptorLight

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General Information

Participating Institutions:
Friedrich Schiller University Jena
Julius Maximilians 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

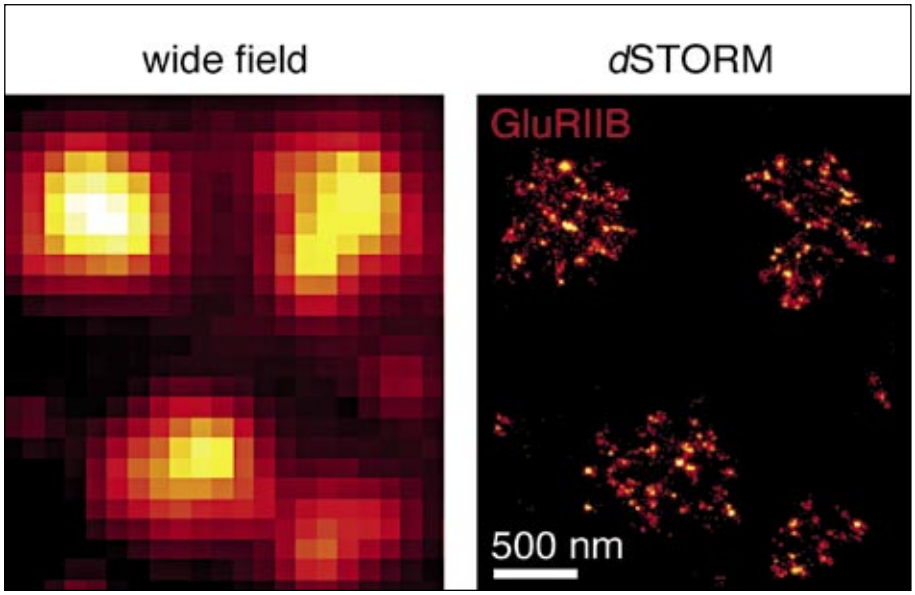

Fig. 1: Antibody staining against an ionotropic glutamate receptor subunit (GluR-IIB) at neuromuscular synapses of Drosophila illustrates the higher spatial resolution delivered by super-resolution microscopy (dSTORM, right) compared to conventional wide field microscopy (left). Images from project B4 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

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Julius-Maximilians-
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Scientific Infrastructure

Interdisciplinary Center for Clinical Research (IZKF) 154
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Core Unit Systems Medicine 161
Clinical Trial Center Würzburg (CTCW) 163

Interdisciplinary Center for Clinical Research (IZKF)

IZKF Würzburg

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Dr. Andrea Thelen-Frölich (Managing Director)
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Tab. 1: Overview IZKF-Project Grants 2014/2015

Project Areas	Funded Projects	Clinical/ Theoretical Departments
Project Area A: Pathophysiology of inflammatory response	**6**	Neurology / Neuroimmunology Gynaecology / Virology Immunology / Rheumatology Neurology / Neurosurgery Internal Medicine II / Rudolf-Virchow-Center Virology / Children's Hospital
Project Area B: Malignant Transformation and Tumor/Host-Interaction	7	Biochemistry / Surgery I Internal Medicine II / Pathology Microbiology / Gynaecology Dermatology / Clinical Biochemistry and Molecular Biology Clinical Biochemistry and Molecular Biology / Internal Medicine II Internal Medicine I / Pharmacology Bioinformatics / Tissue Engineering / Thoracic and Cardiovascular Surgery
Project Area D: Transplantation and Tissue Engineering	6	Surgery II / Pharmacy Surgery II / Functional Materials / Orthopaedics Pathology / Surgery I Internal Medicine II / Tissue Engineering Internal Medicine II/ Pathology / Immunology Musculoskeletal Center / Orthopaedics
Project Area E: Vasculopathies und Myocardial Diseases	2	Neurology / Rudolf-Virchow-Center Anatomy / Internal Medicine I
Project Area F: Novel Diagnostic and Imaging Devices	4	Nuclear Medicine / Radiation Oncology Nuclear Medicine / Neurosurgery Clinical and Experimental Neurology Mathematics / Radiology / Surgery I
Project Area N: Clinical and experimental Neurobiology	8	Anatomy / Anesthesiology Psychiatry / Radiology and Cell Biology Anatomy / Neurology Human Genetics / Psychiatry Physiology II /Neurosurgery Neurology / Physiology II Neurobiology / Anesthesiology Psychiatry / Neuroradiology/ Child and Adolescent Psychiatry

Assignments and Structure

The IZKF Würzburg organizes the Medical Faculty's internal funding for research. Its major goal is to strengthen clinical research by funding interdisciplinary cooperations between clinical research and basic research in biomedical sciences.

Three main instruments characterize the IZKF's work:

- The support of interdisciplinary research projects within its scientific focus (project grants).
- The advancement of a systematic promotion of young researchers in medicine
- The establishment of Core Facilities and the establishment of flexible funding instruments to improve local structural conditions (structural development).

Peer review processes and transparent funds management form the basis for the IZKF's internal research management. Its work is monitored and shaped by three bodies:

- The General Assembly („Zentrumskonferenz"),
- The Executive Board who is responsible for coordinating all funding instruments and allocating the respective grants.
- The External Scientific Advisory Board who sees through the center's activities and who participates in the evaluation of project proposals.

The IZKF Würzburg was founded in 1996 within the federal advancement program "Health Research 2000" of the Federal Ministry of Education and Research. Since 2004, it is funded by the Free State of Bavaria. Since 2010, the annual budget is ~5 M. Euros.

Main Research – Project Grants

The research focus is particularly represented by the IZKF-project grants. The aim of these theme-focused grants is to orient the Medical Faculty's different scientific focuses toward each other and to seize and enhance new topics. A project has to be a cooperation of clinical researchers and basic researchers in biomedicine in order to receive a grant. It is expected to transfer the projects into external third-party funding after receiving up to three years of internal funding from the IZKF. All projects are selected by internal and external peer reviews. Calls for proposals are published every 18 months. The IZKF receives an average of 32 project proposals with each call, up to 12 of which receive a grant which amounts to a funding rate of 38%. In 2014, the IZKF funded 33 projects in its 6 projects areas and in 2015 another 30 projects with a participation of 36 clinical and theoretical departments.

Junior Career Programs

The IZKF-Junior Career Programs offer a specific funding instrument for physicians for an additional research oriented training with a focus on the early dovetailing of clinical and biomedical research. Alongside the Junior Career Programs, the IZKF also supports young and motivated scientists of the Medical Faculty by IZKF-Project Grants.

IZKF-research groups

The IZKF-research groups are part and parcel in the IZKF's portfolio for career enhancement. By giving novel scientific and structural impetus they also provide a long-term and sustainable enhancement of research in our clinical departments. Their thematic foci are oriented at the Medical Faculty's foci. The groups are funded for up to five years.
The group leader position is tendered internationally; the IZKF's External Advisory Board is involved in the selection process.

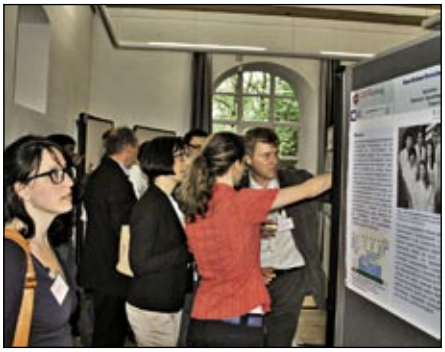

Fig. 2: Poster Session at Kloster Banz, IZKF-Retreat 2015.

Fig. 3: Participants IZKF Retreat 2015.

The research groups in detail:

IZFK Research Group I
„Common pathways of Cardiovascular and Neuropsychiatric Diseases“, promoted as a joint group of the IZKF, DZHI, Psychiatrical Clinic and the Department for Internal Medicine I.
Group leader: Dr. Leif Hommers

Cardiovascular diseases and psychiatric diseases with organic causes (neuropsychiatric diseases) are currently one of the most common reasons for lost disease-free years of one’s life, especially if they occur in combination. The IZKF/DZHI-research group „Common pathways of Cardiovascular and Neuropsychiatric Diseases“ explores basic molecular processes in order to extend the knowledge of similarities and cardiovascular and neuropsychiatric diseases and to obtain new perspectives in the development of therapeutic approaches.

IZKF Research Group II
„In vivo Imaging in preclinical models to develop, establish and validate novel concepts in immune- and tumor therapies“, Department of Internal Medicine II and the Pediatric Clinic
Group leader: Prof. Dr. Andreas Beilhack

The research group’s scientific focus is on the areas of tumor immunology, infection immunology and transplantation immunology. In order to illuminate complex immune processes, the IZKF-research group develops new imaging and microscopy techniques. The aim is to develop, establish, and validate novel concepts in immuno- and cancer therapy.

IZKF Research Group III
“Imaging for molecular biomarkers for clinical heterogeneity and disease progression in Parkinson’s disease”, Neurology and Nuclear Medicine
Group leader: Prof. Dr. Ioannis Isaias

After Alzheimer’s disease, Parkinson is the second most common neurodegenerative disease and affects approximately a percentage of 0,3 of the total population with 8-18 incidences in 100.000 persons/ year. The research group studies the pattern of neurodegeneration, compensatory mechanisms and biomarkers for disease progression in clinically defined subgroups of patients with Parkinson disease.

Fig. 1:Accumulation of lipids in HepG2 hepatoma cells cultured for 24h in the presence of 100mM palmitic acid. Visualization of lipids was achieved by Nile Red staining. (Projekt A-242, Prof. Geier, Dr. Schmitt, (Medizinische Klinik II), PD Dr. Hermanns (RVZ).

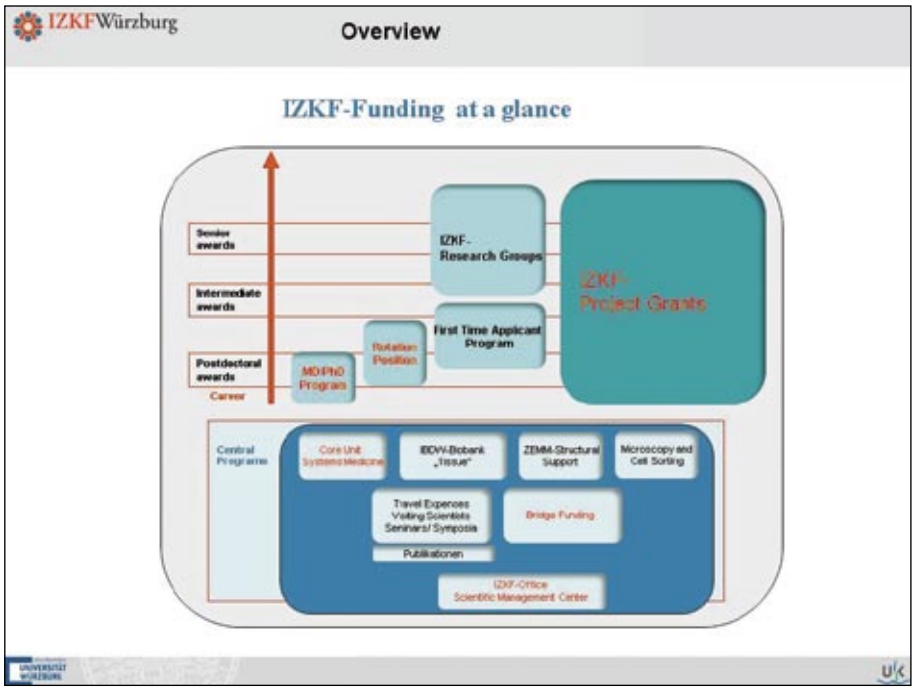

Fig. 4: Chart Research Promotion IZKF.

IZKF Research Group IV
"Mammalian host colonization by the commensal and pathogenic yeast Candida albicans"
Group leader: Dr. José Christian Perez

Our mucosal surfaces are laden with trillions of microorganisms from all three domains of life–microbes that play key roles in human health and disease. Those microorganisms can transition from harmless commensals to life-threatening pathogens. The group studies the most prominent fungal species living in humans, *Candida albicans*, and the underlying principles of interaction of *Candida albicans,* gut microflora and host.

In 2016, the IZKF will calls for a sixth research group with focus on regenerative medicine: „**Tissue Regeneration in Musculoskeletal Diseases**".

Career programs for young physicians

- Würzburg's **MD/PhD Program** is for physicians who already completed their experimental doctoral thesis. The aim of the program is to provide an excellent, postgraduate subject-specific qualification for young physicians by acquiring the Dr. rer. nat. / PhD in accordance with the Doctoral Graduation Regulations of the International Graduate School of Life Sciences (GSLS). The program was established in 1997 on the initiative of the IZKF. Since 2013, the IZKF awards fellowships for outstanding applicants. It is expected that the fellows pursue a career in a clinical environment.

- The **First-time Applicant Program (Erstantragsteller-Programm)** allows young physicians to enhance their own scientific approaches in two years, and to transfer them into an external third party funding with the support of a mentor. The EAST invites tenders bi-yearly. Since 2007, the IZKF has funded 33 EAST-projects and receives an average of 21 proposals with an approval rate of 41%. The program contributes substantially to a successful scientific career for young physicians.

- With the **IZKF-Rotation Program** young resident physicians can leave patient care for up to 12 months in order to focus on own research approaches. The IZKF provides five rotation positions each year. In 2014 and 2015, 11 young physicians received a rotation position.

- In addition to these career development programs, the IZKF and the **Else-Kröner-Forschungskolleg** develop a supporting program for young clinician scientists, e.g individual coachings and consulting for third party funding.

In order to provide direct and local flexible funding opportunities, the IZKF provides bridge funding of up to 25.000 € for research projects that are in the process of being transferred into third party funding. Furthermore, the IZKF promotes visiting scientists, supports the planning and implementation of seminars and symposia, travel expenses for its members to visit meetings and hosts the annual IZKF Retreat for all members of the Medical Faculty. Organization wise, the IZKF office is part of the UKW's department 3.4 „Internal and External Management of Research Funds (FoMM)". Alongside administrative and research coordinative tasks the department provides support and consulting for the acquisition of third party funding for all scientists of the Medical Faculty.

Tab. 2: Structural support and infrastructure

Core facilties	Ansprechpartner	Serviceangebot
Core Unit Systems Medicine	Dr. Sascha Sauer Dr. Claus Jürgen Scholz	Nucleic Acid Sequencing, Microarray-based technologies, Bioinformatics and Single-Cell Analysis
Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw) Subarea: Tissue	Prof. Dr. Roland Jahns Prof. Dr. Andreas Rosenwald Prof. Dr. Christoph Germer	Storage and use of Biomaterials (In 2011, the ibdw was established as a service facility of the Medical Faculty as one of five national Biomaterial Banks funded by the BMBF.
Service-Unit for Confocal Microscopy and Flow Cytometry-based Cell Sorting	Dr. Nora Müller Dr. Christian Linden Prof. Dr. Thomas Hünig	Application of fluorescence techniques (system introduction, support and consulting for experimental designs and optional data analysis)
ZEMM-Structural Support	Prof. Dr. Albrecht Müller	Access to the central animal facility

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Center for Experimental and Molecular Medicine (ZEMM)

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General Information

The *ZEMM* is a facility of the Medical Faculty to provide a platform for experimental research in the field of Molecular Medicine. The *ZEMM* comprises two parts: an animal and a research unit. The building was completed in 2008. In the research unit, well-equipped laboratories are temporarily provided to research groups in biomedicine upon request. The animal facility is in charge of the central breeding, husbandry and supply of non-infectious laboratory animals used by research institutions from the area of medicine and biomedicine. In addition, the animal unit has the tasks to provide clean animal holding areas and to generate gene-modified animals. Furthermore, several operating rooms for small and large animals are available. The lab-zone and the animal facility are available for defined time periods to research groups engaged in clearly defined biomedical research activities.

In 2015 the ZEMM hosted an average of 16,200 mice belonging to 70 different user groups. The number of different transgenic mouse lines was 460. In the past year the different user groups were working on a variety of approved animal experimentation projects, of which about 65 continue to run in the coming years.

Transgenic Technology

The mouse is the most important mammalian model system in basic and translational research. Genetically engineered mice are indispensable tools for basic functional genomics as well as for applied biomedical research and the design of models for human diseases. Research with genetically engineered mouse models is dependant on the availability of specific techniques, highly specialized laboratory equipment and skilled staff. The Transgenic Technology provides the lab infrastructure for the maintenance and generation of transgenic mouse models and the complete set of gene targeting and transgenesis technologies in the setting of specific pathogen free (SPF) animal housing of the ZEMM. The facility offers support, advice and counselling for non-specialists in recombinant embryonic stem (ES) cell technology, *de novo* establishment of mouse ES cell lines and gene targeting experiments.

As a scientific service the Transgenic Technology performs the following experimental techniques:

1. Generation of mouse models by gene targeting/injection of recombinant ES cells into host embryos for the formation of chimeric mice
2. Generation of mouse models by additive gene transfer and new methods of genome editing
3. Mouse rederivation
4. Cryopreservation of mouse lines

Generation of mouse models by gene targeting

The generation of chimeric mice via injection of recombinant ES cells into host blastocysts is the key intermediate step in gene targeting experiments to transform a designed mutant allele from the molecular biology and ES cell level into the complexity of the living mouse model. It demands highly specialized equipments and skills. Our lab is equipped with a laser-assisted microinjection setup. Laser assisted micromanipulation of embryos does not only facilitate standard ES cell injection procedures into blastocysts, but is particularly useful for injections into 8-cell embryos. 8-cell injection has the advantage of showing less interdependence of host embryo and ES-cell background. Our lab uses this technique successfully to inject recombinant ES cell clones of the C57BL/6 background into albino outbred host embryos (Fig. 2). By utilizing recombinant ES clones from the International Mouse Knockout Consortium we increasingly benefit from this valuable scientific resource.

Generation of mouse models by additive gene transfer and new methods of genome editing

The classical approach of additive gene transfer via pronuclear injection of DNA constructs is still an indispensable tool for mouse modelling. Additive gene transfer via infection of zygotes by recombinant lentiviruses has not been requested recently. Instead, adap-

Fig. 1: View of an individually ventilated cage system for the housing of immune-compromised animals.

tation and modification of the originally bacterial CRISPR-Cas9 system has revolutionized the genome editing technology. Compared to the well established Zink finger-nucleases and TALENs, the CRISPR-Cas9 system is more efficient, more versatile, easier and cheaper in application and thus opens completely new possibilities of specifically modifying the genome of eukaryotic cells and organisms in the fields of biomedicine and biotechnology. Using the CRISPR-Cas9 system genetically modified mouse models can be generated by directly editing the mouse genome in fertilized oocytes, either by injecting the corresponding expression vector into one of the pronuclei or by injecting the Cas9 and guideRNA encoding RNAs into the pronucleus and/or into the cytoplasm. The necessary technical equipment is equivalent to that for pronuclear injection. It is available at the ZEMM and was updated with a piezo-driven injector device.

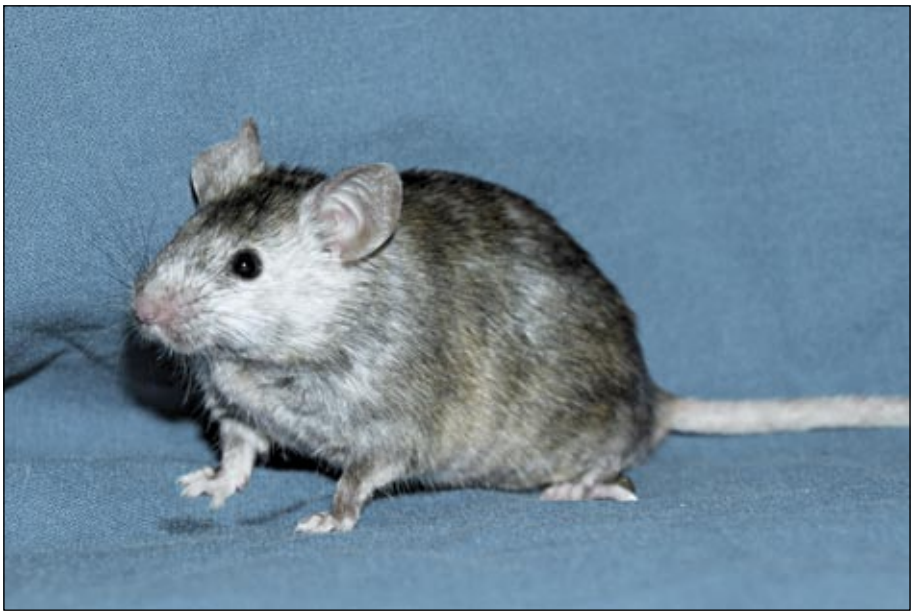

Fig. 2: Chimeric mouse as an intermediate step in gene targeting experiments. The unique coat colour pattern results from the interplay of the different coat colour marker genes of the host embryo and the recombinant ES cells used for microinjection.

Mouse rederivation

Any mouse line imported to the SPF or breeding facilities of the ZEMM is rederived to ensure and maintain the high local hygiene level. Depending on the hygiene status, the animals are either housed in the open facility or in the quarantine station located in the large animal house upon arrival. The males are mated with superovulated donor females; embryos are collected and washed and are transferred into pseudopregnant foster mothers under SPF conditions. Before transfer to the final SPF housing room they undergo a hygiene monitoring control. A similar adopted protocol is used for the rederivation of cryopreserved embryos imported from external sources. Cryopreserved sperms are rederived in a two-step protocol: *in vitro* fertilization and transfer of fertilized 2-cell embryos into foster mothers under SPF-conditions. The import of new mouse lines from external sources is increasingly accomplished by cryopreserved embryos and sperms.

Cryopreservation of mouse lines

Cryopreservation of mouse lines is the method of choice to ensure a backup system that protects against loss due to colony contamination (health or genetic) and for the long term maintenance of lines that are no longer in scientific use and characterization to avoid breeding costs and animal consumption. The golden standard for valuable lines is still the cryopreservation of embryos which is time and material consuming, but allows rapid rederivation by simply thawing the embryos and transferring them into foster mothers. A faster and less expensive alternative is the cryopreservation of sperms. However, the rederivation of cryopreserved sperms by *in vitro* fertilization is more complex and its success rate is strongly influenced by the genetic background of the mouse line with low rates in the commonly used C57BL/6 background. Applying a sperm analyser the quality of sperm preparations and its suitability for *in vitro* fertilization and cryopreservation are assessed. Beyond established protocols the success of cryopreservation is determined by the reliability and safety of long term storage in liquid nitrogen. Supported by the RVZ we purchased two new cryostorage-tanks equipped with electronic surveillance and a fully automated refilling system. In parallel the central utility of the ZEMM for liquid nitrogen supply is technically updated. It is planned to put the new tanks into operation in 2016.

Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw)

INTERDISZIPLINÄRE BIOMATERIAL- UND DATENBANK WÜRZBURG ibdw

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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 and so-called rare multifactorial diseases.

Embedded in the National Biobank Initiative of the Federal Ministry of Education and Research (BMBF) the *Interdisciplinary Bank of Biomaterials and Data Würzburg* (ibdw) was set up as one (out of five) centralized National Biobanks aiming to systematically collect and quality-controlled long-term store both liquid (blood/DNA/serum/urine) and solid bio-materials (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 on a voluntary basis for medical research purposes.

In the developmental concept of the ibdw as an *independent central service unit* of the Medical Faculty 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). In this aim the ibdw puts stepwise into practice a systematic, simultaneous and sequential collection of both liquid and solid BM from patients and study participants of all departments of the University Hospital.

To secure integrity and long-term quality of the collected bio-materials, as one of its paramount tasks the ibdw has implemented (and will department-wise release) highest quality standards according to current OECD- and ISBER-recommendations. Because there are no restrictions with respect to storage-duration and/or the purpose of (medical) research, all bio-materials and data hosted by the ibdw must strictly adhere to the legal framework (including privacy protection) and all current ethical principles. For each stored human bio-sample the ibdw provides the corresponding annotation (core) data and, if required, through the Clinical Data Warehouse access to expandable disease-specific clinical datasets in accordance with current data protection and safety regulations (multi-level authentificated data access model).

Structure, aims, and major research interests of the ibdw

The autonomous ibdw is composed of a central database and two central bio-sample repositories, one for liquid and the other for solid/tissue biomaterials (see Fig. 1), and a limited number of specialized de-centralized Subunits, all adhering to ibdw standards and rules. The Medical Faculty, 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 bio-materials meets highest quality standards according to the current OECD/ISBER recommendations.

Implementation of the ibdw concept is currently achieved jointly with the Service Centre 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 bio-samples in order to correlate them with the patient-specific pseudonymized clinical data sets 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' bio-samples will be accessible only on request by a specified data and privacy protecting regulation.

To secure high automation (Fig. 2) and thus high quality of ibdw-hosted biomaterials (BM) for liquid bio-samples (blood, urine, ascites, cerebrospinal fluid) there is tight cooperation with the Hospital's Central Laboratory.

For tissue samples (tissue, biopsies) there is tight collaboration with the Institute of Pathology and, of course, all surgical departments present in the Centre for Operative Medicine (COM). Therefore, the tissue-bank of the ibdw/CCCM under guidance of the Institute of Pathology (see Fig. 3) has been installed next door to the operation theatres and the rapid section laboratory.

Pre-existing high quality bio-sample collections within the University Hospital have been identified to be step-by-step integrated into the ibdw. In addition, the ibdw manages and operates human bio-materials and through the Clinical Data Warehouse provides access to corresponding clinical and laboratory (analytical) data contributed by existing national and international publicly funded basic and clinical research programs at the University and the University Hospital of Würzburg that have been executed in the past years. 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), the Rudolf Virchow Centre (RVZ), DFG Research Center for Experimental Biomedicine, and the Research Centre for Infectious Diseases (RCID).

The official grand opening of the ibdw was in June 2013 with the hand-over of the keys for the new building A8, which besides a Bio II-laboratory contains two automated cryostores each having a capacity of about 0.5 Mio of liquid bio-samples. In addition, since December 2013 the ibdw participates as a Work Package Leader in the BMBF-funded German Biobank Node (GBN), representing a "bridge head" to the European Biobank Infrastructure (BBMRI-ERIC). Aims of the GBN are to coordinate and harmonize national biobank-activities comprising –amongst others– harmonization of data-acquisition and -exchange (to

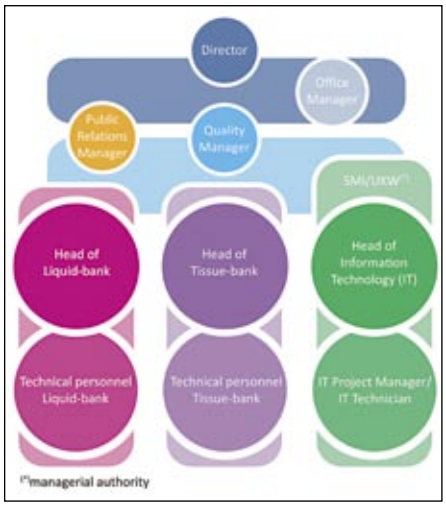

Fig. 1: Functional organigram of the ibdw.

Fig. 2: Pipet-roboter to generate small cryo-tubes from routine blood vials and fully automated -80° C cryo-repositories for the long-term storage of about 1.1 Mio cryo-tubes hosted by the ibdw.

achieve biobank-interoperability), standardization of quality-criteria and rules for the certification of biobanks, but also to develop a joint (national) strategy regarding ethical, legal and social matters of biobanks (including public visibility and public involvement). The ibdw actively participates in all these fields which from autumn 2016 on will be further boosted by a BMBF-initiative aiming to create a German Biobank Alliance (GBA) that will be fully linked to BBMRI-ERIC. These ibdw activities represent an ideal basis for future national, European (BBMRI) and global networking

Fig. 3: Tissue-bank of the ibdw/CCCM situated in the Centre of Operative Medicine. Photos show the online-temperature monitored -80°C freezers of the tissue-bank.

Main principles of the IBDW comprise:

- Concurrent liquid and solid sampling of 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 bio-samples 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 of a multi-level data storage and access concept ensuring consistency of data and bio-sample identity adopting all current data and privacy protection regulations;
- Implementation of hierarchical pseudonymized clinical data sets (core data, and harmonized disease-specific/study-specific datasets available through the Clinical Data Warehouse);
- 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, from 07/2013-03/2016 funded by the TMF);
- Project-based cooperation and networking on a national, European (BBMRI-ERIC) and international level.

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Core Unit Systems Medicine

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General Information

The Core Unit (CU) Systems Medicine is a facility of the Medical Faculty of the University of Würzburg and the Interdisciplinary Center for Clinical Research (IZKF) of the University Hospital of Würzburg. The CU Systems Medicine provides in particular scientists from Würzburg support for the application and development of high-throughput technologies. This will allow for tackling systems biological and systems medical questions at the highest available standards.
Currently the CU Systems Medicine consists of established sub-units for support in diverse genomics analyses – particularly by using "next-generation sequencing" - and associated bioinformatic data analysis. The facility was additionally strengthened in the year 2015 by the purchase and installation of massively parallel and fast sequencing technologies.

Key activities of the CU Systems Medicine comprised 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 gene-regulatory mechanisms with relevance in disease-associated processes in cancer, diabetes and infectious diseases). A particular focus of the unit consists of development and application of highly parallel molecular single-cell analyses.
Further sub-units, in particular for supporting complex systems biological data analyses and for modelling using integration of various data sets (diagnostic markers, proteomic or metabolomic data sets) are being established. For this purpose the CU Systems Medicine conducts pilot studies in the field of systems biology.
In addition to supporting research of researchers of all departments of the University and the University Clinics in Würzburg, the CU Systems Medicine collaborated with external scientists as well as with research consortia to solve demanding systems biological/medical research questions. Amongst others, in addition Dr. Sascha Sauer coordinated the European Sequencing and Genotyping Infrastructure (ESGI; www.esgi-infrastructure.eu), which significantly contributed to technology implementations ("3rd generation sequencing", single-cell sequencing, bioinformatics tools) and various genomics projects of European genome research consortia and groups .

Structure and Major Research Interests

Generally, we conducted in particular bioinformatic sequence analyses and data integration. Therefor we processed data that were obtained from high-throughput methods like "second-generation sequencing" and microarrays. We were mainly focussing on analyses of RNA-seq data to detect and quantify RNA species and interactions of RNA with proteins. While some of our projects focused on clarification of regulatory mechanisms of pathogenic bacteria, we also supported genomic analyses of various research groups that are specialized on other species or domains of life. Moreover, we closely collaborated with experimentally oriented partners to develop (open source) bioinformatic tools.
Among others, we worked on the construction of customized bioinformatics analysis pipelines for high-throughput sequencing experiments, for example in the context of different projects of the Comprehensive Cancer Center (CCC) Mainfranken.
The spectrum of established methods of the CU Systems Medicine amongst others includes panel, exome and genome sequencing, bisulfite sequencing (DNA methylation analysis), transcriptome sequencing (mRNA lnRNA, miRNAs) as well as single-cell RNA sequencing. Another part of our work focussed on the development of new methods and initiating and conducting, disease-ori-

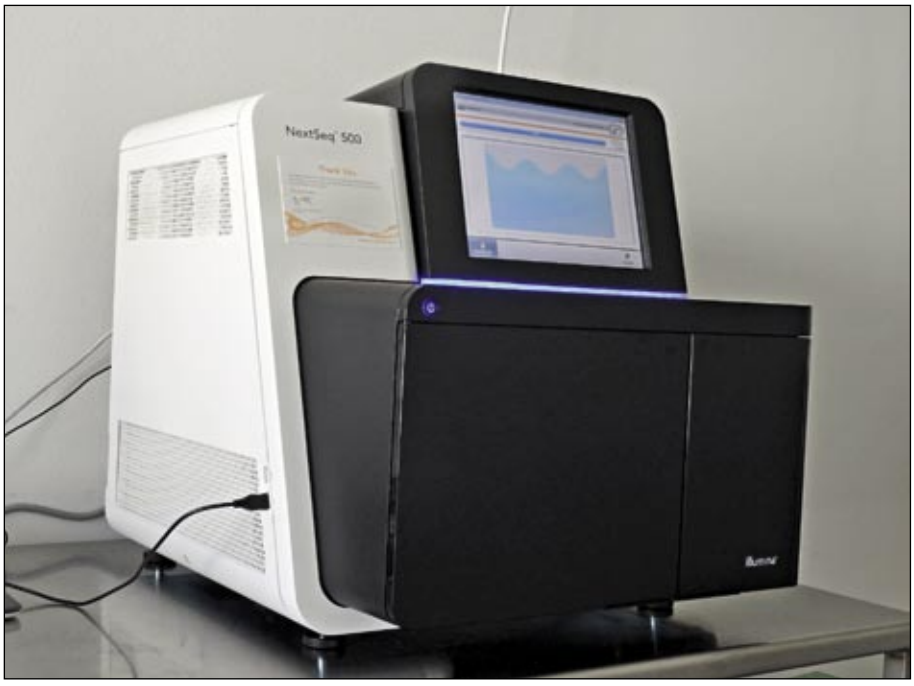

Fig. 1: The NextSeq 500 Sequencer from Illumina is used for rapid, flexible and highly parallel sequencing of biological and medical samples.

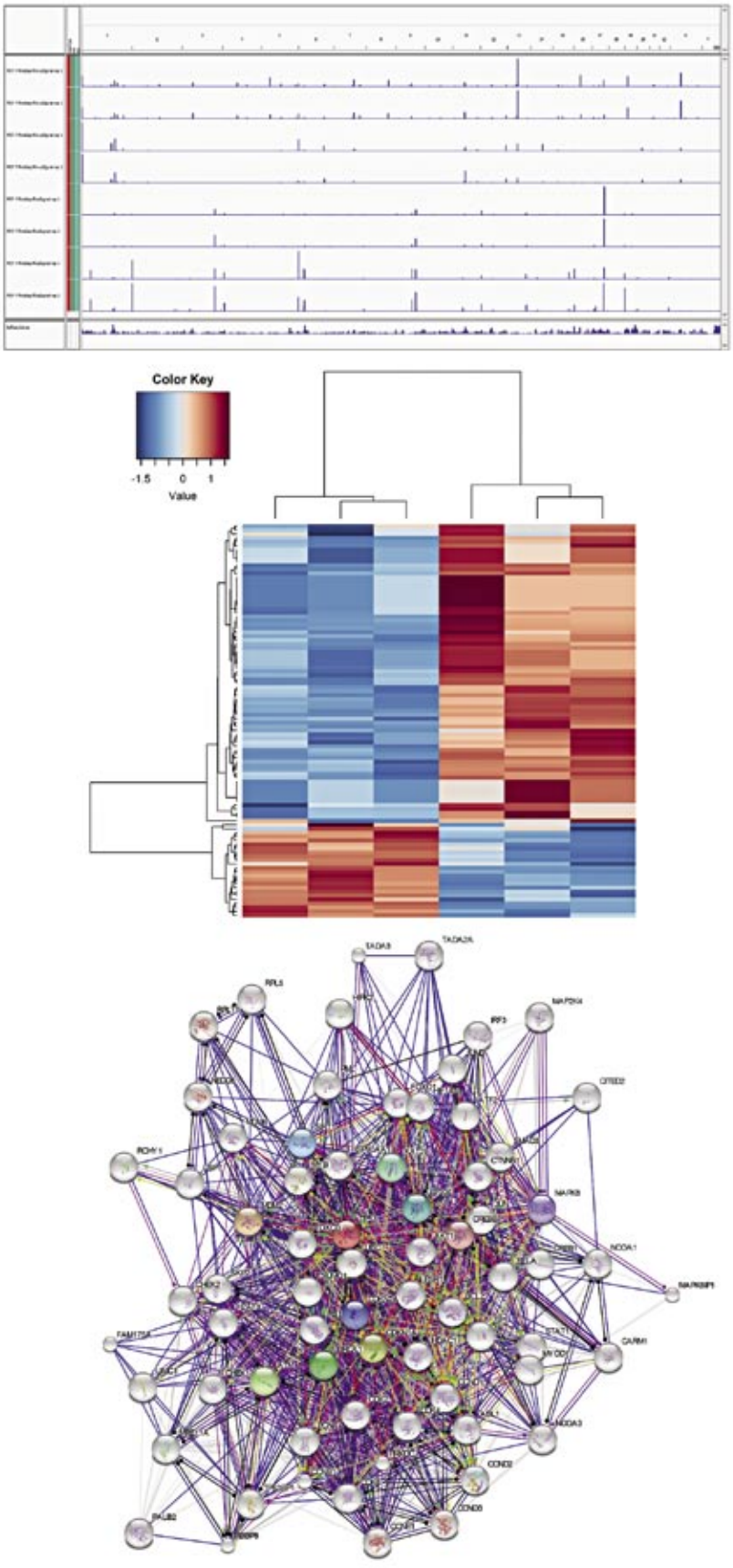

Fig. 2: Complex genomic data sets are prepared by the Core Unit Systems Medicine to gain scientific insights.

ented research and translational research. Moreover, we were committed to teaching (by supporting various IT and bioinformatics courses).

The team consisted of Dr. Silke Appenzeller, Mrs. Margarete Göbel, Dr. Konrad Förstner, Dr. Antoine-Emmanuel Saliba, Dr. Claus-Jürgen Scholz and Dr. Sascha Sauer.

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Clinical Trial Center Würzburg (CTCW)

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Research Portfolio

The Clinical Trial Center Wuerzburg (CTCW) is the central academic clinical research organization (ACRO) of the Medical Faculty Wuerzburg and is integrated in the University Hospital Wuerzburg (UKW).
Due to the CTCW, activities and competencies of the Medical Faculty Wuerzburg with respect to clinical studies are pooled and can be regionally expanded. Especially the infrastructure for the conduct of local and regional studies 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. CTCW´s goal is the support of scientific partners throughout all steps of a clinical trial starting with the initial idea of a clinical study, the development of a viable concept, the joint application of research funds, 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 biometric planning and analysis, legal and regulatory aspects, monitoring, data management, IT and data bases 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, 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 Medicinal Product Directive (MPG) starting with their conception and including planning, execution, and data analysis following Good Clinical Practices. The CTCW also supports the University Hospital Wuerzburg (UKW) in the exercise of their sponsor activities according to the German Medicines Act and Medicinal Product Directive, and is part of the sponsor quality management (sponsor-QA) and sponsor commission of the UKW.
During the time period 2014/2015 CTCWs' services were requested for 25 ongoing clinical study projects and for 31 clinical study projects during their planning period. Advisory services addressing individual questions related to study planning, study execution, preparation and submission of clinical trial applications to the authorities, and biometric-statistic data evaluation were provided for 121 projects.

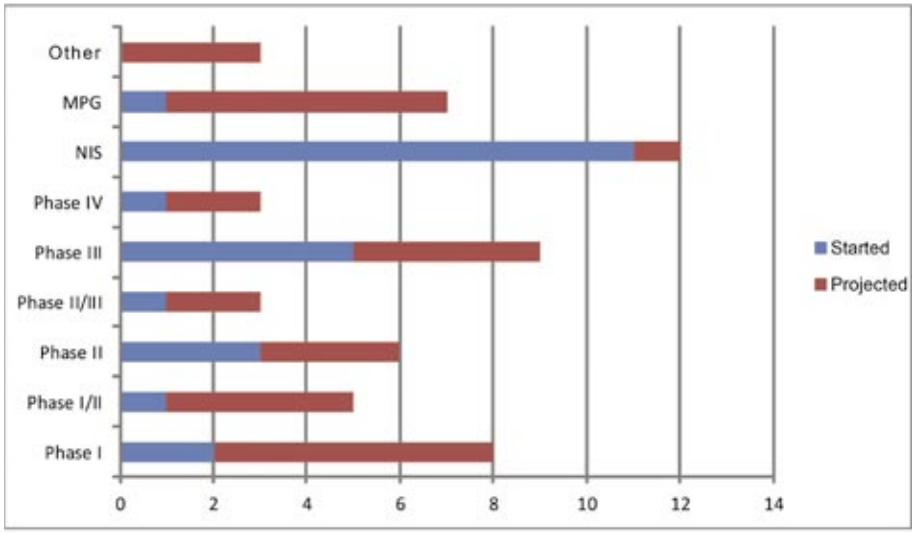

Fig. 1: Distribution of clinical studies according to type and phase. Phases I to IV clinical studies. Medicinal product trials (MPG). Non-interventional studies or e.g. operative studies (NIS) and other activities (Other) during 2014/2015.

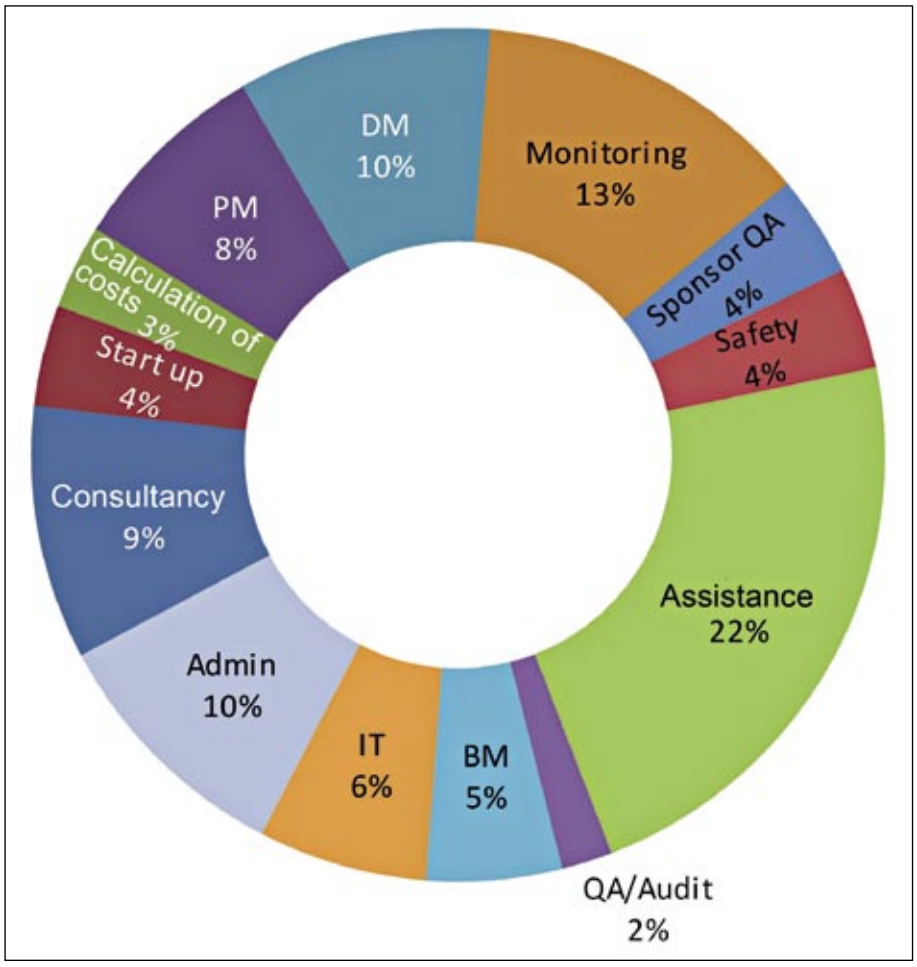

Fig. 2: Distribution of resources of individual services offered by the CTCW. DM = Data management, PM = Project management, BM = Biometrics/Statistics, QA = Quality Assurance, IT = Information technology, Sci = Scientific).

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 Wuerzburg, the University Hospital AöR as well as the academic educational hospitals are important collaboration partners of the CTCW. The number of collaborations with other hospitals, institutes, and centers of excellence is continuously increasing. During the past two years, the CTCW successfully supported 15 hospitals, two interdisciplinary research centers and three clinical profile centers with the coordination of their clinical projects and the realisation of high quality clinical studies according to international standards. The CTCW is also involved in collaborative activities with decentral operational clinical study centers at the University Hospital Wuerzburg. It is closely cooperating with the German Comprehensive Heart Failure Center (DZHI), the Comprehensive Cancer Center Main Franken (CCCMF), the Nephrological Study Center Wuerzburg (NSZ), the Service Center Medical Informatics (SMI), as well as the Institute for Clinical Epidemiology and Biometry (ICE-B).

Education and Training

Other servicesof 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.

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Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

Teaching and Promotion of Young Academics

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Increase in capacity

As a result of the temporary increase in capacity, totals of 155-165 students as opposed to 140-150 were enrolled each semester during the reporting period. These additional students have now reached clinical medical school. The funding provided to finance this increase in student numbers was used to create further beds required to teach the extra students in the "Neurogerontopsychiatric Day Hospital Bürgerspital" in Würzburg as well as the "Main-Spessart-Kliniken" in Karlstadt/Lohr for the years 2014 to 2016.

Evaluation

The tool used to assess the quality of medical teaching was thoroughly revised and simplified to increase response rates. New evaluation software has been developed specifically tailored by the Chair of Computer Science VI (Prof. Puppe). This tool is available in two versions, one suited to PC use and the other suited to mobile devices.

Mobility within the practical year[1]

The national mobility of students has increased drastically thanks to the reforms introduced by the new German Medical Licensure Act (Approbationsordnung, ÄAppO) in 2012, which enables students to complete their practical year at university hospitals and contractually associated teaching hospitals other than those of their home institution. Since the aforementioned changes have tremendously increased the administrative burden on the available staff, new software was developed in collaboration with Prof. Puppe (Chair of Computer Science VI) to simplify the process of distributing vacancies for practical year students. This software is now successfully running in the Office of the Dean of Studies. In addition to our own efforts, we discussed the implementation of a platform provided by the University of Münster, which works on the national level and aims to simplify the processes relating to practical year vacancies and distribution further. The Faculty of Medicine here in Würzburg has been using this platform since November 2015; the initial feedback with respect to usability, support from the providers, as well as student satisfaction is exceptionally positive.

Financial compensation for the practical year

Students embarking on their practical year at the University Hospital have been in receipt of the sum of 200 Euro per month from the University Hospital as financial compensation since the beginning of the practical year rotations in May 2015.

Practical Year "Drivers' Licence"

A "drivers' licence" for practical year students has been introduced within the frame-

[1]The "practical year" in Germany is the final year (last two semesters) of the degree course in human medicine, which is organized as practical training in three 16-week rotations (surgery and internal medicine as compulsory subjects with a third elective subject).

Fig. 1: Learning the various surgical instruments on the course "Conduct in Theatre" in the Teaching Clinic.

work of the "Cooperation for Transparency and Quality in Healthcare" certification of the University Medical Hospital.
The licence is divided into three colour-coded zones following the traffic light model. The red zone denotes activities to be performed solely by a fully qualified clinician and for which students should never be responsible. The green zone comprises medical tasks which students can perform to all intents and purposes independently of supervision. The yellow zone defines activities a student may perform when supervised directly by a clinician. Students not in possession of this licence are not permitted to work in the University Hospital. The licence is acquired by participating in a mandatory course on the first day of the practical year. Among other topics, the course covers guidelines on hygiene, conduct in theatre and during medical emergencies, data security, as well as health and safety issues in the workplace.

Logbooks for the practical year

Geographical mobility during the practical year has forced the need to assure minimum standards of practical education. MFT-Zert, a subsidiary of the German Association of Medical Faculties (Medizinischer Fakultätentag), carried out an examination of the compiled certification criteria for the compulsory disciplines of internal medicine and surgery, as well as for the elective disciplines of paediatrics and gynaecology, in the form of a test inspection at the University Hospital in Würzburg back in July 2014. A recommendation made by the investigation committee was to increase the focus on competencies in the logbooks. Subsequently, a task force comprising clinicians from the fields of surgery and internal medicine, the Dean of Studies, and members of the student council revised the logbooks. The new logbooks were presented to an audience of students as well as clinicians from the University Hospital and affiliated teaching hospitals during the Practical Year Fair in 2015. We began revising the logbooks for elective disciplines in November 2015. These will be made available to the May 2016 practical year cohort. Our future intention is to make the logbooks available for PCs and mobile devices.

The Teaching Clinic in Würzburg

The Teaching Clinic was founded as a skills lab in 2004. Its tenth anniversary was celebrated in the presence of numerous guests on 8 October 2014 in recognition of its remarkable development. Peer teaching is one of the basic principles of the facility. Positions as a student tutor in the Teaching Clinic remain highly sought after; 20% of students in the fifth semester applied for such a position in the summer semester of 2014. The training of these student tutors has been greatly extended and professionalized. The recently produced teaching videos contribute towards quality assurance and standardization of teaching in the mandatory course "Practical clinical examination methods" during the first clinical semester.

The Competence Network for Medical Teaching in Bavaria

During the third period of funding, the Faculty of Medicine in Würzburg has been focussing on projects relating to faculty development, examinations, and e-learning. In the field of faculty development, the Certificate of Medical Didactics in Bavaria was established, which was ratified by the Deans of Studies at each Faculty of Medicine in Bavaria and then presented to the Bavarian State Ministry for Science, Research, and the Arts. This document allows any qualification in medical didactics to be certified on three levels. These levels correspond to those of the Certificate for Higher Education of the Bavarian Universities, but contain a didactic aspect specific to medical education.

Internationalization

With the new Erasmus+ Program introduced in 2014, students now receive a formal guarantee prior to their stay abroad that the courses of study they plan to complete abroad will be accredited in Würzburg. Erasmus student exchanges remain attractive in both directions. Every year, 45 students from Würzburg take up study at an Erasmus partner university with almost 40 students coming to Würzburg for one to two semesters. The total of ten exchange places (for clinical electives and the practical year) at the Universities of Nagasaki and Mwanza are very popular among students with all the available capacity being used. The German Academic Exchange Service (DAAD) has agreed to extend its financial support for a further four years (2015-2018) using financial resources from the Physicians' Program. The program does not only enable student exchanges between Würzburg and Mwanza, but also the continuation of the rewarding cooperation between physicians established and now extended to currently three partner Universities of Würzburg, Mwanza, and Stellenbosch. New impulses to intensify internationalization are expected through the appointment of Prof. Deckert as Vice-Dean for International Affairs. Furthermore, Prof. Deckert heads the new Committee of Internationalization. Thanks to the initiative of the committee member Prof. Higuchi, a new partnership agreement with Kanazawa University (Japan) was signed in the autumn of 2015. Mentoring programs for foreign students were continued and expanded, with funding (Kompass) provided by the German Federal Ministry of Education and Research (BMBF).

Teaching Awards

Since the autumn of 2003, the Albert Kölliker Prize has been awarded twice a year to promote the development of and improve teaching at the Faculty of Medicine in Würzburg. The award amounts to 10,000 Euro which cannot be shared; the funding is earmarked and can only be implemented to improve the quality of teaching. Within the framework of the examination celebrations in the spring and autumn of 2014, Prof. Dr. Esther Asan (Institute of Anatomy and Cell Biology) und Prof. Dr. Klaus Brehm (Institute of Hygiene and Microbiology) respectively received the award for their outstanding teaching achievements. In spring 2015, the Prize was awarded to Prof. Dr. August Stich (Department of Tropical Medicine at the Missionsärztliche Klinik), in autumn 2015 to Prof. Dr. Thorsten Bley (Institute of Diagnostic and Interventional Radiology). Prof. Asan also received the Prize for Excellent Teaching, awarded by the Ministry of Education, Science and the Arts, in Bayreuth in December 2015.

Master of Medical Education

Three members of the Faculty of Medicine have enrolled on the 2015 entry postgraduate degree course "Master of Medical Education". Funded through study grants, the successful participants aim to contribute to the further professionalization of medical teaching.

Chair of General Practice

Modifications to the German Medical Licensure Act (ÄAppO) in July 2012 strengthened the significance of General Practice. The Faculty of Medicine in Würzburg launched the process of establishing a Chair of General Practice, not only in reaction to the abovementioned changes to the law. Meanwhile, the process of appointing the Chair is nearing conclusion.

Chair for Medical Education

After approval by the Bavarian State Ministry for Education, Science, and the Arts, the position of Chair of Medical Didactics was announced at the end of October 2014. Ensuring high standards in the quality of education in human and dental medicine has always been a central aim of the Faculty of Medicine. The Chair of Medical Didactics held by Prof. Dr. med. Sarah König (formerly University Medical Center Göttingen) is to make a substantial contribution to fulfilling this goal. The professorship and the foundation of the Institute of Medical Teaching and Education Research are linked to the establishment of a Centre for Management and Development of Degree Courses and Programs. The new organization is supposed to condense, strengthen, and promote the development of functions previously situated in the Dean of Studies' Office and the Teaching Clinic.

B.Sc/M.Sc. programs in Biomedicine and Biochemistry

The Faculty of Medicine and the Faculty of Biology offer a joint program in **Biomedicine**, where students are trained at the interface between the classical natural sciences and clinical research. The core curriculum consists of a research-oriented training with intensive laboratory courses in small groups and an early immersion in current research topics. Additional internships in individual work groups guarantee an efficient and productive thesis project that concludes with the final Bachelor or Master thesis, respectively, which is written in English.
While the Bachelor curriculum is densely structured, students are rather free to set their own priorities in the Master program after finishing the first semester with a comprehensive course on model organisms. A special feature of the Biomedicine program is the high share of stays abroad. The majority of students use this opportunity to widen their scientific and personal horizon.
The interest in the Bachelor program continues to be impressive with more than 1,000 applications per year for 33 study places. 87 students are currently enrolled in the B.Sc. and another 21 in the M.Sc. program. Most of the graduates opt for further scientific qualifications through a Ph.D. degree, about 40 % of them in Würzburg, while the remaining graduates chose other institutions in Germany or abroad.
Since 2009 the Faculty of Medicine and the Faculty of Chemistry and Pharmacy jointly offer an additional **Biochemistry** B.Sc. program. The demand for these 60 study places is also very high. The focus is on the molecular and functional understanding of basic processes of life. Within the consecutive M.Sc. study program a specialization in "molecular oncology" has been implemented that focusses on the interface between basic research and clinical translation and should attract additional applications from abroad.

Master of Science in Translational Neuroscience

Students have been able to enrol on the Master of Science program in translational neuroscience since the winter term of 2015/2016. This scientifically oriented postgraduate degree course focusses on the link between questions addressing fundamental neurobiological research and those addressing clinically oriented research and the applicability to treatment and clinic. The program accepts up to 25 students per year. The aim is to qualify students for scientific research in the field of the life sciences with a particular emphasis on neuroscience.

Concurrent programs for medical students

For medical students there is the option of parallel supplementary degree programs in **Experimental Medicine** as well as in **Clinical Research and Epidemiology.** In Experimental Medicine in-depth molecular and cell biological knowledge in various fields of biomedicine is taught with concomitant laboratory training. In Clinical Research and Epidemiology, the focus is on patient-oriented clinical research and on the theory and practice of epidemiological and biometric methods. In addition, the interpretation and presentation of scientific results is trained in both programs. With an additional thesis candidates can earn a M.Sc. degree in the corresponding subject. These diverse training opportunities ensure that highly qualified up-and-coming basic and clinical scientists are well trained for medically relevant research.

Bachelor of Science in Academic Speech and Language Therapy

The Bachelor of Science in academic speech and language therapy was introduced in the winter term of 2014/2015. The degree course was realized in cooperation with the Würzburg Vocational College of Speech and Language Therapy (Caritas-Schulen gGmbH). The double degree program accepts 25 students per year. On successful completion, students take the state examination for speech therapists to obtain state certification as a speech and language therapist as well as receiving the academic degree of Bachelor of Science.

Dental medicine

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.
The departments of the dental clinic are equipped according to the newest technical standard. State-of-the-art equipment necessary for a modern dentist training is available. The treatment room of the department of restorative dentistry is the newest facility. The room offers the best equipment for student training since spring 2015. In diverse departments interactive training concepts and problem-based learning integrated in the clinical education are now offered. The National catalog of learning objectives dentistry was published in 2015 and gives further perspectives for the development of the dental education program. 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.
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 with regard to the long-promised introduction of a new order for approval for dentists (ZÄPrO).

Graduate School of Life Sciences (GSLS)

Graduate School
Life Sciences

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(Director, UWGS; Vice Dean, GSLS)
(until 11/2016)

Professor Dr. rer. nat. Dr. med. habil. Heidrun Moll
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General Information

For many years the Faculties of Medicine and Biology have gained experience with structured graduate training through the MD/PhD program and several DFG-funded graduate programs (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. The IGS was established to cover the university's entire academic spectrum, encompassing separate graduate schools, catering to the specific scientific and training needs and cultures of its diverse disciplines.

Section Biomedicine

As a first step, the section of Biomedicine was initiated in the IGS in 2003 by unifying several programs and their doctoral researchers.
These programs 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. Since then, several generations of basic and clinical scientists have successfully completed this program. 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). Recent years, and in particular 2006, have seen major steps towards this goal. The GSLS was successful in the "Excellence Initiative of the Federal and State Governments" and obtained funds to support fellowships and other activities within the GSLS. In addition to the section of Biomedicine and the MD/PhD program three further sections were founded: Infection and Immunity, Neuroscience and Integrative Biology.

The growing Graduate School

Increases in size and scope resulting from the progressive integration of further programs and discussions in the context of the national "Excellence Initiative" called for a number of changes within the IGS in 2006. These changes affected both its internal structure and its formal status. The IGS transformed into an umbrella organization of the independent graduate schools in 2006 and was renamed as the University of Würzburg Graduate Schools (UWGS). Other graduate schools – The Graduate School of the Humanities (GSH), the Graduate School of Science and Technology (GSST) and the Graduate School of Law, Economics and Society (GSLES) have since been added to the UWGS.
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 (see Fig. 1). Each school manages their day-to-day business independently.
The umbrella organization, the UWGS, assures adherence to, and development along common rules. It also provides general services to the individual schools. In this context, graduation 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 programs that is easily adaptable to the needs of the individual graduate schools. The study programs "Life Science" and "Humanities" were approved by the Bavarian State Ministry of Sciences at the end of 2007.

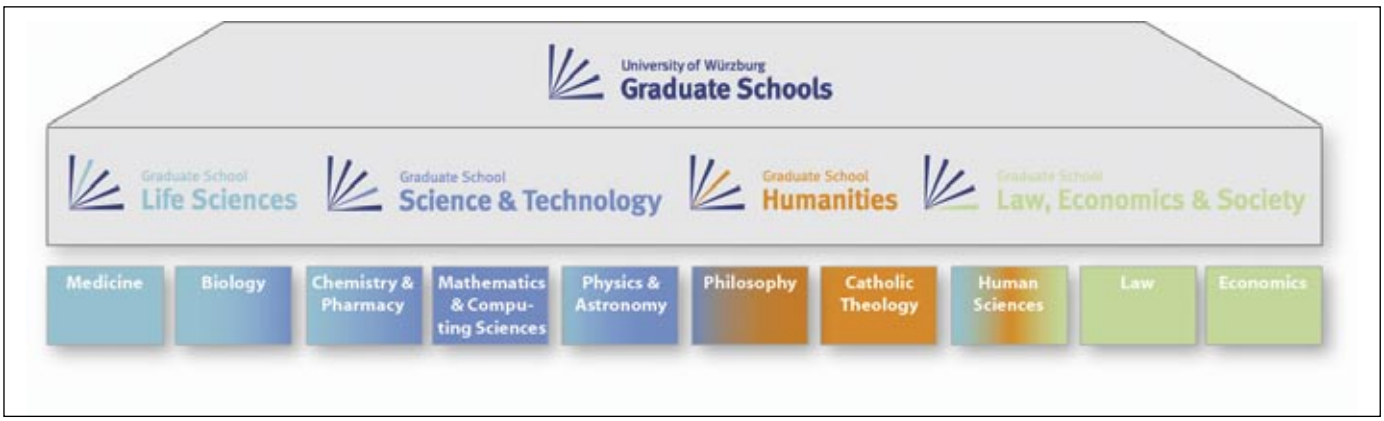

Fig. 1: Structure of the University of Würzburg Schools.

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 application to the Excellence Initiative and have been put into practice.
The GSLS now houses doctoral researchers of all collaborative research programs – such as the DFG-funded collaborative research centers ("Sonderforschungsbereiche"), research training groups ("Graduiertenkollegs") and clinical research groups ("Klinische Forschergruppen"), as well as other collaborative programs funded by the Federal Ministry of Education and Research (BMBF), the European Union and other sources. The school is currently divided into five separate sections. In addition to the sections "Biomedicine", "Infection and Immunity", "Neuroscience" and "Integrative Biology", the section "Clinical Sciences" was established in 2011. Doctoral researchers of the MD/PhD program were integrated into the respective sections according to their research interests. Each section usually comprises individual programs which are the scientific as well as social "home" of the doctoral researchers (see Fig. 2).

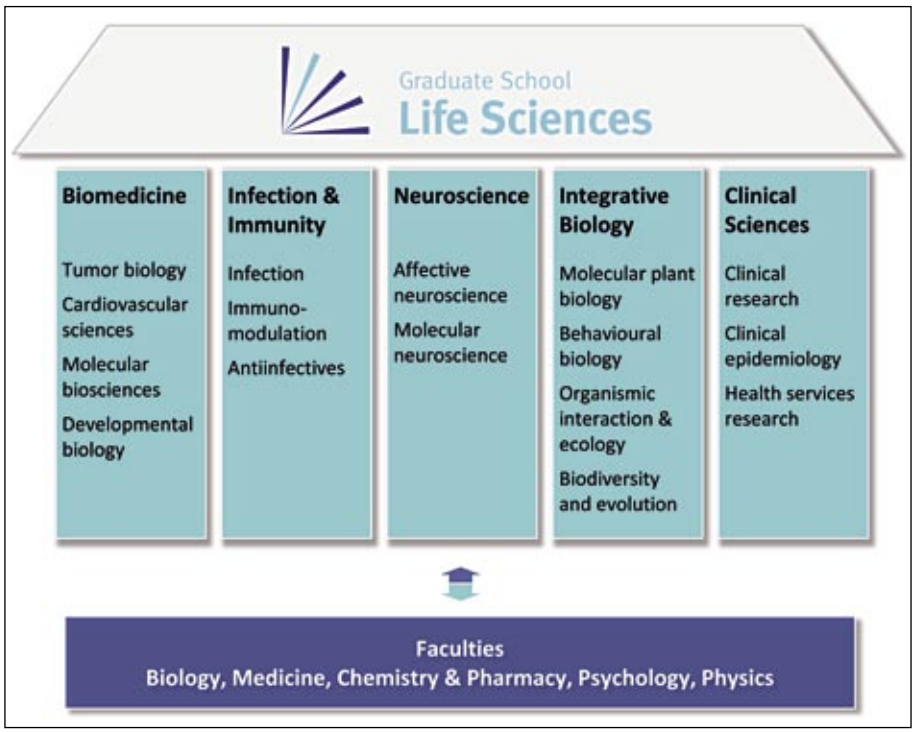

Fig. 2: Structure of the Graduate School of Life Sciences.

GSLS fellowship program: The fellowship program of the GSLS is the core element within the graduate school and funded by the Excellence Initiative. The 10th round of international recruitment began in the fall of 2015. To date, more than 3000 standardized written applications have been evaluated in the recruitment rounds, and interviews with more than 450 candidates have been conducted by the GSLS admission board in Würzburg, by means of video conferencing and abroad. So far 111 fellows from 25 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 220 principal investigators from all participating faculties. In 2015 the number of doctoral researchers registered in the doctoral study program "Life Sciences" rose to more than 360.

Excellence Program for Medical Doctoral Researchers: In July 2012, the renewal proposal of the GSLS in the framework of the second phase of the Excellence Initiative was approved. Besides establishing an international MSc program and a program for postdoctoral fellows to foster their early independence, the introduction of an excellence program for MD doctoral studies was also envisaged, addressing the top ~20% of medical students (Fig. 3).
Since March 2013, 86 MD students have registered in the structured doctoral training program of the GSLS; in 2016 the first students are expected to graduate. For registration the following criteria have to be fulfilled:

- Receipt of an MD fellowship from the Medical Faculty or the GSLS
- The thesis entails an experimental or clinical epidemiological research project
- Successful completion of the First State Exam 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 anytime to the Medical Faculty. All requirements for MD students will amount to a third of those for the natural sciences GSLS doctoral researchers, as the program is expected to last a maximum of one year. The program consists of 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 Program: The usual admission requirement for the doctoral study program 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 exams. To attract excellent international research-minded 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 program has attracted excellent students from around the world. Candidates enter a rigorous selection process before being admitted to the program. In the first semester, students are prepared for active research in the life sciences through two specially-designed lecture series 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 thesis in the second semester. The thesis ideally sets the foundation for a following PhD project which students can start immediately if their master 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 degree parallel to the PhD study, the FOKUS Life Sciences program is

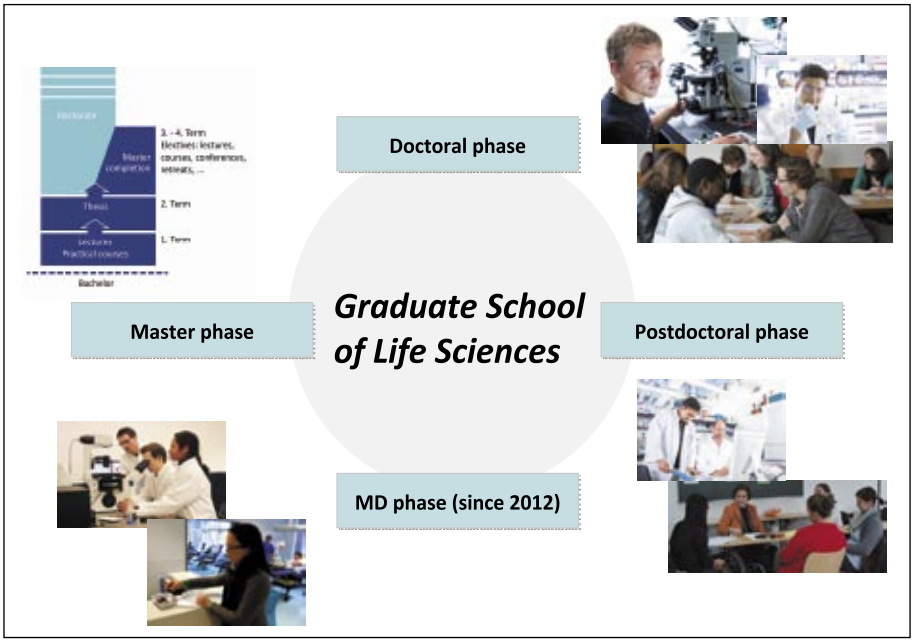

Fig. 3: Programs of the Graduate School of Life Sciences.

able to attract internationally excellent students to Würzburg.
Since the program has been introduced in the winter term 2012/13 31 students have been admitted. In the meantime, twelve students have finished and have all, with only one exception, entered into a PhD program. Five students successfully applied for the GSLS fellowship program, three of whom already started PhD projects in 2015 via the fast-track option, with the other two due to follow in 2016.

The PostDoc Plus Program: It is an important aim of the GSLS to especially support postdoctoral researchers with their first steps towards early independence. In the course of the 2nd phase of the Excellence Initiative, the GSLS successfully submitted a proposal to offer postdoctoral researchers a research grant for the duration of one year. This was designed to provide the basis to achieve preliminary results for the preparation of their own grant proposals. This GSLS program has proven to be quite successful; from 2013 to 2015 15 postdoctoral researchers have successfully applied for the GSLS research grants. Five manuscripts have been accepted for publication and four grant applications have been prepared (e.g. DFG or EU proposals).

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 program is tailored for each doctoral researcher.
- Doctoral researchers actively participate in the program by offering and organizing courses and symposia.
- 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 programs 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, program 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 Medical Faculty and University Hospital

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Aim

MENTORING med is used as a modern instrument in the academic career development in order to recruit and support qualified young scientists on their way to their career and higher achievements. Female scientists are brought together with established seniors scientists and leaders in a so called „one-to-one setting". Networks are formed so that better career chances develop.

Structure

The programme focuses on three elements: it includes a qualification programme (Workshop Series), building of networks (Network Meetings) and meetings between the mentee and the mentor (Mentor-Mentee Relationship).

Participants

The MENTORING med programme is a cooperation of the medical faculty, the clinic and the officer for gender equality issues of the faculty. The programme was co-financed until the 31th of May 2015 by the European Social Fonds (ESF), especially in order to promote female scientists to leading positions. Since 2008 there have been four rounds, each of 18 months duration. A total of 164 female mentees (about 40/round) and 164 female or male mentors have participated. Some mentors have been engaged in more than one round.

Specifically for the time-frame of this report (2014/2015): The fourth round of the MENTORING med took place during this time-frame, namely between October 2013 and May 2015. 40 Mentors (18 females and 22 males) took part in the programme as well as seven external mentors (two from Erlangen, three from Munich, one from Freiburg and one from Hamburg). 29 out of them had a medical background, one was a psychologist, nine were natural scientists and one was a vet. The 47 mentees were all female. 31 had a medical education, one was a dentist, 11 were natural scientists and two psychologists. Three babies were born during this round. Two mentees interrupted the programme and three entered the program after its start. Besides the occasions of the basic program such as get-together, introduction, half-time and final evaluation, also five network meetings took place, 14 workshops and seminars on issues concerning career development. For example: how to apply for grants or how to develop leading competence.

Results

Prof. Dr. Christine Färber from HAW Hamburg performed an evaluation of the programme based on the personal thoughts and feelings of the mentees. She found a very high score of personal satisfaction and acceptance of the programme. Also an evaluation based on objective criteria such as the achievement of a „habilitation"in the medical faculty by the mentees showed high success scores.

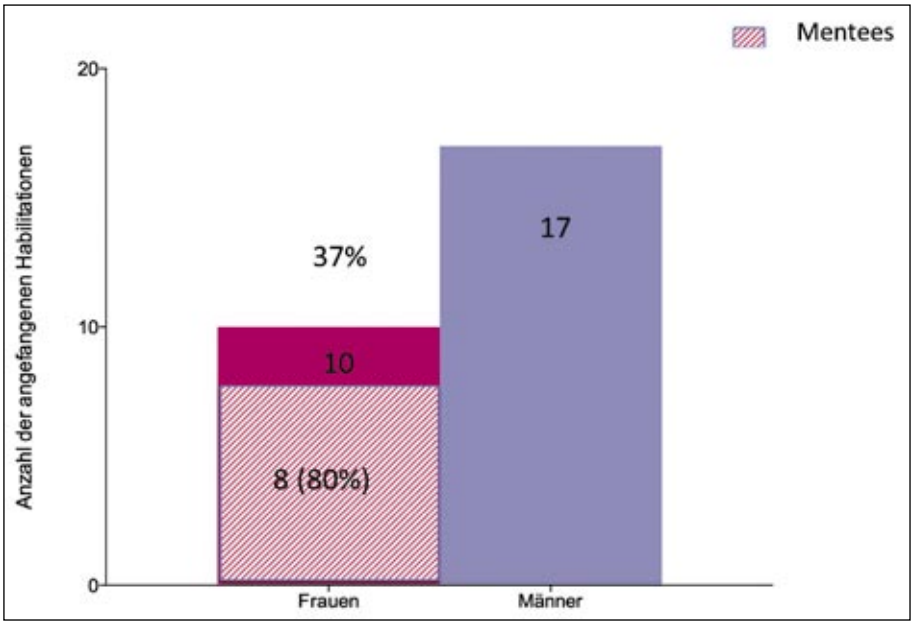

Fig. 1: Starting „habilitations". Source: From the report of the main officer for gender equality issues of the medical faculty, summer 2015.

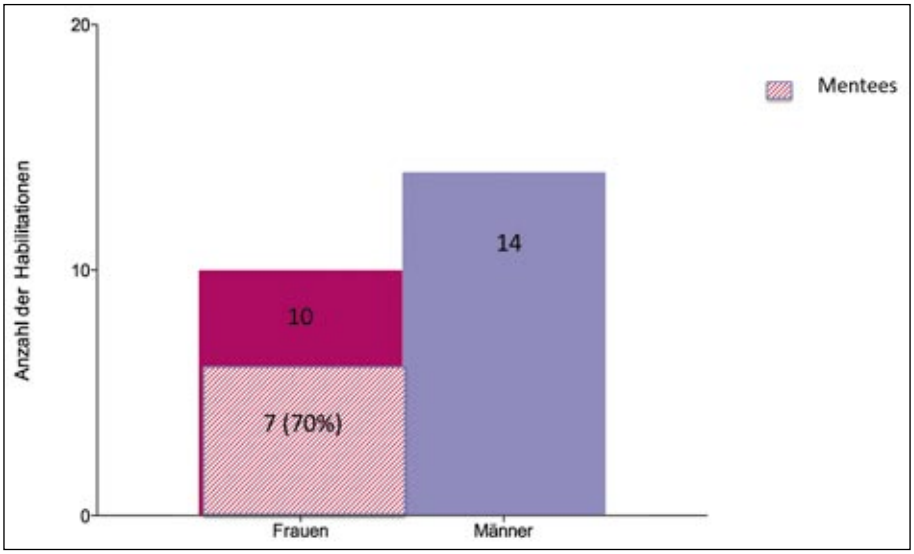

Fig. 2: Proportion of habilitations by female scientists. Source: From the report of the main officer for gender equality issues of the medical faculty, winter 2015.

During the time-frame 2014/2015 10 female and 17 male scientists began with their habilitation (37 % females). Eight out of the 10 female scientists were mentees (80% mentees). Similar were the results concerning accomplished habilitations in 2015.
In 2015 10 female and 14 male scientists were completely ready with their habilitation (41% female scientists). Seven out of 10 female scientists with ready habilitation were mentees. This means that 70% of the ready habilitations come from mentees.

Maintenance

The MENTORING med is since 1. June 2015 an established structure which is permanently continued.

New Concept for the future

Following the fourth round of the programme in May 2015 we started the planning of a new concept which was ready in summer 2015. The new concept includes also male mentees and is called MENTORING med PEER. It starts in the beginning of 2016. There will be 10 male and 10 female mentees in the programme. The very focus of this new concept is networking which will be interdisciplinary and independent of gender. It is planned that the so called peers (colleagues on similar stage in their development) will continuously meet each other in small groups and they will discuss together their career aims and the ways for their achievement. Besides, the peers will exchange their personal experiences. These peer-groups decide themselves which mentors they need to invite for specific issues. The One-to one-concept (MENTORING med ONE to ONE), for female mentees only, starts in 2017 and the two programmes run in this rhythm in parallel further on.

Interdisciplinary Physician-Scientist Program in Translational Immunology

Else-Kröner-Forschungskolleg Würzburg

CONTACT DETAILS

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Professor Dr. rer. nat. Jörg Wischhusen (Speaker)

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Dr. Andrea Thelen-Frölich
Maike Rothgang, M.A.
(Administration and Organization)
Phone: 0931-201-56432

General Information

The Else-Kröner-Forschungskolleg Würzburg for Interdisciplinary Translational Immunology is a multidisciplinary physician scientist program, which aims at providing a structured, science-based training for physician-scientists oriented towards clinical immunology. Under the direction of Prof. Dr. Dr. Andreas Beilhack (Department of Medicine II) and Prof. Dr. Jörg Wischhusen (Department of Obstetrics and Gynecology) the Else-Kröner-Forschungskolleg Würzburg is funded by the Else-Kröner-Fresenius-foundation since 2012. In 2014, the funding has been extended for another three years (starting from December 2015)

The Else-Kröner-Forschungskolleg Würzburg aims at providing optimal support for the careers of young physicians at the interface between patient care and clinical and experimental research. Within the program the eight selected fellows receive an optimized training in medical skills of their respective specialty. Furthermore, the Else-Kröner-Fellows participate in a special research training program, including a 12 month research period, integration into a clinical trial program, and a mentoring program. The eight Else-Kröner-Fellows are introduced to new methods of biomedical research within the eight participating departments and institutes and gain a comprehensive insight into the immunobiological basics of medicine through this curriculum.

Malfunctions of the immune system have a profound impact on various diseases throughout many disciplines of medicine. An improved interconnection between basic immunological research and the translation of those results into clinical applications is imperative for innovative therapeutic approaches. Since the immunological training of young researchers should not be limited to a medical school curriculum it should be also integrated into continuous clinical training.

The Else-Kröner-Forschungskolleg Würzburg recognizes the demand of patient-oriented personalization in immunotherapeutic concepts. Tolerance mechanisms, responsible for insufficient protection from cancer and infectious diseases and excessive immune responses in transplant rejection, autoimmune diseases and allergy, are two sides of the same coin. Thus, all these topics are included in the curriculum of the Else-Kröner-Forschungskolleg Würzburg. The Else-Kröner-fellows get acquainted with the broad impact of immune function on common diseases beyond conventional disciplinary borders.

Although it is a comparatively new program the Else-Kröner-Forschungskolleg turned out to be highly successful in supporting long-term interdisciplinary cooperation. For example, this offers the unique opportunity to promote the translation of therapeutic approaches that have been proven to be successful in some immune related diseases towards new, not yet explored, disease conditions.

Patient-oriented immunological research

To guarantee an ideal interaction between experimental immunological and clinical research, eight different clinical departments and institutes from the Würzburg University Hospital and the Würzburg University joined to collaborate in the Else-Kröner-Forschungskolleg.

State-of-the-art individualized immunotherapy inevitably begins with the identification of target genes. These are analyzed at the Institute of Pathology Würzburg, an internationally recognized center for lymph node pathology with a state-of-the-art sequencing technology (Leukemia and Lymphoma Molecular Profiling Project, International Cancer Genome Consortium). Proteins, essential players in all key functions of the cell and therefore also in the development, diagnosis and treatment of various diseases, are characterized at the DFG Rudolf-Virchow-Centre with various methods including high resolution microscopy and x-ray analysis.

In cooperation with the Department of Internal Medicine I it was demonstrated that autoantibodies against ß1/2-adrenerge receptors can play a major role in the pathogenesis of cardiac insufficiency. The clinical concepts emerging from this research is further explored and developed at the new founded German Center for Heart Failure (DZHI),

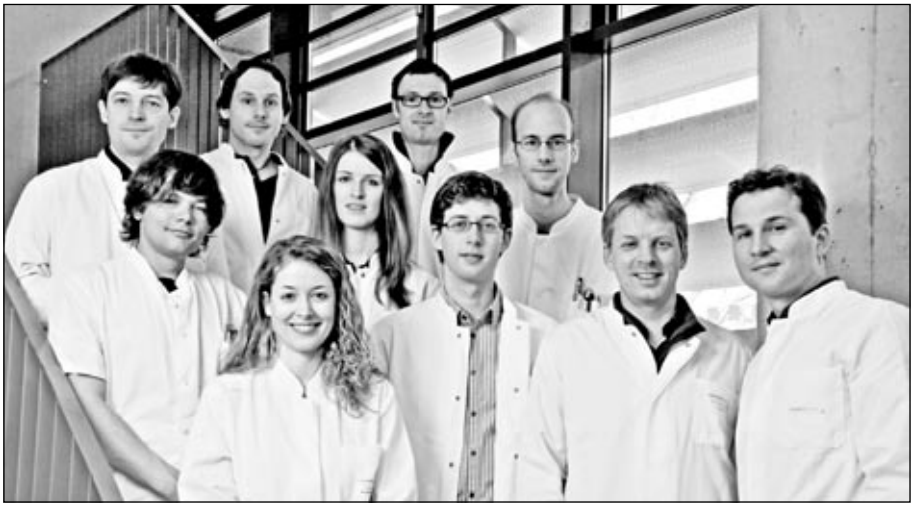

Fig. 1: The fellows of the Else-Kröner-Forschungskolleg for Interdisciplinary Translational Immunology.

which is connected to the Department of Internal Medicine I.

The Department of Internal Medicine II focuses on innovative immunotherapies for hematological malignancies and has initiated the nationwide unique Early Clinical Trial Unit. A center of stem cell transplantation has been built in close collaboration between the Department of Medicine I and the Würzburg University Children´s Hospital where new approaches of stem cell transplantation are evaluated. The IZKF-research group for Experimental Stem Cell Transplantation, established in 2012, is testing new immunological therapeutic concepts for leukemia, solid tumors, infections and graft-versus-host disease after stem cell transplantation in preclinical models.

Adoptive immunotherapies may benefit from novel protocols for efficient generation of tumor-antigen-specific T-lymphocytes under GMP-conditions. Such a special protocol has been developed at the Würzburg University Children´s Hospital. Another focus of the Children´s Hospital is set on dendritic cell-based vaccination for the treatment of pediatric brain tumors.

Immune responses are investigated in close collaboration with the Institute of Virology and Immunobiology. The scientists are testing novel concepts for the regulation of immune responses via cell surface receptors. This approach includes research on the regulatory role of rare T-cell populations such as gamma-delta-T-cells and NK-T-cells.

The Department of Dermatology, Venereology and Allergy has investigated tumor microenvironments as modulator and target structure of anti-tumoral immune reactions. It has successfully carried out trials of peptide based vaccination against tumor-stroma-antigens. Additionally, with the appointment of Prof. Goebeler as the new department chair the field of Allergy research has been strengthened.

At the Department of Obstetrics and Gynecology antibody-based therapies play a key role in the treatment of breast carcinoma. Scientifically the examination of tolerance mechanisms in tumors as well as at the feto-maternal interface forms the primary focus of interest. The section for Experimental Tumor Immunology develops clinically relevant strategies for enhancing T cell infiltration into solid tumors and for the immunotherapeutic targeting of tumor stem cells. Based on mRNA-profiles in the peripheral blood lymphocytes new diagnostic approaches have been developed.

Structured training for physician scientists

The actual participation of the selected fellows in the training program of the Else-Kröner-Forschungskolleg lasts for 3 years. This time frame allows a personalized program in order to suit the individual interests and talents of each participant. Thus, a structured and goal-oriented training as a physician scientist will be adjusted to the individual career paths of the Else-Kröner-fellows. The Else-Kröner-Forschungskolleg embodies three major training components for the young researchers: The clinical training in the individual medical subspecialty, a basic training in biomedical research with an interdisciplinary focus on immunology as well as a profound training in the translation of preclinical results into clinical trials. The mentoring program of the Else-Kröner-Forschungskolleg is supposed to support prospective physician-scientists in mastering the numerous challenges of daily life in the clinics and in academia and help them to improve their individual career options. A first orientation semester with weekly meetings of the Else-Kröner-fellows with clinicians and researchers facilitated the rapid acquisition of a program overview and has also created personal contacts with experts in various disciplines.

During the orientation semester, the Else-Kröner-fellows passed weekly lab rotations in three different research laboratories. This enabled them to make a well-founded decision about their personal research project and also helped them to explore possibilities for collaboration opportunities for their research project.

Together with their supervisors, each fellow designed her/his individual program that should offer her/him an optimized coordination for the 12-18 month research project, consisting of clinical training, including a clinical trial. The supervisory commission, consisting of a scientist, a physician and a clinical director, ensures that both clinical and scientific needs are considered.

An external faculty mentor provides personal guidance to each fellow's individual career development. This policy of external mentors limits potential conflicts of interest between the faculty and the supervisors. Although the fellows of the first round had the possibility to divide their lab rotation into shorter time intervals, all of them chose to complete their secured research time in one cycle.

Because each fellow could pick the lab of their choice, it was ensured that the principal investigators of these laboratories had to accommodate the particular needs of the fellows. During this protected laboratory research period, the fellows were freed from all clinical obligations.

During the three-year training program we had and have weekly lectures and seminars to provide a deeper insight into a variety of relevant topics such as statistics, bioinformatics, methods, applied immunology, guidance in study design, biobanking, bioethics, to name a few. Additional training courses and qualification programs promote work-related social skills and successful coping strategies for challenges related to clinical and research work and optimal work-life balance.

As a perspective, successful Else-Kröner-fellows are expected to advance their research projects sufficiently to secure external research funding. The First-Application-Program of the IZKF Würzburg has offered a good first funding opportunity. Furthermore the IZKF Scientific Management Center supports applicants in the process of grant writing for external funding organizations. This will ensure that the Else-Kröner-fellows will be capable in establishing their own independent research groups and become future leaders as physician-scientists.

Habilitation Grants for Women Physicians of the University of Würzburg

CONTACT DETAILS

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E-mail: esther.asan@uni-wuerzburg.de

Professor Dr. med. Stefanie Hahner
(Head of the Commission for the Advancement of Young Researchers and Women)

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The habilitation grants are awarded to female physicians by the medical faculty to further promote young promising female clinical scientists. Specifically, the aim is to support habilitation projects in order to increase the number of women in leading positions in university medicine. The grant supports female physicians with excellent scientific accomplishments who have completed their medical doctoral thesis and are employed either by the university hospital or by one of the theoretical institutes of the Medical Faculty.
The grants are intended to enable timely completion of all prerequisites needed for habilitation. Accordingly, the funding amount and the funding period are adapted to the individual needs of the respective recipient. Grants include funding of rotation positions, technicians and consumables. Every recipient also participates in the postgraduate program MENTORING med. The grants are awarded for up to two years. The selection is subject to an internal review process by scientists of the Medical Faculty and subsequent evaluation of the proposals and the applicants by the commission for habilitation grants for female physicians.
Since the end of 2010, 15 physicians participated in the program. All six recipients that were supported before 2014 completed their projects successfully and enrolled for their habilitation. Four of them were habilitated in this reporting period, for instance:

PD Dr. med. Christine Hofmann, Department of Pediatrics (2014)
Research topic: Rare inflammatory bone disease in childhood and adolescence

Hypophosphatasia is a rare genetic metabolic bone disease. In severe cases it manifests as a life threatening multisystemic disorder which is characterized by a dysfunction of the enzyme alkaline phosphatase. Within her research project, Christine Hofmann particularly focused on hypophosphatasia and the cellular function of alkaline phosphatase in bone and other tissues. She further investigated intra- and pericellular phosphate metabolism and the genotype/phenotype correlation of affected patients. Since 2011, Christine Hofmann is coordinating an international multicenter phase II trial investigating enzyme replacement therapy in life threatening forms of hypophosphatasia. She is further leading the German Hypophosphatasia Network together with Prof. Dr. Girschick and Prof. Dr. Jakob.

PD Dr. med. Verena Wiegering, Department of Pediatrics (2015)
Research topic: Identification of biomarkers for early detection of chronic Graft-versus-Host-Disease after allogeneic stem cell transplantation – based on the example of impaired B-cell-homeostasis.

Graft-versus-Host-Disease represents a severe complication of allogeneic stem cell transplantation. It is associated with high morbidity and lethality. Impaired B-cell homeostasis is regarded as an important etiological factor. Both biomarkers for early detection of graft-versus-host-disease and specific medication are urgently needed. Verena Wiegering has investigated B-cell subpopulations and cytokine expression in patients with GvHD over time and compared the data with patients not suffering from GvHD. Her research has significantly improved the understanding of the pathogenesis of this disorder and has furthermore led to an optimized risk stratification regarding further clinical decision making.

Six women were included into the program in 2014 and three women were selected for a grant in 2015. Their research topics represent the wide array of research activities of young physicians in the university hospital and theoretical departments of the Medical Faculty: the project topics cover cardiorespiratory aspects of systolic heart failure, pharmacovigilance for an individual benefit-to-risk improvement for children and adolescents, pathophysiological mechanisms in gastric and gastroesophageal carcinoma patients, the role of the gut-liver-axis in the pathogenesis of chronic liver diseases, the role of mitochondria in cell metabolism, cell death and gene transcription, forensic photography and spectrometry, the local glucose metabolism in cardiac remodeling and heart failure, the significance of the node of Ranvier as a central relay in inflammatory neuropathies and the interactive role of comorbidities in heart failure.

SELECTED PUBLICATIONS

Egberts K, Karwautz A, Plener PL, Mehler-Wex C, Kölch M, Dang SY, Taurines R, Romanos M, Gerlach M. (2015) Pharmakovigilanz in der Kinder- und Jugendpsychiatrie. Z Kinder Jugendpsychiatr Psychother 43:21-8.

Güder G, Gelbrich G, Edelmann F, Wachter R, Pieske B, Pankuweit S, Maisch B, Prettin, C, Brenner S, Morbach C, Berliner D, Deubner N, Ertl G, Angermann CE, Störk S. on behalf of the Competence Network Heart Failure Germany (2015) Reverse epidemiology in different stages of heart failure. Int J Cardiol 184C:216-24.

Seidlmayer LK, Juettner VV, Kettlewell S, Pavlov EV, Blatter LA, Dedkova EN. (2015) Distinct mPTP activation mechanisms in ischaemia-reperfusion: contributions of Ca2+, ROS, pH, and inorganic polyphosphate. Cardiovas Res 106:237-48.

Rau M, Schilling AK, Meertens J, Hering I, Weiss J, Jurowich C, Kudlich T, Hermanns HM, Bantel H, Beyersdorf N, Geier A. (2015) Progression from Nonalcoholic Fatty Liver to Nonalcoholic Steatohepatitis Is Marked by a Higher Frequency of Th17 Cells in the Liver and an Increased Th17/ Resting Regulatory T Cell Ratio in Peripheral Blood and in the Liver. J Immunol 196:97-105.

Winkler B, Taschik J, Haubitz I, Eyrich M, Schlegel PG, Wiegering V. (2015) TGFβ and IL10 have an impact on risk group and prognosis in childhood ALL. Pediatr Blood Cancer 62:72-9.

Students' Representatives

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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.

In cooperation with the psychological Institute, the "Anamnesegruppe" ("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 ("Mit-Sicherheitverliebt") 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.

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.

Finally, we work together with the societies of emergency medicine, the European Medical Students' Association (EMSA) and support regional social projects.

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.

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 medical faculty

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

The Medical Faculty: Basic Data

The Medical Faculty: Basic Data

Collaborative Research Centers, Clinical Research Units, Research Training Groups

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

Transregio-Collaborative Research Center 166, High-end light microscopy elucidates membrane receptor function – Receptor-Light

Clinical Research Unit 216, Characterization of the Oncogenic Signaling-Network in Multiple Myeloma: Development of Targeted Therapies

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

Interdisciplinary Centers

Center for Achalasa
Center for Obesity and Metabolic Surgery
ARDS/ECMO Center
Allergy Center
Comprehensive Hearing Center (CHC)
Center for Craniofacial Surgery
Fabry Center for interdisciplinary therapy
Cardiovascular Center Würzburg
Liver Center Würzburg
Interdisciplinary Cleft Lip and Palate Center
Musculoskeletal Center Würzburg (MCW)
Center for Neuromuscular Disorders
Interdisciplinary Center for Palliative Medicine
Perinatal Center (Tertiary Care)
Center for Rheumatic Diseases
Thyroid Center Würzburg
Center for Neurovascular Disorders
Interdisciplinary Pain Center
Center for Developmental Pediatrics
Center for Stemm Cell Therapy and Transplantation
Radiation Emergency Center / WHO REMPAN Collaborating Center
Interdisciplinary Center for Thoracic Diseases Mainfranken
Transplantation Center
Center for Dental Traumatology
Reference Center for Rare Diseases Northern Bavaria

Honorary doctorates awarded by the medical faculty (since 1948)

1948 Dr. Albert Knoll
Ludwigshafen
1952 Prof. Dr. 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 Weckerle
München
2015 Prof. Dr. Dr. Helmut Remschmidt
Marburg

Rinecker-medals awarded by the medical faculty

1890 Prof. Dr. Robert Koch
Berlin
1891 Prof. Dr. Camillo Golgi
Pavia, Italien
1894 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 Kochsieck
Würzburg
2016 Prof. Dr. Christoph Reiners
Würzburg

Carl Caspar von Siebold-medals awarded by the medical faculty

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 The Interessengemeinschaft zur Förderung der Kinder der Würzburger Intensivstation (KIWI e.V.)
Würzburg

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

Winners of the Albert Koelliker-Award for excellent teaching (of the last 10 years)

Semester	Winners
Spring 2007	Professor Dr. M. Böck, Head of the Institute for Clinical Transfusion Medicine and Haemotherapy
Autumn 2007	University lecturers and tutors of the Skills Lab: Professor Dr. W. Voelker (Med. Clinic I), Professor Dr. M. Schmidt (Med. Clinic I), PD Dr. R. Jahns (Med. Clinic I), Dr. J. Schönberger (Med. Clinic I), Dr. W. Burghardt (Med. Clinik II), PD Dr. Dr. U. Dietz (Surgery), PD Dr. T. Meyer (Surgery), PD Dr. E. Gerharz (Urology), S. Böning (Urology), cand. med. S. Beck, cand. med. J. Filser, cand. med. J. Jahn, cand. med. P. Jahn, cand. med. S. Koerdt
Spring 2008	Professor Dr. H. Hebestreit, Department of Pediatrics
Autumn 2008	University Lecturers for General Medicine: Dr. M. Ertel, Dr. P. Rost und Dr. W. Heppner representative for more than fifty contracted physician‘s offices
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

Habilitations

2014

Clinical

Dr. med. Frölich, Katrin	Otorhinolaryngology
Dr. med. Löhr, Mario	Neurosurgery
Dr. med. Morbach, Henner	Pediatrics
Dr. med. Nordbeck, Peter Johann	Internal Medicine
Dr. med. Schneider, Reinhard	Internal Medicine
Dipl.-Ing. Dr. rer. nat. Neuhaus, Winfried	Molecular Medicine
Dr. med. Hofmann, Christine	Pediatrics
Dr. med. Schweitzer, Tilmann	Neurosurgery
Dr. med. Taurines, Regina	Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Dr. med. Kreissl, Michael	Nuclear Medicine
Dr. med. Grigoleit, Götz Ulrich	Internal Medicine
Dr. med. Ginzkey, Christian	Otorhinolaryngology
Dr. med. Buttmann, Mathias	Neurology

Preclinical

Dr. phil. Vogel, Heinrich	Medical Psychology
Dr. med. M.Sc. D.Phil. (Oxon) Langenhan, Tobias	Physiology

2015

Clinical

DDr. med. dent. Kochel, Janka B.	Dental and Oral Medicine, especially Orthodontics
Dr. rer. nat. Schäfer, Arne	Clinical Psychosomatics
Dr. med. Winkler, Beate	Pediatrics
Dr. med. Rauch, Stefan	Anaesthesiology
Dr. med. Häusler, Sebastian F. M.	Obstetrics and Gynecology
Dr. rer. nat. Hagemann, Carsten	Experimental Neurosurgery
Dr. med. Kerstan, Andreas	Dermatology and Venerology
Dr. med. Gräfin Strachwitz, Claudia N.	Ophtalmology
Dr. med. van Oorschot, Birgitt	Palliative Care
Dr. med. Blanke, Philipp	Radiology
Dr. med. Hölscher-Doht, Stefanie	Trauma Surgery
Dr. med. Kraft, Peter	Neurology
Dr. med. Weininger, Markus	Radiology
Dr. med. Weismann, Dirk	Internal Medicine
Dr. med. Wiegering, Verena Amrei	Pediatrics
Dr. med. Zeller, Daniel	Neurology
Dr. rer. nat. Neufang, Susanne	Neuropsychology in Childs and Adolescents
Dr. med. Drechsler, Christiane	Internal Medicine
Dr. med. Liangos, Orfeas	Internal Medicine
Dr. med. Schraven, Philipp	Otorhinolaryngology

Preclinical

Dr. rer. nat. Rost, Simone	Human Genetics
Dr., Ph.D. Iliev, Asparouh	Pharmacology and Toxikology
Dr. rer. nat. Berberich-Siebelt, Friederike	Immunology
Dr., Ph.D. Calebiro, Davide	Pharmacology and Toxikology

Habilitations

2016

Clinical

Dr. med. Sebastian Haferkamp	Dermatology and Venerology
Dr. med. Armin Wiegering	Surgery
Dr. med. Marion Wobser	Dermatology and Venerology
Dr. med. Mia Kim	Surgery
Dr. med. Florian J. D. Seyfried	Surgery
Dr. rer. nat. Malgorzata Burek	Molecular Medicine
Dr. (MD, Ph.D.) Cristina L. Ronchi	Internal Medicine
Dr. med. Daniel Vergho	Urology
Dr. med. Wiebke Fenske	Internal Medicine
Dr. med. Dr. rer. nat. Matthias Kroiss	Internal Medicine
Dr. med. Kristen Rak	Otorhinolaryngology
Dr. med. Petra Roll	Internal Medicine
Dr. med. Stefan Unterecker	Psychiatry and Psychotherapy
Dr. rer. nat. Jörg Geiger	Clinical Biochemistry
Dr. med. Sascha Goebel	Orthopedics
Dr. med. Thorsten Klink	Radiology
Dr. med. Klaus Martin Kortüm	Internal Medicine
Dr. med. Dr. med. dent. Christian Linz	Dental and Oral Medicine, especially Oral and Maxillofacial Surgery
Dr. med. Agmal Scherzad	Otorhinolaryngology
Dr. med. Gülmisal Güder	Internal Medicine
Dr. med. Katica Krajinovic	Surgery

Preclinical

Dr. rer. nat. Matthias Becker	Molecular and Cellular Biology

Registration numbers

Human medicine and dentistry

Jahr	human medicine / thereof female	dentistry / thereof female
SS 2014	170/108	53/33
WS 2014/15	158/94	56/34
SS 2015	153/99	54/35
WS 2015/16	169/105	58/39
SS 2016	180/130	54/40
WS 2016/17	157/93	57/38

Bachelor- and master courses

Jahr	biomedicine Bc. / thereof female	biomedicine Ma. / thereof female	experimental medicine Ma. / thereof female	biochemistry Bc. / thereof female	biochemistry Ma. / thereof female
SS 2014	0	0	0	0	0
WS 2014/15	35/30	5/5	0	75/41	32/21
SS 2015	0	0	1/1	0	2/2
WS 2015/16	36/27	8/8	1/0	95/52	23/10
SS 2016	0	0	1/0	0	0
WS 2016/17	42/34	15/9	0	82/44	32/22

Accompanying courses

Jahr	experimental medicine / thereof female	clinical research and epidemiology / thereof female
SS 2014	1/0	1/1
WS 2014/15	2/1	4/4
SS 2015	0	3/2
WS 2015/16	4/3	5/4
SS 2016	0	0
WS 2016/17	4/0	8/1

Graduations

Human medicine and dentistry

Jahr	human medicine / thereof female	dentistry / thereof female
Spring 2014	143/78	58/28
Autumn 2014	107/55	47/34
Spring 2015	123/61	42/30
Autumn 2015	142/80	43/26
Spring 2016	128/75	48/25
Autumn 2016	154/84	51/36

Bachelor- and master courses

Jahr	biomedicine Bc. / thereof female	biomedicine Ma. / thereof female	experimental medicine Ma. / thereof female	biochemistry Bc. / thereof female	biochemistry Ma. / thereof female
Spring 2014	13/11	4/4	1/0	36/23	4/3
Autumn 2014	2/2	6/6	0	9/7	6/2
Spring 2015	15/15	3/3	2/1	30/14	1/1
Autumn 2015	2/1	9/6	3/2	9/4	6/5
Spring 2016	15/12	2/1	1/0	28/19	12/4

Accompanying courses

Jahr	experimental medicine / thereof female	clinical research and epidemiology / thereof female
Spring 2014	5/1	
Autumn 2014	5/3	
Spring 2015	3/0	
Autumn 2015	1/0	
Spring 2016	3/0	
Autumn 2016	1/0	1/1

Doctorates (without doctorates in natural sciences)

Jahr	preclinical	clinical	total
2014	30	165	195
2015	24	149	173
2016	24	168	192

The deans of the medical faculty 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

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The cover shows figures related to research projects of the medical faculty

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Medical Faculty
University of Würzburg

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WÜRZBURG

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