Institute of Anatomy

Chair of Functional and Clinical Anatomy

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Research focus

- Pathomechanisms of the Meibom Gland Dysfunction
- Biopolymer hydrogels for tissue replacement
- HistoDigital® (HiD) and Cinematic Anatomy
- Mechanisms of tear outflow
- Surfactant proteins
- Test anxiety among medical and dental students
- Diagnostics of neuropathic pain via the eye
- Ocular tissue interactions of a refractive UV femtosecond laser

Structure of the Chair

Professorships: 2
Personnel: 30

- Doctors (of Medicine): 2
- Scientists: 17 (thereof funded externally: 7)
- Graduate students: 35

Special structural features

- Lecture room for lessons in histology with 160 microscopes
- Electron microscopy unit
- Digital Anatomy unit
- Management of the body donation unit

Both chairs collegially lead the Institute of Anatomy.

Research

The Chair of Functional and Clinical Anatomy deals with questions concerning the eye, in particular the ocular surface and the draining tear ducts (ocular surface group) as well as the role of various proteins and peptides (including surface-active proteins) on the ocular surface, in joints (osteoarthritis and rheumatoid arthritis) and in other body localizations. In addition, clinical-anatomical questions are addressed and new methods for anatomy education are intensively developed and teaching research is conducted.

Pathomechanisms of the Meibom Gland Dysfunction
PI: Prof. Dr. F. Paulsen, PD Dr. F. Garreis
Meibomian gland dysfunction (MGD), a term used to describe a diffuse abnormality of the meibomian glands, which are specialized sebaceous glands in the eyelids, is considered the most common cause of dry eye syndrome (DES), a disease with an estimated prevalence of 12 million people alone in Germany. It is currently thought that MGD is caused primarily by terminal duct obstruction due to hyperkeratinization of the ductal epithelium and an increased viscosity of meibum. However, the molecular mechanisms that underlie this process are unclear. We investigate the influence of different hormones on the keratinization process, the importance of the formation of adhesion contacts (Desmosomes) for the maturation process of the meibozytes and the influence of various proteins which contribute to a hyperkeratinization of the ducts and the increasing viscosity of the meibum. Our goal is to gain deeper insights into the pathophysiology of MGD. To this end, experiments will be carried out in an established mouse model of the DED as well as in two and three-dimensional cultivation models with human meibomian epithelial cells. This serves to determine factors that could possibly be used as therapeutic treatment options in MGD.

Novel Biopolymer Hydrogels for Understanding Complex Soft Tissue Biomechanics
PI: Prof. Dr. F. Paulsen (together with Prof. Dr.-Ing. P. Steinmann [Tech], Prof. Dr.-Ing. A. Boccaccini [Tech], Prof. Dr. B. Fabry [Nat])
In a joint project, biopolymer hydrogels are produced and mechanically characterized. These serve as proxy materials to understand and model the highly complex behavior of soft biological tissues. This will result in a proxy material catalog that combines various characteristic features of the mechanical response with a validated modeling approach. It will serve as an important basis for selecting suitable materials for tissue engineering, reducing experiments on human and animal tissues, and increasing the potential of numerical approaches that can be applied in clinical and industrial settings.

HistoDigital® and Cinematic Anatomy
PI: Prof. Dr. M. Scholz, Prof. Dr. F. Paulsen
In close cooperation with Chimaera GmbH (Erlangen), HiD, a digital application is being developed that enables the user to create a digital volumetric reconstruction of the anatomical tissue structures from the data sets of histological section series. The goal is the future use of this application in research and teaching.
The cinematic rendering (CR) technology was originally developed by Siemens Healthineers (Dr. Klaus Engel) as a medical image visualization technology. It enables the generation of 3D photorealistic images of the human body. Existing imaging methods (CT, MRT, etc.) provide the raw data for the volumetric visualizations. In direct cooperation with Siemens, this technology is to be made applicable for teaching and learning the human anatomy.

New insights into the lacrimal pump
PI: Prof. Dr. F. Paulsen, Prof. Dr. M. Scholz
To date, there are many theories on the transport of tears through the canaliculi of the efferent lacrimal system into the lacrimal sac, but few with hard data. We have shown that contraction of the Horner-Duverney muscle leads to closure of the canaliculi in their first two thirds due to the special arrangement of muscle fibers and connective tissue fibers. As a result, the tear fluid in the canaliculi is pushed/transported toward the lacrimal sac. The medial third of the vertical portions of the canaliculi, the canaliculus communis, and the intrasaccal portion of the canaliculus are compressed by the shortening and thickening of the Horner-Duverney muscle from the dorsal side, resulting in compression of the canaliculi lumen in this part of the system, thereby pushing the tear fluid further toward the lacrimal sac. The mixture of rapidly contracting and fatigue-resistant muscle fibers is ideally suited for the blink mechanism, which is complexly regulated by the nervous system. In further studies, we are currently analyzing the lymphatic drainage of the human lacrimal system.

Surfactant proteins
PI: Prof. Dr. L. Bräuer, PD Dr. M. Schicht, Prof. Dr. F. Paulsen
The successive characterization of surfactant proteins, in particular the proteins SP-G and SP-H described by us, demonstrate the immense spectrum of action of these proteins in the human organism. Within the research group it could be shown that SP-H has stimulatory effects on the activity of alveolar macrophages and furthermore leads to an increased phagocytosis activity. Meanwhile, further own studies suggest that both surfactant proteins might play an important role in inflammation and wound healing processes also outside the lung (e.g. at the ocular surface or inside the kidney). The properties described so far could make SP-G and SP-H potential candidates for diagnosis, prophylaxis and possibly therapy of different diseases.

Test anxiety among medical and dental students
PI: PD Dr. C.M. Hammer, Prof. Dr. M. Scholz, Prof. Dr. F. Paulsen
Test anxiety is a common phenomenon among students, often affecting academic performance. To date, there is a scarcity of valid data concerning prevalence, severity, and types of test anxiety among German medical and dental students. Hence, there are only few reports on effective therapeutic or preventive strategies tackling the problem of test anxiety. Repetitive application of a validated psychological test anxiety questionnaire yielded more than 50% of the evaluated students showing pronounced signs of test anxiety. Moreover, it revealed medical hypnosis as a potent intervention to significantly alleviate test anxiety. Medical hypnosis was proved especially effective in the amelioration of the test anxiety subtype “lack of confidence”.

Biomarkers and novel therapeutic approaches for neuropathic pain of different etiologies
PI: Prof. Dr. E. Lütjen-Drecoll, Prof. Dr. F. Paulsen
Within the project, different models of neuropathic pain will be investigated separately, as the mechanisms of neuropathic pain differ considerably depending on the etiology of the pain.

For this reason, therapeutic approaches also differ in the respective neuropathic pain syndromes. For example, effective therapy requires differentiation between tumor- and chemotherapy-induced neuropathic pain. Therefore, to cover the widest possible range of different neuropathic pain types, we are investigating different models of neuropathic pain such as chemotherapy-induced or diabetes-induced neuropathic pain. Results generated therein will be applied to the eye as a window to the peripheral nervous system e.g. by measuring axonal corneal degeneration in neuropathic models, by multi-epitop-ligand mapping as well as tear film lipidomics and -proteomics.

Ocular tissue interactions of a refractive UV femtosecond laser
PI: Dr. C.M. Hammer, Prof. Dr. F. Paulsen
The already established cooperation with the Department of Ophthalmology and WaveLight GmbH was further intensified with regard to this project. Intraoperative gas production and interface quality after extraction of refractive lenticules from porcine eyes was examined and compared between the novel UV-laser and an infrared laser system already established for this procedure (VisuMax). Histological investigations demonstrated the superiority of the UV laser as far as gas production is concerned. Since the UV laser produces significantly less gas than the VisuMax system, it may also have the potential to achieve a much higher degree of surgical precision. Comparative scanning electron microscopical examinations showed similar interface properties with respect to surface smoothness and regularity. This is supportive of the assumption that the UV laser may be as well suited for refractive lenticule extractions as the clinical VisuMax system.

Teaching

The Chair of Functional and Clinical Anatomy is involved in the teaching of macroscopic anatomy at the Institute of Anatomy. Each semester a variety of elective subjects can be offered for medical and dental students in the preclinical semesters. Virtual courses of histology, macroscopy, and embryology are offered in cooperation with the virtual university of Bavaria (vhb).
Moreover, Bachelor's and Master's theses as well as MD and PhD are supervised.

Selected publications
Ali MJ, Zetzsche M, Scholz M, Hahn D, Gaffling S, Heichel J, Hammer CM, Bräuer L, Paulsen F. New insights into the lacrimal pump. Ocul Surf 2020, 18:689-698

Culemann S, Grüneboom A, Nicolás-Ávila JA, Weidner D, Lämmle KF, Quintana JA, Kirchner P, Krljanac B, Eberhardt M, Ferrazzi F, Kretzschmar E, Schicht M, Fischer K, Gelse K, Faas M, Pfeifle R, Rothe T, Ackermann JA, Pachovsky M, Renner N, Haseloff RF, Ekici A, Bäuerle T, Blasig IE, Vera V, Voehringer D, Paulsen F, Schett G, Hidalgo A, Krönke G. Spatiotemporal molecular profiling of synovival macrophages reveals a locally renewing barrier of membrane-forming macrophates shielding the joint. Nature 2019, 572:670-675

Hammer CM, Bischofsberger L, Burger P, Paulsen F, Scholz M. Feasibility of clinical and experimental hypnosis. Int J Clin Exp Hypnosis 2020, 68:511-520

Popp J, Schicht M, Garreis F, Klinger P, Gelse K, Sesselmann S, Tsokos M, Etzold S, Stiller D, Claassen H, Paulsen F. Human synovia contains trefoil factor family (TFF) peptides 1-3 although synovial membrane only produces TFF3: implications in osteoarthritis and rheumatoid arthritis. Int J Mol Sci 2019, 20:E6105

Weizel A, Distler T, Scheidereit D, Friedrich O, Bräuer L, Paulsen F, Detsch R, Boccaccini AR, Budday S, Seitz H. Complex mechanical behavior of human articular cartilage and hydrogels for cartilage repair. Acta Biomater 2020, 118:113-128

International cooperations
Prof Dr. M.J. Ali, FAU Humboldt Fellow, LV Prasad Eye Institute, Hyderabad: India

PD Dr. Dr. P. Burger, Psychiatrische Universitätsklinik Zurich: Switzerland

Prof. C.S. de Paiva, Baylor College of Medicine, Houston, Texas: USA

Prof. Dr. S. Dydekin, Sechenov University, Moskow: Russia

Prof. Dr. M. Ito, National Defense Medical College, Saitama: Japan

Prof. Dr. L. Olewnik, Medical University of Lodz: Poland

Dr. S. Singh, Lala Jagannath Eye Institute, Ambala: India

Dr. S. Wosniak, Wroclaw Medical University, Wroclaw: Poland

Prof. D. Zoukhri, Tufts University School of Dental Medicine, Boston: USA

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Research focus
- Molecular mechanisms of development and progression of malignant melanoma
- Molecular mechanisms of development and progression of hepatocellular carcinoma
- Chondrocytic differentiation and pathophysiological processes in cartilage
- Molecular basis of regeneration and fibrosis in liver and skin
- Molecular mechanisms of hepatic metastasis
- Structure and function of synaptic signaling complexes in the central nervous system
- Pathobiology of non-alcoholic fatty liver diseases

Structure of the Chair

Professorships: 3
Personnel: 50
- Scientists: 35 (thereof funded externally: 23)
- Graduate students: 17

Special structural feature
The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as the professorships of Bioinformatics and of Molecular Medicine with focus on Molecular Imaging.

Research

The research groups of the Chair of Biochemistry and Molecular Medicine study basic physiological and pathophysiological principles in oncological settings and the nervous system using approaches from biochemistry, molecular genetics, embryology, cell biology and bioinformatics. Research interests focus among others on the mechanisms of receptor mediated signal transduction and transcriptional regulation in the tumor cells.

Molecular mechanisms of development and progression of malignant melanoma
PI: Prof. Dr. A.K. Bosserhoff, Prof. Dr. C. Hellerbrand, Prof. Dr. S. Kuphal, PD Dr. Dr. P. Dietrich, Prof. Dr. M. Kappelmann-Fenzl
Malignant melanoma, also called black skin cancer, shows a drastic increase in incidence and an unchanged high mortality in recent decades. Melanoma is a clinically relevant tumor, characterized by gradual progression, metastatic dissemination, rapid and pronounced resistance to therapy. For the analysis of melanoma formation, our analysis also deals with melanocytes and their embryonic precursors, the melanoblasts. As metastatic melanoma curative therapy approaches are still lacking, the 10-year survival rate is below 5%. The pathogenesis of the disease is probably due to an accumulation of specific genetic and epigenetic alterations leading to deregulation of transcriptional regulation and signaling pathways in melanocytes or their precursors. The particular malignancy of melanoma is based on a specific combination of cell cycle autonomy, differentiation defects, apoptosis resistance, deregulated interaction with stromal and immune cells as well as distinctive invasiveness and metastatic ability. We are working in this field performing fundamental studies of pathophysiological changes and covering many areas. In addition to proteins in the cell-matrix association, growth factors, metabolites, and signaling pathways, transcriptional regulators and microRNAs are investigated. Next to the analysis of the function of mature microRNA as key posttranscriptional regulatory elements, their processing in melanoma is in the center of our current research.

Molecular mechanisms of development and progression of hepatocellular carcinoma
PI: Prof. Dr. C. Hellerbrand, PD Dr. Dr. P. Dietrich, Prof. Dr. A.K. Bosserhoff
Hepatocellular carcinoma (HCC) is one of the most frequent types of cancer worldwide. Currently, there are only few therapeutic options that have only a minimal impact on the survival of patients. HCC is frequently resistant against pharmacological therapy or most patients rapidly develop resistance, respectively. We are investigating the molecular mechanisms of the development, progression, and therapy resistance of HCC. We discovered important functions of defined microRNAs and their interactions with therapeutically influenced main signaling pathways of cancer cells, such as the RAS-RAF-ERK signaling pathway.
Furthermore, we are analyzing the interaction of cancer cells with their environment (e.g. immune cells, inflammation mediators, connective tissue cells and factors) mediated by neuropeptides. Such neuroimmunological interactions could decisively influence the tumor microenvironment and thus the progression and therapy resistance of malignant diseases.

Chondrocytic differentiation and pathophysiological processes in cartilage and osteoarthritis
PI: Prof. Dr. A.K. Bosserhoff, Dr. U. Rottensteiner- Brandl
Cartilage is a tissue comprising only a single cell type, namely chondrocytes. In the development of the skeleton, cartilage precedes the bony skeleton and is replaced by the latter in the process of enchondral ossification. In the adult organism, cartilage covers the articular surfaces of our bones and is characterized, among other properties, by high pressure elasticity. Damage to the cartilage is so far not curable until today and inevitably results in osteoarthritis. By better understanding the molecular processes in chondrogenic differentiation, inflammation and cartilage degeneration, we are trying to develop new therapeutic options. As part of our research, we are focusing on different molecular pathways. We study transcriptional regulators, such as AP2Epsilon and YB1. A further focus is on the molecule MIA/CD-RAP, which plays an important role in cartilage differentiation and homeostasis.

Molecular basis of regeneration and fibrosis in liver and skin
PI: Prof. C. Hellerbrand, Prof. Dr. A. Bosserhoff, PD Dr. Dr. P. Dietrich
The liver is the central organ of the metabolism. Nutrients get to the liver from the digestive tract via the portal vein for subsequent degradation and/or metabolization. Thus, the liver supplies the body with vital components such as proteins, carbohydrates, and lipids. Another important function of the liver is detoxification. Alcohol abuse, obesity, metabolic disorders (e.g. hemochromatosis), viral infections (hepatitis B and C), or intoxication with chemicals and environmental toxins are common causes of liver damage. Hepatocellular injury can result in liver inflammation (hepatitis). Hepatitis can progress with hepatic fibrosis which can lead to liver cirrhosis. Cirrhosis is causing organ dysfunction and is the most important risk factor for the development of hepatocellular carcinoma (HCC). Thus, hepatic fibrosis is the central step in the progression of chronic liver injury. Pathological fibrosis resembles impaired wound healing in which the strictly regulated repair processes are impaired after cellular injury. Since the components that are involved in wound healing or fibrosis (connective tissue cells, extracellular matrix, growth factors) are very similar, findings from the physiological wound healing can help to better understand the processes of formation and progression of liver fibrosis/cirrhosis. In this area of our research we focus on the analysis of the newly discovered molecule MIA2 and growth factors of the FGF and BMP families. Furthermore, we could characterize BMP6 as an essential regulator of iron metabolism in recent years.

Structure and function of synaptic signaling complexes in the central nervous system
PI: Prof. Dr. R. Enz
The electric excitability of the central nervous system is regulated by a coordinated interplay of

neurotransmitter receptors and ion channels with enzymes and scaffold proteins that assemble into macromolecular signal complexes at synapses. We analyze structure, expression and function of synaptically localized signal complexes that are associated with receptors for endocannabinoids, GABA and glutamate. Malfunction of these receptors can cause neurodegenerative processes and lead to hearing impairment, tinnitus, night blindness, or epilepsy. Thus, synaptic proteins and their interactions represent interesting targets for therapeutic intervention.
We analyze expression of endoncannabinoid, GABA and glutamate receptors in retina and cochlea and identify new binding partners that regulate these receptors. Interacting protein domains are mapped, the 3D-structure of contact surfaces is analyzed and the function of new protein interactions is elucidated in terms of the activity of receptors and receptor associated signal pathways. Recently, we identified and localized endoncannabinoid and glutamate receptors at pre- and post-synaptic structures of hair cells in the cochlea. Furthermore, we identified the „Cannabinoid Receptor Interacting Protein“ CRIP1 as a new binding partner of glutamate receptors. CRIP1a binds a conserved sequence of 5 amino acids in both receptor types, which regulates their amount in the plasma membrane. Our studies describe new molecular mechanisms at synapses of the central nervous system and pave the ground for the development of new therapeutic approaches targeting neurologic disorders.

Molecular mechanisms of hepatic metastasis
PI: Prof. Dr. C. Hellerbrand, Prof. Dr. A.K. Bosserhoff, PD Dr. Dr. P. Dietrich
Metastasis determines morbidity and mortality in most cancer patients. Most frequently, the majority of tumor entities metastasize into the liver. Only in part this can be explained by the blood flow or the anatomical localization of the liver, respectively. So far it is still unknown, which underlying mechanisms of the liver attract the tumor cells. We are analyzing the reasons of this phenomenon in experimental models and human tissue samples from primary tumors and hepatic metastases. We were able to show that defined non-parenchymal liver cells (hepatic stellate cells) interact with tumor cells and thus induce different steps of metastasis. Our current aim is to identify the mediators of this interaction and to analyze whether such factors can be therapeutic targets.

Pathobiology of non-alcoholic fatty liver diseases
PI: Prof. Dr. C. Hellerbrand, PD Dr. Dr. P. Dietrich
Almost all individuals with obesity develop significant lipid accumulation (steatosis) in the liver. Steatosis can progress with inflammation (steatohepatitis) and fibrosis. The pathological picture is very similar to alcoholic liver injury and is called non-alcoholic fatty liver disease (NAFLD). Today, NAFLD is the most common type of liver disease worldwide. We are analyzing in experimental *in vitro* and *in vivo* models the mechanisms driving the progression of NAFLD, trying to inhibit already early steps of the pathobiological cascade. We could identify defined hop constituents as promising therapeutic targets, which can inhibit the uptake of fatty acids into hepatocytes as well as the development of steatohepatitis.
Application of some chemotherapeutic drugs can cause steatohepatitis, too, which can significantly affect morbidity and mortality of cancer patients. We were able to identify the molecular mechanisms by which irinotecan und fluorouracil (5-FU) cause hepatic steatosis and inflammation. Currently, we are investigating strategies to interfere with these pathomechanisms to improve the tolerability of chemotherapeutic drugs.

Teaching

Both chairs of the Institute jointly carry out the curricular education (lectures, seminars, practical courses) in biochemistry and molecular biology for students of Medicine, Dentistry, and Molecular Medicine as well as the biochemical practical courses of students of pharmacy.
Both chairs supervise Bachelor's and Master's theses as well as PhD students.

Selected publications

Dietrich P, Wormser L, Fritz V, Seitz T, De Maria M, Schambony A, Kremer AE, Günther C, Itzel T, Thasler WE, Teufel A, Trebicka J, Hartmann A, Neurath MF, von Hörsten S, Bosserhoff A, Hellerbrand C. Molecular cross-talk between Y5-receptor and neuropeptide Y drives liver cancer. J Clin Invest. 2020; 130(5):2509-2526.

Seitz T, Freese K, Dietrich P, Thasler WE, Bosserhoff A, Hellerbrand C. Fibroblast Growth Factor 9 is expressed by activated hepatic stellate cells and promotes progression of hepatocellular carcinoma. Sci Rep. 2020; 10(1):4546.

Klotz L, Wendler O, Frischknecht R, Shigemoto R, Schulze H, Enz R. Localization of group II and III metabotropic glutamate receptors at pre- and postsynaptic sites of inner hair cell ribbon synapses. FASEB J. 2019; 33(12):13734-13746.

Liebig JK, Kuphal S, Bosserhoff AK. HuRdling Senescence: HuR Breaks BRAF-Induced Senescence in Melanocytes and Supports Melanoma Growth. Cancers (Basel). 2020; 12(5):1299.

Kappelmann-Fenzl M, Kuphal S, Krupar R, Schadendorf D, Umansky V, Vardimon L, Hellerbrand C, Bosserhoff AK. Complex Formation with Monomeric α-Tubulin and Importin 13 Fosters c-Jun Protein Stability and Is Required for c-Jun's Nuclear Translocation and Activity. Cancers (Basel). 2019; 11(11):1806

Kappelmann-Fenzl M, Gebhard C, Matthies AO, Kuphal S, Rehli M, Bosserhoff AK. C-Jun drives melanoma progression in PTEN wild type melanoma cells. Cell Death Dis. 2019; 10(8):584.

International cooperations
C. Aragón, B. López-Corcuera, Centro de Biología Molecular „Severo Ochoa“, Universidad Autonoma de Madrid, Madrid: Spanien

C. Heilig, Department of Medicine, University of Florida, College of Medicine- Jacksonville, Jacksonville: USA

M. Herlyn, Wistar Institute, Philadelphia: USA
C. Jobin, Department of Medicine, University of Florida, Gainesville, Florida: USA

R. Massoumi, Molecular Tumor Pathology, Medicon Village, Lund University: Schweden

M. Avila, Hepatology Program CIMA, University of Navarra, Pamplona, Spain

R. Schwabe, Department of Medicine, Columbia University, New York, NY, USA

R. Mendez, Institute for Research in Biomedicine, The Barcelona Institute of Science and Technology, Barcelona, Spain

Prof. R. Shigemoto (Institute of Science and Technology, Klosterneuburg, Austria)

Supported by the "Melanoma Research Network", organized by Prof. Dr. A.K. Bosserhoff and funded by the German Cancer Aid, a strong national and international network in melanoma research with many collaboration partners was established.

Institute of Biochemistry – Emil-Fischer-Center

Chair of Biochemistry and Pathobiochemistry

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Research focus
- Sox proteins in glia
- Chromatin-remodeling & histone modifying complexes in glia
- Direct lineage reprogramming
- Cellular decision taking in neural stem cells
- Signal transduction pathways in myogenesis and at the neuromuscular synapse

Structure of the Chair

Professorships: 2
Personnel: 38
- Scientists: 10 (thereof funded externally: 4)
- Graduate students: 18

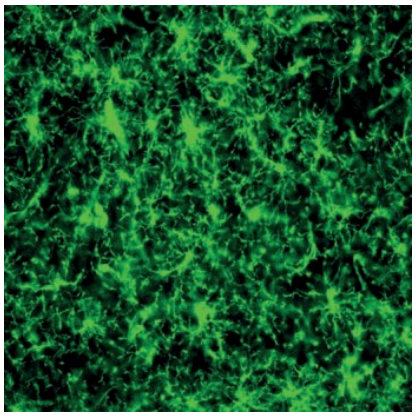
Special structural feature
The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as the professorships of Bioinformatics and of Molecular Medicine with focus on Molecular Imaging.

Research

The groups belonging to the Chair of Biochemistry and Pathobiochemistry work in the field of neuroscience and attempt to unravel regulatory mechanisms of physiological and pathophysiological relevance with a broad spectrum of biochemical, cellular, genetic, bioinformatics and imaging methods. Among others we focus on the impact of transcription factors, chromatin remodelers and histon modifiying enzymes on glial cells and their development, as well as on mechanisms of direct reprogramming and cellular decision taking in neural contexts. An additional group studies neuromuscular signal transduction pathways.

Studying Sox proteins in glia
PI: Prof. Dr. M. Wegner
The three closely related Sox proteins, Sox8, Sox9, and Sox10 (jointly referred to as SoxE proteins), have numerous roles during neural crest development, and ensure survival and pluripotency of neural crest stem cells, generation of melanocytes, enteric nervous system, Schwann cells and satellite glia as well as myelination throughout the peripheral nervous system. In the central nervous system, Sox9 regulates the specification of neural stem cells into oligodendrocytes and astrocytes, whereas Sox10 guides the terminal differentiation of oligodendrocytes and central myelination. Sox10 acts via induction of other transcription factors that are essentially required for oligodendroglial differentiation and cooperate with Sox10 during the process such as Nfat and Myrf proteins. Sox8 gains importance in mature oligodendrocytes for myelin maintenance. SoxE proteins act through recruitment of the basal transcription machinery in a mediator dependent manner as well as through interactions with chromatin-remodeling complexes. Functions of SoxE proteins are also reflected in human disease. Heterozygous haploinsufficient Sox10 mutations lead to Waardenburg-Hirschsprung disease, whereas dominant-negative heterozygous mutations present as a combination of Waardenburg-Hirschsprung disease, peripheral neuropathy, and central leukodystrophy.

Analyzing chromatin-remodeling complexes in glia
PI: Prof. Dr. M. Wegner



Detection of oligodendrocyte precursor cells in the adult brain by staining for NG2

Development and differentiation of myelin-forming glial cells goes along with substantial alterations in chromatin structure that are brought about by chromatin-remodeling complexes. Function and importance of single complexes vary considerably between myelinating glia in central and peripheral nervous systems. In oligodendrocytes, the Brg1-containing BAF complex participates predominantly in the process of specification, whereas in Schwann cells it is essential during maturation by inducing transcriptional regulators of differentiation in cooperation with Sox10. The histone exchanging Ep400/Tip60 complex is required for the timely down-regulation of early regulators during Schwann cell development. In maturing oligodendrocytes, it ensures survival and supports differentiation.

Clarifying the role of histone-modifying complexes in glia
PI: Prof. Dr. E. Sock
Changes in chromatin structure are often accompanied by altered patterns of posttranslational histone modifications. The Rnf20/Rnf40 E3 ligase monoubiquitinates histone 2B. In the absence of Rnf40, Schwann cells in the peripheral nervous system fail to efficiently induce the myelination program despite the fact that all required transcription factors are present including Egr2, the master regulator of myelination. Genome- and transcriptome-wide studies showed that several essential building blocks of the myelin sheath cannot be produced in sufficient amounts and that immaturity factors are not properly turned off. This is caused by failure of Egr2 to recruit the E3 ligase to the corresponding gene promoters, leading to the local absence of histone 2B monoubiquitination and altered gene expression.

Using direct lineage reprogramming to study neural fate acquisition and identity
PI: Prof. Dr. M. Karow
Direct lineage reprogramming entails changing the identity of one cell into the new identity of a target cell. Following this strategy human brain pericytes can be reprogrammed into induced neurons by forced expression of the neurogenic transcription factors Ascl1 and Sox2. By studying the intermediate phases that bridge start and end cell populations, we identified the molecular framework underlying the changes in cell identity. Single cell RNA-sequencing and live imaging technologies are employed to further dissect the sequence of molecular and cellular changes underlying direct lineage conversion. In addition, human induced pluripotent stem cell-derived brain organoids are used as a model system to study the role of specific genes during early human brain development.

Dissecting decision-taking in neural stem cells
PI: Dr. S. Falk
During development a small starting population of neural stem cells (NSCs) gives rise to all neurons and macroglial cells in the mature central nervous system. Hence, controlling NSC decisions is crucial for the accurate production of the precise amount of the desired cell types at the correct time and place. Dynamically orchestrating these stem cell decisions is therefore essential for organogenesis during development, but also represent the key evolutionary mechanism underlying neocortical expansion, in particular in humans. At the very core of the challenge to build a functional nervous system is the cellular choice of NSCs to either divide symmetrically or asymmetrically. Combining time-lapse live imaging and single cell RNA-sequencing of human brain organoid NSCs we aim at uncovering the molecular logic of decision-taking processes governing human brain development.

Studying signal transduction pathways in myogenesis and at the neuromuscular synapse

PI: Prof. Dr. S. Hashemolhosseini

Various molecular signaling pathways participate in myogenesis and guarantee homeostasis and physiology of the neuromuscular synapse. We characterized the activity of Wnt and Hippo pathways including downstream transcriptional effectors in muscle fibers. The signaling pathway activated by the muscle-specific receptor tyrosine kinase (Musk) plays an essential role for the accumulation of postsynaptic proteins at the neuromuscular synapse. We identified the protein kinase CK2 as a MuSK interaction partner. It turned out that CK2 regulates the stability of clusters of acetylcholine receptors by binding and phosphorylation of postsynaptic proteins. CK2 also influences mitochondrial import. In CK2-deficient mice the Pink1- and Parkin-mediated mitophagy is disturbed. Behavioral tests and electro-physiological recordings established a muscle weakness in these mice. The LAP protein Erbin was identified as a second interactor of MuSK and turned out to link MuSK- and ErbB-dependent signaling pathways. Lano und Scribble as further LAP proteins function during maintenance of the neuromuscular synapse, endocytic transport and as scaffold proteins in muscle stem cells. By identifying the molecular causes of neuromuscular pathologies, a foundation is laid for therapeutic interventions in patients.

Teaching

The Chair of Biochemistry and Pathobiochemistry participates in the curricula in Medicine, Molecular Medicine, and Dentistry. Special mention deserves the interdisciplinary teaching in developmental biology and neurosciences in the master degree program Molecular Medicine. Additionally, the chair organizes teaching for the bachelor degree program medical engineering of the Faculty of Engineering. The Chair supervises Bachelor's and Master's theses as well as MD and PhD theses.

Selected publications

Elsesser, O., Fröb, F., Küspert, M., Tamm, E.R., Fujii, T., Fukunaga, R., Wegner, M. Chromatin remodeler Ep400 ensures oligodendrocyte survival and is required for myelination in the vertebrate central nervous system. Nucleic Acids Res. 2019, 47: 6208-6224.

Fröb, F., Sock, E., Tamm, E.R., Saur, A.-L., Hillgärtner, S., Williams, T.J., Fujii, T., Fukunaga, R., Wegner, M. Ep400 deficiency in Schwann cells causes persistent expression of early developmental regulators and peripheral neuropathy. Nat. Commun. 2019, 10: 2361

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Wüst, H.M., Wegener, A., Fröb, F., Hartwig, A.C., Wegwitz, F., Kari, V., Schimmel, M., Tamm, E.R., Johnsen, S.A., Wegner, M., Sock, E. Egr2-guided histone H2B monoubiquitination is required for peripheral nervous system myelination. Nucleic Acids Res. 2020, 48: 8959-8976

Camargo Ortega G*, Falk S*, Johansson PA, Peyre E, Broix L, Sahu SK, Hirst W, Schlichthaerle T, De Juan Romero C, Draganova K, Vinopal S, Chinnappa K, Gavranovic A, Karakaya T, Steininger T, Merl-Pham J, Feederle R, Shao W, Shi SH, Hauck SM, Jungmann R, Bradke F, Borrell V, Geerlof A, Reber S, Tiwari VK, Huttner WB, Wilsch-Bräuninger M, Nguyen L, Götz M. The centrosome protein AKNA regulates neurogenesis via microtubule organization Nature. 2019 567: 113-117

International cooperations

Prof. R. Fukunaga, Osaka University, Osaka: Japan

Prof. S. Dracheva, Icahn School of Medicine at Mount Sinai, New York: USA

Prof. S.A. Johnsen, Mayo Clinic, Rochester: USA

Prof. Q.R. Lu, Cincinnati Children's Hospital Medical Center, Cincinnati: USA

Prof. P Roussos, Icahn School of Medicine at Mount Sinai, New York: USA

Institute of Biochemistry – Emil-Fischer-Center

Professorship of Bioinformatics

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Research focus
- Computational analysis of host-pathogen interactions
- Investigation of the aggregation behavior of the Aβ-peptide of Alzheimer's disease
- Structure-based evaluation of protein variants
- Structure of receptor-ligand complexes

Structure of the Professorship

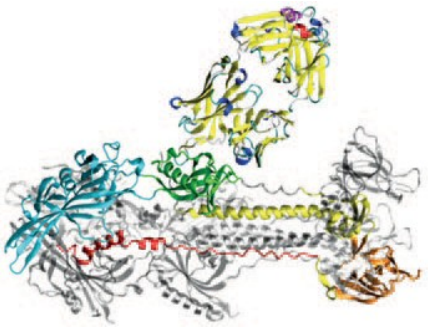
Professorship: 1
Personnel: 7
- Scientists: 3 (thereof funded externally: 2)
- Graduate students: 4

Special structural feature
The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as the professorships of Bioinformatics and of Molecular Medicine with focus on Molecular Imaging.

Research

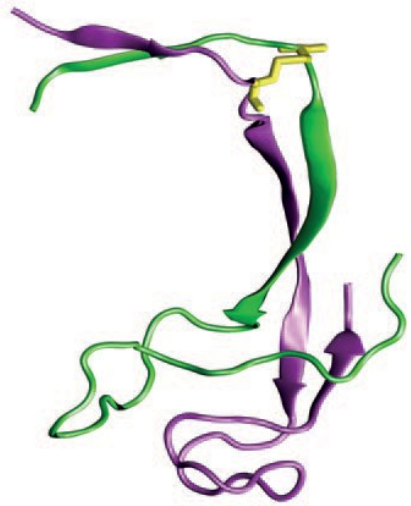
The research focus is on the computational characterization of protein-protein interactions. The identification of the underlying principles of molecular recognition is important for the understanding of regulatory mechanisms as well as for the prediction of novel, physiologically relevant protein interactions. The bioinformatics group investigates molecular interactions by a variety of computational tools (e.g. sequence data analysis, molecular modeling, and molecular dynamics).

Computational analysis of host-pathogen interactions
Specific interactions with host proteins are pivotal for a successful infection by a pathogen. This project focuses on the prediction and structural characterization of host-pathogen protein interactions using computational tools. The recognition processes either occur between short sequence motifs and complementary adapter modules or between pairs of globular protein domains. These types of interactions do not only differ from a structural point of view, but also with respect to the computational tools required for their prediction and analysis.
One particular challenge for the prediction of functional interaction motifs is the short length of the respective sequence patterns resulting in a large number of false-positive hits in conventional predictions, which prove to be non-functional in subsequent experiments. Therefore, we aim at improving the specificity of the predictions by assessing the importance of motif-specific flanking sequence regions.
For the analysis of host-pathogen interactions formed between globular protein domains, a combination of molecular modeling, docking, and molecular dynamics simulations is used. The latter technique provides information about the conformational stability and energetics of an interaction that can hardly be deduced from static structures alone. These methods are for example applied to study the structure of herpesviral glycoproteins that are pivotal for binding to the host cell and following fusion with the cell membrane. Furthermore, we investigate the molecular dynamics of viral regulator proteins and their interaction with cellular targets.



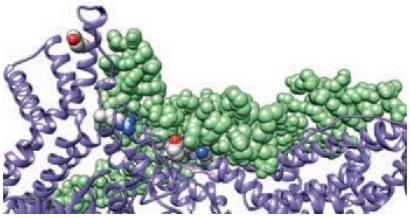
Model of the antigen-binding fragment of a neutralizing antibody bound to Domain-II (green) of the HCMV gB homotrimer
One protomer is colored according to its five domains.

Investigation of the aggregation behavior of the Aβ-peptide of Alzheimer's disease
Protein conformational diseases are unique since they result from a drastic change in protein three-dimensional structure. Most often, the change in conformation involves a structural conversion from primarily α-helical conformation with good solubility to an insoluble β-sheet conformation. Cells have evolved mechanisms to clear these insoluble deposits; however, once clearance pathways are overloaded, these proteins are deposited in the form of insoluble intracellular inclusions or extracellular plaques. Protein deposits or aggregates are also hallmark of many neurodegenerative diseases.
The most prevalent neurodegenerative disease is Alzheimer's disease, which is characterized by extracellular protein deposition of the peptide fragment Aβ from the amyloid precursor protein, and intracellular tau-containing filaments, called neurofibrillary tangles. The 3D structure of the Aβ deposits revealed the overall topology of the fibrils, but gives only limited information about the role of individual residues for fibril formation. The latter type of information, however, is important for the development of novel drugs that can prevent aggregation or of solubilizing aggregates by targeting those residues that represent the hot spots of binding affinity in the fibrillar structure. We address this point by molecular dynamics simulations of Aβ oligomers and thermodynamic analyses of the aggregation interfaces. In addition, we investigate the effect of different solvent environments on the conformational stability of such Aβ oligomers.



Model of the designed S8C variant of the Aß-peptide, which forms neurotoxic dimers
The two peptide chains are shown in magenta and green, respectively, and the disulfide bond is highlighted in yellow.

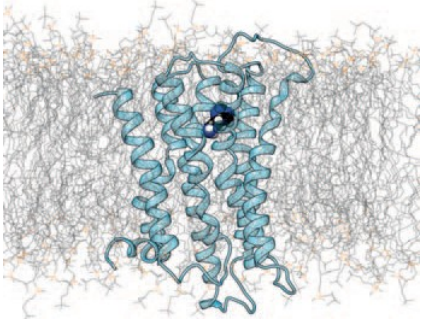
Structure-based evaluation of protein variants
High-throughput DNA sequencing studies revealed a large number of genetic variants between individuals. Many of these sequence variants lead to amino acid exchanges, some of which are linked to disease. Due to their large number (> 10,000 per genome), it is impossible to characterize all sequence variants by experiment, rendering computational prediction tools of utmost importance for the identification of pathogenic variants. Most of the current methods use evolutionary conservation and other sequence-based features to identify damaging variants, but they cannot predict the effects these variants have on protein function. Despite its innate linkage to function, structural information is yet only considered to a very limited extent in the predictions. In addition, the few existing structure-based prediction methods mainly focus on one distinct aspect of protein structure (e.g. protein stability or protein interactions) and do therefore not allow a comprehensive structural and functional annotation. The aim of the present project is to develop a robust computational framework for a comprehensive structure-based analysis and interpretation of high-throughput sequencing data.



Structure of the protein-protein complex between CYFIP (purple) and WAVE1 (green) Mutations of some CYFIP residues, which are located close to the interface, are related to intellectual disability These residues are shown in space-filled presentation and colored by atom-types.

Structure of receptor-ligand complexes

G-protein coupled receptors (GPCRs) are transmembrane proteins that recognize extracellular ligands and thereby trigger intracellular signaling processes. We use methods of molecular modelling and molecular dynamics to study the structure of GPCRs in complex with different small molecule ligands or intracellular interaction partners. Aspects investigated include the prediction of the binding modes of small molecule ligands, conformational changes in GPCRs as a result of ligand binding, and the influence of mutations on GPCR function and interaction. In addition to conventional MD simulation methods, computationally demanding metadynamics simulations are also used. In addition to GPCRs, we also investigate other classes of membrane receptors using similar methodological approaches. Systems studied include the glycine receptor, at which we characterize the binding site of saccharides as allosteric modulators. In the case of the macrophage surface receptor Mincle, we are investigating the binding of synthetic glycolipids, which should support the long-term development of better adjuvants for vaccines.



Structure of the Histamine-H1-Receptor (blue ribbon) with the modelled binding site of histamine (space-filled presentation). The lipids of the cellular membrane are depicted as grey/orange lines.

Teaching

The Professorship of Bioinformatics organizes lectures, seminars, and tutorials in the course program of Molecular Medicine. In addition, the Professorship is involved in interdisciplinary teaching in the master degree programs Life Science Engineering and Integrated Life Sciences in collaboration with the Faculties of Engineering and of Sciences, respectively.
The Professorship also supervises Bachelor's and Master's theses as well as PhD theses.

Selected publications

Söldner CA, Horn AHC, Sticht H. A Metadynamics-Based Protocol for the Determination of GPCR-Ligand Binding Modes. Int J Mol Sci. 2019, 20:1970

Boonsawat P et al. Elucidation of the phenotypic spectrum and genetic landscape in primary and secondary microcephaly. Genet Med. 2019, 21:2043-2058.

Marschall M et al. Nuclear Egress Complexes of HCMV and Other Herpesviruses: Solving the Puzzle of Sequence Coevolution, Conserved Structures and Subfamily-Spanning Binding Properties. Viruses. 2020, 12:683.

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Conrad M, Söldner CA, Miao Y, Sticht H. Agonist Binding and G Protein Coupling in Histamine H2 Receptor: A Molecular Dynamics Study. Int J Mol Sci. 2020, 21:6693.

International cooperations

Prof. Dr. H.-G. Breitinger, German University in Cairo, Cairo: Egypt

Prof. Dr. A. Rauch, Universität Zürich, Zurich: Switzerland

Prof. Dr. H. Durmus, Istanbul University, Istanbul: Turkey

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Professorship of Molecular Medicine with focus on Molecular Imaging

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Research focus
- Transcriptional programs in the regulation of adult neurogenesis
- Role of autophagy and lysosome activity in stem cell function and adult neurogenesis
- Functional characterization of intellectual disability factors
- Hippocampal astrocyte development, dynamics and functional diversity

Structure of the Professorship

Professorship: 1
Personnel: 7
- Scientists: 3 (there of funded externally: 1)
- Graduate students: 5

Dr. Ruth Beckervordersandforth (PI)
- Scientists: 1 (DFG funded)
- Graduate students: 1 (DFG funded)
- medical students: 5 (2 DFG and 3 IZKF funded)

Special structural feature
The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as the professorships of Bioinformatics and of Molecular Medicine with focus on Molecular Imaging.

Research

Neurons and glia cells form functional networks that are the structural basis for learning, cognition, and behavior. Perturbation of the formation, maturation, and plasticity of neural circuits contributes to the pathogenesis of neurodevelopmental disorders, such as intellectual disability and neuropsychiatric diseases, like schizophrenia. Our research aims to better understand the genetic and cell biological mechanisms that regulate development and homeostasis of neural networks.

Transcriptional programs in the regulation of adult neurogenesis
PI: Prof. Dr. D.C. Lie
The discovery of adult neurogenesis, i.e. the lifelong generation of new hippocampal and olfactory bulb neurons from stem cells, has added a new layer of complexity to our understanding of the mechanisms underlying plasticity and regeneration in the mammalian central nervous system. There is strong evidence that adult neurogenesis significantly contributes to hippocampus-dependent learning and memory processes as well as to the pathophysiology of cognitive and affective symptoms during aging and in neurodegenerative and neuropsychiatric diseases. Thus, understanding of the mechanisms regulating adult neurogenesis is of major basic neuroscientific and clinical interest. The generation of new functional neurons from stem cells is a complex multistep process. Current data indicate that each developmental step is controlled by stage-specific transcription factors. We have now found that the Wnt/β-catenin signaling pathway regulates a transcriptional program that controls the functional integration of adult-generated hippocampal neurons. Interestingly, we also observed that ageing-associated impairments in adult hippocampal neurogenesis are paralleled by a decline in Wnt/β-catenin signaling activity. Strikingly, enhancing Wnt/β-catenin signaling activity is sufficient to ameliorate age-associated deficits in adult neurogenesis. In ongoing work, we are investigating the mechanisms regulating Wnt/β-catenin signaling activity in the hippocampus as well as the mechanisms underlying ageing-associated decline in the activity of this key regulatory pathway.
Funding: DFG

Role of autophagy and lysosome activity in stem cell function and adult neurogenesis
PI: Dr. Iris Schäffner, Prof. Dr. D.C. Lie
Degradation and recycling of dysfunctional cellular components are critical pathways for cellular homeostasis. Somatic stem cells are particularly dependent on degradation and recycling pathways to maintain their lifelong capacity for regeneration. We recently demonstrated that the longevity and ageing associated transcription factors of the FoxO family are critical to regulate autophagy, i.e., a central pathway for proteins and organelles, in adult neural stem cells. Loss of FoxOs does not only impair activity of the autophagic pathway, but is associated with stem cell dysfunction and impaired integration of adult-born neurons. We have now found that FoxOs regulate autophagy by controlling lysosome activity and identified molecular targets of FoxOs in this process. Notably, reconstitution of lysosome activity was sufficient to ameliorate FoxO-deficiency associated dysfunction of stem cells and neurons. Inspired by these findings, we are presently testing the hypothesis that enhancing lysosomal activity may counter age-associated deficits in stem cell function.
Funding: IZKF Erlangen

Functional characterization of intellectual disability factors
PI: Dr. Sören Turan, Prof. Dr. D.C. Lie
Sox11 mutations were recently identified in a subset of patients suffering from Coffin-Siris Syndrome, a developmental disorder associated with intellectual disability. Using human pluripotent stem cells to model human neurodevelopment, we found that SOX11 is essential for the generation of neuroectoderm and that SOX11 regulates the balance between proliferation and differentiation in neural stem cells. These findings contribute to a better understanding of the pathogenetic mechanisms in Coffin-Siris Syndrome. This project is conducted in close collaboration with Prof. Dr. B. Winner (Division of Stem Cell Biology) and Prof. Dr. A. Reis (Institute of Human Genetics).
Funding: Bavarian State Ministry for Science and Art, Research Network ForInter

Hippocampal astrocyte development and dynamics
PI: Dr. Ruth Beckervordersandforth
For a long time it has been thought that hippocampal plasticity is predominantly driven by neurons, however, more recent data indicate an active participation of astrocytes. To date it is known that astrocytes contribute to such plasticity in two ways: firstly, by serving as radial glia-like neural stem cells (NSCs) that give rise to new neurons and glial cells, secondly, by serving as niche cells that control the activity of NSCs, and provide structural and functional support to neurons. Besides extensive investigations of the astrocyte-like radial NSC, the niche astrocyte compartment remains understudied and was considered to be static and homogeneous. We recently discovered that the hippocampal niche is constantly changing due to life-long generation of new astrocytes, a dynamic process able to react to external and internal stimuli such as voluntary exercise and aging. Interestingly, we identified that new astrocytes are not only generated by gliogenic division of NSCs, but also by proliferation of local astrocytes. While this mechanism has so far only been described in the developing cortex, our data show that this type of astrogenesis is an ongoing process from hippocampal development to aged stages. We are currently investigating which molecular factors are involved in both NSC- and astrocyte-mediated astrogenesis.
Funding: DFG

Morphological, molecular and functional diversity of hippocampal astrocytes
PI: Dr. Ruth Beckervordersandforth
Investigating astrocyte diversity on morphological, molecular and physiological levels, we present evidence that each anatomical layer of the adult mouse DG is populated by morphologically and molecularly distinct astrocyte populations. Region-specific diversification of astrocytes is further supported

by subtype-specific physiological functions such as the establishment of homotypic astrocyte networks as well as functional differences in Glutamate transport. Importantly, we found a number of key molecular and morphological features of murine astrocyte diversity also in humans, indicating that astrocyte diversity in the DG is highly conserved and relevant for human DG physiology. These findings suggest that diversity of astrocytes goes beyond the broad scale of developmental ancestry and affects - equivalent to what has been shown for neurons - also regional networks.
Funding: DFG

Teaching

The Professorship of Molecular Medicine with focus on Molecular Imaging contributes to the teaching curriculum of Medicine and Dentistry by offering obligatory and elective courses. It provides interdisciplinary training for students of the master degree program Molecular Medicine that is performed together with the departments of Psychiatry and Psychotherapy and of Nuclear Medicine, the Institute of Radiology, and the Division of Molecular Neurology. Aim is to theoretically and practically teach the students state-of-the-art technologies of molecular imaging.
Bachelor and master students as well as medical and scientific graduate students are supervised in our group to successfully finish their thesis projects.

Selected publications

Braun, K., Häberle, B.M., Wittmann, M.T., Lie, D.C. (2020) Enriched environment ameliorates adult hippocampal neurogenesis deficits in Tcf4 haploinsufficient mice. BMC Neurosci. Nov 23;21(1):50. doi: 10.1186/s12868-020-00602-3.

Heppt, J., Wittmann, M.T., Schäffner, I., Billmann, C., Zhang, J., Vogt-Weisenhorn, D., Prakash, N., Wurst, W., Taketo, M.M., Lie, D.C. (2020) β-catenin signaling modulates the tempo of dendritic growth of adult-born hippocampal neurons. EMBO J. Nov 2;39(21):e104472. doi: 10.15252/embj.2020104472. Epub 2020 Sep 15.

Boerstler, T., Wend, H., Krumbiegel, M., Kavyanifar, A., Reis, A., Lie, D.C., Winner, B., Turan, S. (2020) CRISPR/Cas9 mediated generation of human ARID1B heterozygous knockout hESC lines to model Coffin-Siris syndrome. Stem Cell Res. Jun 29;47:101889. doi: 10.1016/j.scr.2020.101889.

von Wittgenstein, J., Zheng, F., Wittmann, M.T., Balta, E.A., Ferrazzi, F., Schaffner, I., Haberle, B.M., Valero-Aracama, M.J., Koehl, M., Miranda, C.J., Kaspar, B.K., Ekici, A.B., Reis, A., Abrous, D.N., Alzheimer, C. & Lie, D.C. (2020) Sox11 is an Activity-Regulated Gene with Dentate-Gyrus-Specific Expression Upon General Neural Activation. Cereb Cortex. doi: 10.1093/cercor/bhz338

Wedel, M., Frob, F., Elsesser, O., Wittmann, M.T., Lie, D.C., Reis, A. & Wegner, M.(2020) Transcription factor Tcf4 is the preferred heterodimerization partner for Olig2 in oligodendrocytes and required for differentiation. Nucleic Acids Res. doi: 10.1093/nar/gkaa218

Turan, S., Boerstler, T., Kavyanifar, A., Loskarn, S., Reis, A., Winner, B. & Lie, D.C. (2019) A novel human stem cell model for Coffin-Siris Syndrome like syndrome reveals the importance of SOX11 dosage for neuronal differentiation and survival. Hum Mol Genet. doi: 10.1093/hmg/ddz089

Fiebig, C., Keiner. S., Ebert, B., Schaffner, I., Jagasia, R., Lie, D.C. & Beckervordersandforth R. (2019) Mitochondrial Dysfunction in Astrocytes Impairs the Generation of Reactive Astrocytes and Enhances Neuronal Cell Death in the Cortex Upon Photothrombotic Lesion. Front Mol Neurosci 12: 40. doi: 10.3389/fnmol.2019.00040

Beckervordersandforth, R. & Rolando, C. (2020) Untangeling human neurogenesis to understand and counteract brain disorders. Current Opinion in Pharmacology 2020.50:67-73. doi: 10.1016/j.coph.2019.12.002

Schneider, J., Karpf, J. & Beckervordersandforth, R. (2019) Role of astrocytes in the neurogenic niches. Methods in Molecular Biology, vol.1938. doi: 10-1007/978-1-4939-9068-9-2

International cooperations

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Prof. A. Ballabio, Telethon Institute of Genetics and Medicine (TIGEM), Neapel, Italien

Dr. A. McNeill, Sheffield University, Sheffield, England

Prof. K. Nakashima, Kyushu University, Fukuoka, Japan

Prof. M.M. Taketo, Kyoto University, Kyoto, Japan

Dr. Jan Beckervordersandforth, Maastricht University Medical Centre, Maastricht, Netherlands

Prof. Dr. Onur Basak, University Medical Centre Utrecht, Utrecht, Netherlands

Dr. Felipe Ortega, Complutense University of Madrid, Madrid, Spain

Institute of Cellular and Molecular Physiology

Chair of Physiology (Systems Physiology)

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Research focus
- Renal sodium and potassium homeostasis
- Epithelial sodium channel (ENaC)
- Regulation of ENaC by hormonal and local factors
- Activation of ENaC by proteases
- Functional characterization of epithelial ion channels

Structure of the Chair

Professorship: 1
Personnel: 21
- Scientists: 9 (thereof funded externally: 3)
- Graduate students: 3

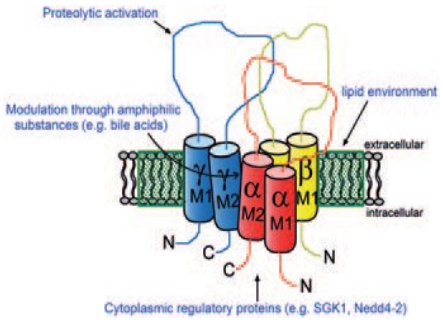
Special structural feature
The Institute of Cellular and Molecular Physiology comprises the Chair of Physiology (Systems Physiology) and the Professorship of Cardiovascular Physiology. The Chair and the Professor of Cardiovascular Physiology serve as director and deputy director of the Institute, respectively.

Research

The research focus of the group of Prof. Dr. C. Korbmacher is the physiology and pathophysiology of renal and epithelial ion channels. In the kidney and other epithelial organs, ion channels are involved in mediating highly selective and regulated transepithelial ion transport. To study these ion channels and their regulation is of physiological and pathophysiological relevance, because an inappropriate function of renal ion channels may cause for example arterial hypertension, renal salt wasting syndromes, or polycystic kidney disease.

Renal sodium and potassium homeostasis
Sodium homeostasis and potassium homeostasis are intimately linked and critically important for the survival of the human organism. Homeostatic regulation primarily depends on the ability of the kidney to match dietary sodium and potassium intake with appropriate renal excretion. Maintaining sodium balance is essential for the control of extracellular fluid volume and blood pressure. Inappropriate renal sodium retention will cause expansion of extracellular fluid volume and may result in arterial hypertension and edema. In contrast, renal sodium wasting causes extracellular volume depletion resulting in a decrease of arterial blood pressure and eventually circulatory collapse. Maintaining potassium balance is critically important for many cellular functions, including neuronal and cardiac excitability. Renal potassium retention or wasting will ultimately lead to hyperkalemia or hypokalemia, respectively, which may cause cardiac arrhythmias and cardiac arrest. Thus, pathophysiological disturbances of renal sodium or potassium homeostasis result in potentially life threatening disorders. Therefore, it is of great interest to understand the function and regulation of ion channels involved in renal sodium and potassium handling.

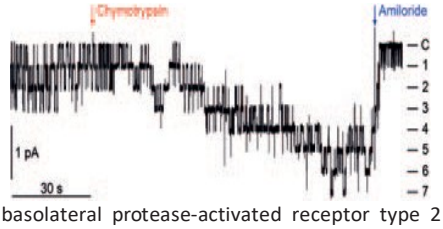
Epithelial sodium channel (ENaC)
A particular focus of this research group is the amiloride-sensitive epithelial sodium channel (ENaC) and the molecular mechanisms involved in its regulation. Ion flux through ENaC is the rate-limiting step for sodium absorption in the so-called aldosterone sensitive distal nephron (ASDN). The pathophysiological importance of ENaC for sodium homeostasis and blood pressure control is evidenced by 'gain of function' and 'loss of function' mutations of the channel causing a hereditary form of severe salt-sensitive arterial hypertension (Liddle syndrome; pseudohyperaldosteronism) or a renal salt wasting syndrome (PHA1; pseudhypoaldosteronism type 1), respectively. ENaC also plays an important physiological and pathophysiological role in sodium and fluid absorption by the respiratory epithelium and distal colon.



Molecular mechanisms involved in the regulation of the epithelial sodium channel (ENaC) consisting of three subunits (α,β,γ)

Regulation of ENaC by hormonal and local factors
A complex network of hormonal and local factors contributes to regulating ENaC. The most important hormone stimulating channel activity is aldosterone which acts through the mineralocorticoid receptor (MR). Many questions remain open regarding regional differences of the action of aldosterone in the ASDN and the molecular mechanisms involved in mediating the aldosterone effect. The differential regulation of sodium absorption and potassium secretion by aldosterone in the ASDN is also incompletely understood. In the ASDN, the secretory potassium channel ROMK (renal outer medullary K^+ channel) is mainly responsible for potassium secretion. An increased ENaC activity favors potassium secretion through ROMK. In contrast, inhibiting ENaC, e.g. by amiloride, reduces ROMK mediated potassium secretion. Therefore, the regulatory interplay of the two channels is of great importance for renal sodium and potassium homeostasis. The appropriate adjustment of the functional interaction of ENaC and ROMK is likely to involve a regional heterogeneity of channel regulation. At the cellular and molecular level, several regulatory proteins (e.g. kinases, proteases, and proteins directly associated with the channel) and the lipid environment of ENaC contribute to its regulation.

Activation of ENaC by proteases
A specific feature of ENaC is its complex proteolytic processing which is critical for channel activation. Proteolytic channel activation can be nicely demonstrated in heterologous expression systems. ENaC activation by locally released proteases may be pathophysiologically relevant in the context of inflammatory kidney disease and may contribute to sodium retention for example in nephrotic syndrome. However, molecular mechanisms contributing to proteolytic ENaC activation are still incompletely understood and (patho)physiologically relevant proteases remain to be identified. In addition to proteases activating ENaC directly by proteolytic channel cleavage at specific sites, interstitial proteases may indirectly modulate ENaC mediated transepithelial sodium transport by activating a

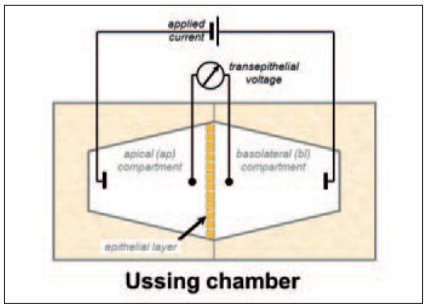


basolateral protease-activated receptor type 2 (PAR2).

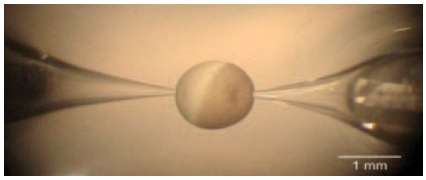
Proteolytic channel activation in an outside-out patch from a Xenopus laevis oocyte heterologously expressing human ENaC

Functional characterization of epithelial ion channels
Above all, electrophysiological methods are used to study the function and regulation of renal and epithelial ion channels. These include transepihelial short circuit current measurements in Ussing chambers, whole-cell current recordings using the two-electrode voltage clamp (TEVC) technique, and patch-clamp experiments which in addition to whole-cell recordings also allow single-channel recordings.

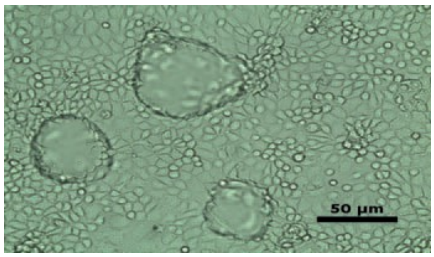
To elucidate the molecular mechanisms involved in ion channel regulation, a range of additional molecular biological and cell physiological methods are employed including the use of *Xenopus laevis* oocytes, cultured cells, native tissue, and animal models (e.g. genetically modified mouse lines). Moreover, the now available structural information in combination with computer simulations and site-directed mutagenesis allows the investigation of functionally relevant channel regions. This integrated approach provides fascinating opportunities to gain novel insights into physiological and patho-physiological mechanisms and a better understanding of molecular disease processes.



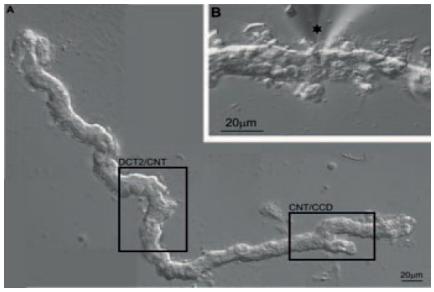
Schematic diagram of a so-called Ussing chamber for short-circuit current measurements to assess electrogenic transepithelial ion transport



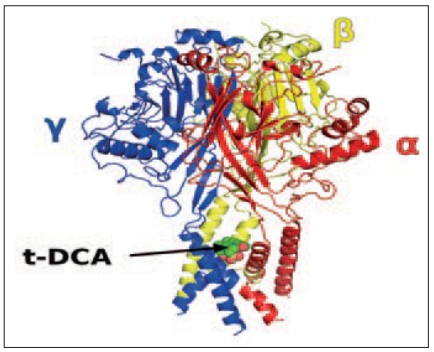
Xenopus laevis oocyte impaled with two microelectrodes to measure whole-cell currents using the two-electrode voltage clamp (TEVC) technique



Phase contrast micrograph of cultured collecting duct cells (mCCD$_{cl1}$ cell line) with dome formation indicating active transepithelial electrolyte and fluid transport



Differential interference contrast image of a microdissected distal mouse nephron. ***A*** *Differential interference contrast image is composed from a series of consecutive photomicrographs. Transitional zone between the distal convoluted tubule and early connecting tubule (DCT2/CNT) and the zone comprising the late CNT and early CCD (CNT/CCD) are indicated.* ***B*** *Split open tubule with patch pipette (*)*



Homology model of human αβγENaC with associated taurodeoxycholic acid (t-DCA) in the pore region of the channel as predicted by molecular docking simulation.

Teaching

The Institute of Cellular and Molecular Physiology is involved in the curricular teaching (lectures, seminars, and practical classes) for medical and dental students and for students following the degree program Molecular Medicine (Bachelor and Master).
The Institute provides research opportunities for medical students working towards a doctoral degree and for bachelor, master, and graduate students.

Selected publications

Mansley MK, Niklas C, Nacken R, Mandery K, Glaeser H, Fromm MF, Korbmacher C, Bertog M. Prostaglandin E2 stimulates the epithelial sodium channel (ENaC) in cultured mouse cortical collecting duct cells in an autocrine manner. *J Gen Physiol*. 2020 Vol. 152 No. 8:e201912525. doi: 10.1085/jgp.201912525. PMID: 32442241

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Bohnert BN, Kanse S, Haerteis S, Korbmacher C, Artunc F. Rebuttal to editorial: Sodium retention by uPA in nephrotic syndrome? *Acta Physiol (Oxf).* 2020 Apr;228(4):e13427. doi: 10.1111/apha.13427. PMID: 31794131

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Ilyaskin AV, Sure F, Nesterov V, Haerteis S, Korbmacher C. Bile acids inhibit human purinergic receptor P2X4 in a heterologous expression system. *J Gen Physiol*. 2019, 151:820-833. PMID: 30988062

International cooperations

Prof. N. W Bunnett, PhD, Columbia University, New York: USA

Prof. E. Hummler, PhD, Université de Lausanne, Lausanne: Switzerland

Prof. Dr. J. Loffing, University of Zurich, Zurich: Switzerland

Prof. L. Martin, PhD, Queen's University Belfast, Belfast: Northern Ireland

Prof. L. G. Palmer, Ph.D., Weill-Cornell Medical College, New York: USA

Prof. S. Somlo, MD, Yale University, New Haven: USA

Institute of Cellular and Molecular Physiology

Professorship of Cardiovascular Physiology

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Research focus
- Cardiac ion channels
- Electromechanical coupling

Structure of the Professorship

Professorship: 1
Personnel: 5
- Scientists: 3
  (thereof funded externally: 1)
- Graduate students: 2

Special structural feature
The Institute of Cellular and Molecular Physiology comprises the Chair of Physiology (Systems Physiology) and the Professoship of Cardiovascular Physiology. The Chair and the Professor of Cardiovascular Physiology serve as director and deputy director of the Institute, respectively.

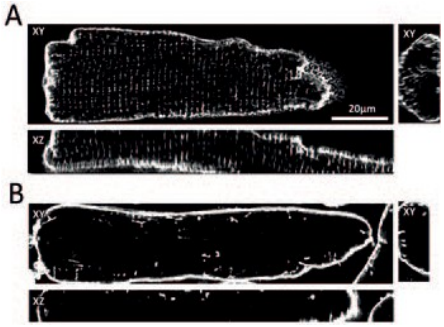
Research

The research focus of the Professorship of Cardiovascular Physiology is the study of the pathophysiology of cardiac arrhythmia and heart failure. Heart failure leads to functional and structural alterations at the macroscopic as well as the microscopic and the molecular level, a process called remodeling. Cardiac remodeling during heart failure alters the electromechanical function of the heart, for example by altering the expression of ion channels that control cardiac excitation and repolarization, which increases the risk for cardiac arrhythmia including sudden death. Structural alterations in heart failure, such as an increase in connective tissue (fibrosis) or an alteration of the myocyte architecture, can decrease cardiac contractility and worsen heart failure. Our primary goal is to further understand the molecular mechanisms that underlie remodeling of the heart. This might lead to new diagnostic, therapeutic, or preventive strategies.

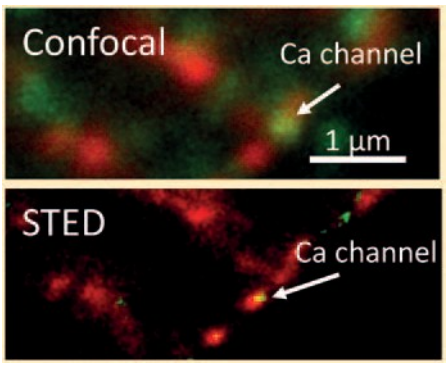
Cardiac ion channels
To investigate function and regulation of ion channels, a broad range of sophisticated electrophysiological, molecular biological, and cell physiological methods is applied on cultured cells, native tissues, animal models (e.g. transgenic mouse lines), and human cells. For example, the patch-clamp technique allows for a detailed analysis of membrane potential and ion channel function by electrically controlling individual cardiac myocytes. Ion channels are particularly important in shaping the action potential and in initiating the contraction. It is well established that regional differences in action potential duration (APD) in different areas of the heart are of great importance for a normal course of repolarization. For example, within the left ventricular free wall, APD is much longer in endocardial than in epicardial myocytes with the consequence that endocardial myocytes repolarize last, although they become depolarized first. Hence, the wave of excitation travels from endocardial to epicardial regions, while the wave of repolarization travels in the opposite direction. Under pathological conditions, such as cardiac hypertrophy or failure, this well-organized sequence of events is altered which is thought to contribute to the increased risk of cardiac arrhythmia and sudden cardiac death of patients with cardiac hypertrophy or failure. In order to further understand the underlying mechanisms, our research group investigates the regulation and pharmacology of ion channels (Na^+, K^+ and Ca^{2+} channels) that are responsible for cardiac excitation and repolarization by using animal models as well as tissue or cell culture. At present, the primary focus lies in the identification of signaling cascades that participate in the regulation of those ion channels under pathophysiological conditions. A promising target is the cardiac mineralocorticoid receptor that participates in the regulation of cardiac Ca^{2+} and K^+ channels.
It is hoped that a more detailed characterization of cardiac ion channels will lead to a better understanding of the mechanisms underlying cardiac repolarization and will help to develop therapeutic strategies to influence the organization of repolarization and hence prevent the development of malignant arrhythmia.

Isolated human ventricular cardiomyocyte during patch-clamp recording

Electromechanical coupling
Electromechanical coupling is the process that links electrical signals from the cell membrane, i.e. action potentials, to the mechanical action of the cell, i.e. the contraction. In the heart, a Ca^{2+}-influx into the cell via L-type Ca^{2+} channels activates ryanodine receptors located intracellularly in the sarcoplasmic reticulum (SR) which in turn release much more Ca^{2+} from the SR. This process, called Ca^{2+}-induced Ca^{2+}-release, activates contraction and controls its magnitude. For example, when not enough Ca^{2+} is released from the SR or the release is too slow, the resulting contraction is inefficient and weak. Multiple mechanisms can cause alterations in electromechanical coupling. In heart failure, alterations in the microarchitecture of cardiac myocytes particularly contribute to a decrease in Ca^{2+} release from the SR.
The transverse tubular system (t-system) in ventricular cardiomyocytes consists of many tube-like membrane invaginations that originate from the cell surface and reach deeply into the cell. L-type Ca^{2+} channels are primarily localized in the t-tubular membrane in close vicinity to the ryanodine receptors. An important task of t-tubules is therefore to facilitate a close contact of L-type Ca^{2+} channels to ryanodine receptors in order to provide the condition for an efficient and quick release of Ca^{2+} from the SR. Three dimensional high resolution microscopy (confocal or STED microscopy) reveals that in heart failure, t-system structure and expression of Ca^{2+} channels is substantially altered. These alterations lead to delayed, reduced, and disorganized Ca^{2+} release from the SR which can also be identified using high resolution microscopy together with Ca^{2+} indicators and computer assisted image analysis.
Using cell- and tissue culture models derived from human heart samples, we investigate the cellular and molecular mechanisms underlying t-system alterations with the aim to stop or even reverse these processes. Furthermore, we link structural and functional alterations at the cellular and molecular level to the clinical picture of patients in order to identify prognostic or diagnostic markers or even new therapeutic strategies.



A 3D confocal microscopic image of the t-system in a cardiomyocyte.
B Cardiomyocyte with loss of t-system, e.g. in heart failure



Immunofluorescence analysis of Ca^{2+} channel expression using confocal and STED microscopy in a cardiomyocyte

Teaching

The Professorship of Cardiovascular Physiology is involved in the curricular teaching (lectures, seminars, and practical classes) for medical and dental students and for students following the degree programs Molecular Medicine (Bachelor and Master).
The Institute provides research opportunities for medical students working towards a doctoral degree and for bachelor, master, and graduate students.

Selected publications

Launhardt M, Ebel N, Kondruweit M, Weyand M, Volk T, Drummer D. Developing a patient individualized flexible silicone implant using SLS and vacuum die casting. AIP Conference Proceedings 2055. 2019. 140005; https://doi.org/10.1063/1.5084908

Seidel T, Fiegle DJ, Baur TJ, Ritzer A, Nay S, Heim C, Weyand M, Milting H, Oakley RH, Cidlowski JA, Volk T. Glucocorticoids Preserve the T-Tubular System in Ventricular Cardiomyocytes by Upregulation of Autophagic Flux. Basic Res Cardiol 2019. 114: 47

Abu-Khousa M, Fiegle DJ, Sommer ST, Minabari G, Milting H, Heim C, Weyand M, Tomasi R, Dendorfer A, Volk T, Seidel T. The Degree of T-System Remodeling Predicts Negative Force-Frequency Relationship and Prolonged Relaxation Time in Failing Human Myocardium. Front Physiol 2020. 11:182

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Bleisinger N, Dittrich R, Strahl O, Brauweiler R, Hoffmann I, Beckmann WM, Volk T. Me2SO perfusion time for whole-organ cryopreservation can be shortened: results of micro-computed tomography monitoring during Me2SO perfusion of rat hearts. PLOS One. 2020. 15:e0238519. doi: 10.1371/journal.pone.0238519

International cooperations

Prof. FB Sachse, University of Utah, Salt Lake City, Utah: USA

Prof. D Alvarez de la Rosa, University of La Laguna, La Laguna: Spain

Dr. R Oakley / Prof. J Cidlowski, National Institute of Health and Environmental Sciences, Research Triangle Park, North Carolina: USA

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Research focus

- Neurophysiologic substrates of higher brain functions
- Systems neurophysiology
- Transduction, integration and plasticity in primary nociceptive neurons
- Trigeminal nociception and headache generation
- Functional imaging of brain activity by fMRI

Structure of the Institute

Professorships: 3
Personnel: 40

- Scientists: 16 (thereof funded externally: 8)
- Doctoral students: 9

Special structural features
The Institute houses experimental set-ups of the Departments of Anesthesiology, Medicine 1 and 4, and Psychiatry, each with close methodical and thematic ties to the research groups of the Institute.

Research

The overarching research objective at our Institute is to understand the bioelectrical and neurochemical processes that constitute the basic language of the nervous systems and enable communication between nerve cells.
What factors elicit an electric impulse in a neuron, if, for instance, pain or temperature stimuli influence the body?
What mechanisms mediate signal transmission between nerve cells and how is information processed in neuronal networks? How do different brain regions communicate with each other? Answers to questions like these will also help to elucidate the underpinnings of cognition, emotion and action and of disorders thereof. We explore such issues with a broad spectrum of methods, ranging from modern electrophysiological, optical, cell and molecular biological techniques to fMRI in healthy volunteers and patients.

Neurophysiologic substrates of higher brain functions
PI: Prof. Dr. C. Alzheimer, Dr. F. Zheng, PD Dr. Dr. T. Huth
Our research focuses on the electric behavior of neurons and neuronal networks under normal and pathological conditions. Using high-resolution neurophysiological and optical techniques, we investigate functions and regulation of ion channels and synapses. Our aim is to understand fundamental neural processes that are essential for cognitive functions as well as for affective behavior and whose dysfunctions might give rise to neuropsychiatric disorders. In particular, we are studying the following topics:
1) Role of activin, a member of the Transforming Growth Factor-ß family, as a ”master molecule” tuning glutamatergic and GABAergic neurotransmission, and its impact on cognition, emotions, and neuroprotection
2) Interaction between BACE1, a crucial enzyme in the amyloid cascade of Alzheimer’s disease, and properties and expression of Na^+ and K^+ channels
3) Neuropsychiatric disease models and mechanisms of drug action (in collaboration with the Department of Psychiatry and Psychotherapy).

Systems Neurophysiology
PI: Prof. Dr. A. Ponomarenko
The motivation for our research is to uncover real-time interactions between neuronal ensembles in the brain supporting experience-dependent and innate behaviours. During these behaviours cortical and subcortical regions display various regimes of networks synchronization, which temporally coordinate neuronal ensembles and is often affected in neuropsychiatric disorders. Combining electrophysiological recording and optogenetic manipulations of neuronal activity in behaving rodents, mouse genetics and mathematical modeling, we study network oscillations and neural coding in brain regions involved in memory, navigation and adaptive behaviour. We further investigate the signaling between cortical and subcortical circuits supporting innate behaviors such as feeding, social interaction and sleep. A recent work focused on the functions of the relevant for obsessive-compulsive disorder coupling of fast and slow oscillations in the prefrontal - subthalamic pathway. Another project addressed the role of signaling between prefrontal cortical interneurons and astrocytes in oscillations, ensemble coding and decision-making.

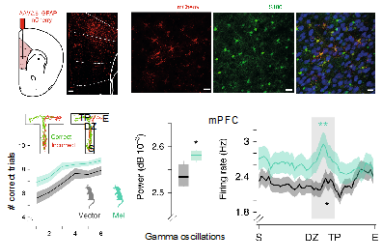

Fig.1: Optogenetic activation of medial prefrontal (mPFC) astrocytes by melanopsin (Mel) improves spatial working memory, facilitates gamma oscillations and increases firing rate of putative excitatory cortical neurons. S100 - astrocytic marker, S – start, DZ – decision zone, TP – turning point, E – end. Modified from Mederos et al., Nat. Neurosci., 2020

Transduction, integration, plasticity in primary nociceptive neurons
PI: Prof. Dr. S. Sauer, Prof. Dr. P.W. Reeh
The research focuses on primary nociceptive neurons, their electrophysiological and neurochemical responses to noxious and pruritogenic stimuli and chemical mediators. Isolated preparations and cultured dorsal root ganglion cells as well as transfected cell lines are used to study action potential discharge, ionic currents, calcium transients, and release of the neuropeptides substance P and calcitonin gene-related peptide. Aim is to elucidate nociceptive transduction and integration of stimuli as well as possible pharmacological interventions. Specific topics are sensitization by tissue acidosis, inflammatory mediators, metabolites as well as their intracellular signal transduction. Transgenic mouse strains lacking different metabotropic and ionotropic receptors or thermally activated ion channels (i.a. TRPV1, TRPA1) are studied. Voltage-controlled ion channels (NaV, Kv7.2, HCN, CaV3.2) came in focus because only few subtypes decide on excitability, i.e. on generation, frequency, and propagation of action potentials to the central nervous system. The group studies mechanisms of painful diabetic neuropathy. One project focus on reactive dicarbonyls, that cause glycation of TRPA1 receptors, the other investigates consequences of calcium channel (Cav3.2) glycosylation. Both processes increase excitability of nociceptors and could by that contribute to pain sensations of diabetes patients

Trigeminal nociception and headache generation
PI: Prof. Dr. K. Messlinger
Our group is working on nociceptive mechanisms in the cranial dura mater, the trigeminal ganglion, and the spinal trigeminal nucleus as the neurobiological basis for the generation of headaches. Extracellular recordings from single afferent fibers in the isolated rodent dura mater are performed to study the sensitivity and response of meningeal afferents and the role for receptors and ion channels that are probably involved in the generation of headaches in humans. In a similar preparation, we examine by which mechanisms the neuropeptide CGRP is released from the cranial dura mater as an indicator for trigeminovascular activation. Using immunohistochemical and molecular biological methods, we aim at detecting the intracellular signal pathways that are induced by these substances. To study the central processes of headache generation, we examine the response properties of neurons in the spinal trigeminal nucleus, record the peripheral and central blood flow, and assess the effects of potential headache therapeutics.

Functional imaging of brain activity by fMRI
PI: Prof. Dr. C. Forster
Functional magnetic resonance imaging (fMRI) is a well-established method to image the activity of the human brain during the processing of various stimuli and tasks. The method is used to identify brain regions involved in the central processing of pain and itch. By variation of the experimental paradigms, the function of various brain regions

and their contribution in the perception of the corresponding stimulus should be determined. Common projects with the Department of Medicine 1 analyze the central changes induced by chronic itch in patients suffering from cholestatic pruritus.

Teaching

In addition to its contribution to the preclinical curricula of students of Medicine, Dentistry, and Molecular Medicine, the Institute gives lectures, seminars, and practical courses in physiology for students of the Faculties of Engineering and of Sciences, in particular courses for the degree programs Medical Technology and Pharmacy. The Institute supervises Bachelor and Master theses as well as MD and PhD theses.

Selected publications

Becker AK, Auditore A, Pischetsrieder M, Messlinger K, Fleming T, Reeh PW, Sauer SK. Reactive dicarbonyl compounds cause Calcitonin Gene-related Peptide release and synergize with inflammatory conditions in mouse skin and peritoneum. J Biol Chem 295:6330-6343, 2020.

Dierich M, Hartmann S, Dietrich N, Moeser P, Brede F, Johnson Chacko L, Tziridis K, Schilling A, Krauss P, Hessler S, Karch S, Schrott-Fischer A, Blumer M, Birchmeier C, Oliver D, Moser T, Schulze H, Alzheimer C, Leitner M, Huth T. β-secretase BACE1 is required for normal cochlear function. J Neurosci 39: 9013-9027, 2019.

Dux M, Babes A, Manchen J, Sertel-Nakajima J, Vogler B, Schramm J, Messlinger K. Eur J Pain. 24:383-397, 2020.

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Mederos S, Sánchez-Puelles C, Esparza J, Valero M, Ponomarenko A, Perea G. GABAergic signaling to astrocytes in the prefrontal cortex sustains goal-directed behaviors. Nature Neurosci, 2020, doi: 10.1038/s41593-020-00752-x.

International cooperations

Prof. S. Werner, Institute of Molecular Health Sciences, ETH Zürich: Schweiz,

Prof. S. Todorovic, U of Colorado School of Medicine, Aurora, CO: USA,

Prof. A. Babes, University of Bukarest, Bukarest: Rumänien,

Dr. M. Dux, Institute of Physiology, University of Szeged: Ungarn,

Prof. E. Jorum, Department for Neurophysiology, Rikshospitalet, University of Oslo, Oslo: Norwegen,

Dr. G. Perea, Instituto Cajal, Madrid: Spanien,

Prof. A.V. Tzingounis, University of Connecticut, Storrs, CT: USA

Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine

Chair of Occupational and Social Medicine

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Research focus
- Work related health research
- Population related health studies
- Biomarker in Occupational Medicine
- Dermatotoxicology
- Molecular markers of exposure to hazardous substances
- Quality assurance of biomonitoring methods
- Quality assurance of health promoting actions
- Healthcare research

Structure of the Institute

Professorships: 2
Personnel: 51
- Doctors (of Medicine): 7
- Scientists: 14 (thereof funded externally: 12)
  Graduate students: 21

Clinical focus areas
- Outpatient-clinic of occupational, social, and environmental medicine
- Biological monitoring
- Occupational medical service for FAU and UK Erlangen (incl. prevention of infection)
- Occupational medical service for teachers at schools in Northern Bavaria

Special structural features
- Chair and scientific secretary of the DFG working group „Setting of Threshold Limit Values in Biological Material“ (Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area)
- Chair and scientific secretary of the DFG working group „Analyses of Hazardous Substances in Biological Material“ (Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area)
- Management and certification center of the quality assessment program for human biological monitoring (German External Quality Assessment Scheme, G-EQUAS)

Research

In different research areas, health hazards derived by occupational and environmental exposure are investigated using clinical, natural-scientific, and sociological methods. The aim of the research of the Institute (IPASUM) is a qualitative and quantitative specification of the effects as well as their determinants and finally evidence-based recommendations of prevention measures. The research approaches vary from cell biological basic research to the scientific evaluation of prevention measures in practice.

Work related health research
Manifest diseases, resulting from chronic exposure at work, often cause substantial social-medical problems. Therefore, IPASUM carries out field studies at the work place that aim at detecting physiological and pathophysiological changes long before manifest diseases appear. Questions always arise when new technologies or working materials are introduced. New welding techniques used in the aluminum processing industry or the replacement of classical solvents by alternative solvents can be listed as examples. Furthermore, allergically mediated diseases at the workplace are still a problem although hygienic conditions have clearly been improved. Therefore, an important focus for IPASUM is on the assessment of exposure and on the effect of toxic, mutagenous, and sensitizing working materials. Many qualified field studies analyze not only the exposure, but also the data of ambient monitoring (inhalative and dermal exposure).
Funding: German employer’s liability insurance association, German State Ministries, German Federal Ministry of Labor and Social Affairs

Population related health studies
Environmental medicine relates to occupational medical questions by critically proving exposure and its possible effects. IPASUM has, amongst others, the task to offer fast and adequate help if the public is postulated with high exposure to chemical agents, like PCB in public facilities, phthalates in pharmaceuticals/toys, or aluminum in deodorants.
Funding: Local authorities, Bavarian State Ministry of the Environment and Public Health, German Federal Environment Agency

Biomarker in Occupational Medicine
PI: Prof. Dr. S. Schmitz-Spanke
This working group examines the cellular response to exposure to hazardous substances in the low dose range. In cellular models, toxicological endpoints (such as cell proliferation, production of oxygen radicals, alterations in the mitochondrial membrane potential, DNA damage) are correlated with alterations on the proteome and metabolome level. Here, the sequence of the cellular defense mechanism is analyzed and the transition from adaptive to adverse effects is characterized. The resultant data sets are comprehensively processed and modeled to simulate different conditions yielding insight into the mechanisms that are involved in this transition.
In a subproject of the project network “Ultra-Fine Particles” (UFP), funded by the Bavarian State Ministry of the Environment and Consumer Protection, the biological response to UFP exposure is being investigated. For this purpose, a state-of-the-art air-liquid interface lung model in situ is exposed to particles of varying sizes and compositions, and the biological response is examined using a high-throughput battery of tests as well as both transcriptomic and metabolomic methods. Cooperating partner: Cooperation Group of Comprehensive Molecular Analytics at Helmholtz Zentrum München.

Dermatotoxicology
Several projects that describe and quantify dermal penetration are conducted by using in vitro (static diffusion chamber, microdialysis on freshly excised human skin) and in vivo models (microdialysis of volunteers). Furthermore one working group deals with the assessment of hazardous substances in the area of skin penetration for the DFG Commission of Investigation of Health Hazards of Chemical Compounds in the Work Area. Clinical research in the area of dermatotoxicology considers procedures to early diagnose subclinical skin damages and irritations. IPASUM developed and validated the Hand Eczema Score for Occupational Screenings (HEROS).

Molecular markers of exposure to hazardous substances
This research group develops and validates procedures for the quantitative assessment of molecular markers of individual exposure to hazardous substances (exposure monitoring), for the disposition for hazardous substances in the metabolism (susceptibility monitoring) and examines the effects of hazardous substances (biological effect monitoring). A special focus is laid on the biological effect monitoring, which particularly quantifies reaction products of mutagenous substances, covalently bound as adducts to macromolecules, like proteins or DNA. The valency of the biomarkers is examined in studies that give information about the specificity, sensitivity, and toxicokinetic behavior.
Funding: DFG, *Chemie-Wirtschafts-förderungsgesellschaft*, German Environment Agency.

Quality assurance of biomonitoring methods
On behalf of the German Association for Occupational and Environmental Medicine, IPASUM currently organizes the most comprehensive external quality assessment scheme worldwide for the evaluation of occupational and environmental biomarkers. The 62nd round robin test of G-EQUAS was finished within the report period. Now G-EQUAS comprises 190 analyses parameters; more than 200 laboratories worldwide (two-thirds of them international) take part in G-EQUAS every six months.

Quality assurance of health promoting actions

Within the framework of company health management, measures are offered and implemented in companies that support the health resources and wellbeing of the employees. IPA-SUM develops concepts to examine the effectiveness and sustainability of health promotion in companies and uses them in practice. The evaluation concepts are developed and implemented for individual companies, networks or for regional programs, like Medical Valley EMN. One evaluation task for these programs is to assess the consistency and feasibility of their objectives. Other tasks are to evaluate the applied measures, their suitability and efficiency and to rate their sustainability.

Psychological strain in the workplace

The changing world of work, as a result of working from home, increased digitalization, constant availability, or the consolidation of tasks, to name a few examples, can lead to a change in general working conditions and social cooperation. In recent years, these changes have led to more focus on mental health, psychological strain, and stress in the workplace with regard to both research and practice. The IPASUM has made a significant effort to develop risk assessment procedures for psychological strain. In this context, relevant content and methods of implementation have been specified, developed, tested, and validated for small and medium-sized businesses as well as for settings like schools and hospitals. Using these evaluative results, measures are derived and concepts are developed which are then further analyzed for success. The goal of this project is to develop methods and concepts for employers to analyze their own current situations (whether independently or with partial support) and improve them as needed.

Healthcare research

In the field of healthcare research, the project “Healthcare in Bavarian schools” was conducted. The project aims to improve occupational healthcare in public Bavarian schools as well as to support the construction of the *Arbeitsmedizinische Institut für Schulen* (Occupational Medicine Institute for Schools, AMIS Bayern). Cooperating partners: Institute for Occupational, Social, and Environmental Medicine of LMU Munich, AMIS Bayern (LGL).

Teaching

The employees of the IPASUM share in the curricular teaching of both compulsory and elective subjects in the study programs Human Medicine and Medical Process Management. In addition to the core subjects of occupational, social and environmental medicine, the IPASUM assists in coordinating complementary subjects Q3 and Q10 as well as career exploration. Moreover, Bachelor and Master theses, as well as dissertations for the medical and natural sciences, are supervised.

Selected publications

Verma N, Pink M, Kersch C, Rettenmeier AW, Schmitz Spanke S. Benzo[a]pyrene mediated time and dose dependent alteration in cellular metabolism of primary pig bladder cells with emphasis on proline cycling. Arch Toxicol. 2019; 93: 2593–2602

Weistenhöfer W, Uter W, Bernet F, Drexler H. The tissue viability imaging system-Suitable method for discovering minimal skin changes in occupational screenings? Results of a cross-sectional field study. Skin Res Technol. 2019; 25(4): 553-563

Hiller J, Klotz K, Meyer S, Uter W, Hof K, Greiner A, Göen T, Drexler H. Systemic availability of lipophilic UV filters through dermal sunscreen exposure. Environ Int. 2019; 132: 105068

Eckert E, Purbojo A, Müller J, Rüffer A, Cesnjevar R, Göen T, Münch F. Plasticizer exposure of neonates by heart surgery. Toxicol Lett. 2020; 330:7-13

Kilo S, Wick J, Vijayan SM, Göen T, Horch RE, Ludolph I, Drexler H. Impact of physiologically relevant temperatures on dermal absorption of active substances - an ex-vivo study in human skin. Toxicol in vitro 2020; 68: 104954

Wischlitzki E, Amler N, Hiller J, Drexler H. Psychosocial risk management in the teaching profession: A systematic review. Saf Health Work. 2020; 11: 385-396

International cooperations

A. LeBlanc, Institute National de Santé Publique du Québec, Québec: Canada

Dr. T. Berman, Department of Environmental Health, Jerusalem: Israel

Dr. K. Jones, Health and Safety Laboratory (HSL), Buxton: UK

Prof. P. Grandjean, MD, Harvard School of Public Health, Boston: USA

Prof. ‘S. Fustinoni, Università degli Studi di Milano, Mailand: Italien

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Research focus
- Clinical nutrition in older persons
- Mobility and function
- Clinical care for geriatric patients

Structure of the Institute

Professorships: 2
Personnel: 30
- Doctors (of Medicine): 2
- Scientists: 22 (thereof funded externally: 20)
- Graduate students: 15

Special structural feature
Prof. Dr. C.C. Sieber is head of the Internal Medicine of the Kantonsspital Winterthur (Switzerland).

Research

The demographic change poses a challenge for the public health care systems. In the future, the approach of diagnose-specific action in older persons will not be enough for the main goal of preservation of independence, mobility, and quality of life in the older population and for prevention and treatment of age-related diseases. The two lifestyle factors, physical activity and nutrition, play a major role – next to medical intervention – to conquer the above-mentioned challenge.
Hence, research at the Institute for Biomedicine of Aging (IBA) is focusing on the areas nutrition and physical activity in older persons and on the improvement of medical care for geriatric patients in a highly interdisciplinary manner.

Clinical nutrition in older persons
PI: D. Volkert
The section of Clinical Nutrition in Older Persons at the Institute for Biomedicine of Aging (IBA) investigates aspects of nutrition related to the maintenance of health and performance into old age and is involved in various national and international research projects with this topic.
In the second funding phase of the BMBF-funded Bavarian competence cluster of nutrition research "enable", an individualized multimodal intervention study was conducted in two nursing homes in Nuremberg to improve the nutritional situation of residents with malnutrition or risk for malnutrition. A senior-specific protein drink and a visually attractive and enriched texture-modified diet were used that had been developed in previous enable projects in collaboration with the Fraunhofer Institute for Process Engineering and Packaging (Freising) and the Weihenstephan-Triesdorf University of Applied Sciences. In addition, the comprehensive database of the enable cohorts was used for further evaluations, e.g. on protein intake and eating motives of older people.
On behalf of the German Nutrition Society (DGE), German data from the worldwide "nutritionDay" project of recent years were analyzed and a chapter on the nutritional situation in German hospitals and nursing homes based on this data was published in the 14th Nutrition Report of the DGE. Prospective international nutritionDay data were used to identify predictors of malnutrition in nursing home residents.
Furthermore, an update of the S3 guideline "Clinical Nutrition in Geriatrics" of the German Society for Nutritional Medicine (DGEM) was started in the reporting period in collaboration with leading German and Austrian experts. Based on the current European ESPEN guideline, recommendations on the prevention and treatment of dehydration are being developed and integrated for the first time.
PI: E. Kiesswetter
Within the BMBF-funded "Effective SLOPE" project, a systematic review with network meta-analysis is conducted to investigate differences in effects and risks of different lifestyle interventions among older people with obesity regarding physical function, body composition and other health-related aspects. Supplementary qualitative interviews were conducted to identify motives, barriers and support needs regarding weight reduction from the perspective of those affected.
In a validation study funded by the Karl-Düsterberg-Stiftung e.V., the suitability of the German translation of the short questionnaire Protein Screener 55+ for identifying low protein intake in community-dwelling older people was tested.
A sub-study of the EFI project "Human Body Odours: Exploring Chemical Signatures" started to analyze differences in body odour between healthy younger and older people.
In February 2020, a FAUconnect on the topic of "Nutrition - Exercise - Digital Health Innovative Intervention Pathways to Maintain Independence in an Aging Society" was organized by the IBA with participants from various FAU institutions as well as external multipliers.

Mobility and function
PI: E. Freiberger
The area of movement and function at the IBA is concerned with the promotion of movement and the preservation of functionality and independence in older people and is involved in various national and international projects.
Internationally, we were partners in the EU project SPRINTT (Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies), an intervention study against loss of muscle mass and physical functionality in older people. The SPRINTT consortium was composed of public and private partners from more than 20 institutions and 11 countries. The 123 elderly, sarcopenic individuals recruited at the study center in Nuremberg, Germany, participated in one of two interventions with and without regular physical activity until the end of 2019. The goal was to prevent loss of mobility as measured by the ability or time required to walk 400 meters continuously.
Another international activity was the participation in the Steering Committee of the "European Network for Action on Ageing and Physical Activity" (EUNAAPA), whose aim was to improve the cross-sectoral networking of organizations from the fields of physical activity, health and social affairs in order to be able to expand and optimize the physical activity offer for older people. Through the EUNAAPA network, the IBA was also involved in the EU project "PROMISS" and acted as a cooperation partner in the dissemination work package.
On a national level, we were involved in the BMBF-funded project PRO PRICARE ("PReventing Overtreatment in PRImary CARE"), which addressed medical overtreatment in older people. The IBA supported the implementation of a systematic review and an expert survey to develop a core set to describe the functional health of a person in general practice.
Also funded by the BMBF was the POWER project ("Prevention by Outdoor-Walking in the Elderly at Risk" under the direction of the General Medicine Department at the University of Marburg, Prof. Donner-Banzhoff). This investigates whether regular walking with the help of volunteers improves functionality in elderly people in nursing homes or assisted living. The IBA was involved in the study planning and supports the project with its expertise in an advisory capacity.
The ADAC Foundation funded two studies by the IBA. In SiFAr ("Safe cycling in old age"), an attempt has being made to improve the competence and safety of seniors over 65 years of age when riding a bicycle or e-bike. For this purpose, a three-month training program was used that combines bicycle-specific and motor exercises. The persistence of the effects will be followed for up to 24 months.
The second project was "Young and Old", which aimed to improve physical functionality through joint projects between nursing home residents and school students in cooperation with a school in Hessen. Due to the Corona pandemic, however, this project was first paused and finally had to be discontinued.
In an internal project, mobility and various gait parameters were assessed in independently living people aged 70 years and older with different levels of physical functioning.
In addition, in a cooperation with the Institute of

Psychogerontology of the FAU, the influence of aging images and place of supply on the commitment to physical activity, which is of great importance for older people to maintain independence, was investigated.
In addition, PD Dr. E. Freiberger was a member of the expert group that developed the expert standard for mobility in nursing care in 2020 (Deutsche Netzwerk für Qualitätsentwicklung in der Pflege /DNQP).
In cooperation with the Institute of Medical Physics, a study was conducted on the safety of training with whole-body electromyostimulation in both young (20-40 years) and older, frail (>75 years) subjects. Various biomarkers were measured closely during the eight-week intervention to show the adaptation to the current stimulus.

Clinical care for geriatric patients
PI: C.C. Sieber
The SCOPE project (Screening for Chronic Kidney Disease among Older People across Europe) is funded by the EU Horizon 2020 program and is being carried out in eight European centers. The two-year follow-up of independently living elderly people recruited in Regensburg and Nuremberg was completed in spring 2020. The data collected will be used to estimate the incidence of chronic kidney disease in the elderly and to develop recommendations for health-economically efficient screening for renal disease in geriatric patients.
The research project TIGER ("Transsectoral Intervention Program to Improve Geriatric Care in Regensburg") investigated whether the number of hospital readmissions can be reduced by providing targeted care that is continuous for 12 months after the transition from hospital to home. The background is the current discontinuity in the transition from inpatient to outpatient treatment. At present, many geriatric patients have only limited success in finding their way back into everyday life after being discharged from hospital, so that they are often quickly readmitted to hospital. Therefore, the need for integrated and cross-sector care for older patients is being increasingly recognized. The project was funded by the Federal Joint Committee (G-BA) as part of the Innovation Fund and has been carried out together with the Barmherzige Brüder Hospital in Regensburg, the Regensburg Physicians' Network, the Bavarian AOK, the German Geriatrics Association and the Institute for Nursing Science at Bielefeld University.

Teaching

The practical geriatric training (Q 7) of the Chair of Internal Medicine provides students with the requirements of medicine in old age. The compulsory elective subjects of the IBA are interdisciplinary with focuses on nutritional issues of older patients as well as physical activity and falls.
Several lectures and courses of the master degree course gerontology (Faculty of Humanities, Social Sciences, and Theology) are organized by the IBA.
IBA supervises Bachelor's and Master's theses as well as MD and PhD theses.

Selected publications
Volkert D, Weber J, Kiesswetter E, Sulz I, Hiesmayr M: Ernährungssituation in Krankenhäusern und Pflegeheimen – Auswertung der nutritionDay-Daten für Deutschland. In: Deutsche Gesellschaft für Ernährung (Hrsg): 14. DGE-Ernährungsbericht Kapitel 2. Bonn (2019) (https://www.dge.de/14-dge-eb/vvoe/kap2)

Ott A, Senger M, Lötzbeyer T, Gefeller O, Sieber CC, Volkert D. Effects of a texture-modified, enriched, and reshaped diet on dietary Intake and body weight of nursing home residents with chewing and/or swallowing problems: An *enable* Study. J Nutr Gerontol Geriatr. 2019 38: 361-376. doi: 10.1080/21551197.2019.1628158.

Seemer J, Kiesswetter E, Blawert A, Fleckenstein D, Gloning M, Bader-Mittermaier S, Sieber CC, Wurm S, Volkert D. An individualised nutritional intervention concept for nursing home residents with or at risk of malnutrition: An *enable* Study. Geriatrics (Basel). 2020 Dec 26;6(1):2. doi: 10.3390/geriatrics6010002

Britting S, Artzi-Medvedik R, Fabbietti P, Tap L, Mattace-Raso F, Corsonello A, et al. Kidney function and other factors and their association with falls. BMC Geriatrics. 2020;20(1):320.

Rempe HM, Sproesser G, Gingrich A, Spiegel A, Skurk T, Brandl B, et al. Measuring eating motives in older adults with and without functional impairments with The Eating Motivation Survey (TEMS). Appetite. 2019;137:1-20.

Drey M, Ferrari U, Schraml M, Kemmler W, Schoene D, Franke A, et al. German Version of SARC-F: Translation, Adaption, and Validation. J Am Med Dir Assoc. 2020.

International cooperations
Prof. Dr. Marjolein Visser, Stichting VU-VUMC, Amsterdam, The Netherlands,

Prof. Dr. Roberto Bernabei, Università Cattolica del Sacro Cuore, Rom, Italy,

Prof. Dr. Michael Hiesmayr, Medizinische Universität Wien, Wien, Austria,

Prof. Dr. Fabrizia Lattanzio, Istituto Nazionale Di Riposo E Cura Per Anziani INRCA, Ancona, Italy

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Research focus
- Retroviral infections
- Herpesviral infections
- Antiviral immunity

Structure of the Chair

Professorships: 4
Personnel: 132
- Doctors (of Medicine): 7
- Scientists: 17 (thereof funded externally: 13)
- Graduate students: 28

Clinical focus areas
- Serological, molecular biological, and virological diagnostics of viral infections
- Drug resistance testing
- Genotyping

Research

Despite substantial progress in our understanding of viral host cell interactions and the interplay between viruses and the immune system, there still is an unmet medical need for the prevention and therapy of persistent viruses and viruses of the respiratory tract. The research focus of the Institute therefore is to explore novel antiviral therapies and preventive measures that are based on molecular analyses of the interaction of viruses with the host cell and the immune system. Specificially, the Institute focused on the following topics:

SARS-CoV-2 Infection
PI: Prof. Dr. K. Überla[1], Prof. Dr. A. Ensser[2], Prof. Dr. T. Gramberg[3], Prof. M. Marschall[4], Prof. Dr. U. Schubert[5], Prof. Dr. M. Tenbusch[6]
In response to the COVID-19 pandemic, diagnostic tests were rapidly established, and a number of research projects were initiated. In a collaborative effort with Prof Jäck, human neutralizing antibodies to SARS-CoV-2 were developed and shown to have prophylactic and therapeutic efficacy in animal models. A seroprevalence study for the hotspot Tirschenreuth was performed together with Prof. Wagner from the University of Regensburg. Recombinant mutants of SARS-CoV-2 were generated that will be important for subsequent studies on virus host interaction and pathogenesis. Several drug candidates inhibiting SARS-CoV-2 replication in cell culture were identified, and their mechanisms of action and therapeutic potential is currently explored. Additional studies aim to get hints on the role of SARS-CoV-2 mutations occurring worldwide. Using animal models, the importance of mucosal immune responses after administration of viral COVID-19 vector and mRNA vaccines is also explored.

Retroviral infections
PI: Dr. A. Thoma-Kreß[1], Prof. Dr. U. Schubert[2], Prof. Dr. K. Überla[3], Prof. Dr. T. Gramberg[4]
Both human pathogenic retroviruses, human T-cell leukemia virus (HTLV) and human immunodeficiency virus (HIV), are the subject of extensive research by the Institute.
The first research group investigates mechanisms of cell-to-cell transmission of HTLV-1.The group identified molecular details of viral transmission and found new cellular players regulating the transport of viral proteins between cells. In the long term, the group aims at developing prevention strategies against mother-to-child transmission. Beyond, the HTLV-1 group studies the regulation of viral transcription.
The second research group investigates the role of small HIV-1 proteins in the pathogenesis of HIV-1, whereby it was shown that the p6 Gag protein represents the first known viral substrate for the insulin degrading enzyme (IDE). Thereby, p6 is ~100-fold more efficiently degraded by IDE than its eponymous substrate insulin. This phenomenon is regulated by the N-terminus of p6 and is specific for the pandemic HIV-1 group M isolates.
One of the questions addressed in the third research group is how intron-containing HIV-1 mRNAs are captured in the cell nucleus. A genome-wide screen using the CRISPR/Cas technology led to the identification of several spliceosome-associated proteins. The inactivation of the corresponding genes increased the cytoplasmic levels of the intron-containing genomic HIV-1 RNA up to 140-fold.
The fourth group focuses on the effects of intrinsic host restriction factors on viral replication and mobile genetic elements . Using knockout mice, the group showed that HIV restriction factor SAMHD1 also blocks MCMV replication in vivo and is counteracted by the viral kinase. Also, the group found that the antiviral factor TRIM5α restricts and senses LINE-1 retroelements and therefore protects the integrity of the host genome. In the field of diagnostics, the focus is on the development of phenotypic drug resistance tests for HIV-1.

Herpesviral infections
PI: Prof. Dr. M. Marschall[1], Prof. Dr. A. Ensser[2], PD Dr. B. Biesinger[3], PD Dr. F. Neipel[4], Prof. Dr. W. Doerfler[5]
The Institute is working on various cell biological aspects of herpesvirus infections.
The first research group studies the regulatory role of protein kinases (PKs) in the replication of human cytomegalovirus (CMV) and further herpesviruses and the utilization of PK inhibitors in antiviral therapy. PK activities play an important role in viral replication processes, such as the nuclear particle egress, interaction with the cell cycle and viral pathogenesis. A multifaceted regulatory contribution of the CMV-encoded PK pUL97, including a pUL97 interaction with cyclins, could be demonstrated. Further viral and cellular components of the nuclear egress complex (NEC) were identified by proteomics approaches and structure-function analyses led to its validation as an antiviral target. Very recently, the prototype of a NEC inhibitory small molecule could be reported.
In their search for antiviral restriction factors, the second group demonstrated that the centrosomal protein TRIM43 restricts herpesvirus infection by regulating nuclear lamina integrity. In a long standing cooperation with Prof. M. Lehner and Prof. W. Holter (Vienna), novel T cell based immunotherapies for CMV infections were investigated.
The third group investigates how oncoproteins of gamma herpesviruses are capable to transform human lymphocytes to permanent growth in culture. The viral oncoproteins interact with TNF receptor-associated factors (TRAF) to activate NF-kappaB, but also to inhibit interferon-inducing signaling pathways. Thereby, the viral oncoproteins may contribute to viral persistence.
The fourth laboratory is studying the oncogenic Kaposi sarcoma-associated herpesvirus (KSHV). The group could show that the Ephrin receptor tyrosinkinase A2 (EphA2) is a receptor for KSHV upon infection of endothelial and epithelial cells. In collaboration with the group of Prof. Felix Rey (Institute Pasteur) the group was able to clarify the structure of the gH/gL/EphA2 complex and experimentally identify single amino acids essential for the interaction. This knowledge is currently used to generate inhibitory antibodies.
The epigenetics group (5) has studied the worldwide rise of SARS-CoV-2 mutations. Analyses of sequences from GISAID revealed 10 frequent mutations in Covid-19 isolates up to late May. Between May to September and on to December 2020, numerous new mutations were selected, including multi-faceted variants from England, South Africa, and Brazil. Up to >50% of mutations were due to C to T transitions, likely caused by deaminases in the cellular APOBEC function. Hence, an antiviral shield seemed perverted to a mutagenic activity.
While herpesviruses are a frequent cause of encephalitis, a completely unexpected pathogen, Borna disease virus 1 (BoDV-1), could be detected by unbiased Next-Generation sequencing of brain tissue of a patient with fatal encephalitis of unknown origin, This was the first evidence demonstrating that BoDV-1, which is transmitted by shrews, is indeed pathogenic in humans.

Antiviral immunity
PI: Prof. Dr. M. Tenbusch[1], Prof. Dr. M. Mach[2],

Prof. Dr. K. Überla[3], PD Dr. V. Temchura[4]
The first research group is developing novel gene-based immunization strategies against viral respiratory tract infections and analyse the important role of local immunity at the mucosal entry site of the pathogens. Potent antigen-specific lung-resident memory T-cells induced by mucosally applied vector vaccines provide efficient protection against a broad panel of influenza A Viruses, the respiratory syncytial virus and most probably against SARS-CoV-2 as well. Furthermore, serological tests for the detection of different immunoglobulin subclasses against Influenza, RSV and SARS-CoV-2 have been established.
The second laboratory has continued its efforts in isolating and defining the mechanisms of protective antibodies against the fusion protein gB of HCMV. By utilizing a panel of virus-neutralizing gB-specific monoclonal antibodies (MAbs), it was demonstrated that syncytium formation of an intrinsically fusion-active gB/VSV-G chimera was inhibited by only a subset of neutralizing MAbs, which target a distinct antigenic domain of gB. This observation argues for differential modes of action of neutralizing anti-gB MAbs and suggests that blocking the membrane fusion function of gB could be one mechanism of antibody-mediated virus neutralization.
The third research group investigates mechanisms of adaptive immunity against HIV and aims at the development of HIV vaccines. The group was able to show in a highly relevant animal model that antibodies against HIV are able to prevent the infection of the very first cells. For vaccine development, the group uses gene-based immunization methods, liposomal vaccines, nanoparticles, and virus particle vaccines. One approach is to exploit T helper cell responses induced by already approved vaccines to optimize the antibody response to the HIV Env protein. The aim of further work is to characterize the influence of HIV infection on vaccine-induced immune responses.
The fourth working group uses B- and T-cell receptor transgenic mice to investigate the influence of nano-particulate vaccine candidates and immunomodulating substances on the activation and differentiation of antigen-specific B cells and follicular T helper cells. The further goal is to characterize the applications of antiviral nano-particulate vaccines to improve antibody responses in small animal models.

Teaching

Curricular lectures and courses on infectiology and immunology for students of Medicine, Dentistry, Pharmacy, and Molecular Medicine are jointly given by the Institute of Clinical and Molecular Virology and the Institute of Clinical Microbiology, Immunology, and Hygiene. In collaboration with further colleagues from theUK Erlangen as well as from Würzburg and Nuremberg, members of the Institute engage in the interdisciplinary course on infectiology and immunology (Q4). Furthermore, the Institute of Clinical and Molecular Virology offers a series of elective and compulsory optional courses for students of the Faculty of Medicine and the Faculty of Sciences. Thus, teaching in virology extends to the B.Sc. und M.Sc. degree programs in Molecular Medicine, Integrated Immunology, Biology, Integrated Life Sciences and Molecular Sciences.
The course offerings are completed by the supervision of Bachelor's, Master's, MD, and PhD theses, amongst others as part of a structured programme within the research training grant GRK2504 "Novel antiviral approaches".

Selected publications

Deutschmann J, Schneider A, Gruska I, Vetter B, Thomas D, Kießling M, Herrmann A, Wittmann S, Schindler M, Milbradt J, Ferreirós N, Winkler TH, Wiebusch L, Gramberg T. A viral kinase counteracts in vivo restriction of murine cytomegalovirus by SAMHD1. Nat Microbiol 2019; 4:2273-228.

Donhauser N, Socher E, Millen S, Heym S, Sticht H, Thoma-Kress AK. Transfer of HTLV-1 p8 and Gag to target T-cells depends on VASP, a novel interaction partner of p8. PLoS Pathog 2020; 16(9):e1008879.

Full F, van Gent M, Sparrer KMJ, Chiang C, Zurenski MA, Scherer M, Brockmeyer NH, Heinzerling L, Stürzl M, Korn K, Stamminger T, Ensser A, Gack MU. Centrosomal protein TRIM43 restricts herpesvirus infection by regulating nuclear lamina integrity. Nat Microbiol 2019; 4:164-176.

Klessing S, Temchura V, Tannig P, Peter AS, Christensen D, Lang R, Überla K. CD4+ T cells induced by tuberculosis subunit vaccine H1 can improve the HIV-1 Env humoral response by Intrastructural Help. Vacccines (2020); 8: 604; doi:10.3390/vaccines8040604.

Lapuente D, Maier C, Irrgang P, Hübner J, Peter AS, Hoffmann M, Ensser A, Ziegler K, Winkler TH, Birkholz T, Kremer AE, Steininger P, Korn K, Neipel F, Überla K, Tenbusch M. Rapid response flow cytometric assay for the detection of antibody responses to SARS-CoV-2. Eur J Clin Microbiol Infect Dis 2020; Oct 20:1-9. doi: 10.1007/s10096-020-04072-7. Online ahead of print.

Muller YA, Häge S, Alkhashrom S, Höllriegl T, Weigert S, Dolles S, Hof K, Walzer SA, Egerer-Sieber C, Conrad M, Holst S, Lösing J, Sonntag E, Sticht H, Eichler J, Marschall M. High-resolution crystal structures of two prototypical β- and γ-herpesviral nuclear egress complexes unravel the determinants of subfamily specificity. J Biol Chem 2020; 295: 3189-3201.

International cooperations

Prof. Dr. Jan Gettemans, University of Ghent, Belgium

Prof. Felix Rey, Institute Pasteur, France

Prof. J. Ung Jung, University of Southern California, Los Angeles: USA

Prof. W.D. Rawlinson, Virology, University of New South Wales, Sydney: Australia

Prof. Dr. D. Burton, Scripps Research, La Jolla: USA

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Research focus

- Mechanism of pathogenic protein cross-seeding in neurodegenerative disorders (Cross- Seeds)
- Characterization of the contribution of trans-glutaminase 6 to Huntington's and Alzheimer's disease
- Examination of behavioral abnormalities in rats after injection with gadolinium based contrast agents: Neurobehavioral findings resulting from experiments
- Characterization of the role of glutaminyl-cyclase and its isoform during Huntington's disease
- Potentiation of Neuropeptide Y mediated effects in stress-associated and neurodegenerative disorders via NPY-degradation inhibitors
- Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition

Structure of the Division

Professorship: 1
Personnel: 7

- Doctor (of Medicine): 1
- Scientist: 1
- Graduate students: 4

Special structural features

- Location within the Preclinical Experimental Animal Center (PETZ)
- Contribution to services and teaching offered by PETZ

Research

Research is focused on experimental therapeutic studies in animal models of human neurodegenerative and psychiatric disorders (Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), Spinocerebellar ataxia type 17, Schizophrenia, stress-induced disorders, attention deficit hyperactivity disorder). After comprehensive phenotyping of a certain disease model, we search for, characterize, and target post-translational protein-modifications by transglutaminases, dipeptidyl-peptidase 4, glutaminyl-cyclase and its isoform ultimately trying to identify novel interventional approaches. A present focus is on neurodegenerative processes in the course of protein aggregation disorders.

Mechanisms of pathogenic protein cross-seeding in neurodegenerative disorders (Cross-Seeds)
This project is based on the hypothesis that a number of brain disorders, including AD, PD, and HD, share common pathogenic mechanisms leading to neurodegeneration. A traditional view on these devastating disorders focuses on individual, disease-specific enzymes and/or aggregating proteins contributing to aspects of neuropathology. Here, we combine interdisciplinary approaches to identify cross-disease pathways leading to pathogenic protein aggregation. All three clinical conditions addressed have at least one feature in common: Aggregation of pathogenic proteins associated with neurodegeneration. We use mice and rats transgenic for AD, PD, and HD in order to screen for cross disease protein aggregation between the pathogenic proteins.

Characterization of the contribution of transglutaminase 6 to Huntington's and Alzheimer's disease
Mammalian transglutaminases (TG) catalyze calcium-dependent irreversible post-translational modifications of proteins and their enzymatic activities contribute to the pathogenesis of several human neuro-degenerative diseases. Our overall hypothesis is that the neuronal isoform of transglutaminases, transglutaminase 6, significantly contributes to protein aggregation in HD and AD. TG6 may interact with polyglutamine (HTT) or amyloid-precursor-derived (Aß) proteins inducing posttranslational modifications via trans-glutaminase-catalyzed intermolecular crosslinks resulting in stable, rigid, and insoluble protein complexes. Focusing on the role of TG6 in HTT and Aß aggregation *in vitro* and *in vivo*, we therefore study TG6 expression and function in HD/AD cell culture systems, transgenic mouse and rat models including novel loss-of-function mutant mice (TG6ko mice). We expect deeper insight into the role of TG6 in the CNS and particular into TG6 dependent mechanisms contributing to HTT/Aß aggregation potentially identifying targets and novel therapeutic approaches in neurodegenerative disorders.

Examination of behavioral abnormalities in rats after injection with gadolinium based contrast agents: Neurobehavioral findings resulting from experiments
The objective of this study was to investigate the potential effect of a signal intensity (SI) increase and the presence of Gadolinium (Gd) in the brain after repeated administration of the Gd-based contrast agents (GBCAs) Omniscan and Gadovist on general health, motor coordination, anxiety-related behaviors as well as cognition. GBCAs represent a family of aminopolyarboxylic acid ligands chelated to gadolinium and are commonly used in patients for T1-weighted magnetic resonance imaging (MRI) for diagnostic purpose. Since a few years it is known that repeated administration of some, but not all GBCAs, is associated with T1-weighted signal intensity increase in the deep cerebral nuclei dentate nucleus and globus pallidus of the patients. Genesis, clinical consequences, reversibility, and potential comorbidity of this Gd-accumulation is not known yet. The American Food and Drug Administration as well as the European Medicines Agency prompted all manufacturer of GBCAs to investigate potential functional consequences of this Gd-accumulation.

Characterization of the role of glutaminyl-cyclase and its isoform during Huntington's disease
Aim of the present project is to investigate the role of glutaminyl-cyclase (QC) and iso-glutaminyl-cyclase (isoQC) during the neuropathological processes associated with HD in the rodent brain. Among other approaches, HD transgenic animals are phenotyped and the impact of the enzyme glutaminy-cyclase (QC) and its isoform (isoQC) is characterized after cross- breeding with QC and isoQC knockout-mice. Furthermore, experimental therapy by active immunization against QC/isoQC posttranslational modified huntingtin fragments is performed.

Potentiation of Neuropeptide Y mediated effects in stress-associated and neurodegenerative disorders via NPY-degradation inhibitors
The concept of stress protection in the CNS via potentiation of endogenous stress-protective signaling is neither fully explored nor clinically translated. Neuropeptide Y (NPY) exerts many stress and neuroprotective actions in the brain and may well be pharmacologically modulated by inhibiting the corresponding enzymatic degradation. In addition, neurodegenerative disorders such as HD may benefit from such approaches. Surprisingly, in the degenerating striatum of HD patients, those medium spiny neurons expressing NPY survive. We will analyze this endogenous NPY-based neuroprotection in animal models of HD. Genetic and pharmacological inhibition of the NPY-degrading enzyme dipeptidyl-peptidase IV will be used to develop a novel HD delaying approach via inhibitor-mediated potentiation of NPY-mediated neuroprotection.

Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition
HD is an autosomal dominant neuro-degenerative disorder caused by expanded CAG repeats in the huntingtin gene. Although mutant HTT is expressed during embryonic development and throughout life, clinical HD usually manifests later in adulthood. A number of studies

document neurodevelopmental changes associated with mutant HIT, but whether these are reversible under therapy remains unclear. We identify very early behavioral, molecular, and cellular changes in preweaning transgenic HD rats and mice. Interventional treatment of this early phenotype with the histone deacetylase inhibitor (HDACi) LBH589 led to significant improvement in behavioral changes and markers of dopaminergic neurotransmission and complete reversal of aberrant neuronal differentiation *in vitro* and *in vivo*. Our data support the notion that neurodevelopmental changes contribute to the prodromal phase of HD and that early, presymptomatic intervention using HDACi may represent a promising novel treatment approach for HD.

Teaching

The Division of Experimental Therapy contributes to the international degree program Molecular Medicine as well as to electives in Medicine. Our seminar on interdisciplinary preclinical studies using animal models of human disorders is much appreciated.
We supervise Bachelor's and Master's theses as well as MD and PhD theses in the fields of neurobiology and neuropathophysiology of neurodegenerative diseases.

Selected publications

Habermeyer J, Boyken J, Harrer J, Canneva F, Ratz V, Moceri S, . . . von Horsten S. (2020). Comprehensive phenotyping revealed transient startle response reduction and histopathological gadolinium localization to perineuronal nets after gadodiamide administration in rats. Sci Rep, 10(1), 22385.

Dietrich P et al. (2020). Molecular crosstalk between Y5 receptor and neuropeptide Y drives liver cancer. J Clin Invest, 130(5), 2509-2526.

Cheong RY, Tonetto S, von Horsten S, & Petersen A. (2020). Imbalance of the oxytocin-vasopressin system contributes to the neuropsychiatric phenotype in the BACHD mouse model of Huntington disease. Psychoneuroendocrinology, 119, 104773.

Konig C, Plank AC, Kapp A, Timotius IK, von Horsten S, & Zimmermann K (2020). Thirty Mouse Strain Survey of Voluntary Physical Activity and Energy Expenditure: Influence of Strain, Sex and Day-Night Variation. Front Neurosci, 14, 531.

Timotius, I. K., Moceri, S., Plank, A. C., Habermeyer, J., Canneva, F., Winkler, J., . . . von Horsten, S. (2019). Silhouette-Length-Scaled Gait Parameters for Motor Functional Analysis in Mice and Rats. eNeuro, 6(6).

Post JI, et al. (2019). Differential Levels and Phosphorylation of Type 1 Inositol 1,4,5-Trisphosphate Receptor in Four Different Murine Models of Huntington Disease. J Huntingtons Dis, 8(3), 271-289.

Minakaki, G et al. (2019). Treadmill exercise intervention improves gait and postural control in alpha-synuclein mouse models without inducing cerebral autophagy. Behav Brain Res, 363, 199-215.

Hartlage-Rubsamen M et al. (2019). Endogenous mouse huntingtin is highly abundant in cranial nerve nuclei, co-aggregates to Abeta plaques and is induced in reactive astrocytes in a transgenic mouse model of Alzheimer's disease. Acta Neuropathol Commun, 7(1), 79.

International cooperations

Dr. A.P. Osmand, Department of Biochemistry and Cellular and Molecular Biology, University of Tennessee, Knoxville: USA

Dr. S. Hunot, Brain & Spine Institute (ICM), Pierre et Marie Curie University, Paris: France

Dr. Å. Petersén, Translational Neuroendocrine Research Unit, Lund University, Lund: Sweden

Prof. Dr. J.G. Bjaalie, Institute of Basic Medical Sciences, University of Oslo: Norway

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Research focus
- Regulation of innate immunity in infection and inflammation
- Innate immunity, macrophages, arginase, and NO synthase
- Genetic and bacterial factors in chronic inflammation
- Pathogenicity of Coxiella burnetii
- Microbial phosphatases
- Innate lymphocytes and tumor necrosis factor in leishmaniasis
- Molecular biology of malaria
- Molecular mycology
- Innate checkpoints of T cell regulation
- Pathogenicity of Salmonella and microbiome analyses

Structure of the Chair

Professorships: 4
Personnel: 93
- Doctors (of Medicine): 10
- Scientists: 12 (thereof funded externally: 1)
- Graduate students: 15

Clinical focus areas
- Accredited clinical-microbiological diagnostics division
- Around the clock microbiological on-call service and emergency diagnostic testing
- Clinical infection related ward rounds for critical cases on the wards of the UK Erlangen
- Accredited hygiene laboratory
- Hospital hygiene related consultation and assistance of the UK Erlangen
- University outpatients' clinic for vaccination and travel medicine

Research

The different research groups of the Institute of Clinical Microbiology, Immunology, and Hygiene study the innate and adaptive immune response during infectious diseases, investigate mechanisms of microbial virulence, and analyze the regulation of basic inflammatory processes, using immunological, cell-biological, and molecular techniques. Various infectious disease models are studied which include infections with bacteria (Coxiella, Listeria, Mycobacteria, Salmonella), protozoa (Leishmania, Plasmodia) and fungi (Aspergillus). The Institute is fully equipped with laboratories, a hypoxia chamber for *in vitro* analyses, fluorescence and confocal laser scanning microscopes, real-time PCR machines, analytical fluorescence activated cell sorters (FACS) for flow cytometry, imaging systems and a next generation sequencing machine.

Regulation of innate immunity in infection and inflammation
PI: Prof. Dr. R. Lang
The question driving our research is how the immune system generates resistance to infection without causing excessive inflammation. We recently showed a pivotal role of TLR-MyD88 in sensing of *Coxiella burnetii* and established a mouse model for studying Q fever in vivo. *Mycobacterium tuberculosis* is another important intracellular pathogen. We have discovered that the cord factor of the mycobacterial cell wall activates macrophages through the MINCLE-SYK-CARD9 pathway, leading to strong Th17 immunity. Dissecting Mincle activation by microbial glycolipids and identification of signaling and transcription factors involved has been a focus of the lab. We are now investigating the functional consequences of CLR regulation by the cytokines IL-4 and TNF. In addition, the role of TDM-Mincle signaling in immune evasion by mycobacteria is addressed in ongoing work.

Innate immunity, macrophages, arginase, and NO synthase
PI: Prof. Dr. C. Bogdan
Nitric oxide (NO), which is synthesized from the amino acid L-arginine by the interferon (IFN)-γ inducible NO synthase (iNOS) in macrophages and other cells, is essential for the defense against intracellular pathogens and a central regulator of the immune system. The enzyme arginase can inhibit the enzymatic activity of iNOS because it competes for the same substrate. Additionally, the arginase reaction allows the synthesis of polyamines that are crucial for cellular growth and differentiation. Ongoing research work of the group focuses on the questions, by which mechanisms host cell and/or parasite arginase contribute to disease development in cutaneous leishmaniasis (*L. major, L. mexicana*) and to the lifelong persistence of *Leishmania* and thereby prevent resolution of the infection. In another project, the group analyses the interaction between iNOS/arginase and iron metabolism and the antimicrobial and immunoregulatory function of reactive chlorine intermediates.

Genetic and bacterial factors in chronic inflammation
PI: Prof. Dr. J. Mattner
Autoimmune responses and inflammatory processes in the intestine and the liver result from complex interactions of genetic, predisposing factors, and distinct environmental cues. Although the autoantigens targeted by the immune system are often ubiquitously expressed in the body, the inflammatory processes are frequently tissue-specific. In this context, the group investigates the genetic and immunological factors (e.g., CD101, Arginase 1 and 2) that govern the immune responses in the intestine and the liver. Furthermore, we analyze the role of microbial antigens in the development of autoimmune responses by applying targeted gene deletion strategies.

Pathogenicity of *Coxiella burnetii*
PI: PD Dr. A. Lührmann
The obligate intracellular bacterium *Coxiella burnetii* is causing Q fever in humans. This zoonotic disease is characterized by a flu-like illness, but can progress to an atypical pneumonia. In rare cases, this disease can become chronic, which mainly manifests itself as endocarditis. The research group aims to clarify how *C. burnetii* infection develops into chronic inflammation. To obtain insights into the pathogenicity of *C. burnetii*, we are analyzing host cell factors and bacterial virulence factors that are necessary for the establishment of the replicative *C. burnetii*-containing vacuole. Additionally, we are investigating the molecular activity of *C. burnetii* virulence factors, in particular those with anti-apoptotic activities, i.e. AnkG.

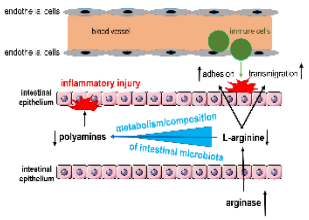

Figure: Overview over the pathological changes in the gut induced by arginase expression and subsequent L-arginine deficiency. The consumption of L-arginine by arginase lowers the diversity of the intestinal microbiota and the production of polyamines resulting in an augmented adhesion and extravasation of inflammatory immune cells and accelerated intestinal epithelial injury. (Adapted from Baier et al., JCI 2020)

Microbial phosphatases
PI: Dr. D. Soulat
Human pathogens have developed numerous strategies to invade their host cell targets. One important virulence mechanism is the secretion of proteins that interfere with host cell signaling (e.g. microbial phosphatases). Pathogen-secreted phosphatases are able to hijack the cellular immune response in a manner that leads to the creation of a pathogen-friendly environment inside the infected host. The research group currently works with two human pathogens: (a) the bacterium *Listeria monocytogenes* causing food-borne disease

and (b) the causative agent of cutaneous leishmaniasis, *Leishmania major*.

Innate lymphocytes and tumor necrosis factor in leishmaniasis
PI: PD Dr. U. Schleicher
Innate lymphocytes contribute to the immune response against Leishmania parasites. In the mouse models of cutaneous and visceral leishmaniasis, the group investigates which of the different subpopulations of the so-called innate lymphoid cells (ILC) is relevant for the defense against Leishmania and by which signals effector functions of ILC are activated and regulated. The prevalence and activation of these cells by Leishmania is also studied in the human system. Furthermore, the group is interested in understanding which protective mechanisms mediated by the cytokine tumor necrosis factor are crucially involved in the healing process of *Leishmania major* infections. Particularly, the role of non-hematopoietic cells is addressed.

Molecular biology of malaria
PI: Dr. M. Petter
Malaria pathogenesis relies on various cellular processes in the life cycle of malaria parasites that each represent promising targets for therapeutic interventions and vaccine development. These include host cell invasion, the expression of virulence factors, and the differentiation of sexual stages that are transmitted by the vector, the Anopheles mosquito. The research group is interested in understanding the molecular mechanisms governing the transcriptional control of these vital processes, focusing on the functional and mechanistic characterization of chromatin-associated proteins such as the bromodomain protein PfBDP1, which contributes to epigenetic gene regulation in malaria parasites by binding to acetylated histones.

Molecular mycology
PI: Prof. Dr. S. Krappmann
Infections with the omnipresent molds of the genus *Aspergillus* and especially with *A. fumigatus* represent a life-threatening complication for immunocompromised patients. Research efforts in this group aim at the characterization of fungal-specific virulence determinants, such as its metabolic versatility or secreted effectors that support infection of a susceptible host by A. fumigatus. Furthermore, the sexual cycle of this ascomycete and its impact on fungal secondary metabolism is investigated. Most recent research efforts in collaboration with Prof. Dr. D. Vöhringer (Division of Infection Biology) aim to elucidate the interplay of *A. fumigatus* with eosinophils, which are relevant in the context of allergic reactions to this fungus.

Innate checkpoints of T cell regulation
PI: Dr. Christian Schwartz
Innate immune cells initiate and shape adaptive immune responses to infections and inflammatory stimuli. Programmed death ligand 1 (PD-L1) is a major regulator of T cell responses – with both inhibitory and activating properties. Different innate immune cells including dendritic cells, macrophages, and type 2 innate lymphoid cells, express PD-L1 and interact with T helper cells. We are investigating the cell-specific function of this immune checkpoint molecule during type 2-biased immune responses found in adipose tissue homeostasis and helminth infections. Furthermore, we study the microbial factors that regulate PD-L1 expression on innate cells during inflammation.

Pathogenicity of Salmonella and microbiome analyses
PI: Dr. R. Gerlach
Salmonellosis is one of the most common bacterial infectious diseases worldwide and in Germany. The research group investigates molecular mechanisms underlying the pathogenicity of Salmonella enterica. In particular, bacterial secretion systems are in focus. Secretion systems play a crucial role in pathogenicity, as Salmonella uses these structures and their substrates to interact with host cells and other bacteria. Furthermore, the research group investigates the influence of host-specific environmental factors on the regulation and function of Salmonella virulence factors. Environmental signals, such as decreased oxygen, play a crucial role in host cell recognition as well as successful adaptation of bacteria to different habitats within the host. For successful colonization, Salmonella and other pathogens must also overcome the barrier function established by the host microbiota. Therefore, another focus of the research group is the analysis of the microbiota composition of humans and using animal models in health and infectious disease.

Teaching

The Institute offers lectures and teaching courses for students of Medicine, Dental Medicine, Molecular Medicine, Biology, and Pharmacy. Particularly noteworthy is the main lecture on immunology within the master degree program Molecular Medicine, the teaching modules within the elite master degree program "Integrated Immunology" and the teaching of the interdisciplinary subject "Infectious Diseases and Immunology" within the clinical part of the training of medical students. In cooperation with the Institute of Clinical and Molecular Virology, our Institute organizes continuous medical education lectures on various infectious diseases for local physicians.
We supervise Bachelor's and Master's theses as well as MD and doctoral theses.

Selected publications
Hayek I, Fischer F, Schulze-Lührmann J, Dettmer K, Sobotta K, Schatz V, Kohl L, Boden K, Lang R, Oefner PJ, Wirtz S, Jantsch J, Lührmann A. (2019) Limitation of TCA-cycle intermediates represents an oxygen-independent nutritional antibacterial effector mechanism of macrophages. Cell Reports 26: 3502-3510.

Saunders SP, Floudas A, Moran T, Byrne CM, Rooney MD, Fahy CMR, Geoghegan JA, Iwakura Y, Fallon PG, Schwartz C. Dysregulated skin barrier function in Tmem79 mutant mice promotes IL-17A-dependent spontaneous skin and lung inflammation. Allergy. 2020 Jul 9;75(12): 3216-3227.

Paduch K, Debus A, Rai B, Schleicher U*, and Bogdan C*. (2019). Resolution of Cutaneous Leishmaniasis and Persistence of Leishmania major in the Absence of Arginase 1. J Immunol 202(5):1453-1464

Binder J, Shadkchan Y, Osherov N, Krappmann S. The essential thioredoxin reductase of the human pathogenic mould Aspergillus fumigatus is a promising antifungal target. Front Microbiol 2020, 11: 1383

Tang J., Chisholm S.A., Yeoh L.M., Gilson P.R., Papenfuss A.T., Day K.P., Petter M. and Duffy M.F. 2020. Histone modifications associated with gene expression and genome accessibility are dynamically enriched at Plasmodium falciparum regulatory sequences. Epigenetics Chromatin. 13. 1: 50

Schick, J., J. Schafer, C. Alexander, S. Dichtl, P. J. Murray, D. Christensen, U. Sorg, K. Pfeffer, U. Schleicher, and R. Lang. 2020. Cutting Edge: TNF Is Essential for Mycobacteria-Induced MINCLE Expression, Macrophage Activation, and Th17 Adjuvanticity. Journal of immunology 205: 323-328

International cooperations
Dr. R. Ostuni, San Raffaele Telethon Institute for Gene Therapy, Milano: Italy

Paul A. Beare (Coxiella Pathogenesis Section, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana, USA

Prof. N. Osherov, Sackler School of Medicine, Tel-Aviv University: Israel

Prof. G. Weiss, University of Innsbruck, Innsbruck: Austria

Prof. Dr. L. Wicker, University of Oxford – Medical Sciences Division, UK

Dr. G. Superti-Furga, Research Center for Molecular Medicine or the Austrian Academy of Science, Vienna, Austria.

Prof. P. Fallon, Trinity Biomedical Sciences Institute, School of Medicine, Trinity College Dublin, Dublin, Ireland

Dr. M. Duffy, University of Melbourne

Prof. P. Andersen, Statens Serum Institut, Copenhagen, Denmark

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Division of Infection Biology

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Research Focus

- Immune response against helminths and allergens
- Functionality and plasticity of memory-like T cells
- Role of dendritic cells for maintenance of immunological tolerance
- IgE response and germinal center reaction

Structure of the Division

Professorships: 1
Personnel: 13
- Scientists: 2 (thereof funded externally: 2)
- Graduate students: 9

Research

The research focus at the Division of Infection Biology aims at characterizing the immune responses against helminths and viruses. In addition, the regulation of immunological tolerance against self-antigens and resolution of inflammation are investigated. We use a variety of infection models and genetically modified mouse strains to dissect the mechanisms that regulate protective immunity and tolerance.

Immune response against helminths and allergens

Main focus of the research activities is the characterization of type 2 immune responses which are elicited by parasitic worms (helminths) and allergens. In both situations, the immune system reacts with an increase in Th2 cells, type 2 innate lymphoid cells (ILC2), mast cells, eosinophils, basophils, and production of IgE. Infection of genetically modified mice with helminths can be used as a model to study the complex interaction between different cell types that orchestrate and execute type 2 immune responses. Work at the Division of Infection Biology during the last year could demonstrate that release of IL-4/IL-13 from basophils plays an important role for protective immunity against different gastrointestinal helminths. These results are based on studies with mixed bone marrow chimeras. We observed that basophils play an important role for protective immunity against helminths especially during secondary infections. Basophils can be efficiently activated by Fc receptors to which helminths-specific antibodies bind. These helminths-specific antibodies are probably generated by long-lived plasma cells that were induced by the primary infection and constitute the immunological memory function. It further became apparent that basophils are essential for chronic allergic inflammation of the skin. This pathologic condition can be induced by passively sensitizing basophils with haptenspecific IgE, followed by antigen-mediated IgE crosslinking. As shown by others before, mast cells are not required for this inflammatory response. The mechanisms that regulate protective and pathological functions of basophils are subject of our current investigations.

Role of the ITT-motif in the cytoplasmic tail of the IgE B cell receptor (BCR) for regulation of the IgE response.

IN a projected funded by the transregio SFB TRR130 we investigated in collaboration with Niklas Engels and Jürgen Wienands (Uni Göttingen) the role of the ITT-motif within the cytoplasmic tail of the IgE-BCR. We compared the primary and secondary immune response against the helminth Nippostongylus brasiliensis in wild-type and mutant mice, in which the cytoplasmic tail of the IgE-BCR was either deleted or the ITT-motif within the tail was inactivated. We could show that the ITT-motif promotes IgE-BCR surface expression and accumulation of IgE-producing plasma cells. Now we go on to characterized the signaling capacity of the IgE-BCR on plasma cells.

Identification of STAT6-regulated genes and proteins in B cells

We recently demonstrated that the transcription factor STAT6 in B cells plays an important role for the germinal center reaction. Following up on this result we performed comparative transcriptome and proteome analysis of wild-type and STAT6-deficient B cells. We observed that more than 200 mRNAs were up-regulated more than 3-fold in a STAT6-dependent manner, and 149 mRNAs were more than 3-fold down-regulated. In collaboration with Prof. Warscheid (Uni Freiburg) we demonstrated that expression of most of the STAT6-dependent proteins is regulated at the transcriptional level. We currently work on the functional characterization of some of the genes identified in this screening. In addition, we generated transgenic mice which express a constitutively active form of STAT6 in B cells. We currently characterize these CD19Cre_STAT6vt mice to gain a better understanding of the function of STAT6 in B cells. B cells of CD19Cre_STAT6vt mice express more CD23 (low-affinity IgE receptor) on the cell surface and a higher frequency of germinal center B cells expresses IgG1. These mice will now be analyzed afer infection with Lymphocytic Choriomeningitis Virus (LCMV) to determine whether constitutively active STAT6 can promote class switch recombination to IgG1 and IgE in this viral infection model.

Regulation of the mold fungus Aspergillus fumigatus-elicited allergic lung inflammation

In collaboration with Sven Krappmann (FAU Erlangen-Nürnberg) we investigated the role of Th2 cells and eosinophils in a mouse model of allergic lung inflammation. We observed that repeated intranasal administration of low amounts of A. fumigatus spores resulted in massive infiltration of eosinophils which was dependent on IL-4/IL-13 secretion from Th2 cells. On the other hand we noticed that eosinophils promote the accumulation of Th2 cells in the lung parenchyma. Currently we investigate the direct interaction between *A. fumigatus* and eosinophils in a DFG-funded project.

Regulation of protective immunity against helminths by STAT6 in gastrointestinal epithelial cells

The role of intestinal epithelial cells for expulsion of helminths is poorly understood. Infection of mice with the gastrointestinal helminth Nippostrongylus brasiliensis results in a STAT6-dependent increase of goblet cells, tuft cells and Paneth cells in the small intestine. To intestigate whether expression of activated STAT6 in intestinal epithelial cells is sufficient for protective immunity against helminths, we generated VilliniCre_STAT6vt mice that express constitutively active STAT6 in intestinal epithelial cells. These mice show a very efficient immune response even in the absence of T cells. Based on these results we will identify and characterize STAT6-regulated genes in intestinal epithelial cells.

Identification and depletion of alternatively activated macrophages

We generated a mouse line to visualize RELMα-expressing cells in tissues by expression of a fluorescent protein. RELMa is mainly expressed in alternatively activated macrophages (AAM) and the reporter mice help to identify these cells by histology and flow cytometry. We observed that in naïve mice AAMs are mainly localized in adipose tissue, the peritoneal cavity and intestinal tissue. By generating mice that allow us to selectively deplete RELMα-expressing macrophages we could show that AAMs are required for protection against secondary N. brasiliensis infection and prevention of an overshooting inflammatory response in the lung.

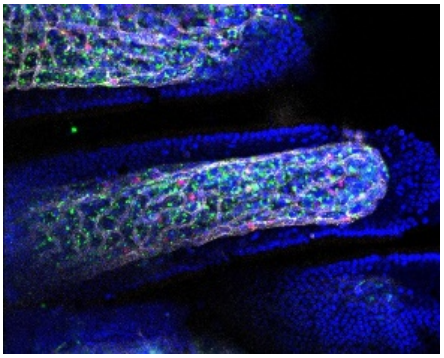

Fig. 1: Immune fluorescence staining from the small intestine of RELMα reporter mice. Grey: endothelial cells (anti-CD31), green: macrophages (anti-CD68), red: RELMα-tdTomato, blue: DAPI.

Teaching

The Division of Infection Biology offers lectures, seminars and teaching courses for students of medicine and molecular medicine as well as various teaching modules of the Faculty of Natural Sciences. Bachelor's and Master's theses are supervised as well as PhD theses.

Selected Publications

Schubart C, Krljanac B, Otte M, Symowski C, Martini E, Günther C, Becker C, Daniel, C, and Voehringer D. 2019. Selective expression of constitutively activated STAT6 in intestinal epithelial cells promotes differentiation of secretory cells and protection against helminths. Mucosal Immunol 12:413-424

Eberle JU*, Radtke D*, Nimmerjahn F, and Voehringer D. 2019. Eosinophils Mediate Basophil-Dependent Allergic Skin Inflammation in Mice. J Invest Dermatol 139:1957-1965.

Krljanac B, Schubart C, Naumann R, Wirtz S, Culemann S, Krönke G, and Voehringer D. 2019. RELMα expressing macrophages protect from fatal lung damage and reduce parasite burden during helminth infection. Sci Immunol May 24;4(35).

Symowski C and Voehringer D. 2019. Th2 cell-derived IL-4/IL-13 promote ILC2 accumulation in the lung by ILC2-intrinsic STAT6 signaling. Eur. J. Immunol. 49:1421-1432.

Schmitt MER, Lutz J, Haase P, Bösl M, Wienands J, Engels N, Voehringer D. 2020. The B cell antigen receptor of IgE-switched plasma cells regulates memory IgE responses. J Allergy Clin Immunol 146:642-651.

Dietschmann A, Schruefer S, Krappmann S, and Voehringer D. 2020. Th2 cells promote eosinophil-independent pathology in a murine model of allergic bronchopulmonary aspergillosis. Eur. J. Immunol. 50:1044-1056.

International Cooperations

Dr. Benjamin Dewals, University of Liége, Liége, Belgien

Dr. Jessica Strid, Imperial College London, London, UK

Dr. J. Kitaura, Universität Tokio, Tokio, Japan

Dr. Andrew McKenzie, MRC Cambridge, Cambridge, UK

Dr. Padraic Fallon, Trinity College Dublin, Dublin, Ireland

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Research focus
- Signal transduction of cardiac rhythmogenesis and hypertrophy
- HCN channels in the nervous system
- Regulation of renal function
- Pharmacological fMRI imaging

Structure of the Chair

Professorships: 2
Personnel: 23
- Scientists: 9
- Graduate students: 5

Special structural feature
The position of the executive director of the Institute rotates between the Chair of Pharmacology and Toxicology and the Chair of Clinical Pharmacology and Clinical Toxicology on a two-year basis.

Research

The chair of pharmacology and toxicology studies physiological and pathophysiological mechanisms in the cardiovascular system as well as in the central and peripheral nervous system of mammals. Research foci are the mechanisms underlying the generation and modulation of the cardiac rhythm and the signal transduction in cardiac hypertrophy. In addition, mechanisms of acute renal failure and other aspects of renal function were analyzed. The role of HCN channels in the nervous system and in particular in nociception and in epilepsy is studied. Finally, brain function under various conditions (drugs, behavioral paradigms, diseases) is studied by non-invasive brain imaging using functional magnetic resonance imaging (fMRI).

Signal transduction of cardiac rhythmogenesis and hypertrophy
PI: PD Dr. J. Stieber, Dr. S. Jamra, Prof. Dr. A. Ludwig
Mice expressing HCN4-channels with a mutant, cAMP-resistant cyclonucleotide-binding domain were characterized. These animals showed a loss of the circadian modulation of the heart rate and an increased arrhythmia propensity. The results suggest that basal cAMP stabilizes the cardiac rhythm by direct binding to HCN4. The role of protein kinase A (PKA) for cardiac function was examined by using a cardiac-specific and inducible mouse mutant of a specific PKA isoform. Mutant animals developed ventricular dysfunction and delayed sarcomere shortening and calcium-decay kinetics. At least part of this phenotype is due to an impaired phosphorylation of contractile proteins and phospholamban. In models of cardiac hypertrophy and failure, we found that the function of this PKA is critical for mediating long-term detrimental adrenergic signal transduction mechanisms. Another important target protein may represent the L-type calcium channel. Therefore, measurements of the L-type calcium current in ventricular myocytes were performed.

HCN channels in the nervous system
PI: PD Dr. J. Stieber, Prof. Dr. A. Ludwig

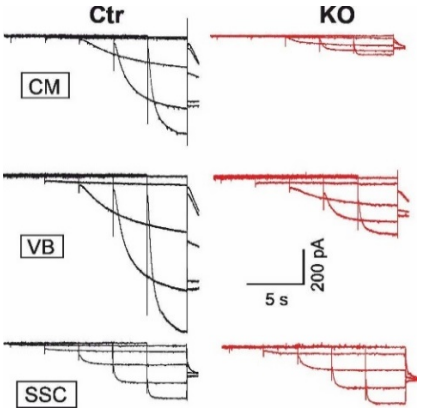

Fig. 1: Ih current in various regions in brain-specific HCN4-deficient mice. The current is strongly reduced in the thalamic centromedial (CM) and ventrobasal (VB) nucleus of knockout animals as compared to controls. In contrast, Ih is unchanged in the somatosensory cortex (SSC) (Zobeiri et al., 2019).

We could show that HCN channels play an important role for pain processing in nociceptive dorsal root ganglion cells. The results indicated that a PKA-mediated activation of HCN2 channels is responsible for the cAMP-dependent sensitization of nociceptors. To directly examine this mechanism, various phosphorylation-deficient HCN2 channels were generated and characterized electrophysiologically. A channel lacking a particular phosphorylation site showed indeed a reduced response to cAMP. Several results regarding the relationship between HCN channels and epilepsy were published. In a cooperation with Prof. M. Biel (LMU München) it was found that the deletion of HCN2 in the ventrobasal complex of the thalamus induced generalized absence epilepsy. Together with Prof. Dr. T. Budde (Westfälische Wilhelms-Universität Münster), we could define the function of HCN4 in the brain. Lack of HCN4 in the thalamus did not result in the occurrence of absence seizures. We determined the specific contribution of HCN4 to the Ih-current in various brain regions and demonstrated, that this isoform is essential for the generation of rhythmic intrathalamic activity. In a collaboration with Prof. C. Reid (University of Melbourne), it was shown that HCN4 constitutes a potential pharmacologically relevant target for anti-seizure drugs.

Renal function and sepsis
PI: Prof. Dr. K. Höcherl
The expression of protease-activated receptors (PARs) has been described in different renal cell types, but the significance of these receptors for renal function is not known yet. We could demonstrate that PAR2-receptors control the secretion of renin in the context of inflammation. However, PAR2 receptors are not involved in the typical physiological regulations of renin secretion and renin gene expression. In addition, pathomechanisms underlying the tubular dysfunction in acute renal failure were examined. In a mouse model of endotoxemia, we studied the metabolism of Mg^{2+}. The results suggest that the observed hypermagnesemia is due to an LPS-induced decrease in renal function. In a renal ischemia/reperfusion model, alterations in the expression of various renal Ca^{2+}-, Mg^{2+}-, and phosphate-transporters in connection with increased fibroblast growth factor FGF23 were characterized.

Pharmacological fMRI imaging
PI: Prof. Dr. A. Hess
Dynamic plastic processes in the central nervous system of laboratory animals (rodents) and humans are analyzed. Brain function is studied primarily by using non-invasive functional magnetic resonance imaging (fMRI). It has been shown repeatedly by our group that fMRI represents an ideal technique for translating experimental findings from laboratory animal to humans and patients. We are working mainly on two neurobiological research areas. Neurotrition, the interaction of food and brain function, was analyzed together with the groups of Prof. M. Pischetsrieder (Food Chemistry, FAU) and Prof. C. Müller (Psychiatry). We could demonstrate that snack food (potato chips) significantly increased the food intake of rats and mice. Together with the Child Psychiatry unit functional brain imaging data from certolizumab in rheumatoid arthritis) was successfully completed. In collaboration with the department of Medicine 1, various patients could be highly specifically differentiated from probands by using newly developed analytical methods which are based on "machine-learning" algorithms and multimodal MRI. This differentiation was most successful when functional markers were used in the brain image analyses. In contrast, a brain signature specific for the fatigue-syndrome of Crohn's disease was observed primarily in anatomical characteristics. All clinical MRI projects were performed in close cooperation with the Division of Neuroradiology. Several additional projects in the pain research field were performed anorectic patients during food intake are collected and analyzed, these results are currently published. In the pain research field, the phase 3-study PreCePra (prediction of treatment success of the TNF-alpha antagonist with various external

partners including analysis of cerebral pain processing in arthritis models (Prof H.-G. Schaible, Universitätsklinikum Jena), bone healing (Prof. S. Grässel, Universität Regensburg) and incision pain (Prof. E. Pogatzki-Zahn and Prof. C. Faber, Universität Münster). Proteom-based analyses were performed together with Prof. M. Schmidt, University of Vienna. In the research field of function MRI, we published in cooperation with Prof. J. Grandjean (Radboud University, Nijmegen) an international multicenter study about the identification of resting-state networks in the mouse brain.

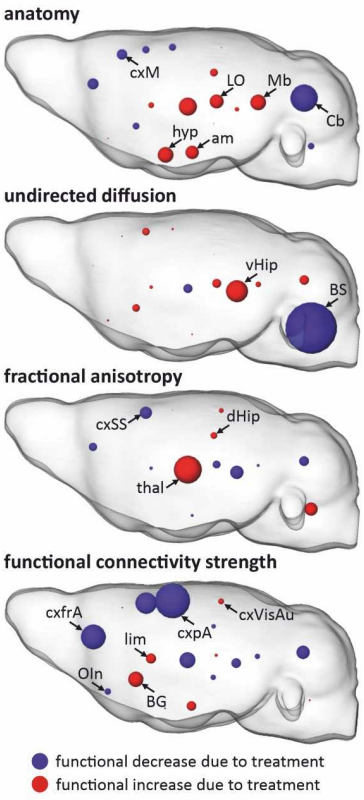

Fig. 2: Depiction of functional brain areas behaving differently in offspring from dams with maternal immune activation as compared to control mice. Shown are significantly changed areas, increases and decreases of relative changes in MRI modalities are indicated by red and blue circles, respectively. Relevant brain regions including brain stem (BS), thalamus (thal), frontal association cortex (cxfrA), etc. are labelled accordingly (Kreitz et al., 2020).

Teaching

In addition to the teaching duties in the degree programs Medicine and Molecular Medicine, the Chair provides the complete training in pharmacology for pharmacy students (as required to acquire the license to practice pharmacy). This includes lectures covering pharmacology and pathophysiology as well as seminars and laboratory internships.
Bachelor's and Master's theses as well as MD and PhD theses are supervised.

Selected publications

Zobeiri M, Chaudhary R, Blaich A, Rottmann M, Herrmann S, Meuth P, Bista P, Kanyshkova T, Lüttjohann A, Narayanan V, Hundehege P, Meuth SG, Romanelli MN, Urbano FJ, Pape HC, Budde T, Ludwig A. The Hyperpolarization-Activated HCN4 Channel is Important for Proper Maintenance of Oscillatory Activity in the Thalamocortical System. Cereb Cortex. 2019, 29:2291-2304.

Kharouf Q, Phillips AM, Bleakley LE, Morrisroe E, Oyrer J, Jia L, Ludwig A, Jin L, Nicolazzo JA, Cerbai E, Romanelli MN, Petrou S, Reid CA. The hyperpolarization-activated cyclic nucleotide-gated 4 channel as a potential anti-seizure drug target. Br J Pharmacol. 2020, 177:3712-3729.

Meurer M, Höcherl K. Endotoxaemia differentially regulates the expression of renal Ca2+ transport proteins in mice. Acta Physiol (Oxf). 2019, 225(1):e13175.

Kreitz S, Zambon A, Ronovsky M, Budinsky L, Helbich TH, Sideromenos S, Ivan C, Konerth L, Wank I, Berger A, Pollak A, Hess A, Pollak DD. Maternal immune activation during pregnancy impacts on brain structure and function in the adult offspring. Brain Behav Immun. 2020, 83:56-67.

Grandjean J, Canella C, Anckaerts C, Ayrancı G, Bougacha S, Bienert T, Buehlmann D, Coletta L, Gallino D, Gass N, Garin CM, Nadkarni NA, Hübner NS, Karatas M, Komaki Y, Kreitz S, Mandino F, Mechling AE, Sato C, Sauer K, Shah D, Strobelt S, Takata N, Wank I, Wu T, Yahata N, Yeow LY, Yee Y, Aoki I, Chakravarty MM, Chang WT, Dhenain M, von Elverfeldt D, Harsan LA, Hess A, Jiang T, Keliris GA, Lerch JP, Meyer-Lindenberg A, Okano H, Rudin M, Sartorius A, Van der Linden A, Verhoye M, Weber-Fahr W, Wenderoth N, Zerbi V, Gozzi A. Common functional networks in the mouse brain revealed by multi-centre resting-state fMRI analysis. Neuroimage. 2020, 205:116278.

Hess A, Kress S, Rakete S, Muench G, Kornhuber J, Pischetsrieder M, Müller CP. Influence of the fat/carbohydrate component of snack food on energy intake pattern and reinforcing properties in rodents. Behav Brain Res. 2019, 364:328.

International cooperations

Prof. C. Reid, Florey Institute of Neuroscience and Mental Health, Melbourne: Australia

Prof. A. Landstrom, Duke University, Durham: USA

Prof. A.Tinker, Queen Mary University, London:UK

Prof. M. Schmidt, Pharmacology and Toxicology, University of VIenna: Austria

Prof. J. Grandjean, Radboud University, Nijmegen: The Netherland

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Chair of Clinical Pharmacology and Clinical Toxicology

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Research focus
- Molecular characterization of drug transporters and transporter-mediated drug-drug interactions
- Molecular and clinical characterization of new cardiovascular risk factors and risk markers
- Quantification of drugs and endogenous substances including metabolomics
- Medication safety

Structure of the Chair

Professorships: 2
Personnel: 26
- Doctors (of Medicine): 2
- Scientists: 12 (thereof funded externally: 8)
- Graduate students: 8

Special structural feature
The position of the executive director of the Institute rotates between the Chair of Pharmacology and Toxicology and the Chair of Clinical Pharmacology and Clinical Toxicology on a two-year basis.

Clinical focus areas
- Drug analysis
- Clinical trial unit
- Drug information service for physicians

Research

The groups at the Chair of Clinical Pharmacology and Clinical Toxicology investigate mechanisms underlying interindividual differences in drug effects using molecular and cellular biology as well as clinical studies. The following topics, funded e.g. by the German Cancer Aid, BMBF, the German Federal Ministry of Health (BMG) and the Wilhelm Sander-Foundation are in the focus of our studies: Uptake and efflux transporters for drugs and endogenous compounds, mechanisms underlying drug-drug interactions, genetic determinants of drug effects (pharmacogenomics), cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism, and medication safety.

Molecular characterization of transporters for drugs and endogenous substances
PI: Prof. Dr. J. König, Prof. Dr. M.F. Fromm
Transport proteins in the plasma membrane of cells are important for the uptake, distribution and excretion of endogenous substances and drugs or drug metabolites. Using double-transfected cell models recombinantly overexpressing an uptake transporter together with an export protein we could demonstrate that the renal uptake transporter OCT2, localized in the basolateral membrane of proximal tubule cells together with the export protein MATE1, located in the luminal membrane mediate the polarized transport of the anticholinergic drug trospium. Transport proteins are also important for the renal handling of arginine metabolites. We could demonstrate that the uremic toxin asymmetric dimethylarginine (ADMA) as well as the cardioprotective biomarker L-homoarginine are substrates of the renal transport protein OATP4C1. Using a double-transfected cell model recombinantly overexpressing basolaterally localized OATP4C1 together with the apically localized export pump P-glycoprotein we could further demonstrate that both transporters mediate the vectorial transport of both arginine metabolites. Supported by the Wilhelm Sander-Foundation we further investigated a splice variant (Ct-OATP1B3 = cancer-type OATP1B3) of an uptake transporter, expressed in several tumor tissues and could demonstrate that the Ct-OATP1B3 protein is localized in intracellular vesicles mediating the sequestration and therefore inactivation of chemotherapeutic agents.

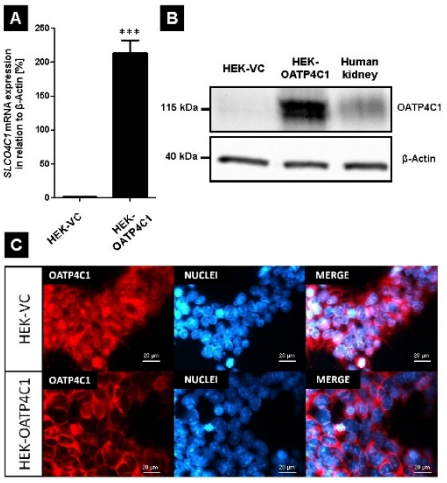

Fig. 1: Characterization of HEK293 cells, which were stably transfected with the renal transporter protein OATP4C1 (Reproduced with permission from Taghikhani E et al, PlosOne 2019)

Molecular and clinical characterization of new cardiovascular risk factors and risk markers
PI: Prof. Dr. R. Maas
A major focus of the group is the experimental and clinical characterization of new cardiovascular risk markers and risk factors as potential targets for therapeutic intervention. Currently the group investigates transport and metabolism of homoarginine, γ-aminoisobutyrate, nitrate and the methylarginines ADMA and SDMA. The investigations are conducted in long standing cooperations with the Department of Medicine 4, the Universities of Dresden and Kiel. In the reporting period we established population-based reference values for the two new biomarkers trimethylamine-N-oxide (TMAO) and N^{ε}-acetyllysine. In 2020 the research was supported by FAU and the Medcial Faculty by a new gas chromatography / mass spectrometer.

Analysis of drugs and endogenous substances including metabolomics
PI: Dr. A. Gessner, Dr. V. Taudte
The mass spectrometry unit uses samples from both, cell culture experiments and clinical and large epidemiological trials (GCKD study, pop-gen). Analytical methods (mostly LC-MS/MS) are developed, optimized, and validated in our laboratory. The spectrum of the analytes ranges from various drugs, such as pravastatin, etoposide, metformin, clopidogrel, and trimethoprim, to endogenous substances, such as derivatives of arginine, N^1-methylnicotinamide, trimethylamine-N-oxide (TMAO), N^{ε}-acetyllysine and γ-aminoisobutyric acid. Recently, the methodological spectrum was broadened to targeted and untargeted metabolomics due to a new mass spectrometer (Q Exactive Focus with UHPLC) funded by the DFG. The available technologies can be used for cooperations within the Faculty and FAU as well as for external cooperations.

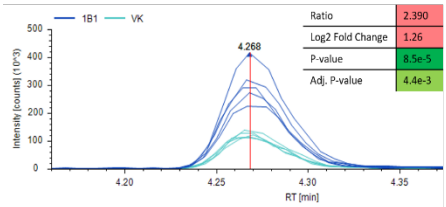

Fig. 2: Metabolomics of HEK-OATP1B1-and HEK-control cells. Intracellular concentration of a detected endogenous molecule is significantly higher in cells expressing the uptake transporter OATP1B1 (dark blue) in comparison to the control cells (bright blue)

Medication safety
PI: Prof. Dr. R. Maas, Prof. Dr. M.F. Fromm

Funding: German Cancer Aid
An innovative, three year clinical study was conducted in patients treated with new oral antitumor therapeutics in collaboration with the pharmacy of UK Erlangen (Prof. Dr. F. Dörje), the Comprehensive Cancer Center Erlangen-EMN (CCC), and collaborating private practices. This prospective, randomized trial showed that intensified clinical pharmacological/clinical pharmaceutical support improves patient safety, convenience and knowledge in patients newly treated with new oral antitumor therapeutics (AMBORA study).

Funding BMG
Clinical Pharmacology in Erlangen coordinates the establishment and evaluation of a ‘medication

safety stewardship' at a large tertiary hospital. The project objective is to optimize the medication process in a sustainable and efficient manner in order to improve medication safety.

Funding BMBF
The use case 'Polypharmacy, drug interactions and risks (POLAR)', which includes all four consortia of the Medical Informatics Initiative Germany, aims to assess using methods and processes of the Medical Informatics Initiative Germany health risks in patients with polypharmacy. Clinical Pharmacology in Erlangen coordinates the Pharmacology / Pharmacy work packages of POLAR.

The Chair participates in a continuing medical education program of the Center of Clinical Studies (CCS) in Good Clinical Practice for physicians, as required for clinical trials of medicines, and medicinal products.

Teaching

The Chair of Clinical Pharmacology and Clinical Toxicology coordinates the interdisciplinary lecture series and seminar clinical pharmacology/ pharmacotherapy for medical students applying problem-based learning. In addition, we teach students of the degree programs Dentistry, Molecular Medicine, Pharmacy, and Medical Process Management. In a cooperation project with the Technical University of Munich, we established two online teaching modules for drug therapy of common diseases. Students of Pharmacy and Medicine are welcome to work with us during their final year.
The Chair of Clinical Pharmacology and Clinical Toxicology offers supervision of Bachelor's and Master's theses as well as of MD and PhD theses.

Selected publications

Gessner A, König J, Fromm MF. Clinical aspects of transporter-mediated drug-drug interactions. Clin Pharmacol Ther, 2019, 105: 1386-1394

Schlichtig K, Dürr P, Dörje F, Fromm MF. New oral anti-cancer drugs and medication safety. Dtsch Arztebl Int, 2019, 116: 775-782

Gessner A, Mieth M, Auge D, Chafai A, Müller F, Fromm MF, Maas R. Establishment of reference values for the lysine acetylation marker N^{ε}-acetyllysine in small volume human plasma samples by a multi-target LC-MS/MS method. Amino Acids, 2019, 51: 1259-1271

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Wiebe ST, Giessmann T, Hohl K, Schmidt-Gerets S, Hauel E, Jambrecina A, Bader K, Ishiguro N, Taub ME, Sharma A, Ebner T, Mikus G, Fromm MF, Müller F, Stopfer P Validation of a drug transporter probe cocktail using the prototypical inhibitors rifampin, probenecid, verapamil, and cimetidine. Clin Pharmacokinet, 2020, 59: 1627-1639

International cooperations
Prof. J. Backman, Prof. M. Niemi, University of Helsinki, Helsinki, Finland,

Prof. R. Masereeuw, Utrecht University, Utrecht, The Netherlands,

Prof. S. Misaka, Fukushima Medical University, Fukushima, Japan,

Prof. R.L. Woosley, The University of Arizona, Phoenix, USA,

Dr. J.A. Zerillo, Harvard Medical School, Boston, USA

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Research focus
- Neurodevelopmental disorders
- Growth disorders
- Psoriasis
- Ophthalmogenetics
- Familial cancer

Structure of the Chair

Professorships: 2
Personnel: 45
- Doctors (of Medicine): 9
- Scientists: 9 (thereof funded externally: 4)
- Graduate students: 10

Clinical focus areas
- genetic outpatient clinic for all aspects of genetic diseases
- Participation in different specialized centers for rare diseases within the Erlangen Center for Rare Diseases
- various interdisciplinary outpatient clinics
- wide range of pre- and postnatal genetic analyses, including genome sequencing

Research

Research at the Institute of Human Genetics focuses on the elucidation of causes and pathomechanisms of genetic disease and genotype/phenotype correlation. In particular, modern genome sequencing technologies are used. For various projects large groups of patients have been recruited and clinically characterized in detail. In addition, cellular models including induced pluripotent stem cells and genome editing are used. The Institute cooperates with numerous departments and institutes within the Faculty and operates the core unit „Next Generation Sequencing“.

Neurodevelopmental disorders
PI: Prof. Dr. C. Zweier, Prof. Dr. A. Reis, Dr. G. Vasileiou
Intellectual disability can occur independently, but also in a syndromic presentation with additional symptoms and malformations. These are summarized as neurodevelopmental disorders (NDDs) and genetic factors are the main cause. Over the years the working groups at the Institute identified numerous single gene defects causing NDDs. In the last reporting season, we discovered that genetic variants in the SCAF4 gene cause a variable neurodevelopmental disorder due to impaired processing of messenger RNA (mRNA). In a study on Borjeson-Forssman-Lehman syndrome, we were able to demonstrate in cell culture models that PHF6 is necessary for proper development of the central nervous system (neuron proliferation, neurite outgrowth and migration). Furthermore, the first international consensus statement for the diagnosis and management of Pitt-Hopkins syndrome was established. Finally, as part of an international cooperation, we were able to significantly broaden the spectrum of the CTCF-associated neurodevelopmental disorder and better characterize its pathophysiology using transcriptome analyses and animal models.

Growth disorders
PI: Prof. Dr. C. Thiel
The elucidation of genetic causes of growth disturbances allows insights into the regulation of fundamental cellular processes. The group focuses on the identification and functional characterization of genes involved in idiopathic short stature and ciliary growth disorders. In a large study group of previously unsolved cases, new candidate genes for idiopathic short stature were identified using a combination of exome sequencing and clustering of evolutionary conserved functional networks.

Psoriasis
PI: Prof. Dr. U. Hüffmeier, Prof. Dr. A. Reis
Complex or multifactorial diseases are caused by a combination of mostly unknown environmental and genetic factors. Numerous genetic variants, each with a small effect size, act as susceptibility factors. At the Institute, both, the more frequent forms of plaque and psoriatic arthritis are studied. In recent years we have expanded our focus to rarer manifestations of pustular psoriasis, for which oligogenic inheritance with stronger allelic effects is suspected. Using exome sequencing, we identified the myeloperoxidase (MPO) gene as a cause of generalized pustular psoriasis. MPO is the main enzyme of neutrophil granulocytes and regulates inflammation by oxidative processes and at the cellular level. Genetic variants impairing the protein lead to partial or complete MPO deficiency. Pharmacological modulation of MPO signaling may thus represent a treatment option for this and other chronic inflammatory diseases.

Ophthalmogenetics
PI: PD Dr. F. Pasutto, Prof. Dr. A. Reis
Glaucoma represents a heterogeneous group of eye disorders characterized by irreversible damage of the optic nerve and usually elevated intraocular pressure, leading to vision loss and ultimately, if untreated, to blindness. Genetic factors are considered to play a key role in all major forms of glaucoma. In recent years, the working group in collaboration with the Department of Ophthalmology and international consortia has made important contributions to elucidate the genetic causes of pseudoexfoliation syndrome, the most common form of secondary glaucoma. Recently, our work focused on targeted deep sequencing of the main PEX predisposition locus (LOXL1) in more than eleven thousand individuals worldwide. We were able to identify a single genetic variant, located adjacent on the same chromosome, modulating the expression of key components of the retinoic acid signaling pathway including STRA6. *In vitro* inhibition of the retinoic acid signaling pathway in PEX-relevant cell types and tissues induced upregulation of PEX-associated matrix genes. Our results indicate that dysregulation of STRA6 and impaired retinoid metabolism are involved in the pathophysiology of PEX syndrome.

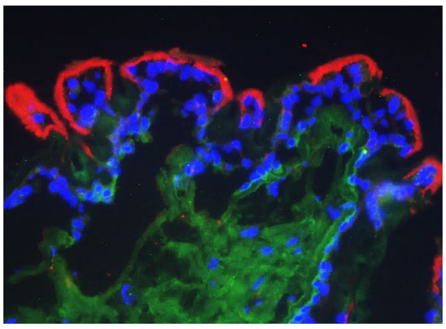

Fig. 1: Reduced expression levels of STRA6 in eye tissues (ciliary body and iris) of PEX patients associated with LOXL1-positive PEX material deposits

Familial cancer
PI: Dr. A. Ekici, Prof. Dr. A. Reis
Some 5 -10% of cancer patients are affected by a familiar cancer syndrome. These are often caused by mutations in cancer susceptibility genes, either inherited or occurring *de novo*. The Institute closely collaborates with several oncology departments on campus to identify mutations in both, highly penetrant and low-penetrant genes, and to correlate genetic findings with patients' symptoms. In particular, in cooperation with working groups at the Department of Obstetrics and Gynecology, we carried out several such systematic mutation screens in large patient groups with familial breast and ovarian cancer. Furthermore, together with the Radiology and Gynecoloy Departments and Siemens Healthineers we explored magnetic resonance imaging methods for early detection of women with genetic predisposition to familial breast cancer. In collaboration with the Institute of Pathology, we characterised biallelic somatic variants of fumarate hydratase in hormone-dependent benign uterine leiomyomas using massive parallel sequencing. Finally, in collaboration with the Childrens´s Hospital, we identified TRIM28 as a predisposing gene for Wilms tumor (nephroblastoma), acting as a tumor suppressor gene.

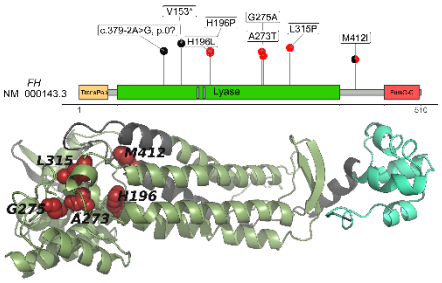

Fig.2: Schematic representation of the fumarate hydratase (FH) protein and its domains with localization of herein identified variants and depiction on the protein crystal structure

Teaching

The Institute of Human Genetics is involved in curricular teaching activities in Medicine and in the B.Sc. and M.Sc. degree programs Molecular Medicine as well as Cellular and Molecular Biology (M.Sc.), respectively. Bachelor's and Master's theses as well as MD and PhD theses are supervised.

Selected publications

Berner D, Hoja U, Zenkel M, Ross JJ, Uebe S, Paoli D, Frezzotti P, Rautenbach RM, Ziskind A, Williams SE, Carmichael TR, Ramsay M, Topouzis F, Chatzikyriakidou A, Lambropoulos A, Sundaresan P, Ayub H, Akhtar F, Qamar R, Zenteno JC, Cruz-Aguilar M, Astakhov YS, Dubina M, Wiggs J, Ozaki M, Kruse FE, Aung T, Reis A, Khor CC, Pasutto F, Schlötzer-Schrehardt U. The protective variant rs7173049 at LOXL1 locus impacts on retinoic acid signaling pathway in pseudoexfoliation syndrome. Hum Mol Genet 2019 28:2531-2548

Diets IJ, Hoyer J, Ekici AB, Popp B, Hoogerbrugge N, van Reijmersdal SV, Bhaskaran R, Hadjihannas M, Vasileiou G, Thiel CT, Seven D, Uebe S, Ilencikova D, Waanders E, Mavinkurve-Groothuis AMC, Roeleveld N, de Krijger RR, Wegert J, Graf N, Vokuhl C, Agaimy A, Gessler M, Reis A, Kuiper RP, Jongmans MCJ, Metzler M. TRIM28 haploinsufficiency predisposes to Wilms tumor. Int J Cancer 2019 145:941-951

Hauer NN, Popp B, Taher L, Vogl C, Dhandapany PS, Büttner C, Uebe S, Sticht H, Ferrazzi F, Ekici AB, De Luca A, Klinger P, Kraus C, Zweier C, Wiesener A, Jamra RA, Kunstmann E, Rauch A, Wieczorek D, Jung AM, Rohrer TR, Zenker M, Doerr HG, Reis A, Thiel CT. Evolutionary conserved networks of human height identify multiple Mendelian causes of short stature. Eur J Hum Genet 2019 27:1061-1071

Fliedner A, Kirchner P, Wiesener A, van de Beek I, Waisfisz Q, van Haelst M, Scott DA, Lalani SR, Rosenfeld JA, Azamian M.S, Xia F, Dutra-Clarke M, Martinez-Agosto JA, Lee H, UCLA Clinical Genomics Center, Noh GJ, Lippa N, Alkelai A, Aggarwal V, Agre KE, Gavrilova R, Mirzaa GM, Straussberg R, Cohen R, Horist B, Krishnamurthy V, McWalter K, Juusola J, Davis-Keppen L, Ohden L, van Slegtenhorst M, de Man SA, Ekici AB, Gregor A, van de Laar I, Zweier C. Variants in SCAF4 Cause a Neurodevelopmental Disorder and Are Associated with Impaired mRNA Processing. Am J Hum Genet 2020 107: 544–554

Haskamp S, Bruns H, Hahn M, Hoffmann M, Gregor A, Löhr S, Hahn J, Schauer C, Ringer M, Flamann C, Frey B, Lesner A, Thiel CT, Ekici AB, von Hörsten S, Aßmann G, Riepe C, Euler M, Schäkel K, Philipp S, Prinz JC, Mößner R, Kersting F, Sticherling M, Sefiani A, Lyahyai J, Sondermann W, Oji V, Schulz P, Wilsmann-Theis D, Sticht H, Schett G, Reis A, Uebe S, Frey S, Hüffmeier U. Myeloperoxidase Modulates Inflammation in Generalized Pustular Psoriasis and Additional Rare Pustular Skin Diseases. Am J Hum Genet 2020 107:527-538

Popp B, Erber R, Kraus C, Vasileiou G, Hoyer J, Burghaus S, Hartmann A, Beckmann MW, Reis A, Agaimy A. Targeted sequencing of FH-deficient uterine leiomyomas reveals biallelic inactivating somatic fumarase variants and allows characterization of missense variants. Mod Pathol 2020 33:2341-2353

International cooperations

Nur Aydinli, Department of Pediatric Neurology, Istanbul University School of Medicine, Istanbul, Turkey

Rikard Holmdahl, Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden

Anita Rauch, Institute of Medical Genetics, University of Zurich, Zurich, Switzerland

Tin Aung, Singapore National Eye Centre, Singapur, Singapur

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Research focus
- Stem cell modeling of Parkinson's disease
- Stem cell models of motor neuron disease
- CRISPR/Cas9 gene editing of human pluripotent stem cells

Structure of the Division

Professorship: 1
Personnel:
- Doctor: 4
- Scientists: 3
  (thereof funded externally: 2)
- Graduate students: 12

Clinical focus area
Speaker of the Center for Rare Diseases (ZSEER)

Research

The research of the Department of Stem cell biology focuses on modeling CNS disorders using genome editing and human stem cell technology. The physiological and pathological function of the human brain is still unsolved. Post mortem analyses are available for a structural investigation. In order to better understand brain development and degeneration, it is important to study the interaction of human brain cells. The generation of brain cells from human stem cells in multidimensional cultures enables novel relationships in structural and complex interactions. Our research focuses on neurodegeneration and regeneration in neurodegenerative and other neurological diseases.

Parkinson's disease Stem Cell Modeling
PI: PD. Dr. I. Prots, Prof. Dr. B. Winner
Parkinson's disease (PD) is a progressive, neurodegenerative disease characterized by the loss of midbrain neurons. It is believed that both alpha-synuclein (aSyn) accumulation and inflammation can play critical roles in neurodegeneration in PD. We investigate how this can lead to neuronal loss. We also investigate the interaction of neurodegeneration and neuroinflammation for PD pathology. To model PD pathology in a human model, we differentiate neurons from induced pluripotent stem cells (iPSC) from patients in cooperation with the molecular neurology department. We were able to show that the formation of smaller oligomer aSyn aggregates reduces axonal mitochondrial transport and compromises axonal and synaptic integrity in human neurons, including iPSC-derived neurons from PD patients. Axonal transport defects could be improved by using a substance that inhibits the formation of aSyn oligomers. To uncover the role of neuroinflammation in human PD pathology, we developed a human autologous co-culture from peripheral T-cells and iPSC-derived midbrain neurons from PD patients and controls. We were able to show that T cells induce the cell death of midbrain neurons in sporadic PD through IL-17 dependent signaling pathways, upregulate the IL-17 receptor and activate the activation of NF von B. More IL-17-producing T-cells were seen in the blood of PD patients, and an increased number of T cells was detected in post-mortem PD midbrain tissues. Blocking IL-17 or IL-17R decreased neuronal cell death in cell culture. A possible involvement of IL-17-producing T-cells in PD could reverse our understanding of how PD neurodegeneration can be promoted by systemic inflammation. We are currently investigating the influence of neuroinflammation on axonal transport in synucleinopathies.

Stem Cell Models of Hereditary Spastic Paraplegia (HSP)
PI: Dr. M. Regensburger, Prof. Dr. B. Winner
The group of HSPs comprises a heterogeneous symptom complex with the common characteristic of degeneration of the upper motor neuron. Using different paradigms, pluipotent stem cells are differentiated into different motor neurons. We compare patient cells with controls. This enables the analysis of gene expression, proteins, neuronal integrity, network formation and electrophysiological properties in neurons generated by patients in the cell culture. In the most common form of hereditary spastic paraplegia (HSP), which is caused by mutations in the SPG4 gene, we are investigating changes in the functional interaction between the endoplasmic reticulum and the cytoskeleton. Mutations in SPG11 are the most common cause of an autosomal recessive complex HSP, which is characterized by multisystem neuronal degeneration. We analyze the effect of SPG11 mutations in various neuronal models including three-dimensional cerebral organoids. Various affected cellular signaling pathways could be identified (lysosomal metabolism, mitochondrial function, GSK3), which are examined for potential therapeutic targets. Our overarching goal is to better understand the mechanisms of motor neuron disease and to identify therapeutic goals for future translation into the clinic.

Research into ALS using stem cell models
PI: Dr. F. Krach, Prof. Dr. B. Winner
Amyotrophic lateral sclerosis is characterized by the degeneration of the upper and lower motor neurons. At the molecular level, aberrant alternative splicing is believed to be the key mechanism of the disease. In order to shed light on these processes in more detail, we generate alpha motor neurons from iPSC from patients and controls and analyze the alternative splicing on a global level using RNA sequencing. To determine the cause of the splice changes, we integrate data sets on the RNA binding of various proteins that are known to influence alternative splicing. We want to use this knowledge to specifically identify RNA binding proteins, the modulation of which can represent a targeted target for future therapies.

CRISPR/Cas9 gene editing of human pluripotent stem cells
PI: Dr. S. Turan, Prof. Dr. B. Winner
Genome editing is becoming increasingly important in order to create human-specific disease models in human stem cell-based models. Inefficient and labor-intensive gene editing techniques such as zinc finger nucleases or TALENs have been replaced by the CRISPR / Cas9 technique, which enables efficient genome editing in stem cells. Therefore, this method is of crucial importance for examining models for neural developmental diseases and neurodegeneration. Our laboratory uses the CRISPR method to generate knockout or knockin models of multiple genes that play critical roles in nervous system development and cognitive impairment (SOX11, ARID1B, TCF4), motor neuron disease (SPG4, SPG11) and PD (SNCA). We succeeded in generating haploinsufficiency models for SOX11 or ARID1B. For proteins for which antibodies are not specific enough, we use CRISPR / Cas9 genome editing in order to create endo-genously marked reporter lines with FLAG or fluorescence reporter with the aim of generating new protein-protein or protein-DNA-Find interactions.

Teaching

The stem cell biology department participates with compulsory and elective subjects in the curriculum of medicine, cell and molecular biology and molecular medicine. Bachelor and master theses as well as medical and scientific doctorates are supervised.

Selected publications
Brazdis, R. M., Alecu, J. E., Marsch, D., Dahms, A., Simmnacher, K., Lorentz, S., . . . Prots, I. (2020). Demonstration of brain region-specific neuronal vulnerability in human iPSC-based model of familial Parkinson's disease. Hum Mol Genet, 29(7), 1180-1191. doi:10.1093/hmg/ddaa039
Perez-Branguli, F., Buchsbaum, I. Y., Pozner, T.,

Regensburger, M., Fan, W., Schray, A., . . . Winner, B. (2019). Human SPG11 cerebral organoids reveal cortical neurogenesis impairment. Hum Mol Genet, 28(6), 961-971. doi:10.1093/hmg/ddy397

Pozner, T., Regensburger, M., Engelhorn, T., Winkler, J., & Winner, B. (2020). Janus-faced spatacsin (SPG11): involvement in neurodevelopment and multisystem neurodegeneration. Brain, 143(8), 2369-2379. doi:10.1093/brain/awaa099

Simmnacher, K., Krach, F., Schneider, Y., Alecu, J. E., Mautner, L., Klein, P., . . . Winner, B. (2020). Unique signatures of stress-induced senescent human astrocytes. Exp Neurol, 334, 113466. doi:10.1016/j.expneurol.2020.113466

Sommer, A., Marxreiter, F., Krach, F., Fadler, T., Grosch, J., Maroni, M., . . . Winner, B. (2019). Th17 Lymphocytes Induce Neuronal Cell Death in a Human iPSC-Based Model of Parkinson's Disease. Cell Stem Cell, 24(6), 1006. doi:10.1016/j.stem.2019.04.019

International cooperations

Prof. F. H. Gage, Salk Institute for Biological Studies, La Jolla: USA

Prof. E. Masliah, National Institute of Aging, Bethesda: USA

Prof. G. Yeo, University of California San Diego: USA

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Chair of Medical Biometry and Epidemiology

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Research focus
- Computational biostatistics
- Statistical learning methods and medical data analysis
- Dermatoepidemiology
- Cooperative epidemiological and clinical studies

Structure of the Chair

Professorships: 2
Personnel: 13
- Scientists: 12 (thereof funded externally: 5)
- Graduate students: 5

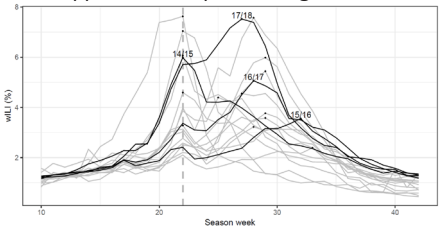
Research

The focus of the Chair's scientific activity is on three distinct areas: Methods development in the realm of machine learning (Computational Biostatistics), statistical modelling of infectious diseases, Statistical learning methods and medical data analysis, and dermato-epidemiological research, respectively. Moreover, the Chair cooperates with numerous research projects addressing different topics with different departments or institutes. Usually, the Chair is responsible for statistical aspects of study design and analysis.

Computational biostatistics
PI: Dr. E. Waldmann
The statistical analysis of high-dimensional data containing large numbers of features has become increasingly important in biomedical practice. Consequently, statistical methods for analyzing data with complex dependency patterns and for separating informative features from non-informative ones are needed. Boosting is a promising statistical method to address these issues. The project focuses on improving and developing boosting methodology for data structures that cannot yet be analyzed with the help of classical boosting techniques. For example, classical boosting methods were further extended to generalized additive models for location, scale, and shape (GAMLSS). GAMLSS is a popular statistical approach for simultaneously modeling multiple parameters of a response distribution in regression models. Current fitting procedures for GAMLSS are infeasible for high-dimensional data setups and require heuristic (or potentially biased) feature selection methods. The new algorithm allows for simultaneous estimation of predictor effects and feature selection in GAMLSS. In the course of the project, boosting methods were further analyzed with regard to their general performance as optimization method for AUC-based performance criteria in classification and survival analysis. Furthermore, boosting methods are developed and evaluated which target the analysis of so-called joint models, addressing modeling of two related outcome variables, one a time-to-event- component, the other a longitudinally observed outcome, related by a parameter of association.

Statistical learning methods and medical data analysis
PI: PD Dr. W. Adler
In the statistical evaluation of clinical studies in collaboration with the University Hospital Erlangen, in addition to the usual questions that can be solved with conventional test procedures and multiparametric models, studies with very small sample sizes and / or complex data structure often arise, for which, in addition to complex statistical models, non-parametric analysis procedures that do not rely on statistical distribution assumptions are also suitable. Among the latter, especially the bootstrap method plays an important role, which, in addition to the estimation of confidence intervals or the determination of statistical significance when examining the group difference of different statistical measures, can also be used, for example, to generate ensembles of classification and regression trees, since a flexible adaptation to the data structure at hand is possible. Mixed linear models, by suitable manipulation of the covariance matrix, allow the determination of correlation for data with appropriate data structure, such as the presence of repeated measures. Moreover, GEE models have an important role, for example, for efficient evaluation of data sets where both eyes are partially available from glaucoma patients. GEE models take the data structure into account not so much by modeling the magnitude of parameters, but rather by determining their uncertainty.

Statistical analysis of infectious disease spread
PI: Dr. S. Meyer
Infectious pathogens such as influenza and noro viruses cause epidemics. Public health surveillance records age-stratified and spatial data on the occurrence of notifiable infectious diseases; in Germany, this is handled by the Robert Koch Institute. Based on such surveillance data, statistical models enable probabilistic forecasts of key measures relevant to public health authorities, eg. the incidence or peak week of the epidemic. A particular scientific focus was to investigate proper scoring rules for such probabilistic forecasts. Furthermore, epidemic models can support the understanding of disease spread, for example to estimate the impact of environmental or socioeconomic factors and vaccination coverage on disease dynamics. For this purpose, we have developed specialized regression models and associated statistical software, which has already been employed also by other epidemiological research groups. We are working on extensions of these methods for multidimensional time series of proportions, for example, regionally stratified consultation rates of influenza-like illness or influenza-attributable hospitalization rates in different age groups. Moreover, we evaluate statistical models for point processes, which allow for a more detailed picture of epidemic spread given individual-level surveillance data. All methodological developments are implemented in open source research software to facilitate scientific progress and broad application in epidemiological research.



Seasonal flu activity in the USA, 1998-2017, as measured by the (population-weighted) proportion of patients with influenza-like illness (ILI) among all monitored outpatient visits. Season week 22 (calendar week 52) is indicated with a vertical dashed line, where a peak or secondary peak occurs in most seasons. A forecasting challenge of different statistical models was performed for the last four seasons (black lines). From: Lu & Meyer, IJERPH, 2020. License: CC BY 4.0.

Dermatoepidemiology
PI: Prof. Dr. A. Pfahlberg, Prof. Dr. W. Uter
In clinical contact allergy research, a close co-operation with the German contact dermatitis group (DKG) e.V. and the multi-centric project Information Network of Departments of Dermatology (IVDK), maintained by an institute at the University of Göttingen, has been established. Pooled data collected in the participating allergy departments are analyzed in terms of contact allergy surveillance, i.e. early detection of trends in contact allergy (increase, possibly in particular subgroups). Moreover, the network European Surveillance System on Contact Allergies – Data Centre (ESSCA-DC) has been collecting and analyzing such data on a European level since 2002, with the data center located at the Chair of Medical Biometry and Epidemiology. Currently, the so-called European Baseline Series for patch testing is being updated based on ESSCA results.
The epidemiology of malignant melanoma and acquired melanocytic nevi is a further research interest: Acquired melanocytic nevi, surrogates or potential precursors of malignant melanoma, are addressed by the current MONA-study which

includes standardized assessment of student cohorts. Currently, results of two surveys ("Erlking Sun", "Francis") addressing knowledge on prevention of UV exposure in kindergarten staff and actual protective measures (shading etc.) in the institutions are being analyzed with the aim of identifying targets of improvement of primary prevention, with a special focus on the concept of the UV-index.

Cooperative epidemiological and clinical studies

This area of activity comprises diverse research topics addressed in cooperation with different departments and institutes. Usually, biometrical aspects of study design and statistical analysis have been performed by the Chair in these co-operative projects. The most important projects in the reporting period include:

- Studies in cooperation with the Center for medical healthcare research of the Chair of Psychiatry and Psychotherapy concerning nonpharmacological interventions for dementia (DeTa-MAKS, Senior-Go, MAKS-kog-ls, MAKS-s)
- A multi-centric European studying on "Accelerated Partial Breast Irradiation" and a controlled clinical trial on radiochemotherapy in patients with locally advanced head/neck tumors stage III and IVA-B (PACCIS) and radiochemotherapy after induction chemotherapy with gemcitabine and FOLFIRINOX, resp. (CONKO-007 study), all chaired by the Department of Radiation Oncology
- The research network PRO PRICARE (see separate report) targeting the identification of unnecessary diagnostic and therapeutic interventions, their causes, and possible strategies for a future reduction of such measures. The Chair is involved in a sub-project addressing so-called cascade effects and their causes in thyroid disease
- A European multicenter study "SCOPE" ("Screening for Chronic Kidney Disease among Older People across Europe") in co-operation with the Institute for Biomedicine of Aging
- The transsectoral TIGER Study assessing daily home support of elderly patients by "pathfinders" to reduce re-admission rates after discharge from inpatient treatment
- The ANFOLKI-36 study, which examines the effects of general anesthesia in children on their cognitive function, in cooperation with the Department of Anesthesiology and the Chair of Medical Informatics
- The clinical study EUPHORIA to enhance ultrasound & photoacoustic for recognition of intestinal abnormalities using a new imaging modality called Multispectral Optoacoustic Tomography (MSOT).
- The population-based epidemiological cohort study TiCoKo examining the seroprevalence of SARS-CoV-2 longitudinally in the county of Tirschenreuth based on a random sample of more than 4200 inhabitants as well as determinants of morbidity
- A qualitative study regarding knowledge and use of the UV-index during consultations on the subject of sun protection in pharmacies in the Rhine-Main region in cooperation with the Institute for Public Health at Mannheim University Medical Center
- The statistical-epidemiological study SUSPend to analyse the impact of social distancing policies on the spatio-temporal spread of COVID-19.

Teaching

The Chair of Medical Biometry and Epidemiology contributes to curricular teaching in terms of mandatory and optional courses in Medicine, Molecular Medicine, Medical Technology, Life Science Engineering, Logopedics, and Medical Process Management. Concerning inter-disciplinary teaching, the cooperation in the context of "Querschnittsbereich I" with the Chair of Medical Informatics and the Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine is of note.
The Chair supervises Bachelor's and Master's theses as well as MD and PhD doctoral theses.

Selected publications

Gayawan E, Adebayo SB, Waldmann E. Modeling the spatial variability in the spread and correlation of childhood malnutrition in Nigeria. Stat Med. 2019 May 10;38(10):1869-1890.

Kaiser I, Pfahlberg AB, Uter W, Heppt MV, Veierød MB, Gefeller O. Risk Prediction Models for Melanoma: A Systematic Review on the Heterogeneity in Model Development and Validation. Int J Environ Res Public Health. 2020 Oct 28;17(21):7919.

Lehmann M, Sandmann H, Pfahlberg AB, Uter W, Gefeller O.. Erythemal UV Radiation on Days with Low UV Index Values-an Analysis of Data from the German Solar UV Monitoring Network over a Ten-year Period. Photochem Photobiol 2019;95(4):1076-1082

Lu J, Meyer S. Forecasting flu activity in the United States: Benchmarking an endemic-epidemic beta model. International Journal of Environmental Research and Public Health. 2020;17(4):1381

Uter W, Aalto-Korte K, Agner T, Andersen KE, Bircher AJ, Brans R, Bruze M, Diepgen TL, Foti C, Giménez Arnau A, Gonçalo M, Goossens A, McFadden J, Paulsen E, Svedman C, Rustemeyer T, White IR, Wilkinson M, Johansen JD. The epidemic of methylisothiazolinone contact allergy in Europe: follow-up on changing exposures. J Eur Acad Dermatol Venereol. 2020;34(2):333-339

Uter W, Gefeller O, Mahler V, Geier J. Trends and current spectrum of contact allergy in Central Europe: results of the Information Network of Departments of Dermatology (IVDK) 2007-2018. Br J Dermatol. 2020 Nov;183(5):857-865.

International cooperation

Multicentric:
Prof. J.D. Johansen (1), Prof. C.M. Bonefeld (1), Dr. I. R. White (2), Prof. J.-P. Lepoittevin (3), Prof. M.B. Veierød (4)
(1) Copenhagen University, (2) Kings College London, (3) Université de Strasbourg, (4) University of Oslo

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Research focus
- Process support through health information systems
- Medical ontologies and medical knowledge processing
- Evaluation of health information systems
- Analysis, assessment, and visualization of medical data
- IT-infrastructure applications for medical research
- Clinical bioinformatics

Structure of the Chair

Professorship: 1
Personnel: 20
- Doctor (of Medicine): 1
- Scientists: 16 (thereof funded externally: 12)
- Graduate students: 10

Research

Various working groups are concerned with the development and the introduction of electronic medical records, the integration of clinical decision support functions into hospital information systems (HIS), the modelling and optimization of clinical workflows, both data warehouse and data mining applications, the evaluation of the effect of health technology interventions on processes and persons involved in the health system, the development of IT infrastructures for research and teaching and with clinical bioinformatics. The integration of clinical and research data within hospitals and data sharing within large networks, e.g. in the context of the German Medical Informatics Initiative and the German Biobank Alliance, are a particular focus of our research activities.
Prof. Dr. H.-U. Prokosch is as Chief Information Officer also responsible for the strategic development of information processing at UK Erlangen.

Process support through health information systems
One of the major challenges in the design, establishment, and management of health information systems (HIS) is the intersectoral interoperability which is important to optimize the cooperation of the various health service providers across institutional boundaries in outpatient and inpatient care in order to deliver the best patient care. For an additional reduction of patient risks, we integrate clinical decision support functionalities into HIS. Clinical information flow and communication functionalities should ultimately involve and benefit patients, e.g. by the application of medication plans or by the use of a personal electronic health record. In addition to grant funded projects, the Chair also pursues and supports several innovative pilot projects embedded in the SOARIAN®/Meona® HIS environment of Erlangen University Hospital. The direct integration of the patient by means of an online-based capturing of follow-up information and the vision of a patient portal which is integrated into HIS, additionally supports a patient´s eConsent processes and provides transparent information about the use of his data in research projects completes the range of research in this field.

Medical ontologies and medical knowledge processing
In our projects, providing knowledge processing systems in medicine always comprises knowledge modeling and the implementation of standardized knowledge modules for example to support drug therapy and drug prescription or to reduce patient risks within intensive care units (ICU). Within the patient data management system of an ICU, a clinical decision support system has been integrated to monitor the exceedance of threshold values or to monitor critical trends of various laboratory values and, as a consequence, to have a direct feedback sent as a text message to the DECT telephone of the clinician on duty. Within the MIRACUM project one focus is the integration of molecular analysis results with clinical data and its efficient visualization for physician´s support in therapy decisions. Further research aims on the AI-based development of classification and prognosis algorithms, as well as the provision of medication dosage recommendations. In the context of those developments we are also concerned with all aspects of the use of software as a medicinal product.

Evaluation of health information systems
When introducing new information technologies, it is essential to evaluate their effect on user satisfaction, work processes, and process costs to avoid adverse effects of these technologies on medical care. Successful use of IT in medicine may be hindered by negative user attitudes, user-unfriendly interfaces, and insufficient usability in general. In numerous evaluation studies, we have applied methods, such as usability questionnaires, observations, thinking aloud, and cognitive walkthrough, to both optimize and evaluate the acceptance of different kinds of IT artefacts. In cooperation with the Department of Anesthesiology, as well as further German anesthesiologists and the foundation German anesthesiology (“Stiftung Deutsche Anästhesiologie”) we perform usability analysis of different levels of prototypes and mockups for a computerized emergency checklist. Further, we cooperate with the Department of Pediatrics and Adolescent Medicine in the stepwise development and usability analysis of a web-based medication information system to support drug therapy for children. In the context of developing user interfaces for searching biospecimens and for feasibility analyses, we cooperate very closely with the Institute for Medical Informatics and Biometry at the TU Dresden in conducting usability evaluations.

Analysis, assessment, and visualization of medical data
An increasing amount of data is documented electronically in clinical IT systems during routine patient care. To avoid information overload or overlooking of essential facts, appropriate and flexible visualization methods are required. We have been creating a learning health system by reusing such data for research projects. In cooperation with Harvard University Medical Center, the i2b2 (informatics for integrating biology and the bedside) platform has been integrated with UK Erlangen Clinical Data Warehouse and enhanced with semantic ontology annotations as well as timeline-based visualization methods. It has been established as a research integration platform for several projects at UK Erlangen, but also within national collaborations. Furthermore, we have provided the tranSMART platform for different research groups at our Faculty for the purpose of integrating genomic data into clinical data. Here we are also evaluating the use and the usability of the platform for its application in the fields of cohort identification and data exploration. In the MIRACUM consortium (Medical Informatics in Research and Care in University Medicine) we evaluate and enhance the translational platform cBioPortal (originally developed at the Memorial Sloan Kettering Cancer Center, New York, USA), which aims at integrating and visualizing clinical findings and genomic analysis data. The final goal is to provide an optimized information presentation for enhanced IT supported therapy decisions in molecular tumor boards.

IT-infrastructure applications for medical research
Today, medical research is often pursued within networked multi center structures, which require efficient and safe IT-infrastructures. Amongst others current activities comprise IT infrastructures to support biobanking and the development of biobank networks on a national (German Biobank Node, German Biobank Alliance) and international (BBMRI-EIRC Common Service IT) level. A further focus was laid on the single-source reuse of patient data for clinical and translational research. The Chair is member and active partner in many projects and working groups of the TMF (German technology and methods platform for networked medical

research). We lead the MIRACUM consortium, in which we design, develop, and implement an ecosystem of open source software tools (MIRACOLIX: e.g. ID-management, consent-management, federated authentication, several research data repositories and research data management based on the FAIR principles), which form the building blocks for the establishment of data integration centers at each of the MIRACUM university hospitals.

Clinical bioinformatics
Another research focus includes bioinformatics analysis and modeling of medical data. Our work focuses on high-dimensional omics and imaging data (bulk/single-cell transcriptomics, proteomics, metabolomics, interactomics, ATAC-Seq, FACS, CyTOF), which we systematically analyze using methods of integrative and comparative bioinformatics and machine learning. The goal is to gain a comprehensive understanding of molecules (e.g. non-coding RNAs, RNA-binding proteins) and signaling pathways in the pathogenesis and their pharmacological applications. The thematic focus of our work is in particular (auto)immune, fibrosis and tumor diseases. In this context, we have developed innovative methods and integrative analysis tools and successfully applied them in various collaborative projects and research alliances. For example, we have identified markers for various cardiac and lung diseases as well as novel mediators in fibroblast activation in systemic sclerosis, but also elucidated mechanism of immune cells in the pathogenesis. Another aspect of the work involves disease modeling. Here, we identified a blood-based metabolome signature for the diagnosis of adrenocortical tumors using machine learning approaches. In addition, we have developed computer models for various tumor diseases that reflect the underlying mutations and involved signaling pathways of a tumor and can be used, for example, for targeted therapy decisions in the context of molecular tumor boards.

Teaching

The Chair of Medical Informatics is involved in the education of students of Medicine, in the degree programs of informatics (minor subject: medical informatics) of the Faculty of Engineering as well as in the interdisciplinary degree program Medical Process Management and in the cross-faculty courses of the degree programs in medical engineering. In all these courses, the innovative laboratory for medical informatics and eHealth which is an established feature at the Chair of Medical Informatics is used as the Erlangen laboratory of medical informatics (“EMIL”) in the form of a Skills Lab and in the context of an innovative teaching concept.

Selected publications
Gruendner J, Wolf N, Tögel L, Haller F, Prokosch HU, Christoph J. Integrating Genomics and Clinical Data for Statistical Analysis by Using GEnome MINIng (GEMINI) and Fast Healthcare Interoperability Resources (FHIR): System Design and Implementation. JMIR 2020; 22:e19879.

Gulden C, Kirchner M, Schüttler C, Hinderer M, Kampf M, Prokosch HUP, Toddenroth D. Extractive summarization of clinical trial descriptions. Int J Med Inform. 2019;129:114-121.

Vey J, Kapsner LA, Fuchs M, Unberath P, Veronesi G, Kunz M. A toolbox for functional analysis and the systematic identification of diagnostic and prognostic gene expression signatures combining meta-analysis and machine learning. Cancers (Basel), 2019 Oct; 11(10). pii: E1606. doi: 10.3390/cancers11101606

Kunz M, Wolf B, Fuchs M, Christoph J, Xiao K, Thum T, Atlan D, Prokosch HU, Dandekar T. A comprehensive method protocol for annotation and integrated functional understanding of lncRNAs. Brief Bioinform., 2020; 21(4):1391-1396. doi: 10.1093/bib/bbz066

Fuchs M, Kreutzer FP, Kapsner LA, Mitzka S, Just A, Perbellini F, Terracciano CM, Xiao K, Geffers R, Bogdan C, Prokosch HU, Fiedler J, Thum T, Kunz M. Integrative Bioinformatic Analyses of Global Transcriptome Data Decipher Novel Molecular Insights into Cardiac Anti-Fibrotic Therapies. Int J Mol Sci., 2020; 21(13):4727. doi: 10.3390/ijms21134727

International cooperations
Prof. Dr. E. Ammenwerth, Private Universität für Medizinische Informatik und Technik (UMIT), Innsbruck: Österreich

Prof. Dr. T. Bürkle, Berner Fachhochschule, Biel: Schweiz

Prof. Dr. I. Kohane, National Center for Biomedical Computing, Boston: USA

Prof. Dr. C. Sawyers, Dr. A. Zehir, Memorial Sloan Kettering Cancer Center, New York: USA

Prof. Dr. George Hripcsak. Columbia University, New York: USA.

Institute of Medical Informatics, Biometry, and Epidemiology

Chair of Digital Health

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Research focus

- Wearable health systems
- Context recognition
- Digital Biomarker estimation
- Digital Twins of humans and systems

Structure of the Chair

Professorship: 1
Personnel: 11

- Scientists: 9 (thereof funded externally: 6)
- Graduate students: 5

Research

The Chair of Digital Health is pursuing research on sensor-based embedded medical systems, including wearables and implants. Research is done on machine learning algorithms to estimate Digital Biomarkers and decision support systems related to patient behavior, physiology, and exposure in out-of-lab settings. Work focuses on algorithms for context awareness and knowledge mining from clinical, multimodal data to support diagnosis and treatment. The algorithm bandwidth stretches from time series analysis to dynamically adaptive pattern modeling. A further strand of research addresses novel digital design methods and procedures to implement wearable and implantable sensor and actuator systems, employing digital co-simulation of digital human twins and system twins, 3D printing, and multi-process additive manufacturing methods. In collaborative projects with various medical and industry partners, novel algorithms, models, and technology are getting validated.

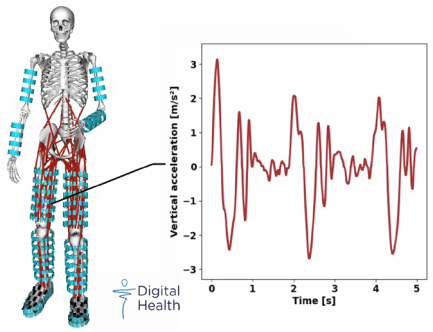
Wearable medical systems
Mobile and wearable systems provide access to health-related patient behavior and exposure information, thus support medical professionals and patients in diagnosis and treatment. The Chair investigates the potential of new wearable and implantable systems that provide specific and reliable health, behavior, and exposure data. Among the wearable device developments are 3D-printed regular-look smart eyeglasses with frame-integrated electronics and sensors to continuously acquire physiological data (e.g. heart beat via in-frame optical sensors), behavior (e.g. meal timing via in-frame acoustic sensors), and exposure (e.g. ambient light via optical sensors). Another development of the Chair is the GastroDigitalShirt that is being investigated in a clinical study for acoustic monitoring of the intestinal tract. With its continuous, long-term monitoring of the abdomen and algorithms to interpret the acoustic signal patterns, the diagnosis of inflammatory bowel diseases will be supported.

GastroDigitalShirt system with embedded microphone array and computing device won the 2019 DGVS Innovation Award "Digital Gastroenterology". The system is being evaluated in a clinical study at UK Erlangen (Baronetto et al., 2020).

Context recognition
The Chair develops and evaluates new algorithms to analyze large, multi-modal continuous time series from mobile and wearable sensor systems. Research activities include pattern spotting of rare known patterns and mining of new relationship/association rules among events in data. Recent investigations combined context information and compressive sensing techniques to create a dynamically adaptive pattern recognition system for resource-constrained embedded systems, in particular wearables and implants. Investigations on the new context-adaptive sensing approach yielded energy savings of more than 50% compared to state-of-the-art non-adaptive systems and still improve significantly over sub-Nyquist sampling methods. The results are vial for future medical systems, as size and continuous runtime are directly related to the required energy storage.
The Chair is furthermore investigates dynamic design space exploration methods that include runtime-adaptive algorithms, where static approximations do not yield tight bounds. Instead, our system simulations include complexity estimation and sensor data to estimate the performance loss in under-powered systems.

Digital Biomarker estimation
Digital Biomarkers often combine different pattern analysis algorithms to estimate clinical relevant parameters in unsupervised, free-living conditions, thus supporting decision making by patients and/or medical professionals. The Chair develops methods for estimating new Digital Biomarkers and procedures to derive known ones with mobile and wearable systems, in collaboration with clinical partners. For example, from body-worn motion sensor data, we developed a novel biomarker to analyze the convergence prognosis between affected and less-affected body sides in hemiparesis patients, called Convergence Point (CP). In addition, a range-of-motion marker was developed in collaboration with therapists, based on quantifying upper extremity postures assumed over measurement days, called Cubic Quantizer. Currently, various smartphone app projects explore platform-independent designs in connections with a new course "Digital Health" and seminar "Digital Health App Design", which have been well-received by students in computer science and medical engineering.

Co-simulate digital human twins
The Chair's research on digital human twins has intensified in topology modeling and dynamic body motion analysis. A particular interest is to co-simulate digital health twins with technical twins of medical systems, to maximize insight and system design optimization before physical prototyping and testing. For example, gait motion twins of athletes and patients with a hemiparesis, e.g. after stroke, were co-simulated with wearable inertial sensor systems to evaluate sensor position and Digital Biomarker estimation performance, e.g. stride duration and step count. The investigation is a first step towards exploiting the potential of digital twin and co-simulation. Further projects on digital human twins are under preparation.



Example co-simulation of digital human twins and system twins. Virtual inertial sensors, e.g. acceleration, are being simulated to explore robust body locations and Digital Biomarker estimations (Derungs & Amft, 2020).

COVID-19 and Digital Health
Prof. Amft is a co-founder of the "Corona Datenspende" initiative of the Robert Koch Institute. The initiative is leading worldwide, having more than 500k users that provide resting heart rate and step count data of their wearable device. No other initiative has gained so many participants. The data shows that wearable data can anticipate COVID-19 reports by approx. one week. Another initiative of the Chair is a novel behavior simulation approach that describes proximity between individuals in a virtual world. The simulation framework enables us to estimate the performance of digital and manual contact tracing as well as

study intervention methods, such as the closure of restaurants and schools.

System modeling
Modeling of body-worn systems becomes an important research area for our Chair. So far, the Chair has been investigating system modeling already, either to estimate performance before implementing prototypes or to personalize wearable systems. For example, head modeling and head parameter estimation was used to fit eyeglasses frame sensors to anatomically relevant positions at the head.

Teaching

The Chair of Digital Health contributes to education in Computer Science, minor in Medicine, and in Medical Engineering curricula, through courses, exercises, seminars, and practicals. Among the course offerings are foundational classes on ubiquitous sensor technology, biomedical signal processing, context recognition, and selected topics in machine learning. In addition, applied offerings include seminars and internships on wearable medical system design, 3D printing, and monitoring studies. Within the Medical Engineering curriculum, the Chair provides education for all tracks, covering medical devices, electronics, and computer science. The Chair utilizes their currently available laboratory rooms to let a few students each year explore and learn about novel personal medical device construction and fabrication technologies and methods.
Bachelor's and Master's theses topics as well as PhD theses are offered, crossing disciplines of engineering and computer science with medicine.

Selected publications
Amft, O., Lopera Gonzalez, L.I., Lukowicz, P., Bian, S., and Burggraf, P. (2020). Wearables To Fight COVID-19: From symptom tracking to contact tracing. IEEE Pervasive Computing 19, 53–60.

Derungs, A., and Amft, O. (2020). Estimating wearable motion sensor performance from personal biomechanical models and sensor data synthesis. Nat Sci Rep 10.

Baronetto, A., Graf, L.S., Fischer, S., Neurath, M.F., and Amft, O. (2020). GastroDigitalShirt: A Smart Shirt for Digestion Acoustics Monitoring. In ISWC '20: Proceedings of the 2020 International Symposium on Wearable Computers, (Virtual Conference: ACM), pp. 17–21.

Lopera Gonzalez, L.I., Derungs, A., and Amft, O. (2019). A Bayesian Approach to Rule Mining. arXiv.org.

Schiboni, G., Suarez, J.C., Zhang, R., and Amft, O. (2020). DynDSE: Automated Multi-Objective Design Space Exploration for Context-Adaptive Wearable IoT Edge Devices. Sensors 20, 6104.

Tansaz, S., Baronetto, A., Zhang, R., Derungs, A., and Amft, O. (2019). Printing Wearable Devices in 2D and 3D: An Overview on Mechanical and Electronic Digital Co-design. IEEE Pervasive Computing 18, 38–50.

International cooperations
Prof. GZ Yang, Imperial College London: UK

Prof. D. Kotz, Dartmouth College, Hannover, NH: USA

Prof. K. de Graf, Wageningen University: The Netherlands

Prof. M.A. Spruit, Maastricht University: The Netherlands Prof. L. Chen, De Montfort University, Leicester: UK

Prof. Dr. I. Korhonen, TU Tampere: Finland

Institute of Neuropathology

Chair of Neuropathology

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Research focus
- Neuropathological classification of focal epilepsies in humans
- Epigenetic mechanisms of epileptogenesis
- Molecular myopathology
- Deep Learning Morphology

Structure of the Institute

Professorships: 2
Personnel: 17
- Doctors (of Medicine): 4
- Scientists: 4 (thereof funded externally: 3)
- Graduate students: 2

Clinical focus areas
- European Reference Center for rare and complex epilepsies "EpiCare"
- Neuropathological reference center for epilepsy surgery and host of the European Epilepsy Brain Bank
- Member of the panel of the German reference center for brain tumors
- Disease of skeletal muscle (Member of the Muscle Research Center Erlangen)

Research

The Institute of Neuropathology scientifically addresses diseases of the central nervous system and the skeletal musculature. Our internationally highly visible research expertise is in the area of human epilepsy and neuromuscular disorders. Our Institute welcomes visiting scientists to train them in studying human tissue samples for research purpose, but also for clinical diagnostics (no exchange possible during the COVID-19 pandemic in 2020-2021).

Neuropathological classification of focal epilepsies in humans
PI: Prof. Dr. I. Blümcke
This research project is focused on drug-resistant focal epilepsies in humans to decipher pathomechanisms and clinically define brain lesions associated with chronic seizures, e.g. hippocampal sclerosis, glio-neuronal tumors, and focal cortical dysplasia. We perform systematic analysis in surgically resected human brain specimens in correlation with clinical histories and postsurgical follow-up data, and our work contributed in establishing new international standards for clinico-pathological diagnosis of focal cortical dysplasia (ILAE classification 2011) and hippocampal sclerosis (ILAE classification 2013). Extensive collaboration with our clinical and neuropathology colleagues from Germany and many other European countries were helpful to establish the European Epilepsy Brain Bank (EEBB), a reference and consultation center for neurosurgical epilepsy tissue specimen. The EEBB is also part of the European Reference Network "EpiCare". The collection of more than 10.000 specimens and collaboration with 40 European centers will help us to finally integrate genetics and histopathology for a better understanding of etiology and pathogenesis of epilepsy-associated brain lesions and also develop a state-of-the-art disease classification in the near future. Another DFG-funded collaborative research project with the Cologne Center for Genomics and the Cleveland Clinic Epilepsy Center aims at a comprehensive genotype-phenotype characterization of epileptogenic human brain lesions in order to develop better diagnostic tools for patient stratification in research studies or targeted therapies.
Funding: EU, DFG

Epigenetic mechanisms of epileptogenesis
PI: PD Dr. K. Kobow

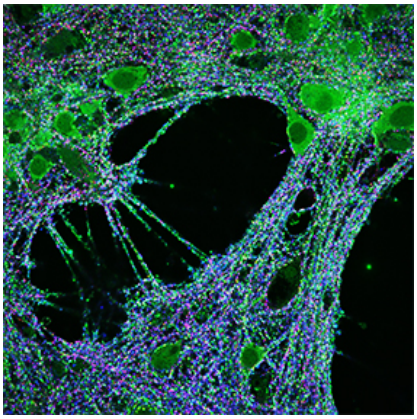

Fig.1: Neuronal cell culture model „epilepsy-in-a-dish". Triple-fluorescence microscopy of antibodies bound to VGLUT1 (blue, demonstration of excitatory synapses), VGAT (green; demonstration of inhibitory synapses) and Bassoon (red, demonstration of active pre-synapses). With permission from Lucas Hoffmann.

Our work specifically addresses genome-wide DNA methylation profiles and the epigenetic signaling machinery, i.e. histone code modifications or miRNA, in relation to epileptic neuronal activity using human surgical brain specimens. This approach includes the development of a novel DNA methylation classifier using Illumina 850k EPIC arrays to support a genotype-phenotype diagnosis based on formalin-fixed and paraffin-embedded human epilepsy surgery tissues. The integration of our data with histomorphological studies obtained from the European Epilepsy Brain Bank as well as the development of machine learning algorithm by our Deep Learning working group (see below) will help to develop new biomarker for disease mechanisms. Another topic of our research explores new therapeutic strategies addressing the epigenetic signaling machinery in our experimental cell culture model 'epilepsy-in-a-dish', such as the ketogenic diet or specific molecular targets thereof.

Deep Learning Morphology
PI: PD Dr. S. Jabari
We have established a new working group addressing innovative deep learning algorithms in the arena of digital pathology. It is the long-term goal of the group to build online solutions for pattern recognition in the histopathological assessment of difficult-to-diagnose epilepsy surgery specimens. We program and train neuronal networks with routine H&E specimens retrieved from the collection of more than 10.000 well-characterized surgical specimens enrolled into the European Epilepsy Brain Bank. All microscopy slides were fully digitized (WSI – whole slide imaging) and submitted to our enhanced deep learning algorithms in order to correctly classify the microscopic image. We use SHAP (SHapley Additive exPlanations) to retrieve and review morphological features identified by the network. We first applied our algorithms to the spectrum of low-grade epilepsy-associated brain tumors (LEAT) to differentiate ganglioglioma from dysembryoplastic neuroepithelial tumors and other LEAT w/o known genetic driver mutations. This approach will be translated into an open access online tool and subsequently extended to the entire spectrum of epilepsy-associated brain lesions to support the resource-intense histopathological genotype-phenotype work-up of surgical human brain specimens.
Funding: IZKF

Molecular myopathology
PI: Prof. Dr. R. Schröder
The central research topic of this group is the pathogenesis of myofibrillar myopathies, which are morphologically characterized by the presence of pathological protein aggregation in cross-striated muscle cells. This group of genetic myopathies and cardiomyopathies is clinically marked by a progressive course and premature death. To date, no specific treatment is available for these disorders. The main focus of our group is the generation and characterization of transgenic mouse and cell models for desmin-, and filamin C-related myopathies and cardiomyopathies. The clinical, morphological, biochemical, and molecular analysis of these models provides deeper insights into the molecular "sequence" that leads to pathological

protein aggregation and progressive muscle damage in these disorders. This work is the basis for the evaluation of novel targeted treatment strategies.
Funding: Deutsche Forschungsgemeinschaft, Deutsche Gesellschaft für Muskelkranke e.V., Association Française contre les Myopathies.

Teaching

The Institute of Neuropathology offers lectures and teaching courses in histopathology for students in Medicine, Dentistry and Molecular Medicine. Comprehensive lectures (clinico-pathology conferences) are organized together with the Departments of Neurology and Neurosurgery. In addition, we annually organize the International Summer School for Neuropathology and Epilepsy Surgery. The 10th Summer School took place from 24.7.-27.7.2019 at UNICAMP in Campinas (Brasil). In total, we have trained more than 300 participants from over 40 countries in our summer schools on the subject of epilepsy-associated brain lesions in hands-on workshops at the microscope and through innovative digital pathology platforms. We supervise Bachelor's and Master's theses as well as doctoral theses of the Faculties of Medicine and Sciences, respectively.

Selected publications

Herrmann et al. H, Dual Functional States of R406W-Desmin Assembly Complexes Cause Cardiomyopathy With Severe Intercalated Disc Derangement in Humans and in Knock-In Mice. Circulation. 2020;142:2155–2171.

Kobow et al. Mosaic trisomy of chromosome 1q in human brain tissue associates with unilateral polymicrogyria, very early-onset focal epilepsy, and severe developmental delay. Acta Neuropathol. 2020 Dec;140(6):881-891

Kobow et al. Genomic DNA methylation distinguishes subtypes of human focal cortical dysplasia. Epilepsia. 2019 Jun;60(6):1091-1103
Kubach et al. Same same but different: A Web-based deep learning application revealed classifying features for the histopathologic distinction of cortical malformations. Epilepsia. 2020 Mar;61(3):421-432

Lamberink et al. European Epilepsy Brain Bank writing group; study group; European Reference Network EpiCARE. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. Lancet Neurol. 2020 Sep;19(9):748-757

International cooperations

International League against Epilepsy

Prof. F. Cendes, Department of Neurology, UNICAMP, Campinas: Brazil

Prof. A. El-Osta, The Alfred Center, Monash University, Melbourne: Australia

Drs. D.Lal, I.Wang, L.Jehi and I.Najm; Epilepsy Center, Cleveland Clinic, Cleveland, Ohio: USA

Dr. J. Zurmanova, Dept. of Physiology, Charles University Prague: Czech Republic

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Research focus
- Diagnostic molecular pathology
- Experimental tumor pathology – gastrointestinal tumors
- Breast and gynecological tumors
- Tumors of the head and neck region
- Clinical and predictive molecular pathology of urogenital carcinomas
- Pathology of immune and inflammatory reactions

Structure of the Chair

Professorships: 5
Personnel: 102
- Doctors (of Medicine): 18
- Scientists: 8 (thereof funded externally: 3)
- Graduate students: 20

Clinical focus areas
Histopathology with specific expertise in
- Breast pathology
- Gynecological pathology
- Urogenital pathology
- Head and neck pathology
- Soft tissue pathology
- Molecular pathology

Research

The main research focus of the Institute of Pathology is the identification of molecular alterations in different malignant tumors. In different research groups, gastrointestinal tumors, breast cancer, gynecological tumors, tumors of the head and neck region, urological tumors, and sarcomas are investigated for both, diagnostic markers and new therapeutic targets. The aim is the integration of the identified molecular alterations into diagnostic molecular pathology. An additional focus is the characterization of immune and inflammatory cell infiltration in tumors and the importance of this immune response for tumor development and response prediction to immunotherapy.

Diagnostic molecular pathology
PI: Prof. Dr. F. Haller, PD Dr. E.A. Moskalev, Dr. L. Tögel, Dr. C. Schubart, Prof. Dr. R. Stöhr
The aim of the group is the development and functional validation of novel genetic and epigenetic markers with diagnostic, prognostic, or predictive impact in solid tumors. The successful establishment of next-generation sequencing technology enabled the group to identify novel key molecular events in different salivary gland tumors and soft tissue neoplasms. Whole genome sequencing in collaboration with the German Cancer Research Center identified recurrent translocations in acinic cell carcinomas of the salivary glands. Another focus of the group is the massive parallel sequencing of multi-gene panels in lung cancer, soft tissue tumors, cancer of the urogenital tract, and head and neck cancer to correlate the presence of mutations among distinct genetic pathways with specific histomorphological subtypes, clinical behavior, and therapy response. The functional characterization of novel genetic or epigenetic aberrations in cell culture systems is another aim to develop the basis for future therapeutical options. Since 2016 the inter-disciplinary molecular tumor board has been successfully installed which aims to detect genetic aberrations in patients with advanced cancer that can be used as therapeutic targets. Since 2018, >600 patient samples presented in the molecular tumor board are analyzed in collaboration with the routine diagnostic molecular pathology group.

Experimental tumor pathology – gastrointestinal tumors
PI: Prof. Dr. R. Schneider-Stock, Dr. K. Erlenbach-Wünsch, Dr. M. Eckstein, Dr. C. Geppert, Prof. Dr. A. Hartmann, Prof. Dr. A. Agaimy
The main focus of our group is the molecular and biochemical characterization of genetic and epigenetic alterations in initiation and progression of colorectal tumors. We aim at identifying new valid biomarkers for tumor transformation in colorectal carcinogenesis that could be of potential therapeutic interest. We are interested in tumor invasion front and thus in regulation of EMT and stemness to drive invasion and metastasis. For translation we are equipped with diverse tissue mircroarrays of CRC patients and immunostainings can be already digitally analyzed. A broad spectrum of 2D and 3D models, patient-derived 3D organoids, co-culture models of tumor cells and immune cells, and CRISPR-ko cell lines is established. The chorioallantoic membrane assay is used as an alternative in vivo test model. Novel experimental conditional ko mice were generated. Since many years we have been studying successfully the anti-cancer effects of novel plant-derived compounds for colorectal tumor cells especially in combination treatment with clinically used drugs.

Breast and gynecological tumors
PI: Prof. Dr. A. Hartmann, Dr. R. Erber
In collaboration with the Department of Gynecology and Obstetrics, we aim to analyze molecular-biological changes of breast cancer and gynecological tumors. Regarding breast cancer, identification of molecular prognostic and predictive biomarkers that can be used in the clinical-pathological differential diagnosis and therapeutical stratification of malignant breast cancer is the main focus. Therefore, we predominantly investigate tumor probes included in large multicentric therapy studies. Besides immunohistochemistry, molecular-pathological techniques like gene expression analyses and sequencing are deployed. Furthermore, we consider immunoncological aspects. The second main focus of our working group includes investigation of molecular-biological features of malignant endometrial and ovarian cancer for potential therapy stratification, e.g. investigation of fumarat hydratase deficient uterine leiomyomas and mismatch repair deficient/microsatellite instable endometrial cancer.

Tumors of the head and neck region
PI: Prof. Dr. A. Agaimy, Prof. Dr. F. Haller
We investigate the molecular changes in tumors of the head and neck region in cooperation with the Departments of Otorhinolaryngology – Head and Neck Surgery and of Oral and Cranio-Maxillofacial Surgery. This research project has two objectives: One is to compile a molecular-pathological and histopathological classify-cation of salivary gland tumors with low and high risk of relapse and progression, the second is to identify early molecular markers to identify dysplastic changes as tumor precursors in the mucosa of the head and neck region.

Clinical and predictive molecular pathology of urogenital carcinomas
PI: Prof. Dr. A. Hartmann, Prof. Dr. Dr. R. Stöhr, PD Dr. Dr. C. Stöhr, PD Dr. S. Bertz, Dr. M. Eckstein, Dr. I. Polifka, Dr. V. Weyerer, Dr. E. Erlmeier, K. Bende, Dr. F Ferrazzi, M Angeloni
The group investigates the basic molecular principles of the development, progression, and subtyping of urothelial carcinoma of the urinary bladder, prostate cancer, squamous cell carcinoma of the penis, and renal cell carcinoma. There is a close cooperation with the Department of Urology, the Institute of Clinical and Molecular Virology and with numerous national and international cooperation partners. The objective is the identification of genomic and epigenetic changes in urothelial carcinomas of the urinary bladder and kidney tumors to identify new markers for early diagnosis and new therapeutic target molecules. In addition, gene expression analyses are used to establish a risk stratification of the tumors that should support the finding of the ideal treatment option for a patient in daily clinical routine. Another focus of the groups' work is the molecular investigation of patients with early-onset disease. These analyses should clarify if tumors in young patients have distinct molecular developmental pathways as compared with tumors from aged patients. Moreover, molecular investigation of tumors from patients with early-onset disease could allow the identification of predisposing factors and disease-initiating events helping to

define individuals with high disease risk. In addition, the group is closely involved into the multi-institutional BRIDGE-Consortium, which main goal is the characterization and clinical implementation of new therapeutic targets for treatment of urothelial carcinoma of the bladder.

Selected main topics of the group are:

- Histologic and molecular characterization of rare subtypes of urothelial cancers
- Histologic and molecular characterization of urothelial cancers of the upper urinary tract in context of an EU-funded multi-institutional TRANSCAN project
- Identification of relevant therapeutic targets using retrospectively selected patient cohorts after adjuvant chemotherapy and multimodal therapies
- Identification of progression and disease initiating markers for bladder cancer using a whole-organ mapping approach on cystectomy specimens
- Analyses of urothelial tumors from patients with early-onset disease (< 45 years of age) to identify disease initiating and predisposing factors
- Histologic, immunohistochemical and molecular characterization of renal cell carcinomas with focus on non-clear cell subtypes (cooperative project with Prof. Dr. M Schwab, Stuttgart, partly in cooperation with the German Network Renal Cell Carcinoma).
- Characterization of the immune cell infiltration and tumor cell metabolism of renal cell carcinoma (cooperative project with Prof. Dr. B. Seliger, Halle)
- Identification of molecular risk factors and prognostic relevant alterations of squamous
- cell carcinoma of the penis
- Digital pathology and development of diagnostic and predictive deep learning approaches

Pathology of immune and inflammatory reactions

PI: Dr. M. Eckstein, Dr. C. Geppert, Prof. Dr. A. Hartmann

This group focusses on the characterization of immunological interactions of different tumors (in particular: colon carcinoma, Barrett's carcinoma of the esophagus, muscle invasive urothelial carcinoma, squamous cell carcinoma of the head and neck) with their immunological microenvironment. There are numerous national and international cooperations. In particular, the characterization of antitumorally active immune cell populations and their immunosuppressive antagonists are the focus. Based on differentially expressed immune cell populations and their activity status, which is largely controlled by immune-checkpoints, different immunophenotypes should be identified which potentially harbor both, prognostic and a predictive significance. Another key topic is the establishment and harmonization of predictive diagnostic tools to predict immunotherapy response such as immuno-checkpoint protein expression (especially PD-L1) and other next generation immuno-oncological biomarkers (e.g. digital pathological assessment of cytotoxic immuncell-infiltrates).

Teaching

The Institute of Pathology is involved in the compulsory and elective curricular teaching of Medicine and Dentistry and of the degree programs Molecular Medicine and Medical Process Management. Particularly noteworthy is the interdisciplinary teaching in the context of crosscutting subjects Q5 and Q6 together with the Departments of Obstetrics and Gynecology, Medicine 1, Urology, Surgery, Nuclear Medicine, and the Institute of Radiology. Bachelor's and Master's theses as well as MD and PhD theses are looked after.

Selected publications

Eckstein M, Erben P, Kriegmair MC, Worst TS, Weiß CA, Wirtz RM, Wach S, Stoehr R, Sikic D, Geppert CI, Weyerer V, Bertz S, Breyer J, Otto W, Keck B, Burger M, Taubert H, Weichert W, Wullich B, Bolenz C, Hartmann A, Erlmeier F. Performance of the Food and Drug Administration/EMA-approved programmed cell death ligand-1 assays in urothelial carcinoma with emphasis on therapy stratification for first-line use of atezolizumab and pembrolizumab. Eur J Cancer. 2019 Jan;106:234-243

Haller F, Bieg M, Will R, Körner C, Weichenhan D, Bott A, Ishaque N, Lutsik P, Moskalev EA, Mueller SK, Bähr M, Woerner A, Kaiser B, Scherl C, Haderlein M, Kleinheinz K, Fietkau R, Iro H, Eils R, Hartmann A, Plass C, Wiemann S, Agaimy A. Enhancer hijacking activates oncogenic transcription factor NR4A3 in acinic cell carcinomas of the salivary glands. Nat Commun. 2019 Jan 21;10(1):368.

Fasching PA, Gass P, Häberle L, Volz B, Hein A, Hack CC, Lux MP, Jud SM, Hartmann A, Beckmann MW, Slamon DJ, Erber R. Prognostic effect of Ki-67 in common clinical subgroups of patients with HER2-negative, hormone receptor–positive early breast cancer. Breast Cancer Research and Treatment 2019 Jun;175(3):617-625. doi: 10.1007/s10549-019-05198-9.

Pfannstiel C, Strissel PL, Chiappinelli KB, Sikic D, Wach S, Wirtz R, Wullweber A, Taubert H, Breyer J, Otto W, Worst T, Burger M, Wullich B, Bolenz C, Fuhrich N, Geppert CI, Weyerer V, Stöhr R, Bertz S, Keck B, Erlmeier F, Erben P, Hartmann A, Strick R, Eckstein M The Tumor Immune Microenvironment Drives a Prognostic Relevance That Correlates with Bladder Cancer Subtypes Cancer Immunol Res. 2019; 7(6): 923-938.

Woerl AC, Eckstein M, Geiger J, Wagner DC, Daher T, Stenzel P, Fernandez A, Hartmann A, Wand M, Roth W, Foersch S Deep Learning Predicts Molecular Subtype of Muscle-invasive Bladder Cancer from Conventional Histopathological Slides. Eur Urol. 2020; 78(2): 256-264.

International cooperations

Prof. F. Real, Spanish National Cancer Research Centre, Madrid: Spain

Prof. J. Galon, French National Institute of Health and Medical Research, Paris: France

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Research focus

- Afferent renal innervation
- Complement-mediated cross-talk between tubular and interstitial cells in renal transplantation.
- Analysis of the pathological effects of light chains and AL protein forms
- The role of DPP4 in crescentic glomerulonephritis
- Chronic kidney disease of unknown etiology (CKDu)
- SriKid H_2O – Investigation of correlations between localized chronic kidney diseases and water quality in Sri Lanka
- Pathology work-up of GvL and GvHD in mice and man
- Role of the receptor GPR126 in heart and kidney development
- Establishment and function of non-centrosomal MTOCs in striated muscle
- Heart regeneration
- Cardiac tissue engineering
- Zebrafish as cancer model

Structure of the Division

Professorships: 2
Personnel: 32

- Doctors (of Medicine): 4
- Scientists: 4 (thereof funded externally: 0)
- Graduate students: 18

Clinical focus areas

- Diagnosis on kidney biopsies
- Diagnosis on peritoneal biopsies
- Diagnosis on iliac crest
- Diagnosis of heart diseases
- Lightmicroscopy, immunohistology, electron microscopy

Research

Clinical and experimental cooperations are well established with clinical partners and research groups of UK Erlangen and FAU as well as external cooperators, working in the field of nephrology. Main focus of the Division of Nephropathology is to test molecular hypotheses on experimental and human kidney biopsy material.

Afferent renal innervation
PI: Prof. Dr. K. Amann
In spite of clear evidence of its importance, a basic feature of renal innervation – the regulation of sympathetic activity by afferent renal nerves – is not yet understood. It is particularly unclear whether renal afferents, i.e. the dorsal root ganglion neurons with renal projections, stimulate or inhibit sympathetic activity. We want to demonstrate in a model of experimental hypertension that afferent renal nerve activity acts rather sympathoinhibitory, but not sympathoexcitatory. This project will be done in collaboration with Prof. Dr. R. Veelken (Department of Medicine 4). Funding: IZKF

Complement-mediated cross-talk between tubular and interstitial cells in renal transplantation
PI: Prof. Dr. M. Büttner Herold, Prof. Dr. C. Daniel, Prof. Dr. K. Amann
In this project the activation of the complement pathway, in particular the lectin signaling pathway, during renal transplantation and thereby the interaction with renal tubular epithelial and inflammatory cells will be investigated. Human renal biopsies and kidney tissue from experimental studies in rats will be used for this purpose. Using an inhibitory antibody directed against the activator of the lectin-activated complement pathway MASP-2 or a C5 blocker inhibiting the terminal pathway of all complement pathways, we aim to prevent graft deterioration and graft loss. In addition, the interaction of different complement factors with renal tubule cells will be investigated in vitro. Funding: SFB 1350

Analysis of the pathological effects of light chains and AL protein forms
PI: Prof. Dr. K. Amann
In this project we investigate the cellular response of amyloidosis light chain (AL) peptides in the heart and kidney, which are important for understanding tissue pathology. Attempts will be made to separate the effect of the various AL peptides themselves from environmental factors, i.e., changes in the milieu or differentiation of cells. In addition, these in vitro data will be the basis for subsequent in vivo analyses in animal models. The work is embedded in a research group consisting of researchers in Kiel, Heidelberg, Ulm and Munich. Funding: FOR 2969

The role of DPP4 in crescentic glomerulonephritis
PI: Prof. Dr. C. Daniel
In this project, we investigate the role of dipeptidyl peptidase IV (DPP4) in pathogenesis of crescentic glomerulonephritis. DPP4 is an exoprotease cleaving incretins as well as different chemokines, but can also act as a co-receptor for cell-cell recognition. Therefore, we induce an anti-GBM model in rats and compare disease propagation in DPP4-inhibitor treated animals with untreated controls. Analysis will focus on the role of DPP4 in crescent formation and changes in kidney function. Funding: Boehringer Ingelheim GmbH

SriKid H_2O – Investigation of correlations between localized chronic kidney diseases and water quality in Sri Lanka
PI: Prof. Dr. K. Amann
Together with nephrologists (Dr. N. Nanayakkara, Prof. Dr. K.-U. Eckardt), hydrogeologists (Prof. J. Barth, Prof. R. Chandrajith) and toxicologists (Prof. C. Zwiener) from Germany and Sri Lanka, we investigate in this interdisciplinary project causes and pathogenesis of chronic kidney dis- ease of unknown etiology (CKDu) that is restricted to dry areas in tropical regions. Beside histopathological characterization of renal biopsies using immunohistology and electron microscopy, comprehensive analysis of drinking water will be done. The aim of this project is to uncover the causes and pathogenesis of this life- threatening disease. Funding: BMBF

Pathology work-up of GvL and GvHD in mice and man
PI: Prof. Dr. M. Büttner-Herold
Diagnosis of GvHD is challenging due to its high variability of clinical and histopathological manifestations and insufficient validation of diagnostic criteria, even for experienced transplant pathologists. Therefore this project aims to better define diagnostic criteria of GvHD by using a round robin test with participation of four different institutes of pathology focusing on GvDH in colon. In addition, together with Prof. Dr. M. Evert (Regensburg) and Prof. Dr. A. Rosenwald (Würzburg) this project will support other sub-projects of the SFB/TRR 221 (compare own report) by production and evaluation of immune-histological sample analysis including human as well as murine GvDH. Funding: DFG, IZKF A84

Role of the receptor GPR126 in heart and kidney development
PI: Prof. Dr. F.B. Engel
Adhesion GPCRs are characterized by large N-termini and a GPS motif at which they are autoproteolytically cleaved into a C-terminal and N-terminal fragment (CTF and NTF, respecttively). Following the discovery that the adhesion GPCR Gpr126 is essential for trabeculation during heart development, Gpr126 was shown to play a critical role in the organization of the endocardium and its differentiation. Analysis of various zebrafish mutants has further shown that the CTF and NTF have distinct roles regulating separate cellular processes during trabeculation. Analysis of Gpr126 zebrafish mutants has also shown that Gpr126 plays a role in kidney development. Funding: DFG, IZKF

Establishment and function of non-centrosomal MTOCs in striated muscle
PI: Prof. Dr. F.B. Engel
Microtubule organization plays a pivotal role in cellular architecture and biological processes such as intracellular transport, signal transduction, mitotic spindle assembly, and organelle positioning. Recently, we have shown that the centrosome - the dominant microtubule organizing center (MTOC) in most proliferating vertebrate

cells - is disassembled in cardiomyocytes during development and that the nuclear envelope adopts the MTOC function. This relocalization of the MTOC was associated with a decline of cardiomyocyte proliferative capacity. MTOC relocalization to non-centrosomal (nc) sites has been described in a wide variety of differentiated cell types. Yet, despite this phenomenon is well known and mutations in related genes cause severe human disease, the formation and function of ncMTOCs are poorly understood. We have now elucidated the molecular mechanism underlying the establishment of nuclear MTOC in muscle cells. Furthermore, we could show that this mechanism is also used by osteoclasts. In rat cardiomyocytes, AKAP6 anchors centrosomal proteins to the nuclear envelope through its spectrin repeats, acting as an adaptor between nesprin-1α and Pcnt or AKAP9. In addition, AKAP6 and AKAP9 form a protein platform tethering the Golgi to the nucleus. Both Golgi and nuclear envelope exhibit MTOC activity utilizing either AKAP9, or Pcnt-AKAP9, respectively. AKAP6 is also required for formation and activity of the nuclear envelope MTOC in human osteoclasts. Moreover, ectopic expression of AKAP6 in epithelial cells is sufficient to recruit endogenous centrosomal proteins. Finally, AKAP6 is required for cardiomyocyte hypertrophy and osteoclast bone resorption activity. Collectively, we decipher the MTOC at the nuclear envelope as a bi-layered structure generating two pools of microtubules with AKAP6 as a key organizer. Funding: DFG

Heart Regeneration
PI: Prof. Dr. F.B. Engel
The loss of cardiomyocytes after heart injury cannot be corrected by conventional treatment methods. Mammalian cardiomyocytes establish a cell cycle arrest after birth and the final cell cycle results in binucleation or polyploidization. In contrast, cardiomyocytes of zebrafish and amphibians maintain their ability to proliferate and can regenerate their hearts by inducing cell division of existing cardiac muscle cells. The research group has recently developed new methods to distinguish cell division and binucleation (failure of cytokinesis) in cardiomyocytes. In addition, we have characterized these processes and demonstrated that also binucleated cardiomyocytes can be induced to proliferate. Our results indicate that postnatal binucleated cardiomyocytes upon stimulation can enter mitosis, cope with their multiple and/or unpaired centrioles by forming pseudo-bipolar spindles, and divide. Funding: DFG, ELAN

Cardiac tissue engineering
PI: Prof. Dr. F.B. Engel
Materials for the generation of artificial heart tissue are tested for tissue replacement therapy. In close collaboration with Prof. Dr. A.R. Boccaccini (Department of Biomaterials, Faculty of Engineering) and Prof. T. Scheibel (Bayreuth Materialzentrum, University of Bayreuth), we cur- rently focus on the analysis of electroconductive materials, collagen, and recombinantly produced silk. We are now able to produce beating heart tissue from human pluripotent stem cells that beat for weeks without external stimulation and respond to various pharmaceuticals. In addition, we have started to integrate endothelial cells into our fabrication strategy to pre-vascularize the tissues. Funding: DFG, TRR 225, Foundation Medicine

The zebrafish as cancer model
PI: Prof. Dr. F.B. Engel
Since cardiomyocytes establish a strict cell cycle arrest after birth – and thus cardiac tumors are very rare - cardiomyocyte differentiation appears to be an excellent model to identify new potential targets for cancer treatment. To determine the role of candidate genes such as IQGAP3 in cancer cell proliferation and migration, a zebrafish xenograft model will be used and live cell imaging will be performed. We study IQGAP3 in colorectal cancer as: 1) IQGAP3 is downregulated during heart development and mis-localized during the last cell cycle resulting in binucleation. 2) It is expressed in proliferating transit-amplifying cells in crypts and is upregulated in colorectal cancer; one of the most common and lethal cancers. During the last decade the zebrafish model has been established as a powerful tool for cancer biology. In addition to its general advantages, the embryonic zebrafish is an excellent xenograft model as its adaptive immune system matures not before 4 weeks post-fertilization. Therefore, injection of mouse or human cells will not cause an immune rejection. Moreover, xenografts can be performed in zebrafish 48 hours post-fertilization and results will be obtained 4 days later at 6 days post-fertilization. Funding: Wilhelm Sander Foundation

Teaching

The Division of Nephropathology participates in the teaching of the Institute of Pathology and acts as "Advanced Training Center for Nephropathology" of the European Society of Pathology.
Bachelor's and Master's theses as well as MD and PhD theses are supervised.

Selected publications

Daniel C, Leppkes M, Munoz LE, Schley G, Schett G, Herrmann M. Extracellular DNA traps in inflammation, injury and healing. Nature reviews Nephrology. 2019; 15(9):559-575.

Balasooriya S, Munasinghe H, Herath AT, Diyabalanage S, Ileperuma OA, Manthrithilake H, et al. Possible links between groundwater geochemistry and chronic kidney disease of unknown etiology (CKDu): an investigation from the Ginnoruwa region in Sri Lanka. Exposure and Health. 2020; 12(4):823-834.

Rodionova K, Veelken R, Hilgers KF, Paulus EM, Linz P, Fischer MJM, et al. Afferent renal innervation in anti-Thy1.1 nephritis in rats. American journal of physiology Renal physiology. 2020;319(5):F822-f832.

Rodionova K, Hilgers KF, Paulus EM, Tiegs G, Ott C, Schmieder R, et al. Neurogenic tachykinin mechanisms in experimental nephritis of rats. Pflugers Archiv : European journal of physiology. 2020;472(12):1705-1717.

Vergarajauregui S, Becker R, Steffen U, Sharkova M, Esser T, Petzold J, Billing F, Kapiloff MS, Schett G, Thievessen I, Engel FB. AKAP6 orchestrates the nuclear envelope microtubule-organizing center by linking golgi and nucleus via AKAP9. Elife. 2020; 9:e61669.

Roshanbinfar K, Vogt L, Ruther F, Roether JA, Boccaccini AR, Engel FB. Nanofibrous Composite with Tailorable Electrical and Mechanical Properties for Cardiac Tissue Engineering Adv Funct Mater. 2020; 30(7): 1908612.

Musa G, Srivastava S, Petzold J, Cazorla-Vázquez S, Engel FB. miR-27a/b is a post-transcriptional regulator of Gpr126 (Adgrg6). Ann N Y Acad Sci. 2019; 1456(1):109-121.

Leone M, Engel FB. Pseudo-bipolar spindle formation and cell division in postnatal binucleated cardiomyocytes. J Mol Cell Cardiol. 2019; 134:69-73.

Roshanbinfar K, Mohammadi Z, Mesgar AS, Dehghan MM, Oommen OP, Hilborn J, Engel FB. Carbon nanotube doped pericardial matrix derived electroconductive biohybrid hydrogel for cardiac tissue engineering. Biomater Sci. 2019; 7(9):3906-3917.

International cooperations
Prof. S. Shankland, Department of Nephrology, University of Washington, Seattle: USA

Dr. N. Nanayakkara, Kandy University Hospital, Kandy: Sri Lanka

Prof. M. van den Hoff, Department of Anatomy, Academic Medical Center Amsterdam, Amsterdam: The Netherlands

Prof. M. Kapiloff, Stanford Cardiovascular Institute, Stanford University: USA

Prof. J. Hilborn, Department of Chemistry, Angstrom Laboratory, Uppsala University: Sweden

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Research focus

- Clinical Ethics and Ethics Consultation
- Medicine and Human Rights
- Human Rights in Healthcare
- Global Health Ethics and Philosophy of Medicine

Structure of the Professorship

Professorship: 1
Personnel: 13

- Doctors (of Medicine): 2
- Scientists: 8
  (thereof funded externally: 5)
- Graduate students: 20

Special structural features
The autonomous Professorship for Medical Ethics is responsible for management of the Clinical Ethics Committee at UK Erlangen and a Graduate School. The Chair of the History of Medicine and the Professorship for Medical Ethics constitute the Institute for the History of Medicine and Medical Ethics.

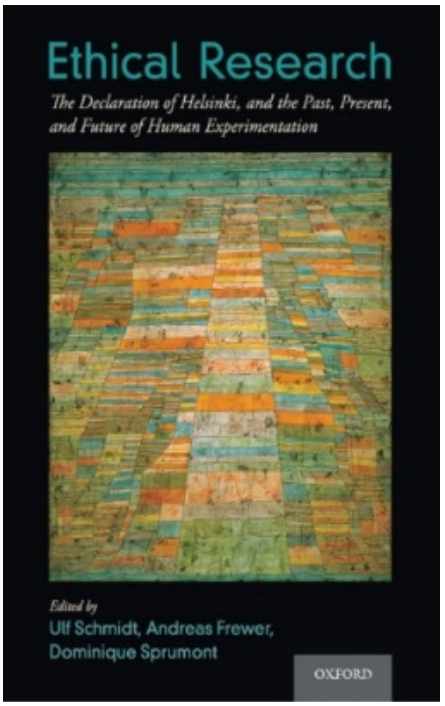
Research

The main areas of research are clinical ethics and ethics consultation, medicine and human rights, and global health ethics and philosophy of medicine. The field of clinical ethics deals with foundational ethical questions concerning the adequate care for patients, motivation of the acts of physicians during the daily routine, and conflict situations in hospital and other medical facilities. Central questions are ethical issues at the beginning of life (prenatal diagnosis, pregnancy challenges, neonatology etc.), during a crisis (oncology, genetic advice, psychiatry, transplantation), and at the end of life (advance directives, dementia, terminal care, euthanasia etc.). Some important means of clinical ethics are the analysis of arguments of applied medical ethics and bioethics, advice via ethics committees, and empirical research. The Professorship chairs the Graduate School "Human Rights and Medical Ethics for the Elderly" (Josef and Luise Kraft Foundation), runs the "Forum Medicine and Human Rights" and edits twelve book series.

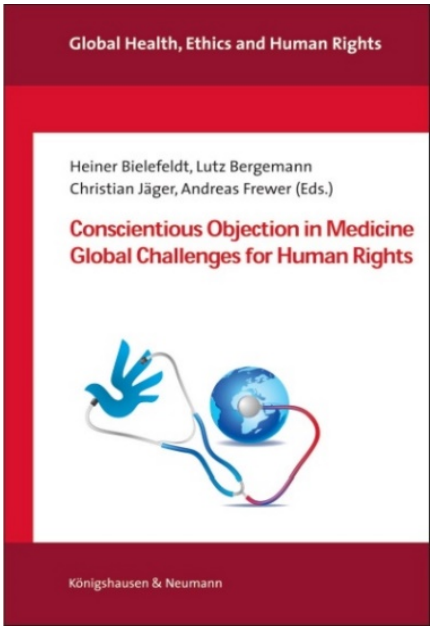
Clinical Ethics and Ethics Consultation
PI: Prof. Dr. A. Frewer, PD Dr. L. Bergemann, Dr. C. Hack, Elisabeth Langmann, M.A.
A main field of expertise of the Professorship for Medical Ethics is research concerning clinical ethics consultation whereby a close cooperation with the Clinical Ethics Committee is given. Theoretical groundwork and documentation of ethics consultation and the evaluation of ethical consultation belong to this field of inquiry. Files of patient's advocates are being dealt with in the project "Clinical Ethics from the Patient's Perspective". Further fields of research, particularly using methods of empirical ethics, are end of life conflicts, e.g. projects on ethical consultation, cultures of dying, and advance directives.
As part of this field of research, an annual "Ethics Day" and an intensive course "Clinical Ethics" (BMBF) were organized, the "Yearbook Ethics in Clinics" and the book series "Clinical Ethics" are being edited.
In context of strategies against the Covid-19-Pandemic the project "Clinical Ethics Consultations in Covid-19. Current and Future Challenges" was funded by the WHO in the year 2020.

Medicine and Human Rights
PI: Prof. Dr. A. Frewer, PD Dr. L. Bergemann, Dr. C. Hack, Elisabeth Langmann, M.A.
This field of research bears on problems of determining the place of human dignity and human rights in the area of medical and bioethical controversy. The possibilities and limits of a rights-based medical ethics and bioethics are considered from a theoretical perspective and several dimensions of the concepts of human dignity and human rights are studied in this context. In a practical vein, this area of research involves questions of medical investigation and the documentation of human rights violations, application of the Istanbul Protocol of the United Nations to document torture, but also the participation of physicians in human rights violations. Not least of all, it inquires into the therapy and prevention of human rights violations, such as wartime sexual violence, torture, recruitment of children as soldiers, and female genital mutilation. In connection with this area of research, a public lecture series (in cooperation with "CHREN") is being organized and three academic book series are being edited.

Human Rights in Healthcare
PI: Prof. Dr. A. Frewer, PD Dr. L. Bergemann, Dr. C. Herrler, Dipl.-Polit. S. Klotz
The project "Human Rights in Healthcare" focuses on highly relevant issues in the intersection of human rights, medicine, and medical ethics. The project deals with conflicting claims to receive support for personal autonomy in healthcare. The general purpose is to better understand the implicit criteria which guide decisions taken in clinical practice and to develop normative criteria based on human rights and medical ethics. Practical examples are studied intensively with issues of dialysis, transplantation, new conflicts arising from international patient mobility, health literacy education, contributions to health empowerment of vulnerable groups and end-of-life-questions. Beyond raising public awareness on complicated and important issues, the aspiration is to provide practical orientation based on ethical principles, internationally binding human rights' norms, and professional experience in the field. The field develops an intensive cooperation between researchers from different disciplines, including medicine, human rights, ethics, law, philosophy, social sciences, political science, and literature studies.



Global Health Ethics and Philosophy of Medicine
PI: Prof. Dr. A. Frewer, M.A., PD Dr. R. Erices, Dr. C. Herrler, PD Dr. A. Reis, M.Sc.dThis field deals with questions concerning the notion ”disease” and human aging, moral evaluations of various aspects of human enhancement, preimplantation diagnosis, and deep brain stimulation. In this context, two academic book series are being edited.



Teaching

The Professorship for Medical Ethics contributes with obligatory and facultative subjects to the education of the students. Special units are offered within the Graduate School “Human Rights and Medical Ethics for the Elderly” and the interdisciplinary seminars “Q2” and “Q13”. The seminars on “Ethical Communicative Competencies“ – with role plays for students and simulated patients, some inter-professional – deserve to be mentioned particularly. This broad offer on the complex ethical questions with the modules “Breaking Bad News”, “Talking about Death and Dying”, “Intercultural Communication”, “Acting at borders – Coping with Dementia” and “Communicative Competencies for Errors in Medicine” is unique at medical faculties in Germany.
Bachelor’s and Master’s theses and medical or philosophical dissertations as well as “Habilitations”/PhD studies are supervised.
Prof. Dr. A. Frewer is Senior Advisory Consultant of the World Health Organization (WHO) and gives international lectures as well as courses.

Selected publications
Frewer A. Conflicts of Interest? The World Medical Association, Research Ethics, and Industry in the 1950s and 60s. In: Schmidt et al. (2020). Oxford/New York, pp. 131-166

Frewer A. Ältere Menschen in der Sprache der Medizin. Ethische Fragen von Ausgrenzung und Ageism. In: Gute Behandlung im Alter? (2020), pp. 67-94

Frewer, A. (Hrsg.) Psychiatrie und „Euthanasie“ in der HuPfla. Debatten zu Werner Leibbrands Buch „Um die Menschenrechte der Geisteskranken“. Nürnberg, 2020

Frewer A, Bergemann L, Langmann E (Hrsg.) Unsicherheit in der Medizin. Zum Umgang mit Ungewissheit im Gesundheitswesen. Jahrbuch Ethik in der Klinik, Band 13. Würzburg, 2020

Frewer A, Klotz S, Herrler C, Bielefeldt H (Hrsg.) Gute Behandlung im Alter? Menschenrechte und Ethik zwischen Ideal und Realität. Human Rights in Healthcare 8. Bielefeld, 2020

Jungert M, Frewer A, Mayr E (Hrsg.) Wissenschaftsreflexion. Interdisziplinäre Perspektiven zwischen Philosophie und Praxis. Paderborn

Schmidt U, Frewer A, Sprumont D (Eds.) Ethical Research. The Declaration of Helsinki, and the Past, Present and Future of Human Experimentation. Oxford University Press, Oxford/New York, 2020

Wittwer H, Schäfer D, Frewer A (Hrsg.) Handbuch Sterben und Tod. Geschichte – Theorie – Ethik. 2. Auflage/Second Edition. Stuttgart/Heidelberg, 2020

International cooperations
PD Dr. A. Reis, M.Sc. Health Ethics & Governance Unit, Research for Health Department, World Health Organization (WHO), Geneva: Switzerland

Prof. U. Schmidt, PhD., Centre for the History of Medicine, Ethics and Medical Humanities, University of Kent, Canterbury: UK

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Research focus

- Cellular plasticity as driving force of metastasis
- EMT-activators in cancer-associated fibroblasts (CAF) and macrophages (CAM)
- Nuclear co-factors of the tumorigenic EMT-activator ZEB1
- Role of the EMT-activator ZEB1 in pancreas development und homeostasis
- Role of the EMT-activator ZEB1 in skeletal development and osteosarcoma
- EMT-transcription factors as regulators of cell-metabolism and DNA-repair
- EMT-dependent transcriptional enhancers in cancer metastasis

Structure of the Chair

Professorship: 1
Personnel: 15

- Doctor (of Medicine): 1
- Scientists: 5
- (thereof funded externally: 4)
- Graduate students: 4

Special structural feature
Managing Director of the Nikolaus-Fiebiger Center (NFZ), alternating biannually with the Chair of Experimental Medicine II

Research

Our research is focused on the development and malignant progression of solid cancers, particularly on the molecular mechanisms of tumor invasion and metastasis. The aim is to develop novel therapeutic concepts to fight these processes. We integrate cell-/molecular-biological, epigenetic, and genetic methods, in vitro and in vivo model systems, as well as analyses of human tumor samples and patient data.

Cellular plasticity as driving force of metastasis
PI: Dr. M. Stemmler, Dr. S. Brabletz, Prof. Dr. T. Brabletz
We have shown that the ability of cancer cells to adapt to changing conditions und demands is a major determinant of malignant progression towards a therapy-resistant, metastatic disease. This ability is termed aberrant cellular plasticity. The molecular basis in many cases is a molecular motor which we identified, i.e. the ZEB1/miR200 feedback loop. By this molecular motor, the transient expression of ZEB1 in cancer cells activates stemness properties and a partial epithelial-mesenchymal transition (EMT), which stimulates invasion, therapy resistance dissemination, and finally metastasis in solid cancer types. The central role of ZEB1 in tumorigenicity, plasticity, and metastasis was proven by us by a conditional knockout of ZEB1 in a genetic mouse model of pancreatic cancer.

EMT-activators in cancer-associated fibroblasts (CAF) and macrophages (CAM)
PI: Dr. M. Stemmler, Dr. S. Brabletz, Dr. H. Schuhwerk, Prof. Dr. T. Brabletz
The observed high plasticity in cancer cells implies that not only genetic alterations, but also regulatory inputs from the tumor environment are major driving forces of tumor progression. Thereby the interaction of cancer cells with cancer associated fibroblasts (CAF) and macrophages (CAM) plays an important role. We could show that the EMT activator ZEB1 is highly upregulated in CAFs and CAMs as compared to their normal counterparts and regulates the expression of central genes of these cell types. By using conditional ZEB1 knockout mice, we investigate the effect of a ZEB1 depletion on development and progression of gastrointestinal tumors.

Nuclear co-factors of the tumorigenic EMT-activator ZEB1
PI: Dr. S. Brabletz, Dr. M. Stemmler, Dr. R. Eccles, Prof. Dr. T. Brabletz
We demonstrated that ZEB1 is an important tumorigenic factor. ZEB1 is a transcription factor and by unknown mechanisms it can switch from a transcriptional repressor to an activator. We postulated the recruitment of unknown nuclear co-factors as underlying mechanism and identified a number of potential binding partners by mass spectrometric analyses. In this project we validate and characterize their binding to ZEB1. In addition we investigate their mutual functional effects. Thereby we also determine changes in whole genome expression patterns and epigenetics by applying ChIPSeq analyses. On the basis of the results, the long term aim is to develop inhibitors of ZEB1 function also for potential therapeutic usage.

Role of the EMT-activator ZEB1 in pancreas development und homeostasis
PI: Dr. M. Stemmler
Based on the data that ZEB1 is crucial for the pathogenesis of pancreatic cancer, we hypothesized that it also regulates normal pancreas development and adult pancreas homeostasis. This is investigated in a conditional ZEB1 knockout mouse model. First results showed no strong effect of ZEB1 on pancreatic development, but indicate a role of ZEB1 in pancreatic homeostasis under stress conditions. We now investigate this by applying different stress conditions (high fat, high glucose, pancreatitis, etc.).

Role of the EMT-activator ZEB1 in skeletal development and osteosarcoma
PI: Dr. S. Brabletz, Dr. M. Ruh, Prof. Dr. T. Brabletz
In a conditional ZEB1 knockout mouse model we identified, besides other affects, strong defects in embryonic bone development. We subsequently demonstrated that mesenchymal stem cells (MSC) need ZEB1 to maintain their stemness state. Consequently ZEB1 had to be downregulated to allow differentiation to osteoblasts. This regulatory mechanism also affects the generation of osteosarcoma. We could show that the expression of ZEB1 correlates with a particular aggressiveness of osteosarcomas. Depletion of ZEB1 in osteosarcoma cells reduces their stemness competence, tumorigenicity, and aggressiveness.

EMT-transcription factors as regulators of cell-metabolism and DNA-repair
PIs: Prof. Dr. T. Brabletz, PD Dr. S. Brabletz, PD Dr. M. Stemmler, Dr. H. Schuhwerk, Dr. J. Kleemann
A new project is dedicated to our recently discovered relationship between the expression of EMT transcription factors and the regulation of cellular metabolism, in particular fatty acid metabolism, and DNA replication or associated DNA repair mechanisms. Both subfields aim to define EMT-dependent bottleneck factors for cancer cell survival, which then serve as targets for therapeutic attacks.

EMT-dependent transcriptional enhancers in cancer metastasis
PIs: PD Dr. S. Brabletz, Dr. Nora Feldker.
Phenotypic plasticity enables tumor cells to metastasize. The EMT transcription factor Zeb1 mediates this plasticity and drives metastasis, which is accompanied by substantial enhancer reprogramming. Because Zeb1 functions as a transcriptional coactivator in putative enhancer regions, we are examining the enhancer landscape in metastatic cell lines to determine Zeb1-dependent enhancers, their target genes, and their relevance to metastasis development. The results will be validated in human cell lines and organoids. This will allow us to understand the molecular context of metastasis and use it as a basis for new prognostic and therapeutic approaches.

Teaching

The Chairs of Experimental Medicine I and II organize lectures, seminars, and experimental classes in cell, molecular, and developmental biology at basic and advanced levels for students of Molecular Medicine, Medicine, and biology. Bachelor's and Master's theses are supervised.

Selected publications
Feldker N, Ferrazzi F, Widholz SA, Guenther K, Lukassen S, Kleemann J, Riegel D, Bönisch U, Eccles RL, Schmidl C, Stemmler MP, Brabletz T*, Brabletz S*. Genome-wide cooperation of the EMT-activator ZEB1 with YAP and AP-1 factors in breast cancer. EMBO J, 39(17):e103209 (2020). * joint senior authors.

Stemmler MP, Eccles RL, Brabletz S, Brabletz T. Non-redundant functions of EMT-transcription factors. (invited review) Nat Cell Biol, 21: 102-112 (2019)

Liu M, Zhang Y, Yang J, Cui X, Zhou Z, Zhan H, Ding K, Tian X, Yang Z, Fung KA, Edil BH, Postier RG, Bronze MS, Fernandez-Zapico ME, Stemmler MP, Brabletz T, Li YP, Houchen CW, Li M. ZIP4 Increases Expression of Transcription Factor ZEB1 to Promote Integrin α3β1 Signaling and Inhibit Expression of the Gemcitabine Transporter ENT1 in Pancreatic Cancer Cells. Gastroenterology. 2020 Feb; 158(3): 679-692.

Haensel D, Sun P, MacLean AL, Ma X, Zhou Y, Stemmler MP, Brabletz S, Berx G, Plikus MV, Nie Q, Brabletz T, Dai X. An Ovol2-Zeb1 transcriptional circuit regulates epithelial directional migration and proliferation. EMBO Rep. 2019 Jan;20(1): e46273.

International cooperations

Prof. Dr. G. Berx, University of Ghent VIB, Gent: Belgium

Dr. M. Conacci-Sorrell, UT Southwestern Medical Center, Dallas: USA

Prof. A. Ben Ze'ev, Weizman Institute, Rehovot: Israel

Dr. F. Siebzehnrübl, Stem Cell Institute, Cardiff: UK

Prof. Dr. A. Puisieux, Cancer Research Center, Lyon: France

Nikolaus-Fiebiger-Center of Molecular Medicine

Chair of Experimental Medicine II (Molecular Oncology)

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Research focus
- Molecular oncology of Wnt signaling
- Amer proteins
- Role of Axin/Conductin as negative Wnt regulators

Structure of the Chair

Professorship: 1
Personnel: 9
- Scientists: 3 (thereof funded externally: 0)
- Graduate students: 2

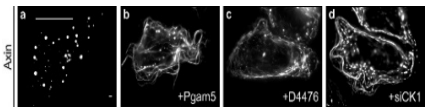
Special structural feature
Managing Director of the Nikolaus-Fiebiger-Center (NFZ) alternating biannually with Chair of Experimental Medicine I

Research

The focus of research is on the molecular analysis of signal transduction pathways causally involved in tumor diseases. Over the last years, central components of the oncogenic Wnt signaling pathway were identified through special screening approaches and analyzed in molecular detail. These efforts have contributed to the identification of novel targets for therapy aimed at inhibition of the pathway, which are currently intensively investigated worldwide.

Molecular oncology of Wnt signaling
The Wnt signaling pathway controls the stability of β-catenin and thereby regulates various processes during embryonic development and can lead to cancer. Wnt are secreted glycoproteins, which induce the accumulation of β-catenin in cytoplasm and nucleus by binding to frizzled and LRP receptors. β-Catenin interacts with TCF transcription factors and activates target genes. The destruction of β-catenin is induced by phosphorylation in a multi-protein complex consisting of the scaffold components axin or conductin, the serine/threonine kinase GSK3β, and the tumor suppressor APC (Adenomatous Polyposis Coli). The Wnt signal inhibits phosphorylation of β-catenin and thereby leads to its stabilization. In colorectal tumors, mutations of APC or of the serine/threonine phosphorylation sites of β-catenin lead to stabilization of β-catenin and trigger constitutive signaling to the nucleus. Such β-catenin mutations are also found in a multitude of other tumor types suggesting that aberrant activation of Wnt signaling is a key mechanism of oncogenic transformation. We are analyzing the molecular roles of central components of the pathway, which are mostly involved in β-catenin degradation. Among these are Amer1, Axin, Conductin as well as the phosphatase PGAM5 that all modulate β-catenin phosphorylation.

Role of Axin/Conductin as negative Wnt regulators
PI: Dr. D. Bernkopf
Axin and conductin (also known as axin2) are structurally related inhibitors of Wnt/β-catenin signaling that promote degradation of β-catenin. Whereas axin is constitutively expressed, conductin is a Wnt target gene implicated in Wnt negative-feedback regulation. By proteome analysis we could demonstrate an interaction of axin with the mitochondrial phosphatase PGAM5. PGAM5 gets cleaved and released to the cytoplasm after damage of the mitochondrial membrane potential. Cytoplasmic PGAM5 interacts with axin, and the resulting complex induces dephosphorylation of β-catenin leading to its stabilization and activation of β-catenin-dependant transcription. Since Wnt signaling is known to increase mitochondrial numbers, we proposed that the release of cytoplasmic PGAM5 from damaged mitochondria induces formation of new mitochondria by activating the Wnt pathway (Bernkopf et al., 2018). In the course of these studies we noticed that Pgam5 alters the localization pattern of axin. Whereas transiently expressed axin formed the typical axin puncta, co-expression of PGAM5 frequently induced the formation of long elongated axin polymers resembling fibrils (Fig. 1, a,b). Importantly, inhibition or knockdown of a central kinase in the Wnt/β-catenin signaling pathway, casein kinase 1 (CK1) also induced the formation of axin fibrils (Fig. 1c, d), suggesting that endogenous CK1 controls the axin polymerization mode. These data revealed the existence of a yet uncharacterized fibrillary form of axin polymers besides the well-studied punctate form, and show that the transition between both is a regulated process involving phosphorylation. Of note, Pgam5-induced axin fibrils co-localized with microtubules (MTs) and were destroyed by depolymerization of MTs with nocodazole (not shown).
We also noticed that puncta of transiently expressed axin as well as of endogenous axin were in close proximity and appeared associated to MTs These data suggest that MTs provide a platform for fibril formation by axin, and might be involved in degrading β-catenin, which is suggested by preliminary data of our group. Although conductin is strongly upregulated in colorectal cancer as a target of Wnt signaling, its activity apparently does not suffice for blocking β-catenin. We noticed that conductin per se is less active that axin in degrading β-catenin. We found that axin and conductin differ in their intracellular distribution with axin polymerizing into microscopically-visible puncta while conductin was distributed diffusely all over the cytoplasm. This became of functional interest because axin-mediated β-catenin degradation depends on polymerization. By exchanging domains between both homologs, we could map the differential distribution to the regulator of G-protein signaling (RGS) domain (Bernkopf et al., 2019).
We discovered a predicted aggregation site in the RGS domain of conductin that is lacking in the RGS domain of axin and showed that RGS mediated aggregation blocks conductin polymerization. Importantly, inactivation of this aggregon by specific amino acid mutation allowed polymerization of conductin and led to increased activity of conductin in degrading β-catenin. Together, these data suggest that interfering with RGS-mediated aggregation promotes DIX-mediated polymerization of conductin and inhibits Wnt signaling. In order to develop a strategy to promote conductin polymerization, we designed short peptides containing the aggregation site, which would compete with RGS-RGS aggregation of conductin. Indeed, co-expression of such a peptide induced polymerization of conductin, reduced Wnt signaling and suppressed growth of colorectal cancer cells in vitro (Bernkopf et al., 2019).
We are currently optimizing the peptide for in vivo use and plan to screen chemical libraries of FDA-approved small-molecules for compounds inducing conductin polymerization. These could serve as peptide alternatives and potential chemotherapeutic drugs in the future.



Puncta of axin (a), and fibril formation after Pgam5 expression (b), CK1 inhibition (c), or CK1 knockdown (d).

Teaching

The Chairs of Experimental Medicine I and II are primarily responsible for the training of bachelor and master students of Molecular Medicine in cell biology and molecular oncology.
Bachelor's and Master's theses are supervised.

Selected publications
Bernkopf DB, Jalal K, Bruckner M, Knaup KX, Gentzel M, Schambony A, Behrens J. Pgam5 released from damaged mitochondria induces mitochondrial biogenesis via Wnt signaling. J Cell Biol 2018, 217, 1383-1394

Bernkopf DB, Brückner M, Hadjihannas MV, Behrens J. An aggregon in conductin/axin2 regulates Wnt/β-catenin signaling and holds potential for cancer therapy. Nat Commun. 2019, 18; 4251.

International cooperation
Prof. V. Katanaev, University Geneva, Geneva: Switzerland

Department of Orthopedics in the Malteser Waldkrankenhaus St. Marien gGmbH

Chair of Orthopedics and Orthopedic Surgery

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Research focus

- Roentgen-Stereophotogrammetric-Analysis (RSA) for quality control in total hip and knee arthroplasty
- Neuromuscular disorders
- Gait- and posture analysis

Structure of the Department

Professorship: 1
Personnel: 9

- Doctors (of Medicine): 3
- Scientists: 1
- Graduate students: 32 / Graduations 9
- post-doctoral qualification applicants: 1 / post-doctoral qualifications 3

Clinical focus areas

- Hip, knee and shoulder arthroplasty
- Knee and shoulder surgery
- Arthroscopic surgery
- Foot surgery
- Pediatric orthopedics
- Neuromuscular disorders
- Conservative and technical orthopedics
- Orthopedic pain management

Research

The Department of Orthopedics deals with innovative research questions concerning in vivo diagnostics and therapy within the field of total hip and knee arthroplasty. Main topics represent the assessment of in vivo implant migration and implant safety, the preoperative planning of total hip and knee arthroplasty and spinal intervertebral fusions as well as gait and posture analysis. Additionally clinical studies within the field of neuromuscular diseases were performed.
Research staff is organized within the „Research Network Musculoskeletal Biomechanics (MSB-NET)“ of the German Society for Orthopedics and Traumatology (DGOU) and have exchange opportunities with similar national research institutions.

Roentgen-Stereophotogrammetric-Analysis (RSA) for quality control in total hip and knee arthroplasty
PI: Prof. Dr. R. Forst, PD Dr. F. Seehaus
Implantation and revision statistics for total hip and knee arthroplasty have shown a continuous increase within the recent years. Aseptic implant loosening is a clinical challenge and still one of the most common causes of total joint arthroplasty revision surgery. By Roentgen-Stereophotogrammetric-Analysis (RSA) method, it is possible to assess clinically the in vivo implant fixation of a new implant designs or coatings within the first two postoperative years. The RSA method allows an accurate in vivo measurement of the relative implant-to-bone movement, the so-called implant migration. It has been shown scientifically that the continuously increasing early implant migration correlates very well with a later aseptic loosening within the first two postoperative years, which predicts RSA as a reliable surrogate marker for later aseptic loosening of the implant. The current focus of RSA research at the Department of Orthopedics is on the experimental validation of new RSA approaches as well as the clinical assessment of in vivo migration of total hip arthroplasty.
Currently, an RSA approach is being experimentally and clinically validated, which uses a generated implant model based on elementary geometrical shapes (EGS) and uses this to determine migration. Methodological limits and further possibilities for assessing implant safety using the RSA-EGS approach were demonstrated.
In addition to the classic application of the RSA method to assess the in vivo implant fixation, the Department of Orthopaedics uses RSA approach to determine the in vivo wear behaviour of THA bearings and to determine the in vivo implant kinematics.
The Department of Orthopedics collaborates with the Laboratory for Biomechanics and Biomaterials of Hannover Medical School, Laboratory for Biomechanics and Implant Research of the Orthopedic University Hospital Heidelberg and the Institute of Medical Technology of Ostbayerische Technische Hochschule Amberg-Weiden.

Neuromuscular disorders
PI: Prof. Dr. J. Forst, Dr. A. Fujak, Prof. Dr. R. Forst
The research group for neuromuscular disorders is engaged in an evaluation of orthopedic symptoms, conservative and operative treatment in children and adult patients with neuromuscular disorders. The aim of research is the optimization of orthopedic treatment, improvement of the medical care and quality of life of these patients. The studies are particularly focused on anterior horn cell diseases, spinal muscular atrophies, post-polio syndrome, hereditary neuropathies and muscular dystrophies. Although knowledge of the gene defect and the coded protein – the dystrophin – is given, there is no causal therapy of Duchenne muscular dystrophy (DMD) – the most common neuromuscular disease. The natural history of this disease includes beside the obligatory restrictive respiratory insufficiency the cardiomyopathy contractures of the extremities and progressive scoliosis in almost all patients.
The results of operative treatment of contractures of lower extremities particularly in early course of the disease are investigated in a prospective study in a collective of more 500 patients with genetically confirmed diagnosis of DMD. Positive effect of this treatment could be proven, and a stage-oriented therapy concept could be developed.
In close cooperation with the Department of Anesthesiology, the special features in anesthesia and pain therapy in patients with the neuromuscular disorders are investigated. In common projects with the Division of Pediatric Cardiology and the Institute of Radiology, the participation of the heart musculature in DMD is examined.

Gait and posture analysis
PI: PD Dr. F. Seehaus, Prof. Dr. R. Forst, PD Dr. A. Fujak
The Department of Orthopaedics cooperates here on a national level with the gait laboratory of the Orthopaedic Children's Hospital in Aschau (Dr. C. Dussa; PD Dr. habil H. Böhm), and internationally with the University of Physical Education in Warsaw, Poland.
Questions onto the assessment and classification of gait pathologies, applicability and efficiency of orthopaedic aids or the review of surgical treatments. For the assessment of in vivo implant kinematics, an initial measurement and information system was set up and validated as part of a student project in the medical technology course.

Teaching

The Department of Orthopedics participates within the curricular teaching of Medicine. To increase interdisciplinary teaching at FAU, interdisciplinary courses for students of Medicine and medical technology are held in cooperation with the Faculty of Engineering. Lecture and seminar are open to students of medical technology, as well as materials scientists, industrial engineers, mechanical engineers, or mechatronics.
The existing curriculum for medical students (internship at Department of Orthopedics) is continuously expanded by practical exercises/ laboratories, likewise the „Skillslab Fractue Treatment”. Within this course, students should be trained first practical skills in the field of plate osteotomy and or the implantation of total knee and hip arthroplasty using Saw-Bones.
In addition Bachelor’s and Master’s theses from students of the Faculty of Engineering as well as medical dissertations are supervised. Currently, five Chinese guest physicians (PhD Fellowships), 32 doctoral students, and 1 postdoctoral qualification applicant are supervised by the Department of Orthopedics.
Results of current projects were presented by research staff and PhD students at national and international conferences.

Selected publications
Xu J, Sonntag R. Kretzer JP, Taylor D, Forst R, Seehaus F. Model-based Roentgen Stereophotogrammetric Analysis to monitor in vivo the Head-Taper junction in Total Hip Arthroplasty – and they do move. Materials. 2020, 13(7):1543.

Seehaus F, Sonntag R, Schwarze M, Jakubowitz E, Sesselmann S, Kretzer JP, Hurschler C. Früherkennung des Risikos der späteren Implantatlockerung mittels der Röntgen Stereophotogram-metrischen Analyse (RSA). Orthopäde. 2020, 49(12):1042-1048.

Hüttel M, Golditz T, Mayer I, Heiss R, Lutter C, Hoppe MW, Engelhardt M, Grim C, Seehaus F, Forst R, Hotfiel T. Effects of Pre- and Post-Exercise Cold-Water Immersion Therapy on Passive Muscle Stiffness. Sportverletz Sportschaden. 2020, 34(2):72-78.

Dussa CU, Böhm H, Döderlein L, Forst R, Fujak A. Does an overcorrected clubfoot caused by surgery or by the Ponseti method behave differently? Gait Posture. 2020, 77:308-314.

Böhm H, Döderlein L, Fujak A, Dussa CU. Is there a correlation between static radiographs and dynamic foot function in pediatric foot deformities? Foot Ankle Surg. 2020, 26(7):801-809.

International cooperation

Dr. I. Wiszomirska, Józef Piłsudski University of Physical Education, Warsaw: Poland

Department of Orthopedics in the Malteser Waldkrankenhaus St. Marien

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Research Focus
- Arthroscopic synovectomy
- Dynamic pedobarography
- Endoprostheses for degenerative and inflammatory joint diseases
- Mechanisms of chondrocyte differentiation and endochondral ossification

Structure of the Division

Professorships: 1
Personnel: 3
- Doctors (of Medicine): 2
- Scientists: 0
- Graduate students: 0

Clinical focus areas
Clinical activities focus on arthritis surgery of patients with degenerative and inflammatory joint diseases. Besides joint preserving operations the Division of Orthopedic Rheumatology concentrates on joint arthroplasties of the lower extremities (hip and knee). Furthermore, this division treats patients with rare diseases of the synovia (synovial joint chondromatosis, pigmented villonodular synovitis, etc.). The division of orthopedic rheumatology is audited as a center for arthritis surgery since June 2015.

Research

Clinical research still focusses on the outcome of arthroscopic synovectomies as well as joint replacements of hip and knee. Basic osteoarthritis research (in cooperation with Prof. Dr. K. Gelse, department of traumatology) works on chondrocyte differentiation in human osteoarthritis. Dynamic pedographic measurements, which started on rheumatoid patients, investigate meanwhile also pathologies in soccer players.

Arthroscopic synovectomy
Project managers: Prof. Dr. B. Swoboda
Clinical studies investigated the effect of arthroscopic synovectomies in patients with rheumatoid arthritis. Arthroscopic synovectomies of the knee joint were combined with a radiosynoviorthesis. The long-term effect of this procedure was evaluated using joint replacement as an endpoint.

Endoprostheses for degenerative and inflammatory joint diseases
Project managers: Dr. A. Jendrissek, Prof. Dr. B. Swoboda
Clinical studies are conducted on the clinical outcome of large joint arthroplasty, especially in patients with degenerative and inflammatory joint diseases. For this purpose, different preoperative findings, surgical requirements, postoperative outcome, and patient satisfaction are compared.

Dynamic Pedobarography
Project managers: Dr. T. Hotfiel,
Dynamic Pedobarography has been considered as an important measurement device and has been used in various orthopedic and biomechanic investigations. Dynamic pedobarography enables to assess various kinetic parameters such as pressure, force or contact-time in the interface between the plantar skin and the measurement surface. It can be used in different conditions such as walking, running or specific movements. Increased and asymmetric plantar pressure conditions can be seen as risk factors for the development of metatarsal stress fractures or plantar ulcers and is associated with prolonged and complicated recurrence of existing tissue damages. Moreover the assessment of foot loads can be helpful for the evaluation of orthotic devices or given weight bearing conditions in the field of rehabilitation.
- Systematic comparison of foot pressure conditions between insole and platform based pedobarography systems
- Plantar pressure distributions in adolescent and professional adult soccer players
- Assessing foot load distribution during rehabilitation and strengthening exercises

Teaching

The Division of Orthopedic Rheumatology offers lectures on obligatory and optional topics.
Students can take part in orthopedic operations. The division offers hands on examination courses.

Selected Publications
Mazur F, Swoboda B, Carl HD, Lutter C, Engelhardt M, Hoppe MW, Hotfiel T, Grim C. Plantar pressure changes in hindfoot relief devices of different designs. J Exp Orthop. 2019; 6 (1):7

Krüger K, Schmid S, Paulsen F, Ignatius A, Klinger P, Hotfiel T, Swoboda B, Gelse K.Trefoil Factor 3 (TFF3) Is Involved in Cell Migration for Skeletal Repair. Int J Mol Sci. 2019; 20(17):4277.

Stolz B, Grim C, Lutter C, Gelse K, Schell M, Swoboda B, Carl HD, Hotfiel T. Assessing Foot Loads in Continuous Passive Motion (CPM) and Active Knee Joint Motion Devices. Sportverletz Sportschaden. 2019 Feb 21. doi: 10.1055/a-0648-8699. Online ahead of print. PMID: 30791084

Hotfiel T, Golditz T, Wegner J, Pauser J, Brem M, Swoboda B, Carl HD. A cross-sectional study on foot loading patterns in elite soccer players of different ages. J Back Musculoskelet Rehabil. 2020; 33(6):939-946.

Kiltz U, Braun J; DGRh, Becker A; DEGAM, Chenot JF, Dreimann M; DWG, Hammel L; DVMB, Heiligenhaus A; DOG, Hermann KG; DRG, Klett R; DGMM, Krause D, Kreitner KF, Lange U; DGPMR/DGRW, Lauterbach A; Physio Deutschland, Mau W, Mössner R; DDG, Oberschelp U; DGOOC, Philipp S, Pleyer U, Rudwaleit M, Schneider E, Schulte TL, Sieper J, Stallmach A; DGIM, Swoboda B; DGOOC/DGORh, Winking M; DGNC. [Long version on the S3 guidelines for axial spondyloarthritis including Bechterew's disease and early forms, Update 2019 : Evidence-based guidelines of the German Society for Rheumatology (DGRh) and participating medical scientific specialist societies and other organizations]. Z Rheumatol. 2019 ;78(Suppl 1):3-6

International Cooperations
Prof. Dr. T. Kirsch, PhD, Department of Orthopedic Surgery, Director of the Musculoskeletal Research Center NYU Hospital for Joint Diseases, New York City: USA

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Research focus
- Clinical and experimental pharmacology of anesthesia
- Experimental pain research
- Medical technology of diagnostic and therapeutic procedures
- Clinical research in perioperative medicine
- Research projects furthering the medical education

Structure of the Chair

Professorships: 2
Personnel: 479
- Doctors (of Medicine): 151
- Scientists: 8 (thereof funded externally: 3)
- Graduate students 2019: 9
  Graduate students 2020: 13

Clinical focus areas
- Clinical anesthesiology
- Operative intensive care medicine
- Pain management center
- Emergency medicine
- Palliative medicine

Special structural features
- 50 anesthesia workplaces
- Anesthesia outpatient department
- Pain outpatient department, pain ward (four hospital beds)
- Two intensive care units (35 critical care beds), during the covid pandemic two more intensive care units with 22 critical care beds.
- Pain management unit (in cooperation with the Department of Neurology)
- Medical management of the emergency service (Erlangen, administrative district Erlangen-Höchstadt, Herzogenaurach)
- Medical care in air rescue services and in transport within UK Erlangen

Research

Research at the Department of Anesthesiology is focused on the clinical and experimental pharmacology of anesthesia and on the experimental and clinical pain research. In addition, innovative techniques for drug administration and patient monitoring are investigated, and projects dealing with the quality improvement of teaching and training are part of the Department's research program.

Clinical and experimental pharmacology of anesthesia
In a clinical phase I study in young healthy volunteers, the pharmacokinetics and clinical pharmacodynamics (including sedation, hemodynamics, respiration and electrocardiogram) of the new short acting benzodiazepine remimazolam were investigated. An integrated pharmacokinetic model for remimazolam and its metabolite and a pharmacodynamic model for the sedative effect of remimazolam were developed within this study.
During the reporting period and within the framework of a research cooperation with the Department of Anesthesiology, Wenzhou Medical University, China, the pharmacokinetics of dexmedetomidine, a selective α2 adrenergic receptor agonist for sedation, was investigated after intranasal administration during general anaesthesia in Chinese children aged 4 to 10 years.

Experimental pain research
The Heisenberg professorship of Experimental Pain Research was tenured in 2019. Research topics of this program included the pathomechanism of cold pain as well as the investigation of the role of TRP channels in the somatosensory system and in thermoregulation. To investigate afferent nerves innervating striated muscle tissue, a new muscle-nerve preparation was established which allows to stimulate receptive fields in the muscle specifically and locally. This allowed to investigate the effect of lactate and rising temperature, such as in the working muscle, on metaboreceptors and other muscle afferents, such as muscle spindles. Further projects addressed the differences in mouse behavioral activity patterns, food intake, and energy consumption in a large number of inbred strains which are commonly used in mouse pain behavioral models and our currently ongoing haplotype mapping studies. In these studies, differences between mouse strains were quantified and serve as a basis for the interpretation of future haplotype-based studies.
Another research area deals with the analysis of rare hereditary pain syndromes using human induced pluripotent stem cells (hiPSCs). In cooperation with the Department of Stem Cell Biology, we differentiate hiPSC-derived pain sensing neurons (nociceptors) from skin biopsies of healthy donors and affected pain patients. These sensory neurons are hardly available for analysis in humans and have therefore mainly been investigated using animal models. Species-specific differences are likely to be one explanation for the poor translation of preclinical findings into effective pain therapeutics. This project aims to contribute to bridge this gap. In our *in vitro* disease model we found that hiPSC-derived nociceptors of our patients show pathological spontaneous activity in electrophysiological recordings which is also found in patients suffering from neuropathic pain.

Medical technology of diagnostic and therapeutic procedures
The main research focus in this area was the processing and analysis of the EEG signal recorded during sedation with the new benzodiazepine Remimazolam in a phase I study in volunteers. Using an artificial neuronal network trained on specific artifact patterns of EEG signals and new processing techniques in the time-frequency domaine, it was able to identify concentration-induced remimazolam-characteristic changes in the EEG activity of Beta, Alpha and Delta frequency bands. Concentration dependent changes of a processed parameter in the Beta frequency band (BetaRatio) highly correlated with the remimazolam-induced sedation. Thus, BetaRatio can be used as a surrogate parameter for monitoring remimazolam sedation.
During the reporting period, we further investigated the analgesic efficiency of the new therapeutic algorithm Patient-Controlled-Analgesia with Target-Controlled-Infusion. For the opioid hydromorphone, the algorithm showed analgesic equivalence but higher patient comfort compared to standard Patient-Controlled-Analgesia.

Clinical research in perioperative medicine
The research in perioperative medicine was focused on the evaluation of airway devices and complex procedures to secure the airway and following intraoperative ventilation in the field of thoracic surgery. Videolaryngoscopy as a relevant tool for anesthesia and emergency medicine was studied comparing different designs. Results revealed favorable designs for safe care. In the field of anesthesia during thoracic surgery a complex combination of neuromonitoring to prevent harm from intraoperative nerv lesions and providing single-lung-ventilation simultanenously was described and studied in terms of feasibility und safety. This topic was addressing patient safety in both anesthesiology and surgery. A systematic development of a cognitive aid representing the anesthesiological issue of emergency medicine. The cognitive aid was supported by the professional society of anesthesiology and is now implemented nationwide. Another focus in emergency medicine was set on physical and psychological loads of EMS personnel. Results delimited occupational reality of EMS professionals as well as required support more precise.

Research projects furthering the medical education
A major focus of research on patient safety was the further development of a cognitive aid for crisis management in Anaesthesia which had been implemented in the department several years ago. Since there are currently no officially endorsed cognitive aids for intraoperative emergencies available in Germany, the Professional Association of German Anesthesiologists (BDA) and the German Society of Anesthesiology and Intensive

Care (DGAI) set up a project to develop such a comprehensive set of digital cognitive aids for intraoperative emergencies under the leadership of staff from the Erlangen department of Anesthesiology. Within the scope of this project, clinicians from different university hospitals („German Cognitive Aid Working Group“) worked together with human factors engineers and software developers. The development of the cognitive aid „eGENA“ (elektronische Gedächtnis- und Entscheidungshilfe für Notfälle in der Anästhesie) was based on the user-centered design (UCD) process of ISO 9241-210, that has been performed for the development of other applications in the medical context. A thorough analysis of the physical and organizational environment, the application context, and the technical and task-specific requirements of the end-users was performed. The project resulted in a progressive web application that runs with multiple software platforms as well as stationary and mobile devices.
As the main function of cognitive aids consists in supporting expert teams to remember and excel, rather than helping novices perfom procedures beyond their expertise, a qualitative study explored how novice and expert anaesthetists understand expertise in anaesthesia.
As a result of the COVID-19 pandemic and the related restrictions on face-to-face teaching for students, new concepts to qualify medical students to support intensive care staff during a pandemia (TIP) were developed and evaluated.

Teaching

The Department of Anaesthesiology is involved in the curricular and extracurricular student teaching of the Medical Faculty of the Friedrich Alexander University in many ways. In 2019, two digitisation projects within the framework of the QuiS II funding phase (Quality in Study and Teaching) were the focus of the further development of teaching. Triggered by evaluation and student surveys, two project groups created blended learning concepts in the form of flipped classrooms for the cross-sectional area 14 "Pain Medicine" and Q8 "Emergency Medicine 6th Semester". Interactive learning modules preparing for the attendance phase were created in the StudOn learning platform. With the Covid-19 pandemic in 2020, the teaching and learning conditions changed rapidly. The two projects were now able to unfold their full effectiveness. Due to the complex requirement profile of emergency medicine of theoretical knowledge, technical skills in combination with non-technical skills and high interactivity in the team, classroom training is indispensable. Flipped classroom concepts set knowledge impulses in advance and activate latent knowledge. In the classroom phase, these knowledge impulses are applied in practical case scenarios. The focus of the concept is on a concentrated presence phase at the simulation manikin. This concept and the experiences from QuiS II were also transferred to the block practical course "Anaesthesia, Intensive Care Medicine and Emergency Management" (10th semester). In a similar way, teaching was implemented for the block practical course in pain medicine. Here, students work out contents in advance in case-based learning modules in order to reflect on them in a video seminar (Zoom) with a lecturer and to deepen them in practice on a simulation patient (SP). Evaluations were linked to these curricular seminars and practical courses, which were always evaluated very positively and contributed to further optimisation of the courses. Building on these experiences, lectures, seminars and practical courses could be offered in digital or hybrid form. The concept of blended learning as a flipped classroom offers the opportunity for concentrated, in-depth attendance phases and will continue to play an important role in curricular development in order to prepare students for their medical work.

Selected publications

Schüttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers: Part I. Pharmacokinetics and clinical pharmacodynamics. Anesthesiology. 2020; 132(4): 636-651. doi: 10.1097/ALN.0000000000003103

König C., Plank A., Kapp A., Timotius I., von Hörsten S., Zimmermann K. (2020) Thirty mouse strain survey of voluntary physical activity and energy expenditure: Influence of strain, sex and day-night variation. Frontiers in Neuroscience 14:531. doi: 10.3389/fnins.2020.00531.

Lampert A., Bennett D.L., McDermott L.A., Neureiter A., Eberhardt E., Winner B., Zenke M. Human sensory neurons derived from pluripotent stem cells for disease modelling and personalized medicine. Neurobiology of Pain 8:100055 (2020)

Eisenried A, Schüttler J, Lerch M, Ihmsen H, Jeleazcov C. Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers: Part II. Pharmacodynamics of Electroencephalogram Effects. Anesthesiology. 2020;132(4):652-666. doi:10.1097/ALN.0000000000003102

Wehrfritz A, Ihmsen H, Fuchte T, Kim M, Kremer S, Weiß A, Schüttler J, Jeleazcov C. Postoperative pain therapy with hydromorphone; comparison of patient-controlled analgesia with target-controlled infusion and standard patient-controlled analgesia: A randomised controlled trial. Eur J Anaesthesiol 2020 Dec;37(12):1168-1175. doi: 10.1097/EJA.0000000000001360.

St Pierre, M. and J. M. Nyce (2020). "How novice and expert anaesthetists understand expertise in anaesthesia: a qualitative study." BMC Med Educ 20(1): 262.

International cooperations

Prof. E. Jørum, Department of Neurology, Oslo University Hospital-Rikshospitalet, Oslo: Norwegen

Prof. G. Peltz, Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, Stanford: USA

Prof. Teijo Saari, Department of Anesthesiology and Intensive Care at Turunyliopisto - University of Turku, Finnland

Dr. Hua-Cheng Liu, MD, Department of Anesthesiology, the Second Affiliated Hospital & Yuying Children’s Hospital of Wenzhou Medical University, Wenzhou, China

Prof. Johan Bergstrom, PhD, Division of Risk Management and Societal Safety, Director MSc. Programme in Human Factors & Systems Safety, Lund University, Sweden

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Research focus

- Immunopathogenesis of lung tumor
- Immunopathogenesis of allergic asthma

Structure of the Division

Professorship: 1
Personnel: 13

- Scientists: 9 (thereof funded externally: 3)
- Graduate students: 8

Research

The Division of Molecular Pneumology studies the mechanisms underlying the immune responses in allergic asthma and lung tumors.

Immunopathogenesis of lung tumor
Lung cancer is one of the most common cancers worldwide. Factors contributing to its development include smoking and specific genetic characteristics. Treatment options include surgical removal of the tumor, chemotherapy and radiotherapy, which have a low treatment success rate and result in a 5-year survival rate of only 15%. Current studies are focusing on immunotherapies as a new breakthrough treatment option in oncology. Effector and cytotoxic T cells play an indispensable role in ensuring a successful anti-tumor immune response.
In recent years, our group has been involved in the analysis of T cells present in the tumor microenvironment that influence the development and progression of lung carcinomas.
In most tumors, effector functions of tumor-infiltrating lymphocytes (TIL) are inhibited by various factors, such as accumulation of immunosuppressive cells or increased expression of inhibitory receptors, such as programmed cell death protein 1 (PD-1). PD-1 contributes to the functional impairment of T cell activation. Furthermore, inhibitory receptors are used by tumor cells to evade an immune response. For this reason, immunotherapies have been developed to reactivate effector immune cells by blocking so-called checkpoint receptors on immunoregulatory cells. In order to identify possible targets of immunotherapy, our group is investigating the influence of different genes and signaling pathways on tumorigenesis and development.
To this end, we are currently analyzing samples from more than 150 patients with non-small cell lung cancer (NSCLC) in collaboration with the Department of Thoracic Surgery. Tissue samples were taken from three different areas of the lung: the tumor region, the peri-tumoral region surrounding the tumor at a distance of 2 cm, and a control area free of tumor cells. Histological sections are generated from these tissue samples, RNA and proteins are extracted and various cell types are isolated. Further investigations are performed on peripheral blood mononuclear cells (PBMC). These procedures are necessary to understand specific tumor characteristics and to develop new therapeutic strategies.
Furthermore, using murine models of lung cancer by deleting different genes in specific cell types, we want to investigate what role these might play in the regulation of the immune response to lung cancer.
Current projects include the following:

- Role of STAT5 NSCLC
- Role of PU.1 in NSCLC
- Role of glucose in the initiation and development of NSCLC
- Role of Blimp-1 in NSCLC

Immunopathogenesis of allergic asthma
Allergic asthma is an increasing chronic-inflammatory disease of the airways that affects millions of people worldwide. It is characterized by increased airway inflammation, hyperresponsiveness, and remodeling after allergen and rhinovirus challenge.
While the classical model of allergy-induced airway inflammation focuses on a Th2 driven immune-reaction, Th1 and T regulatory cells play instead a protective role in this disease. Th2 cytokines can also influence B cells which then develop into plasma cells producing IgE which activates mast cells via binding to the high affinity IgE receptor, resulting in the release of bronchoconstrictors, like histamine.
In the course of the European asthma study PreDicta (Post-infectious immune reprogramming and its association with persistence and chronicity of respiratory allergic diseases; since 2011) with healthy and asthmatic pre-school children aged between 4 to 6 years, we have gained insight into important immunological processes during asthma development in general and in context to viral infections in particular. Since 2016, a local follow-up study (AGENDAS: Genetic, age, gender, and environmental factors that modify immuno-responses and the development of allergic asthma during the school age in childhood) has been recruiting healthy and asthmatic school children (6 to 10 years) during symptomatic or convalescent visit with the aim to substantiate and extend the results obtained in PreDicta. Especially the connection between rhinovirus infections and interferon type I and type III responses are a major research focus in our Division, but also T and B cell responses as well as innate lymphoid cells (ILC) are of interest to our group. Here we concentrate on cytokine patterns released by the different cell populations, e. g. IL-4 release from Th2 cells, and the expression of key transcription factors, such as T-bet in Th1 cells or Foxp3 in Tregs. Since 2020 we also conduct a new human study with healthy and asthmatic adults. In the AZCRA study they are invited to come to a baseline and a symptomatic visit comparable to AGENDAS. Here our focus lies on different chemokines and their receptors, as well as cytokines which are important in the immune response. In a third group we investigate the influence of the diet on the immune response. Here the asthmatic patients will change their diet into a healthy nutrition for 12 weeks in Cooperation with the hector center. To support our findings from the human studies, also mouse models of allergic asthma are used. Here, mouse models lacking e.g. single transcription factors, cytokines or cytokine receptors, e.g. IL-3, NFATc1 or CCR3 deficient mice contribute to determine the role of these factors/mediators in allergic asthma. As a model antigen we use ovalbumin (OVA) and the human relevant allergen house dust mite (HDM) in these experiments. These studies should contribute to the development of new therapeutic approaches and prevention strategies for asthma.
Current projects include the following:

- Role of the transcription factor NFATc1 in allergic asthma
- Role of the chemokine Rantes and its receptors in allergic asthma
- Interferon type I and III immune responses to rhinovirus infections in asthma
- Role of vitamine D3 in asthma

Teaching

The Division of Molecular Pneumology supervises Bachelor's and Master's theses as well as MD and PhD theses.

Selected publications

Sopel N, Kölle J, Dumendiak S, Koch S, Reichel M, Rhein C, Kornhuber J, Finotto S. Immunoregulatory role of acid sphingomyelinase in allergic asthma. Immunology. 2019 Apr;156(4):373-383

Kölle J, Haag P, Vuorinen T, Alexander K, Rauh M, Zimmermann T, Papadopoulos NG, Finotto S. Respiratory infections regulated blood cells IFN-β-PD-L1 pathway in pediatric asthma. Immun Inflamm Dis. 2020 Sep;8(3):310-319

Krug J, Kiefer A, Koelle J, Vuorinen T, Xepapadaki P, Stanic B, Chiriac M, Akdis M, Zimmermann T, Papadopoulos NG, Finotto S. TLR 7/8 regulates Type I and Type III Interferon Signalling in RV1b induced Allergic Asthma. Eur Respir J. 2020 Dec 10:2001562

Jakobi M, Kiefer A, Mirzakhani H, Rauh M, Zimmermann T, Xepapadaki P, Stanic B, Akdis M, Papadopoulos NG, Raby BA, Weiss ST, Finotto S. Role of nuclear factor of activated T cells 2 (NFATc2) in allergic asthma. Immun Inflamm Dis. 2020 Dec;8(4):704-712

Koch S, Knipfer L, Kölle J, Mirzakhani H, Graser A, Zimmermann T, Kiefer A, Melichar VO, Rascher W, Papadopoulos NG, Rieker RJ, Raby BA, Weiss ST, Wirtz S, Finotto S. Targeted deletion of NFAT-Interacting-Protein-(NIP) 45 resolves experimental asthma by inhibiting Innate Lymphoid Cells group 2

(ILC2). Sci Rep. 2019 Oct 30;9(1):15695

International cooperations

T. Vuorinen, Department of Virology, University of Turku, Turku: Finland

Prof. S.T. Weiss, Translational Genomics Core, Partners HealthCare, Cambridge, MA: USA

Prof. Dr. M.L. Kowalski, Department of Immunology, Rheumatology and Allergy, Medical University of Łódz, Łódz: Poland

Prof. T. Jartti, Department of Pediatrics and Adolescent Medicine, Turku University Hospital, Turku: Finland

Prof. N.G. Papadopoulos, Allergy and Clinical Immunology Unit, National and Kapodistrian University of Athens, Athens: Greece

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Division of Palliative Medicine

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Research focus
- Ethical aspects in palliative care
- Family caregivers in palliative care and quality of care in the end of life
- Clincial-experimental research

Structure of the Division

Professorship: 1
Personnel: 50
- Doctors (of Medicine): 8
- Scientists: 6
  (thereof funded externally: 5)
- Graduate students: 24

Clinical focus areas
- Care for terminally ill and dying patients
- Pharmacological and non-pharmacological interventions for symptom alleviation and pain relief
- Support in finding reasonable therapy goals
- Coordination of care
- Consultation on advance directives and comparable documents

Research

Health services research in palliative care examines the „reality“ of palliative care. It provides information about healthcare concepts under everyday conditions. In this way, health services research in palliative care answers questions that neither biomedical basic research nor classical clinical research can answer.
Clinical-experimental research at the Division of Palliative Medicine deals with innovative approaches to optimize the treatment of patients with severe diseases, e.g. technical applications in palliative medicine.

Ethical aspects in palliative care
PI: Prof. Dr. C. Ostgathe, Dr. C. Klein
One possible option for patients with symptoms refractory to treatment is palliative sedation (PS) that can be offered and performed after careful consideration of the clinical situation. Despite ethical implications, PS is seen as integral part of palliative care (inter-)nationally.
- The Division has been investigating PS since 2012. A documentation recommendation was completed and published in 2018.
  Funding: Staedtler foundation
- A consortium project on sedation in specialized palliative care has been coordinated from Erlangen since 2017. The discussion on sedation in specialized palliative care in Germany and other countries has so far lacked a framework that differentiates between the various forms of sedation, taking into account clinical, ethical, and legal aspects. There is also a lack of data on the sedation practice and the experiences and assessments of different institutional representatives involved in decisions regarding sedation. Reliable empirical data with a detailed analysis of ethical and legal challenges are necessary, as well as an approach involving representatives of relevant professional groups (such as nurses and physicians) to develop conceptually and empirically substantiated recommendations for good practice in different forms of sedation in Germany. In order to address the deficits of sedation in the specialized palliative care in Germany, the consortium aims to develop conceptually and empirically justified recommendations for different forms of sedation in the inpatient and outpatient specialized palliative care.
  Funding: BMBF
- Continuous sedation until death is particularly discussed from an ethical point of view. Experiences and attitudes towards continuous sedation until death of physicians will be assessed in an international project.
  Funding: ELAN Fonds

Family Caregivers in palliative care and quality of care in the end of life
PI: Prof. Dr. C. Ostgathe, Dr. M. Heckel, PD Dr. S. Gahr
- Validation of the „Care of the Dying Evaluation (CODE)“ for deceased patients‘ informal caregivers in the German-speaking area

In 2018, the validation study on the „Care of the Dying Evaluation“ (CODE) assessing the quality of care by relatives of deceased patients in palliative medicine and other departments was completed. The study was conducted in collaboration with the university hospital Mainz. The questionnaire was answered in writing by relatives who had accompanied the patient during the last three days of his life. The validation study and the results on the quality of care during the last three days of life in two German hospitals has been published in 2020. The questionnaire fulfils the statistical quality criteria of validity and reliability for survey instruments. It can be used for research and in practice and allows for international comparability. An international project (iCODE) incorporates the results of the present validation study.
Funding: DFG
- Coordination Office Palliative Care in the network of German Comprehensive Cancer Centers

In the first project phase from 2014 – 2017, a „best practice strategy“ for a structured integration of specialized palliative care in a Comprehensive Cancer Center (CCC) was developed using scientific methods. This includes both the integration of palliative medicine into the course of treatment and into the research and teaching activities of the individual CCCs. Since 2017, the implementation of best practice recommendations, the implementation and evaluation of the jointly developed standard operation procedures (SOP), joint documentation for the identification and evaluation of quality indicators, and the development of a needs-oriented medical education and training program have been started. A third phase of funding (4 years) started in November 2020 focusing on timely integration of palliative care in cancer care, screening of palliative care needs, care of the dying and the care for family and informal caregivers.
Funding: German Cancer Aid
- National Strategy for Palliative Care in Pandemics (PallPan) in Germany

The Network University Medicine was founded by the Charité Berlin and the German Government as response to the current SARS-CoV2 pandemic. It is funded by the German Ministry of Education and Research. The Network aims to connect German Medical Schools and German University Hospitals to jointly develop a pandemic preparedness for the current as well as for future pandemic situations. The PallPan project explores pandemic effects in all settings of palliative care on patients with and without Covid-19, their families and health care professionals. The Division of Palliative Medicine Erlangen contributes in the work package on SARS-CoV2 pandemic response teams at micro, meso and macro level with regard to the care of severely ill patients with far advanced disease at the end of life and their families in the current pandemic. Purposeful sampled pandemic board members will be interviewed nation-wide regarding the composition, organization and authority of pandemic crisis teams with a focus on palliative care expertise and staff experiences on end of life care issues, solutions and challenges.
Funding: BMBF

Clinical-experimental research
PI: Prof. Dr. C. Ostgathe, Dr. T. Steigleder
Clinical-experimental research at the Division of Palliative Medicine deals with innovative approaches to optimize the treatment of patients with severe diseases.
One research focus is medical applications in palliative medicine. This focus is represented by the working group PallMeT.
- GUarded by Advanced Radar technology-based DIagnostics Applied in palliative and intensive care Nursing (GUARDIAN)

In the care of seriously ill people, the recording of respiration and heartbeat may be necessary for crisis detection. The previously necessary derivation via electrodes on the patient's body and the connected cables limit the self-determination and quality of life of palliative and

intensive care patients and lead to false alarms and complications such as mental confusion. GUARDIAN should enable the contactless monitoring of vital parameters to ensure health. Patients can change their position in the bed at will and move freely in a GUARDIAN-protected room. By using six-port interferometry as a new concept, all body movements are recorded in a contactless manner from a distance of up to several meters with previously unattained distance resolution in the micrometer range. Respiration and heartbeat are extracted from the temporal signal curve. The aim of the project is the research and prototypical development of a radar-based sensor that makes it possible to measure the vital signs heart rate and respiration of a patient without physical contact over distances of up to several meters. In 2017, collaborators from the Chair for Electronics Engineering at FAU developed a prototype of the radar sensor, which was tested by PallMeT in a clinical study with 30 healthy volunteers in 2018. Based on the study data, the radar system was adapted for a study with palliative patients at UK Erlangen that was conducted in 2019 and 2020.
Funding: BMBF

- Evaluation of non-drug therapies using the example of music therapy

Music therapy is frequently used in palliative medicine among other no-drug therapies, like physiotherapy, arts therapy, and psychological and spiritual care. Since 2018, the work group PallMeT has been investigating the effects of music therapy on physiological parameters, likeheart rate, breathing rate, blood pressure, and the activity of the autonomic nervous system. The heart activity is measured by touchless radar-based monitoring (see project GUARDIAN). This project is executed in collaboration with University of Augsburg.

- Bio-interferometry for epilepsy diagnostics in pediatrics

By using six-port interferometry it is possible to record heart beat and respiration without physical contact through materials such as blankets, mattresses, clothes, wooden parts of the bed. Our working group is the only one worldwide exploring six-port interferometry in context of vital signs. The activity of the autonomic nervous system (determined by heart rate variability) is a possible biomarker in different diseases, eg in monitoring epileptic activity. During and immediately preceding an epileptic seizure ECG-analysis showed significant changes of heart rate variability. In 2020 we started to investigate the potential use of radar-based, touchless epilepsy diagnostics. The aim is to provide continuous monitoring and monitoring for patients who are restricted to interact such as toddlers and newborns.
Funding: BMBF

Patient and Public Involvement Committee of the Division of Palliative Medicine. Members are volunteers who share their perspectives as citizens and support the research team in different ways throughout the research process. (Image: I. Gheith, 2019-05-09)

Teaching

The Division of Palliative Medicine is an integral part of the teaching force for Medicine, psychogerontology, and Medical Process Management. In addition to the comprehensive curricular teaching, it offers workshops for medical students as part of the clinical team on treating palliative care patients with simulated patients under constant supervision and with structured feedback. Furthermore, we established a multi- professional seminar in 2013 that takes place once each term. Tutors and participants both comprise many different health professions.
The Division of Palliative Medicine offers the chance to accomplish a MD thesis or a dissertation in human biology as well as Bachelor's and Master's theses of many degree programs. A research workshop is also held for students writing their final thesis in the division.

Selected publications

Vogt A, Stiel S, Heckel M et al. Assessment of the quality of end-of-life care: translation and validation of the German version of the "Care of the Dying Evaluation" (CODE-GER) - a questionnaire for bereaved relatives. Health Qual Life Outcomes 2020; 18: 311. doi:10.1186/s12955-020-01473-2

Shi K, Schellenberger S, Will C, Steigleder T, Michler F, Fuchs J, Weigel R, Ostgathe C, and Koelpin A (2020) A dataset of radar-recorded heart sounds and vital signs including synchronised reference sensor signals, Scientific Data, Feb 13;7(1):50

Kurkowski S, Radon J, Vogt AR et al. Hospital end-of-life care: families' free-text notes. BMJ Support Palliat Care 2020. doi:10.1136/bmjspcare-2020-00239.

Heckel M, Vogt AR, Stiel S et al. The quality of care of the dying in hospital-next-of-kin perspectives. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2020; 28: 4527-4537. doi:10.1007/s00520-020-05465-2

Heckel M, Sturm A, Stiel S et al. '. . . and then no more kisses!' Exploring patients' experiences on multidrug-resistant bacterial microorganisms and hygiene measures in end-of-life care A mixed-methods study. Palliative Medicine 2020; 34: 219-230. doi:10.1177/0269216319881603

Gahr S, Loedel S, Berendt J et al. Implementation of Best Practice Recommendations for Palliative Care in German Comprehensive Cancer Centers. Oncologist 2020; 25: e259-e265. doi:10.1634/theoncologist.2019-0126

UNIVERSITY HOSPITAL

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Chair of Cardiac Surgery

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Research Focus
- Chronic rejection of allografts
- Therapy of end-stage heart failure: Heart transplantation or support with a left or right ventricular assist device
- Electromechanical coupling in heart failure
- Development of a non-blood contacting heart actor
- High speed camera investigations on heart valves in a pulse duplicator

Structure of the Department

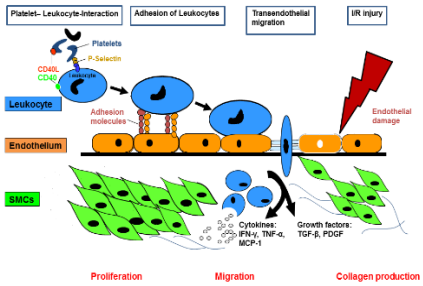
Professorships: 1
Personnel: 100
- Doctors (of Medicine): 15
- Scientists: 4 (thereof funded externally: 1)

Clinical focus areas
- Adult cardiac surgery
- Heart transplantation in adults and children
- Minimally invasive valve surgery
- Mechanical circulatory support
- Wound management
- Heart insufficiency therapy
- Rhythm surgery
- Surgery in grown-up with congenital heart disease
- Interventional heart valve surgery
- Interventional aortic surgery

Research

Main research topics are on the one hand basic research in transplantation and on the other hand clinical research in mechanical circulatory support and the development of new heart assist devices in close cooperation with the Faculty of Engineering.

Chronic rejection of allografts
PI: PD Dr. C. Heim
Transplant vasculopathy is the main reason for late graft failure after heart transplantation. In order to develop effective therapeutic strategies and translate them into clinical success, a detailed understanding of the mechanisms responsible for the development of transplant vasculopathy is essential. We have recently established and characterized the abdominal aortic allograft model as a suitable tool to study the development of transplant vasculopathy. Ongoing projects involve the role and importance of platelets and their inhibition in the development of transplant vasculopathy. Immunmodulatory effects of Clopidogrel could be shown in small animal models. The results of these preclinical studies could be translated into a multi-center study (CEDRIC). Additionally, microvascular integrity of pulmonary grafts was shown to be essential for the long-term success of animal transplant models. In cooperation with the Department of Medicine, another major aim of this working group is the use of antiproliferative substances to explore potential strategies to avoid the development of transplant vasculopathy in experimental transplant models.
Additionally an ISHLT grant investigates the serostatus of cytomegalovirus as risk factor for transplant vasculopathy in a international heart transplant register.



Mechanisms in CAV
After I/R injury, endothelial damage is likely to occur. Adhesion molecules are upregulated and after platelet–leukocyte interaction, leukocytes transmigrate through the endothelial layer. There they produce several cytokines and growth factors. As a result, SMC produce collagen, proliferate, and migrate into the neointima. This finally leads to a progressive narrowing of the transplanted vessels and to subsequent graft failure. CAV, cardiac allograft vasculopathy; IFN-γ, interferon-γ; I/R, ischemia/reperfusion; MCP-1, monocyte chemoattractant protein-1; PDGF, platelet-derived growth factor; SMC, smooth muscle cell; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor α. (Reproduced from Heim et al., Thorac Cardiovasc Surg 2018, with permission from Thieme)

Therapy of end-stage heart failure: Heart transplantation or support with a left or right ventricular assist device
PI: Dr. R. Tandler
Orthotopic cardiac transplantation is the therapy of choice for cardiac insufficient patients. Due to an increasing shortage of donor organs, these cardiac insufficient patients need to be bridged with an implantable ventricular assist device until a suitable donor organ is available. In some cases heart disease has already progressed to such an extent that the patients need to be stabilized with a left ventricular assist device or – in case of additional right heart failure – with a biventricular assist device.

Electromechanical coupling in heart failure
PI: PD Dr. C Heim
Remodelling of cardiomyocytes in heart failure patients is well described in the literature, but not completely understood. The calcium delivery in cardiomyocytes may be altered in heart failure patients. In previous studies the remodeling of the T-system of the cardiomyocytes was discussed as responsible for cardiac recovery in ventricular assist device patients. Therefore the aim of the ongoing projects in cooperation with the Institute of Physiology and Pathophysiology is to further analyze underlying mechanisms of the T-system remodeling using human heart tissue from VAD or transplant patients.

Development of a non-blood contacting heart actor
PI: Prof. Dr. M. Weyand
The support of the insufficient heart muscle function by artificial support systems is worldwide an intensive field of research and an aim seeked for for about 60 years. Rising life expectancy and the growing number of heart-insufficient patients on the one hand as well as restricted availability of donor organs and damping of the increase of the health costs will further raise the need in innovative support systems in the future. On account of the risks of the existing, invasive, clinical methods, a carefully implantable technology is necessary. It must be functioning reliably as well as permanently and intervene not invasive in the heartcirculatory system. Within a clinical-medical setting, the investigation of a research project pursues from the interpretation over the production up to the clinical validity of the system function more new, actoric, and patient-individual heart muscle support systems for the purposes of an external compression of the heart. Therefore the main focuses are the investigation of a biomechanically efficient, mechanical system as well as the development of dior piezoelectric based actor material patterns.

High speed camera investigations on heart valves in a pulse duplicator
PI: Dr. M. Kondruweit
High-speed camera investigations on heart valves in an animal model are an already established model. In this project these proceedings are applied into a pulse duplicator to be able to compare several heart valve types in a standardized procedure. Special situations, as for example the Ventricle Assist Devices support and the effect on the hemodynamic on the heart valves, are examined. The results should show possible reasons for heart valve attrition by measuring power vectors. If possible, these reasons shall be corrected by changing the valve design.

Teaching

The Department of Cardiac Surgery takes part

in compulsory and elective subjects for the curricular teaching of the human medicine and dentristy.
Bachelor's and Master´s theses especially from the Faculty of Engineering are supervised as well as MD and PhD theses.

Selected publications

Heim C, Kuckhahn A, Ramsperger-Gleixner M, Nicolls MR, Weyand M, Ensminger SM. Microvasculature in murine tracheal allografts after combined therapy with clopidogrel and everolimus. Interact Cardiovasc Thorac Surg. 2020

Fritz NM, Stamminger T, Ramsperger-Gleixner M, Kuckhahn A, Müller R, Weyand M, Heim C. Cytomegalovirus chemokine receptor M33 knockout reduces chronic allograft rejection in a murine aortic transplant model. Transplant Immunology. 2020

Rivinius R, Kaya Z, Boeken U, Provaznik Z, Heim C, Knosalla C, Schoenrath F, Rieth A, Berchtold-Herz M, Barten MJ, Rauschning D, Grinninger C, Warnecke G, Schulze PC, Katus HA, Kreusser MM, Raake PW. COVID-19 among heart transplant recipients in Germany: A multicenter survey. Clinical Research in Cardiology. 2020; 109(12):1531-1539

Abu-Khousa M, Fiegle DJ, Sommer ST, Minabari G, Milting H, Heim C, Weyand M, Tomasi R, Dendorfer A, Volk T, Seidel T. The degree of t-system remodeling predicts negative force-frequency relationship and prolonged relaxation time in failing human myocardium. Frontiers Physiology. 2020; 11:182

Seidel T, Fiegle DJ, Baur TJ, Ritzer A, Nay S, Heim C, Weyand M, Oakley RH, Cidlowski JA, Volk T. Glucocorticoids preserve the t-tubular system in ventricular cardiomyocytes by upregulation of autophagic flux. Basic Res Cardiol. 2019; 114(6):47

Heim C, Khan MA, von Silva-Tarouca B, Kuckhahn A, Stamminger T, Nicolls MR, Weyand M, Ensminger SM. Preservation of microvascular integrity in murine orthotopic tracheal allografts by clopidogrel. Transplantation. 2019; 103:899-908

International cooperations

Dr. M. Nicolls, Professor in Pulmonary and Critical Care Medicine, Stanford University, CA: USA

Dr. J. Stehlik, Director of ISHLT Registry, University of Utah, UT: USA

Dr. K. Kush, Professor in Cardiology and Cardiac Transplantation, Stanford University, CA: USA

UNIVERSITY HOSPITAL

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Division of Pediatric Cardiac Surgery

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Research focus area

- Organ protection: cerebral perfusion / beating-heart-surgery / distal thoracic aorta perfusion (descendens perfusion)
- Heart valve surgery
- Extracorporeal circulatory support
- Thymus immunology
- Migration of plasticizers into patient's blood

Structure of the Division

- Professorship: 1
- Personnel: 7
- Doctors (of Medicine): 4
- Graduate students: 19

Clinical focus areas

- Surgery for children and adult patients with congenital heart disease
- Extracorporeal support for children with severe heart and/or lung failure
- Surgical reconstruction of cardiac valves and "physiological" cardiac valve replacement

Research

The aim of our research efforts is to achieve highest possible level of safety for our patients especially in the context of complex operations. The same goal applies for routine operations in order to optimize outcomes of congenital cardiac procedures with special focus on organ protective methods during cardiopulmonary bypass.

Heart valve surgery
In the context of surgery for congenital heart defects, it is often necessary to reconstruct the right ventricular or, less often, the left ventricular outflow tract with the aid of different heart valve prostheses. The still postulated gold standard for pulmonary valve replacement are pulmonary homografts which is only feasible to a certain extent due to their limited availability. On the left side, the autologous pulmonary valve is often used for aortic valve replacement (Ross operation), and a valved RVPA conduit is implanted between the right ventricle (RV) and pulmonary artery (PA). Xenogeneous pulmonary valve prostheses offer an alternative to homografts, but are only available in limited sizes due to their diameter - often too large for small patients and sometimes too small for teenager or adult patients. This is particularly often the case in patients after Fallot repair with significantly enlarged right ventricular outflow tracts and dilated pulmonary arteries. For this group of patients, stented, xenogenic aortic valve prostheses are available, that can also be used as pulmonary conduits after being sewn into a Dacron tube graft. In addition to a low transvalvular gradient, the advantage of this method is an ideal "landing zone" for later trans-femoral pulmonary valve interventions or replacements.
Decellularized aortic homografts (DAH, cell-free aortic valves from human donors) for aortic valve replacement have been used clinically in children and young adults since 2002. In clinical studies, the 10-year data show very good medium-term results without calcification compared to conventional homografts. The potential of DAH for recellularization in children can be illustrated by the example of a 2.4-year-old child whose DAH was explanted during a heart transplant. Significant recellularization of the macroscopically normal appearing homograft by non-immunogenic cells was observed 8 months after the implantation. The explanted DAH was 75% similar to a normal aortic valve. The latest data suggest that DAH offer a promising additional option for pediatric aortic valve replacement. Reported preliminary DAH outcome data in children are comparable to results of contemporary pediatric Ross procedures or mechanical AVR and better than those of cryopreserved allografts. These grafts were implanted in twenty children and young adults in our institution as aortic valve replacement with great success since 2018. A relevant advantage of these novel conduits compared to mechanical heart valves is that patients do not have to take anticoagulants for lifetime. These valves further seem to have the potential to grow with the patient's body. Decellularized pulmonary valve homografts are meanwhile available as well and have been applied to eleven patients since 2019 so far.

Plasticizer migration from medical synthetic products into patient's blood
A continuous research focus of our department is the investigation of phthalate (e.g. DEHP) migration and other similar substrates from stored blood products into patient's blood. These plasticizers have a toxic potential in the bloodstream, especially in children. The pediatric cardiac surgery department has implemented various experimental models to investigate how the entire circulating amount of plasticizers could be reduced or eliminated.
These projects could show that longer stored blood products are more significantly contaminated with plasticizers that further migrate into erythrocytes. Migrated plasticizers could be clearly and specifically reduced by "washing" before transfusion. Blood products older than 7 days could be cleaned by Cell-Saver-washing to reduce the entry of plasticizers 2.3 up to 14.8-fold. It has been proven that plasticizers serve as "endocrine disruptors" in children, with great influence in the development of reproductive organs and fertility, which is why they have already been banned in toy manufacture.

Organ-protective procedures: monitoring of cerebral perfusion
Organ-protective measures during aortic arch surgery are an essential research focus of the Division of Pediatric Cardiac Surgery. After experimental validation in an animal model for selective brain perfusion during aortic arch operations, statements on intraoperative cerebral perfusion could be made with the help of intraoperative transfontanellar ultrasound in infants with open fontanels. In particular, the quantitative assessment of cerebral blood flow in different phases of neonatal cardiac surgery with and without extracorporeal circulation was investigated in vivo using transfontanellar contrast enhanced ultrasound (T-CEUS). The particular advantage is a valid "real-time monitoring" of cerebral perfusion, so that intraoperative measurements help to continuously investigate brain perfusion during every phase of the surgical procedure. This method helped us to evaluate and quantify different flows to both hemispheres in patients first in man. T-CEUS parameters in patients operated on cardiopulmonary bypass were not different to those in patients operated without extracorporeal circulation. When flows in to the heart-lung machine were reduced, brain perfusion significantly changed as expected.
The optimization of cardioproductive measures as well as the care of the entire organs, especially the brain, during the surgical treatment of congenital heart defects with aortic arch hypoplasia or interruption remain our focus. Selective perfusion of the descending aorta during aortic arch corrections ("descending aortic perfusion") represents a further development of the selective, optimized regional perfusion concept on cardiopulmonary bypass (CPB). According to our primary clinical data, this technology leads to improved outcomes for newborns and infants who are particularly sensitive to CPB. Finally, our further special focus is on the imparing effects of cardiopulmonary bypass to the neonatal brain and later neurodevelopmental issues and how they can be possibly avoided by optimized CPB-concepts.

Extracorporeal circulatory support
Extracorporeal circulatory support systems are used in terminal heart and / or lung failure. VAD therapy (Venticular Assist Device) has emerged as a promising bridge to transplantation option with improvement in quality of life and survival on the waiting list. However, VAD therapy for patients with univentricular hearts before and after Fontan circulation with protein losing enteropathy (PLE) or other types of Fontan failure remain a challenge. In patients with preserved ventricular function, implantation of a right ventricular assist device (RVAD) as a bridge to transplantation with improved endorgan function has been described. RVAD support represents a promising palliative method for Fontan patients with circulatory failure ("Failing-Fontan") up to a transplant or perhaps

even as a permanent palliation. The validation and development of such concepts is currently being collaboratively developed together with many other heart centers and industrial support (BerlinHeart/Berlin, Germany).

Thymus immunology
In cooperation with the Department of Dermatology (Prof. Dr. D. Dudziak), a project related to the differentiation of immunocompetent cells of children with congenital heart defects has been established. Routinely removed thymus tissue is processed systematically in order to examine its immune-competent cells. The same characterizations are carried out in the peripheral blood of patients. Research is focused on thymus subpopulations in order to gain information related to the natural maturation of the immune system.

Teaching

Main lectures, internships, electives and final year clinical rotations are being held throughout the year.
Special surgical techniques, anatomic considerations, and pathogenesis of congenital heart disease are being taught in small group student tutorials.
Teaching is supported by modern technical equipment. All surgical steps could be followed on additional screens in the operating room. We supervise Bachelor's and Master's theses as well as MD and PhD theses.

Selected publications
Rüffer A, Tischer P, Munch F, Purbojo A, Toka O, Rascher W, Cesnjevar RA, Jungert J. Comparable Cerebral Blood Flow in Both Hemispheres During Regional Cerebral Perfusion in Infant Aortic Arch Surgery. Ann Thorac Surg. 2017, Jan;103(1):178-185

Ambarsari YA, Purbojo A, R. Blumauer, Glockler M, Toka O, Cesnjevar RA, Ruffer A. Systemic-to-Pulmonary Artery Shunting Using Heparin-Bonded Grafts. Interact Cardiovasc Thorac Surg. 2018 Oct 1;27(4):591-597

Heger L, Balk S, Luhr JJ, Heidkamp GF, Lehmann CHK, Hatscher L, Purbojo A, Hartmann A, Garcia-Martin F, Nishimura SI, Cesnjevar RA, Nimmerjahn F, Dudziak D. Clec10a Is a Specific Marker for Human Cd1c(+) Dendritic Cells and Enhances Their Toll-Like Receptor 7/8-Induced Cytokine Secretion. Front Immunol. 2018 Apr 27;9:744

Kellermann S, Janssen C, Munch F, Koch A, Schneider-Stock R., Cesnjevar RA, Ruffer A. Deep Hypothermic Circulatory Arrest or Tepid Regional Cerebral Perfusion: Impact on Haemodynamics and Myocardial Integrity in a Randomized Experimental Trial. Interact Cardiovasc Thorac Surg. 2018 Apr 1;26(4):667-672

Stonawski V, Vollmer L, Kohler-Jonas N, Rohleder N, Golub Y, Purbojo A, Moll GH, Heinrich H, Cesnjevar RA, Kratz O, Eichler A. Long-Term Associations of an Early Corrected Ventricular Septal Defect and Stress Systems of Child and Mother at Primary School Age. Front Pediatr. 2018 Jan 15;5:293

Münch F, Hollerer C, Klapproth A, Eckert E, Ruffer A, R. Cesnjevar RA, Goen T. Effect of Phospholipid Coating on the Migration of Plasticizers from Pvc Tubes. Chemosphere. 2018 Jul;202:742-749

International cooperations
Prof. M.D. Rodefeld, MD, Department of Surgery, Indiana University School of Medicine, Indianapolis: USA

Dr. O. Miera, EEPIG (European Excor Pediatric Investigator Group): multizentrisch

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Research focus

- Cellular immune intervention
- RNA electroporation to improve DC vaccines and to generate antigen-specific T cells
- Functional role of DC subpopulations and antigen presentation
- Role of miRNA in cancer and immune-related diseases
- Composition, function, and clinical relevance of plasma extracellular vesicles (pEV)
- Characterization of the toponome of tissue and cells by multi-epitope ligand cartography (MELC)
- Pathomechanisms of chronic inflammatory skin diseases
- Identification of biomarkers in malignant melanoma
- Regulatory T cells for cell-based therapy in inflammatory bowel disease (IBD)
- Cellular motility and migration of NK cells and regulatory T cells

Structure of the Chair

Professorships: 4
Personnel: 212

- Physicians: 40
- Scientists: 24 (with external funding: 17)
- Graduate students: 10

Clinical focus areas

- Targeted and Immunotherapy of melanoma and uveal melanoma (checkpoint blockade, DC vaccination)
- Treatment of inflammatory and autoimmune skin diseases
- Experimental treatment with regulatory T cells
- Recombinant allergens for diagnosis and therapy
- Certified care of chronic wounds

Research

A major focus of research activities at the Department of Dermatology is melanoma. The studies deal with pathogenesis, immune defense, cellular immunotherapy, transcription factors and biomarkers of the tumor. A particular interest is in dendritic cells (DC), CAR T cells, extracellular vesicles in plasma, and MELC technology for tissue section analysis. There are also funded research projects on inflammatory skin diseases and autoimmune diseases. Across projects, we use the special expertise of network analyses and computer simulations.

Cellular Immunotherapy
PI: Prof. Dr. B. Schuler-Thurner
The aim of this working group, consisting of the GMP laboratory (manufacture of cellular therapeutics) and a clinical unit (patient application), is the production and clinical application of advanced therapy medicinal products (ATMPs). After seven phase I and II trials using DC vac- cines, a multicenter adjuvant phase III trial using tumor mRNA as vaccine antigen was started in July 2014 in cooperation with the Department of Ophthalmology in Erlangen and other major uveal melanoma centers, NCT01983748). Since the start of the trial, 226 patients have been screened and 115 have been included.
Current improvements are the use of Next Generation Exon and RNA sequencing in conjunction with HLA epitope prediction in order to improve the vaccination strategy as well as an optimized maturation of DC with the help of mRNA coding for NFkB. Such an optimized vaccine is now used within a phase I clinical trial in metastatic uveal melanoma ((NCT04335890).
The GMP quality team (M. Kummer) has successfully developed the implementation of all cellular therapies.

RNA electroporation to generate antigen-specific T cells
PI: PD Dr. N. Schaft
This research focusses on the use of electroporation of T cell receptor- (TCR) and chimeric antigen receptor- (CAR) encoding mRNA to reprogram T cells to enable them to directly recognize tumor cells or virus-infected cells. For the clinical application of these cells to treat (uveal) melanoma patients, the clinical-scale production of CSPG4-specific CAR-T cells under full GMP compliance was developed. Moreover, preparations for the application to the Paul-Ehrlich-Institute for a phase I clinical trial authorization are running. Next to the classical format of a CAR (i.e. scFv antigen-binding moiety linked to intracellular co-stimulatory (e.g. CD28, 4-1BB) and T-cell-signaling (CD3ζ) domains), alternative CAR formats using non-canonical signaling domains (e.g. NKG2D, DAP-10, CD32A, CD16A) are preclinically developed and investigated. This also enables the functional testing of such new CARs in alternative cellular vessels like NK/NKT cells or myeloid cells, to broaden the possibilities of cellular therapy against cancer.

RNA electroporation to improve therapeutic DC vaccines
PI: PD Dr. J. Dörrie
This project aims to preclinically and translationally optimize DC as therapeutic vaccine against cancer, especially uveal melanoma and Merkel cell carcinoma. To this end, the DC are electroporated with mRNA to load them with tumor antigens and to activate them functionally. The latter is achieved with a mutated activator of the NFκB pathway that was rendered constitutively active and generates DC, which induce immune responses of higher potency. Additionally, in collaboration with Prof. J. Vera-González, innovative methods to analyze NGS data for identification of ideal tumor antigens are developed.

Functional role of DC subpopulations and antigen presentation
PI: Prof. Dr. D. Dudziak
This working group focuses on the functional characterization of primary DC subpopulations and their modulation of immune responses. Studies are being conducted on how the cytokine profile, surface profile, but also the migratory behavior of DCs can be controlled. The aim is to modify the DC subpopulations by different stimulators in such a way that the DCs generate an enhanced TH1, TH2 or TH17 CD4+ T cell response or cytotoxic CD8+ immune responses. The group works in both murine and human systems. So-called antigen-targeting antibodies are used, with which antigens are targeted to DC subsets, as well as cutting-edge technologies such as multi-color flow cytometry, multi-color confocal immunofluorescence and RNA sequencing. In cooperation with different clinical departments, human DC subpopulations are characterized. Since 2020, Prof. Dudziak is coordinator of the Bayresq.Net initiative IRIS to analyze new checkpoints to fight multidrug-resistant bacteria. Prof. Dudziak has also been recently appointed to be responsible for public relations in the German Society for Immunology and in the review board 'Cell Biology' of the DFG.

Systems Medicine of skin diseases
PI: Prof. Dr. J. Vera-González
Multifactorial diseases are not controlled by single genes, but instead by dense networks of interacting genes, proteins and RNAs. We combine clinical data, molecular profiling of patient samples and computational modelling to detect the key gene networks controlling pathogenesis and therapy response in melanoma and autoimmune diseases (www.vcells.net/melanoma). We have algorithms for detecting and selecting tumor epitopes for anticancer therapy in melanoma (www.curatopes.com). Network and pharmacogenomics approaches are utilized to design miRNA-based anticancer therapies (www.synmirapy.net) and network analysis and computer simulations are used to engineer immune cells therapy for cancer.

Predictive diagnostics with biomarker patterns from plasma extracellular vesicles (pEV) using methods of artificial intelligence (AI)
PI: Prof. Dr. A. Baur
The group investigates the composition of plasma extracellular vesicles (pEV), in conjunction with AI algorithms, to establish predictive diagnostic tests, particularly for cancer patients. The project focuses on the assessment of protease activities and immune markers using novel and patented pEV isolation and analysis systems. The basis for this research were observations showing that the number of vesicles and the content of these factors increase significantly in the course of disease

development, as for example in cancer, infectious and neurodegenerative diseases. Conversely, healthy individuals lack these factors. Moreover, we obtained good evidence, that these factor and protease activity patterns discriminate different stages of a given disease. The project was selected by the BMBF in 2018 and was funded in 2020, including a partner specialized in technical development of novel test systems. Aim of the Corporation is the foundation of a startup company.

Characterization of the toponome of tissue and cells by multi-epitope ligand cartography (MELC)
PI: Prof. Dr. A. Baur, Dr. C. Ostalecki
The research group focuses on the tissue characterization using the innovative MELC (Multi-epitope ligand cartography) technology, which allows the staining of up to 100 antigens via antibodies on one tissue section or slide. Digital imaging of these tissue markers generates multiplexed datasets that provide an ideal basis for the application of data mining algorithms. Thus, the development of early melanoma has been analyzed, and novel expression patterns have been identified. In addition, clonal dedifferentiation of primary melanoma was revealed for the first time using these data mining algorithms, providing new insights into melanoma pathogenesis. New prognosis-determining parameters will be elaborated and provide new opportunities to conventional histological analysis.

Pathomechanisms of chronic inflammatory skin diseases
PI: Prof. Dr. M. Sticherling
Chronic inflammatory diseases make up a major part of skin diseases. Apart from e.g. psoriasis, atopic eczema, and granulomatous diseases, autoimmune mediated diseases restricted to the skin, like bullous autoimmune skin disorders, as well as specific skin involvement among multi- organ diseases, like collagenous skin diseases (inflammatory connective tissue diseases), may be addressed. Scientifically, the involvement of B-cells is addressed ex vivo and in vitro by molecular biological and immunohistochemical methods in the inflammatory process of psoriasis and cutaneous lupus erythematosus as model diseases. In addition, the differential involvement of Toll-like receptors (TLR) and their modulation in cutaneous inflammatory processes is examined.

3D imaging of pigmented nevi and therapy-induced skin lesions during sytemic therapy of cutaneous malignancies
PI: Dr. M. Erdmann
Sequential high resolution 3D photography can exactly monitor initial changes in patients with many nevi. Additionally cutaneous effects of immune-oncologic as well as targeted therapies can be analyzed by this technique. We could demonstrate development and response of disseminated skin metastases under systemic therapy of melanoma.

Evidence-Based Dermato-Oncology and Health Services Research
PI: PD Markus Heppt, M.Sc., MHBA; Theresa Steeb, MPH
Projects on evidence-based dermato-oncology and health services research aim at contributing to better treatment decisions for both skin cancer patients and their treating physicians. Medical guideline projects with a focus on dermato-oncology (e.g. the evidence- and consensus-based ("S3") guideline on actinic keratosis and squamous cell carcinoma of the skin) are conducted as well as systematic reviews, meta-analyses, and network meta-analyses according to the principles of evidence-based medicine on topics of dermato-oncology, primarily on actinic keratosis. Additionally, the group deals with topics relevant to health care using both quantitative and qualitative research approaches, such as the evaluation of websites and videos on skin cancer. The projects are funded by the German Cancer Aid and the Skin Cancer Council Germany (Nationale Versorgungskonferenz Hautkrebs e.V.)

Transcription factors in melanoma
PI: PD Dr. med. Markus Heppt, M.Sc., MHBA; Anja Wessely, M.Sc.
This research group investigates how neural crest transcription factors contribute to the development and progression of cutaneous and uveal melanoma. Especially, the functional role of SOX10 is analyzed in uveal melanoma, which differs from cutaneous melanoma both clinically and genetically. Furthermore, the epigenetic regulation of the transcription factor Brn3a, which contributes to melanoma cell survival and promotes tumorigenesis, is investigated. The group generates uveal melanoma cell lines from fresh tumor tissue of primary tumors and metastases.

Standard of care for patients with chronic wounds
PI: PD Dr. C. Erfurt-Berge, Prof. R. Renner
This research group investigates diagnostic and therapeutic approaches in the care of patients with chronic wounds. The main focus is on rare dermatoses as cause of chronic wounds such as pyoderma gangrenosum or necrobiosis lipoidica. In addition to the care situation within but also beyond specified wound centers, the group investigates factors influencing wound healing such as mobility, quality of life and develops new concepts for patient education. Cooperations exist with the study course Medical Process Management at FAU, as well as the University of Coburg (Master study course Health Promotion). Currently, two projects are funded by the Initiative chronische Wunde e.V. on the topics of patient information and education, as well as recording mobility and sleep in patients with chronic wounds. In cooperation with the University of Applied Sciences Osnabrück (Research Group Informatics in Health Care), a grant was recently approved within the BMBF task "Adaptive Technologies for Society - Intelligent Interaction of Humans and Artificial Intelligence". The group is also involved in teaching and has been able to implement and scientifically evaluate both new practical teaching concepts and digital learning opportunities on the subject of wound management in teaching at FAU.

Regulatory T cells for cell-based therapy in inflammatory bowel disease (IBD) and cellular motility in a three-dimensional network
PI: PD Dr. C.J. Bosch-Voskens, PhD
The focus of this project, funded by KFO 257 and since July 2018 by SFB/Trans Regio 241, is on regulatory T cells (Treg). In inflammatory bowel disease, it is postulated that insufficient numbers of regulatory T cells (Treg) that attenuate local proliferation of effector T cells in the gut can be corrected by infusion of autologous Tregs. Together with the Medical Department 1, a phase I fast-track dose-escalation clinical trial was initiated late 2020 (NCT04691232) and is currently actively enrolling patients. In another project, we study motility and migration of NK cells and regulatory T cells in 3-D collagen gels and were able to show that NK cell motility is dramatically impaired after cryopreservation, which leads to a significant reduction of the cytotoxic function.

Mechanisms to improve CAR T cell therapy in solid tumors
PI: Dr. med. U. Uslu
After the success of chimeric antigen receptor (CAR) T cells in hematological malignancies, its efficacy is currently evaluated in different solid tumors. However, first results were not as compelling as for hematological malignancies, due to the fact that CAR T cells need to cope with several challenges, e.g., the insufficient engineered T cell migration and the unfavorable tumor microenvironment. Thus, this group has worked on mechanisms to improve CAR T cell therapy. In addition, stable DNA based receptor transfer for permanent receptor expression on T cells with tumor antigen-specific receptors was established in-house by this group, which will be crucial for moving this therapy towards a clinical use.

Teaching

The Chair of Skin and Venereal Diseases teaches students of medicine, dentistry, molecular medicine, integrated immunology, integrated life sciences, and cellular and molecular biology in dermatology, molecular and cellular immunology in combination with translational applications (GMP laboratory). The educational program is organized in seminars, practical training courses in the clinics and laboratories, lectures, as well as Bachelor's, Master's, and MD theses. The Department of Dermatology is responsible for the organization of dermatological advanced training courses for physicians.

Selected publications

Mark C, Czerwinski T, Roessner S, Mainka A, Hörsch F, Heublein L, Winterl A, Sanokowski S, Richter S, Bauer N, Angelini TE, Schuler G, Fabry B, Voskens CJ. Cryopreservation impairs 3-D migration and cytotoxicity of natural killer cells. Nat Commun. 2020 Oct 16;11(1):5224. doi: 10.1038/s41467-020-19094-0. PMID: 33067467; PMCID: PMC7568558.

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Steeb T, Wessely A, Schmitz L, Heppt F, Kirchberger MC, Berking C, Heppt MV. Interventions for Actinic Keratosis in Nonscalp and Nonface Localizations: Results from a Systematic Review with Network Meta-Analysis. J Invest Dermatol. 2021 Feb;141(2):345-354.e8. doi: 10.1016/j.jid.2020.06.021. Epub 2020 Jul 6.PMID: 32645365.

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Research focus
- CD83 induced immune regenerative processes and resolution of inflammation
- Immune-modulation in autoimmunity and transplantation
- Transcriptional *in vivo* targeting of Dendritic cells (DC)
- Cell-specific biologic function of CD83 expressing immune cells
- Interaction of DC and viruses

Structure of the Division

Professorship: 1
Personnel: 18
- Scientists: 10 (thereof funded externally: 8)
- Graduate students: 5

Research

The *translational research*, i.e. the translation of basic research findings into new and applicable therapeutic strategies for patients, is the prime focus within our research Division. Immune modulation in the context of autoimmune disorders and transplantation as well as tumor- and infectious diseases are in the center of our research projects. In addition, we focus our research efforts torwards immune-mediated regenerative processes during wound healing and resolution of inflammation.

CD83 induced immune-regenerative effects and resolution of inflammation
PI: Dr. D. Royzman, Prof. Dr. A. Steinkasserer
The timely coordinated and site specific resolution of inflammation and the subsequently induced immune-mediated regeneration processes of cells and tissues, are absolutely vital to inhibit chronification and long term damage. This is true for inflammatory disorders of the joint and intestinal tissues, such as in rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), as well as for wound healing processes. Since the recombinantly expressed soluble CD83 (sCD83) molecule has been shown to induce antigen-specific immune tolerance and resolution of inflammation, we investigated the effects of sCD83 in the context of preclinical RA models. Herein, sCD83-treated mice showed a significantly ameliorated disease progression, a reduced inflammatory milieu as well as an accelerated resolution of inflammation. Noteworthy, sCD83 treated animals were even protected from a flare up reaction, without any additional sCD83-applications. Furthermore, we discovered for the first time, that sCD83 treated animals show an inhibitory effect on the formation of bone-resorbing cells, i.e. osteoclasts. Based on these results, the major focus of the research group lies now in the translation of these basic murine results into the human setting, in order to establish new sCD83 based therapeutic strategies for RA patients. In addition, we investigate the pro-regenerative capacities of sCD83 in the context of wound healing. This project is based on the previous observation that both the systemic as well as the local sCD83 application resulted in a significantly improved and accelerated wound closure, using a murine model. In particular, this was characterized by an increased vessel formation within the wound areas and accelerated regenerative healing processes. Currently, we investigate the sCD83-mediated molecular and cellular processes in the course of wound healing, to elucidate the underlying mechanisms. In addition, the potential of sCD83 to induce long lasting wound healing and regeneration processes, for future treatment options for elderly patients suffering from chronic wounds or patients with wound-healing disorders, will be investigated.

Immunmodulation in autoimmunity and transplantation
PI: PD Dr. E. Zinser
The project group focuses on the immuno-modulatory properties of soluble CD83. Using this molecule, we inhibited the inflammation and disease associated symptoms in different murine autoimmune models. Furthermore, also the rejection of heart-, skin-, and cornea-transplants was reduced/ prevented by the sCD83 treatment. Regarding the mode of action, we found, that sCD83 induces regulatory T cells (Treg) and that the indoleamine 2,3-dioxygenase (IDO) plays a major mechanistic role.
Using conditional KO animals, where CD83 is specifically deleted in CX3CR1^{+} macrophages (MΦ), we are currently investigating the role of CD83 within these important immune cells. MΦ are the body's own phagocytes, responsible for detecting, engulfing and destroying pathogens as well as apoptotic/necrotic cell debris. Moreover, MΦ play an important role upon tissue regeneration after injury. Distinct MΦ populations will be characterized under steady state and inflammatory conditions by modern high resolution microscopy, immunological assays and proteomics analyses.
In addition, the group is actually investigating the precise function of sCD83-mediated immune-regulatory mechanisms using a murine model of corneal allograft transplantation. Within this subproject, we analyse whether the pre-treatment of donor tissue with sCD83 induces corneal allograft tolerance and inhibits rejection within the acceptor. Data established in the context of this project provide the basis for new therapeutic strategies in the field of transplant immunology.

Transcriptional *in vivo* targeting of Dendritic cells (DCs)
PI: Dr. I. Knippertz
This research group focuses on two main key topics: (i) transcriptional targeting of dendritic cells for the development of new vaccination strategies, and (ii) the activation of the aryl hydrocarbon receptor (AhR) for the induction of tolerogenic DCs.
Regarding the first topic, we aim to develop a new vaccine for the treatment of patients suffering from cancer or chronic viral infections (e.g. HIV). Currently, new therapeutic vaccination strategies, using adenoviral vectors as well as nanoparticles, are in development to target DCs directly in patients. To ensure specific therapeutic gene expression only in mature immune-stimulating DCs, we use the DC-specific human CD83 promoter, which allows the transcriptional targeting of these DCs. Hence, different therapeutic adenoviruses as well as nanoparticles will be generated, allowing the induction of potent anti-tumoral or anti-viral immune responses, directly in patients.
The second emphasis of our group is to study the mechanisms by which different AhR agonists modulate the phenotype and function of DCs, thereby influencing the immune response in physiology and pathophysiology. In this context, we recently showed, that DCs treated with the AhR ligand Quercetin, a naturally occurring flavonoid, developed a tolerogenic phenotype. Currently, we analyse the underlying molecular mechanisms of AhR activation by Quercetin and other endogenous agonists. The long term aim is the development of new treatment options for patients suffering from autoimmune diseases.

Cell-specific biologic function of CD83 expressing immune cells
PI: Dr. A. Wild
This group focusses on the biologic function of the CD83 molecule, expressed by specific immune cells, including DCs, Tregs as well as microglia. Using cell-type specific conditional KO (cKO) mouse strains, we demonstrated that DC-expressed CD83 plays an important part in resolution of inflammation, since autoimmune responses are severely aggravated in these cKO mice. On the other hand, due to this over activation, bacterial infections are cleared much better. On cellular level, we found that CD83-deficent DCs are characterized by a pro-inflammatory cytokine profile and inhibited tolerogenic and regulatory processes. The underlying molecular mechanisms, leading to the differentiation of this particular cellular phenotype, are currently under investigation. In studies, using CD83 cKO Tregs, we have shown that CD83 is essential for the differentiation and stability of this particular T cell subset, and now we investigate the underlying mechanisms. Moreover, we analyze cKO-strains, in which CD83 is specifically depleted in microglial cells, of the central nervous system (CNS). Using these mice, we have discovered that CD83 is associated with both, a homeostatic and a reparative phenotype in these CNS cells.

Currently, we are investigating the effect of CD83 deletion, using preclinical models for autoimmune neuro-inflammation. Preliminary data show, that CD83 cKO mice develop axacerbated disease symptoms. Within this basic research project, we will generate valuable insights to development new therapies for inflammatory autoimmune disorders of the CNS, in the future.

Interaction of DCs and viruses

PI: Dr. A. Birzer

This research group focuses on the interaction of DCs and specific viruses, including herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and HCMV. To induce potent immune responses against pathogens, e.g. viruses, DCs play a pivotal role. Thus, it is not surprising that many viruses developed specific immune escape mechanisms during their coevolution with the host. We are particularly interested to elucidate the molecular mechanisms leading to such immune escape strategies. In this regard we recently reported, that both adhesion and migration of human DCs are targeted by HSV-1 and HSV-2. Enhanced DC-adhesion leads to impaired migration of these cells into the draining lymph nodes and subsequently to reduced anti-viral immune responses.

Moreover, we discovered that HSV-1 specifically modulates the IL-6 signaling pathway in human mature DCs (mDCs). Using FACS analyses we showed that IL-6 receptor surface expression was strongly impaired on directly HSV-1-infected mDCs. Surprisingly, this was also the case when we analyzed uninfected, bystander mDCs. This is facilitated by so called non-infectious light (L)-particles, which in comparison to infectious heavy (H)-particles do not contain the viral capsid and thus miss the viral genome. However, these particles contain many viral proteins which are sufficient to down-modulate IL-6 receptor expression on mDCs. To obtain further insights regarding the precise protein composition of these non-infectious L-particles, we performed mass spectrometry analyses and compared L- particles with infectious H-particles.

In addition, we are interested in the DC-specific viral replication cycle and compared immature DCs (iDCs) with mDCs, and observed a very interesting difference between these cells. Surprisingly, only iDCs generate infectious H-particles, while mDCs only facilitate the production of non-infectious L-particles. Mechanistically, we found that HSV-1 capsids are trapped within the nucleus in mDCs, thereby inhibiting the viral replication cycle. In sharp contrast, iDCs facilitate an autophagy-dependent degradation of the nuclear lamin layer and thus induce the completion of the viral replication cycle, leading to the generation of infectious viral particles. This represents a new and very interesting mDC-specific mechanism to inhibit viral replication.

Teaching

We teach students from the degree courses “molecular medicine” as well as “biology”, in the fields of molecular and cellular immunology. The teaching takes place in form of lectures, seminars as well as practical courses. In addition, we supervise Bachelor, Master and PhD students.

Selected publications

Birzer A, Krawczyk A, Draßner C, Kuhnt C, Mühl-Zürbes P, Heilingloh CS, Steinkasserer A, Popella L. HSV-1 Modulates IL-6 Receptor Expression on Human Dendritic Cells. Front Immunol. 2020 Aug 26;11:1970. doi: 10.3389/fimmu.2020.01970. PMID: 32983130; PMCID: PMC7479228.

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Turan A, Grosche L, Krawczyk A, Mühl-Zürbes P, Drassner C, Düthorn A, Kummer M, Hasenberg M, Voortmann S, Jastrow H, Dörrie J, Schaft N, Kraner M, Döhner K, Sodeik B, Steinkasserer A, Heilingloh CS. Autophagic degradation of lamins facilitates the nuclear egress of herpes simplex virus type 1. J Cell Biol. 2019 Feb 4;218(2):508-523.

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International cooperations

Prof.Dr. M. Berezovski, Department of Chemistry and Biomolecular Sciences: Canada

Prof. Dr. R.D. Everett, MRC-Center for Virus Research, University of Glasgow, Glasgow: GB

Prof. Dr. C.C. Figdor, Nijmegen Center for Molecular Life Sciences, Nijmegen: The Netherlands

Prof. Dr. U. Grohmann, University of Perugia, Perugia: Italy

Prof. Dr. M. G. Manz, University of Zurich, Zurich: Switzerland

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Forschungsschwerpunkte

- Intestinal diseases
- Experimental hepatology
- Epithelial cytoskeleton dynamics in the gut
- Therapeutic targets for treatment of IBD and colorectal cancer
- Division of clinical and experimental pulmonology
- Molecular gastroenterology
- Molecular hepatology and GI-oncology
- Patient-oriented research and innovative therapeutic strategies in IBD
- Cell trafficking and T cells in IBD
- Cytokines and transcription factors in IBD and CAC
- Clinical and experimental nutritional and sports medicine – Hector-Center

Structure of the Department

Professorships: 10
Personnel: 478

- Doctors (of Medicine): 69
- Scientists: 23
  (thereof funded externally: 14)
- Graduate students: 61

Clinical focus areas

- Gastroenterology
- Pneumology
- Endocrinology and diabetology
- Hepatology
- Nutritional medicine
- Intensive care
- Emergency reception

Research

The research focus of the Medical Clinic 1 is a better understanding of the physiology and pathophysiology of the gut, liver and lung. In particular, we are investigating how cells and their functions contribute to the development of diseases such as inflammation and cancer, and which molecular targets may be suitable for therapeutic intervention. In addition to established immunological, molecular biological and cell biological techniques, innovative and interdisciplinary detection methods are being developed.

Intestinal diseases
PI: PD Dr. Dr. C. Neufert, Prof. Dr. M. Waldner
Our research focus is on the pathogenesis of intestinal inflammation and colorectal cancer. Herein, we evaluate molecular mechanisms promoting disease development. Current investigations address the role of the intestinal immune system and its interaction with other gut cell populations. Through an increasing knowledge about these processes, our studies could help to improve the therapeutic options for patients suffering from intestinal inflammation and colorectal cancer.

Experimental hepatology
PI: PD Dr. Wirtz, Prof. Dr. C. Günther, PD Dr. A. Kremer
We work on pathophysiological processes that drive the initiation and progression of acute and chronic liver disorders and their attendant symptoms such as pruritus and fatigue. We are particularly interested in novel signal transduction pathways that trigger the occurrence of massive hepatocyte death, which is a common feature of acute hepatic inflammation and toxin-dependent liver injury. In this context, we could demonstrate that besides apoptotic cell death, programmed necrosis substantially contributes to hepatocellular death during liver inflammation. Therefore, we currently evaluate in preclinical studies and patient cohorts how regulated necrosis contributes to gradual accumulation of extracellular matrix components and hepatic tissue remodeling.

Epithelial cytoskeleton dynamics in the gut
PI: Dr. R. Lopez-Posadas
This group aims at the description of cytoskeleton-dependent molecular mechanisms regulating epithelial integrity in the gut. This knowledge might be exploited in order to develop innovative diagnostic and therapy strategies for the benefit of IBD and CRC patients, and contribute to current efforts in the context of epithelial restitution for the clinical management of chronic intestinal diseases.

Therapeutic targets for treatment of IBD and colorectal cancer
PI: PD Dr. I. Atreya
We intend to achieve improved insights into the imunopathogenesis of inflammatory bowel diseases (IBD) and the antitumor immune response in colorectal cancer. In this context, we in particular focus on T lymphocytes and innate lymphoid cells in the peripheral blood, inflamed intestinal mucosa or tumor tissue and their capacity to interact locally with epithelial cells, different types of mucosal immune cells or other tissue-resident cells. Supported by innovative experimental settings, we are able to perform detailed functional analyses and advanced imaging of primary human immune cells derived from the peripheral blood or tissue biopsies of affected patients. Overall, our investigations aim on the identification of new therapeutic target structures for an improved treatment of IBD and colorectal cancer.

Division of clinical and experimental pulmonology
PI: Dr. F. Fuchs, Prof. Dr. K. Hildner
The lung tissue bank established and located at our Department allows us to study the immunological micromilieu of the lung in greater detail. For example, the presence and functionality of innate immune cell subpopulations in the broncho-alveolar lavage is assessed in current research projects. Our clinical research unit currently focusses on the state-wide establishment of the infrastructure for a research data network to study lung cancer within the Bavarian cancer research centre (BZKF). Clinical studies within this network are under way.

Molecular gastroenterology
PI: Prof. Dr. C. Becker
The research group focuses on immunological and molecular mechanisms in the development of gastrointestinal infections, inflammation and cancer. During the reporting period, several studies were performed on the role of cell death in the development and resolution of intestinal inflammation and colon cancer. It has been shown that necroptosis in the intestinal epithelium plays a crucial role in the development of intestinal inflammation and that necroptosis can be regulated by the immune system. Important goals in the research of necroptosis were not only the elucidation of cellular signaling pathways and the study of the significance of necroptosis in various diseases, but also the development of specific detection methods for necroptosis and for the differentiation of necroptosis from other forms of cell death.

Molecular hepatology and GI-oncology
PI: PD Dr. Dr. P. Dieterich
The group addresses molecular mechanisms of acquired therapy resistance in hepatocellular carcinoma (HCC). HCC mostly develops in cirrhotic livers. During the reporting period, the group also investigated underlying molecular mechanisms of liver metastasis of gastrointestinal (GI) tumors such as colon cancer. Liver metastasis majorly contribute to the poor prognosis of GI-cancers. The group focused on small RNA molecules that strongly affect main cancer- and therapy resistance-associated signaling pathways like the RAS-RAF-ERK-pathway. Moreover, the group revealed novel cellular cross-talk mechanisms mediated by neuropeptide-signaling in GI-cancer types that affect the tumor microenvironment and important neuro-immunologic interactions driving cancer progression and metastasis.

Patient-oriented research and innovative therapeutic strategies in IBD
PI: Prof. Dr. R. Atreya
This group aims at characterizing the molecular mechanism of action of anti-inflammatory therapies in IBD and the identification of biomarkers for the prediction of therapeutic response. The translational identification and characterization of immunological resistance mechanisms against biologics is another research

focus of the group. The clinical application of molecular endoscopy for the individual prediction of therapeutic response in IBD represents another field of our group.

Cell trafficking and T cells in IBD

PI: Dr. S. Zundler

The main interest of this group is to understand processes of cell trafficking in intestinal immunology with special focus to IBD and related translational applications. Moreover, the team examines the impact of cell trafficking originating from the gut for inter-organ communication, e.g. with the joints or the brain and explores the modulation of the intestinal microbiome by chemotactic peptides. During the reporting period, the researchers characterized the role of α4β7 integrin-mediated gut homing of monocyte subpopulations for intestinal wound healing, which is clinically relevant in the context of therapeutic integrin blockade in IBD. Another focus was the analysis of cell type-specific dose response profiles of anti-integrin antibodies, which could serve as the basis for optimized treatment protocols.

Cytokines and transcription factors in IBD and CAC

PI: PDDr. Dr. B. Weigmann

The main research areas of the working group are T-cell-specific transcription factors and the associated cytokines. Transcription factors of the NFAT family in particular are important modulators of Th2 cells and are closely related to ulcerative colitis (UC). They are the subject of studies with intestinal inflammation models. Another focus of the working group is the cytokine interleukin-9, which was identified a few years ago in connection with UC and which is produced by Th9 cells. IL-9 is being investigated as a mediator for CAC (colitis-associated colon carcinoma) in the working group. Furthermore, the fabrication of stimuli sensitive, bio-functionalized PLGA nanocarriers incorporating surface attached bio-molecules for more specific targeting of inflamed colon tissue through active/passive mechanisms is the aim of another research area of the working group. Finally, the effect of cyclosporine A, which is used in UC, is the focus of current studies. Our data indicate that by specifically switching off the Tec-Kinase, Itk, the activation of T cells can be prevented and thus the resolution of the inflammatory reaction in the intestine can be induced.

Clinical and experimental nutritional and sports medicine – Hector-Center

PI: Prof. Dr. Y. Zopf

The working group examines the influence of nutrition and sports on body composition, performance, muscular metabolism, and the molecular mechanisms of inflammation in oncological and obese patients. We could show that even patients with advanced cancer profit from a high-protein nutrition and sports. In our experimental model, we demonstrated that myokines activate muscular metabolism, reduce the proliferation of tumor cells and induce their cell death. We could further show that our innovative sports and nutritional interventions reduce the systemic inflammation in obese patients, increase the physical performance, and improve the metabolic risk profile. In the field of food intolerance, we examine the influence of food on mucosal integrity. We focus on the detection of molecular pathomechanisms of mucosal inflammation and on the effects of anti-inflammatory food.

Teaching

The Department of Medicine 1 is involved in the curricular teaching of human medicine with compulsory and elective courses. Particularly noteworthy is the interdisciplinary teaching within the cross section lectures together with the Departments of Medicine 2 and 5 as well as the Institutes of Clinical Microbiology, Immunology, and Hygiene and of Clinical and Molecular Virology, respectively. The Department of Medicine 1 offers a student ultrasound training with exclusive devices for this propose. MD and PhD doctorates are supervised.

Selected publications

Kreiß L, Thoma O, Dilipkumar A, Carlé B, Longequeue P, Kunert T, Rath T, Hildner K, Neufert C, Vieth M, Neurath MF, Friedrich O, Schürmann S, Waldner MJ. Label-Free In Vivo Histopathology of Experimental Colitis via 3-Channel Multiphoton Endomicroscopy. Gastroenterology. 2020 Sep;159(3):832-834.

Heichler C, Scheibe K, Schmied A, Geppert A, Schmid B, Wirtz S, Thoma O, Kramer V, Waldner MJ, Büttner C, Farin HF, Pešić M, Knieling F, Merkel S, Grüneboom A, Gunzer M, Grützmann R, Rose-John S, Koralov SB, Kollias G, Vieth M, Hartmann A, Greten FR, Neurath MF, Neufert C. STAT3 activation through IL-6/IL-11 in cancer-associated fibroblasts promotes colorectal tumour development and correlates with poor prognosis. Gut. 2020 Jul;69(7):1269-1282.

Schleier L, Wiendl M, Heidbreder K, Binder M, Atreya R, Rath T, Becker E, Schulz-Kuhnt A, Stahl A, Schulze L, Ullrich K, Merz SF, Bornemann L, Gunzer M, Watson AJM, Neufert C, Atreya I, Neurath MF, Zundler S. Non-classical monocyte homing to the gut via α4β7 integrin mediates macrophage-dependent intestinal wound healing. Gut. 2020 Feb;69(2):252-263.

Zundler S, Becker E, Spocinska M, Slawik M, Parga-Vidal L, Stark R, Wiendl M, Atreya R, Rath T, Leppkes M, Hildner K, López-Posadas R, Lukassen S, Ekici AB, Neufert C, Atreya I, van Gisbergen KPJM, Neurath MF. Hobit- and Blimp-1-driven CD4 + tissue-resident memory T cells control chronic intestinal inflammation. Nat Immunol. 2019 Mar;20(3):288-300.

Schmitt H, Billmeier U, Dieterich W, Rath T, Sonnewald S, Reid S, Hirschmann S, Hildner K, Waldner MJ, Mudter J, Hartmann A, Grützmann R, Neufert C, Münster T, Neurath MF, Atreya R. Expansion of IL-23 receptor bearing TNFR2+ T cells is associated with molecular resistance to anti-TNF therapy in Crohn's disease. Gut. 2019 May;68(5):814-828.

Günther C, Ruder B, Stolzer I, Dorner H, He GW, Chiriac MT, Aden K, Strigli A, Bittel M, Zeissig S, Rosenstiel P, Atreya R, Neurath MF, Wirtz S, Becker C. Interferon Lambda Promotes Paneth Cell Death Via STAT1 Signaling in Mice and Is Increased in Inflamed Ileal Tissues of Patients With Crohn's Disease. Gastroenterology. 2019 Nov;157(5):1310-1322.e13.

International cooperations

M. Lacucci, MD, PhD, Institute of Translational Medicine, University of Birmingham, Birmingham: Großbritannien

R. S. Blumberg, MD, Brigham Research Institute Division of Gastroenterology, Brigham and Women`s Hospital, Boston: USA

Prof. A. Kaser, Department of Medicine, University of Cambridge, Cambridge: Großbritannien

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Department of Medicine 2 – Cardiology and Angiology

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Research focus
- Molecular and experimental cardiology
- Interventional cardiology
- Interventional valve therapy
- Electrophysiology
- Cardiac computed tomography

Structure of the Department

Professorship: 1
Personnel: 228
- Doctors (of Medicine): 54
- Scientists: 4 (thereof funded externally: 2)
- Graduate students: 45

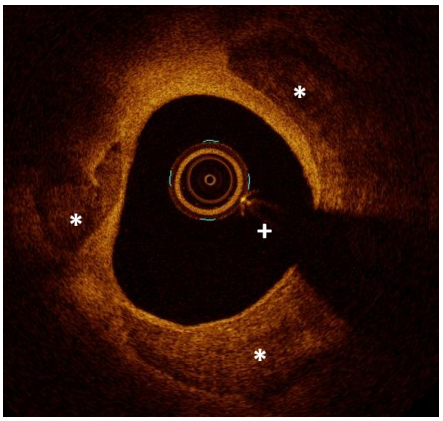
Clinical focus areas
- Interventional cardiology
- Electrophysiology
- Intensive care medicine
- Cardiac imaging

Research

The Department of Medicine 2 - Cardiology and Angiology conducts clinically oriented research with three special areas of focus. The working group for molecular cardiology, located in the „Translational Research Center“, explores the development and progression of atherosclerosis and in particular the mechanisms by which shear stress influences atherosclerotic lesions. In the field of interventional cardiology, coronary and structural interventions, their optimizarion, and predictors of outome constitute the major areas if research. Finaly, in cardiac imaging, methodological and clinical aspects of cardiac computed tomography, in particular in connection to risk prediction and the optimization of cardiac interventions, constitute a major focus. In addition, the Department of Medicine 2 is involved in a large number of national and international multicenter trials, primarily in the fields of interventional cardiology, invasive electrophysiology, pacemaker and ICD therapy.

Molecular and experimental cardiology
PI: Dr. B. Dietel, Dr. M. Tauchi-Brück
In the “Translational Research Center”, researchers explore the role of wall shear stress in atherosclerosis development and the mechanisms by which it influences atherogenesis. One of the main interests is the investigation of cellular signaling cascades mechanically activated by blood flow. Specific glycocalyx proteins, which build a surface layer on endothelial cells and are involved in mechanosensing of shear stress, affect atherosclerotic plaque progression. The respective mechanism are being explored. To translate basic knowledge into clinical practice, the laboratory works in close collaboration with medical and basic researchers in various disciplines.

Interventional cardiology
PI: Dr. L. Gaede
The working groups focuses on the optimization of intravascular coronary diagnostics and coronary intervention. Single and multi-center studies include patients with acute as well as chronic coronary syndrome, to evaluate the benefit of new techniques. This includes, for example, OCT (optical coherence tomography) guided stent implantation or intravascular coronary lithoplasty for the treatment of calcified lesions. Additionally, pressure wire assessment of coronary lesion hemodynamics represents an important topic. Conventional pressure wire measurements are one one hand evaluated in specific anatomic lesion subsets and on the other hand compared to new invasive (angiography-based FFR) and non-invasive imaging-based approaches (CT-based FFR).



Calcified stenosis visualized in OCT.
**calcified plaque, +vessel lumen*

Interventional valve treatment
PI: PD Dr. M. Arnold
In addition to the analysis of procedural parameters and outcome after transcatheter aortic valve implantation (TAVI), the treatment of mitral and tricuspid valve regurgitation with transcatheter techniques is a particularly intensive field of research. This prominently includes interventional and imaging aspects of catheter-based tricuspid annuloplasty. The Department of Medicine 2 has a leading role in several national and international registries.

Electrophysiology
PI: PD Dr. M. Arnold, Dr. L. Anneken
Scientific activities include the evaluation of new ablation techniques in patients with atrial fibrillation in the framework of international multicenter studies. New approaches to cardiac resynchronization therapy encompass the use of two separate left ventricular stimulation leads for cardiac resynchronization therapy in order to obviate the need for a lead in the right ventricle. This is particularly relevant for patients with tricuspid valve regurgitation. New techniques for holter ECG documentation, including textile-based approaches and algorithms for automated ECG analyses, are being investigated.

Cardiac computed tomography
PI: PD Dr. M. Marwan
CT angiography-based simulation of coronary flow and in particular its prognostic relevance is evaluated in a large cooperative project with Cleveland Clinic, USA. The potential influence of coronary plaque inflammation on fatty deposits around the coronary arteries as a marker of plaque instability, including its impact on long-term prognosis is explored in collaboration with the University of Oxford. In addition, the research group actively investigates the role of patient-specific CT findings to predict outcome and avoid complications in catheter-based aortic valve replacement.

Teaching

The Department of Medicine 2 participates with compulsory and elective subjects in the curricular teaching of Medicine, with a special emphasis on bedside and interactive teaching. We supervise 45 MD theses.

Selected publications
Bittner DO, Mayrhofer T, Budoff M, Szilveszter B, Foldyna B, Hallett TR, Ivanov A, Janjua S, Meyersohn NM, Staziaki PV, Achenbach S, Ferencik M, Douglas PS, Hoffmann U, Lu MT; PROMISE investigators. Prognostic value of coronary CTA in stable chest pain: CAD-RADS, CAC, and cardiovascular events in PROMISE. JACC Cardiovasc Imaging. 2020, 13(7), 1534-1545

De Backer O, Dangas GD, Jilaihawi H, Leipsic JA, Terkelsen CJ, Makkar R, Kini AS, Veien KT, Abdel-Wahab M, Kim WK, Balan P, Van Mieghem N, Mathiassen ON, Jeger RV, Arnold M, Mehran R, Guimarães AHC, Nørgaard BL, Kofoed KF, Blanke P, Windecker S, Søndergaard L; Reduced Leaflet Motion after Transcatheter Aortic-Valve Replacement. GALILEO-4D Investigators. N Engl J Med. 2020 Jan 9;382(2):130-139.

Fearon WF, Achenbach S, Engstrom T, Assali A, Shlofmitz R, Jeremias A, Fournier S, Kirtane AJ, Kornowski R, Greenberg G, Jubeh R, Kolansky DM, McAndrew T, Dressler O, Maehara A, Matsumura M, Leon MB, De Bruyne B; FAST-FFR study investigators. Accuracy of fractional flow reserve derived from coronary angiography. Circulation. 2019 Jan 22;139(4):477-484

Oikonomou EK, Desai MY, Marwan M, Kotanidis CP, Antonopoulos AS, Schottlander D, Channon KM, Neubauer S, Achenbach S, Antoniades C. Perivascular Fat Attenuation Index Stratifies Cardiac Risk Associated With High-Risk Plaques in the CRISP-CT Study. J Am Coll Cardiol. 2020 Aug 11;76(6):755-757.

Oikonomou EK, Williams MC, Kotanidis CP, Desai MY, Marwan M, Antonopoulos AS, Thomas KE, Thomas S, Akoumianakis I, Fan LM, Kesavan S, Herdman L, Alashi A, Centeno EH, Lyasheva M, Griffin BP, Flamm SD, Shirodaria C, Sabharwal N, Kelion A, Dweck MR, Van Beek EJR, Deanfield J, Hopewell JC, Neubauer S, Channon KM, Achenbach S, Newby DE, Antoniades C. A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography. Eur Heart J. 2019 Nov 14;40(43):3529-3543

Smits PC, Chang CC, Chevalier B, West NEJ, Gori T, Barbato E, Tarantini G, Kocka V, Achenbach S, Dudek D, Escaned J, Wlodarczak A, Abdel-Wahab M, Esposito G, Tijssen JGP, Morice MC, Onuma Y, van Geuns RM. Bioresorbable vascular scaffold versus metallic drug-eluting stent in patients at high risk of restenosis: the COMPARE-ABSORB randomised clinical trial. EuroIntervention. 2020 Oct 23;16(8):645-653

International Cooperations

Dr. U. Hoffmann, Massachusetts General Hospital, Boston: USA

Prof. Dr. D. Berman, Damini Dey, Cedars Sinai Medical Center, Los Angeles: USA

Prof. Dr. S. Neubauer, University of Oxford, Oxford: Great Britain

Prof. Dr. P. Smits, Maasstad Hospital, Rotterdam: Netherlands

Prof. Dr. Milind Desai, Cleveland Clinic, Cleveland, OH: USA

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Research focus
- Tissue and Bone Destruction
- Autoimmunity
- Metabolism
- Tissue Homeostasis
- Innate Immunity
- Fibrosis Research
- Clinical Research
- COVID-19 and Inflammation

Structure of the Chair

Professorships: 8
Personnel: 246
- Doctors (of Medicine): 31
- Scientists: 52
  (thereof funded externally: 22)
- Graduate students: 36

Clinical focus areas
- Rheumatology (In- and outpatient department)
- Immunology (In- and outpatient department)

Research

The Department of Medicine 3 focuses on translational and clinical inflammation research to decipher the mechanisms that are responsible for pathogenesis and perpetuation of rheumatic inflammatory and autoimmune diseases. The emphasis of the experimental research is on the interaction between immune cells and cells of affected organs. The main focus of the clinical research is innovative drug trial studies and early recognition of rheumatic diseases, e.g. by imaging methods.

Tissue and Bone Destruction
Chronic inflammation often leads to bone loss. Responsible for this are mediators released by inflammation that have a destructive effect on the joints and the bone.

PI: Prof. Dr. A. Bozec
We delineate that macrophages are skewed into an anti-inflammatory and bone protective phenotype by Fra-1 expression via the induction of L-arginine. We have also shown that HIF1a is essential in regulating B cells, which influences autoimmune responses and bone homeostasis. Recently, we have uncovered a new crosstalk between osteocyte death and the induction of bone loss by increasing osteoclastogenesis via activation of the c-type lectin receptor Mincle.

PI: Dr. U. Steffen
The group investigates the interplay between antibodies and bone loss in rheumatic diseases. We showed the regulation of bone resorption by Siglec-9 and the effects of IgA subclasses on immune cells and bone. For instance, the IgA subclass IgA2 acts proinflammatory and aggravates rheumatoid arthritis.

PI: Dr. S. Frey
The group showed that JAK inhibitors relieve pathological bone loss and promote the repair of affected bone substance. In addition, the group could decipher the mechanism that is responsible for osteoblast differentiation allowing bone repair during arthritis.

Autoimmunity
The origin of autoimmunity leading to chronic inflammation is essential for developing strategies that allow to prevent autoimmune disease.

PI: Prof. Dr. G. Krönke
A new mechanism and function has been discovered that allows the joint cavities remain cell free: Using light sheet fluorescence microscope, we were able to visualize a closed mantle of resident macrophages along the synovium, which isolates the joint from the surrounding tissue and is a protective membrane against inflammatory reactions.

Metabolism
Misdirected metabolic processes such as in obesity, diabetes and chronic intestinal diseases appear to have a major influence on inflammatory activity in joint and bone diseases.

PI: Prof. Dr. M. Zaiss
Interactions between intestinal and bone cells play an important role in the pathogenesis and progression of rheumatoid arthritis. In this context, metabolic products of the intestinal bacteria such as short chain fatty acids influence the immune system and therefore have an effect on autoimmune diseases such as rheumatoid arthritis. We were able to show that a diet rich in fibres has an anti-inflammatory effect. Also the immunomodulatory effect of moderate alcohol consumption was described by the group.

Tissue Homeostasis
Inflammation leads to fast tissue responses that can either prevent or promote inflammation.

PI: Prof. Dr. S. Uderhardt
The use of intravital imaging and multiplex microscopy enabled us to demonstrate that tissue-resident macrophages can actively protect stromal tissue damage and prevent the activation of inflammatory effector cells. This "cloaking" mechanism prevents inflammatory collateral damage and maintains tissue homeostasis during local stromal injury.

PI: PD Dr. M. Hoffmann
We could show that the so-called "inflammatory tissue priming" is based on a metabolic reprogramming of tissue-derived synovial fibroblasts (SF). Inflammatory tissue priming develops following activation of intracellular complement C3 and the complement C3a receptor, which initiates the mTOR/HIF1α pathway, resulting in increased glycolysis and oxidative phosphorylation and activation of the NLRP3 inflammasome in SF. This new concept may be a basis for new therapeutic approaches that seek to reset tissue priming and would thus allow suspension of anti-inflammatory therapies at low risk of relapse.

Innate Immunity
Neutrophil extracellular traps (NETs) play a crucial role in the pathogenesis of autoimmune diseases and are essential for the immune system.

PI: Prof. Dr. Dr. M. Herrmann, PD Dr. L. Munoz
Neutrophils, NETs and aggregated NETs (aggNETs) are double-edged swords that orchestrate the innate immune response but also carry the risk of causing autoimmunity, epithelial damage and vascular blockages. We showed that gallstone formation essentially requires NETs. In accordance with the physicochemical process of crystal formation, NETs promote their aggregation into larger aggregates and eventually into gallstones. Similarly, they promote calcium crystal aggregation in the salivary gland ducts and trigger concrement formation. They are particularly important for patrolling and monitoring the external and internal body surfaces and exhibit anti-inflammatory characteristics in the oral cavity and eye. In contrast, excessive aggNET formation can directly block vessels and ducts, causing thrombi, like those observed in COVID-19 or duct obstruction such as gallstones. We describe how NET formation influences diseases and how NET formation can be therapeutically inhibited.

Fibrosis Research
Fibrotic diseases are characterized by aberrant activation of fibroblasts with progressive deposition of extracellular matrix.

PI: Prof. Dr. J. Distler
We demonstrated that fibroblast growth factor receptor 3 (FGFR3) and its ligand FGF9 are induced by the profibrotic cytokine transforming growth factor β (TGF-β) in patients with systemic sclerosis (SSc) with a corresponding FGFR3 signature in SSc skin. Activation of FGFR3 induces a profibrotic phenotype in fibroblasts by inducing multiple profibrotic signals, while inhibition of FGF9/FGFR3 shows antifibrotic effects in different models. We also demonstrated that activation of DNA

methyltransferase 3A (DNMT3A) and DNMT1 in fibroblasts turns off the expression of the antifibrotic factor Suppressor of Cytokine Signaling 3 by promoter hypermethylation in the sense of tissue memory, and the resulting hyperactivation of the JAK/STAT signaling cascade promotes fibrotic tissue remodeling.

PI: PD Dr. A. Ramming
In fibrotic diseases, fibroblasts synthesize large amounts of extracellular matrix. However, fibroblasts in arthritis are also characterized by the degradation of the extracellular matrix. We identified the transcription factor PU.1 as an essential regulator of the pro-fibrotic gene expression program. The interplay between transcriptional and post-transcriptional mechanisms that normally control PU.1 expression is disrupted in several fibrotic diseases, leading to upregulation of PU.1, induction of fibrosis-associated gene sets and a phenotypic switch to extracellular matrix-producing pro-fibrotic fibroblasts.

Clinical Research
In order to transfer innovative diagnostic and monitoring methods as well as targeted therapies into routine practice, we conduct phase Ib-IV therapy studies as well as phase II studies on the safety and efficacy of drugs.

PI: PD Dr. A. Kleyer, PD Dr. D. Simon, PD Dr. M. Pachowsky
Structural changes in the joints result from chronic inflammatory arthritis. By using state-of-the-art imaging techniques such as MRI or high-resolution peripheral quantitative computed tomography (HR-pQCT), we are able to identify early bone changes associated with the onset of arthritis. Hereby, we combine advanced imaging with computer technology (cinematic rendering). Furthermore, we showed that certain bone changes in the finger joints, such as erosions and osteophytes, are age-dependent and that the biomechanical properties of the peripheral bone are relevantly reduced in patients with hand osteoarthritis. In addition to bony changes, we investigated whether sequences in MRI, such as T2 mapping, detect cartilage damage in patients with RA. These innovative diagnostic and monitoring methods as well as targeted therapies are being investigated in ongoing studies (Phase II-IV) to evaluate disease progression and treatment response in patients with rheumatoid arthritis or psoriatic arthritis and to transfer them into clinical routine.

COVID-19 and Inflammation
We identify factors influencing the humoral immune response to SARS-CoV-2 in patients with immune-mediated inflammatory diseases.

PI: Prof. Dr. Dr. M. Herrmann
We showed that severe COVID-19 is characterized by pronounced formation of NETs within the micro-vessels. The intravascular aggregation of NETs leads to rapid occlusion of the affected vessels, impaired microcirculation and organ damage. In severe COVID-19 infections, the neutrophil granulocytes are highly activated and adopt a so-called low-density phenotype, which tends to spontaneously form NETs.

PI: Prof. Dr. G. Schett, Prof. Dr. B. Manger, PD Dr. D. Simon
SARS-CoV-2 antibody testing showed that patients with inflammatory diseases, including rheumatoid arthritis, Crohn´s disease and psoriasis receiving cytokine inhibitor therapy have a low risk for COVID-19 infection. This finding has been surprising and indicated that immune modulatory treatment of such patients should not be stopped but maintained during the pandemics.

Teaching

The Department of Medicine 3 is embedded into the curriculum-based teaching of Medicine. In the course of interdisciplinary teaching, the lecture “Dr. House in Erlangen – surgical and internal differential diagnosis” for first-year students is to highlight particularly.
Furthermore, master’s theses as well as medical and scientific doctorates are supervised.

Selected publications

Simon D, et al. Patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have low prevalence of SARS-CoV-2 seroconversion. Nat Commun. 2020 Jul 24;11(1):3774.

Schett G, et al. COVID-19 revisiting inflammatory pathways of arthritis. Nat Rev Rheumatol. 2020 Aug;16(8):465.

Tajik N, et al. Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. Nat Commun. 2020 Apr 24;11(1):1995.

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Leppkes M, et al. Vascular occlusion by neutrophil extracellular traps in COVID-19. EBioMedicine. 2020 Aug;58:102925.

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Muñoz LE, et al. Neutrophil Extracellular Traps Initiate Gallstone Formation. Immunity. 2019 Sep 17;51(3):443.

Culemann S, et al. Locally renewing resident synovial macrophages provide a protective barrier for the joint. Nature. 2019 Aug;572(7771):670.

Wohlfahrt T, et al. PU.1 controls fibroblast polarization and tissue fibrosis. Nature. 2019 Feb;566(7744):344.

International cooperations
Prof. L. Klareskog, Karolinska Institutet, Stockholm: Sweden

Prof. M. Hansson, Uppsala Universitet, Sweden

Prof. I. McInnes/Prof. C. Goodyear, University of Glasgow, Great Britain

Prof. R. Lories, Universiteit Leuven, Belgium

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Research focus

- The role of miRNA in B cell maturation and pathogenesis of multiple myeloma
- Nonsense-mediated decay of nonfunctional mRNA
- Molecular control of peripheral B cell and plasma cell differentiation
- Selection of B cells
- Metabolic control of B cells

Structure of the Division

Professorship: 1
Personnel: 18

- Scientists: 4 (thereof funded externally: 1)
- Graduate students: 6

Research

The Division of Molecular Immunology concentrates on the development of mature B cells and their differentiation in effector cells. In addition, we develop human monoclonal antibodies against tumors of the B cell lineage.

The role of miRNA in B cell maturation and pathogenesis of multiple myeloma
PI: H.-M. Jäck, J. Wittmann
One research focus is on the role of microRNA (miRNA) during central and peripheral development of B cells, the antigen-induced differentiation of mature B cells, as well as the pathogenesis of diseases, such as multiple myeloma or Epstein-Barr virus infection. MiRNA are small, 22-nt long, non-coding RNA (ribonucleic acid) that control the expression of specific target genes at the post-transcriptional level. MiRNA bind to the 3'untranslated region of mRNA (messenger RNA) which results either in a block of translation or an acceleration of the degradation of the target mRNA. MiRNA play a significant role in the regulation of cell fate and cell differentiation processes in animals and plants. Dysregulation of miRNA expression was detected in various tumors. Therefore, we are investigating the function of miRNA during development of normal B cells as well as the pathogenesis of multiple myeloma and B cell autoimmune diseases. Currently, we are analyzing miRNA expression profiles in different B cell stages and myeloma as well as lymphoma cells by high-throughput-sequencing of miRNA libraries which will serve as a platform for further functional analysis of specific miRNA involved in the B cell maturation and the generation of multiple myeloma or B cell lymphoma.

Nonsense- mediated decay of non-functional mRNA
PI: H.-M. Jäck, J. Wittmann
Another research focus is the molecular control of recognition and decay of non-functional immunoglobulin (Ig)-mRNA, a pathway that is termed nonsense-mediated decay (NMD) of nonfunctional mRNA (mRNA surveillance). Nonsense Ig mRNA is encoded from non-productively rearranged Ig genes during B cell development because of a defective VDJ recombination. As faulty mRNA can be translated into potentially toxic proteins, the elucidation of control mechanisms and factors involved in mRNA decay is of interest for B and T cell maturation. The role of NMD in central B cell maturation is analyzed in a mouse line in which a specific NMD factor which was discovered in our laboratory can be conditionally deleted in developing B cell progenitors. In parallel, immunoprecipitation analyses followed by mass spectrometry analyses are carried out to identify novel interaction partners and their role in the degradation of faulty mRNAs and early B cell maturation.

Molecular control of peripheral B cell activation and plasma cell differentiation
PI: H.-M. Jäck, W. Schuh
Immune responses are strictly dependent on proper positioning of immune cells in the body. The transcription factor Krüppel-like factor 2 (KLF2) plays an important role in the differentiation, activation and correct positioning of B cells in the lymphatic organs. Investigations of a mouse model with a B-cell-specific deletion of KLF2 showed that KLF2 is essential for the migration of plasma cells to their survival niches in the bone marrow. The molecular mechanisms of plasma cell migration and plasma cell survival are currently being investigated through the identification and verification of new as well as known target genes of KLF2. For this purpose, comparative transcriptome and single cell sequencing analyses of "normal" plasma cells and KLF2-deficient plasma cells from different tissues are carried out. Furthermore, the function of KLF2 in B-cell activation and plasma cell homeostasis in the gut-associated lymphoid tissues (GALT) and in the context of an IgA immune response will be investigated.

Selection and differentiation of B cells in the germinal center
PI: D. Mielenz
In specialized structures, so-called germinal centers, the B cell memory and plasma cells secreting high affine antibodies are generated. Both are required to establish a long-lasting, highly specific immunity. The germinal center reaction demends a finely tuned intracellular signal transmission machinery and a flexible adaptation of the metabolism because signals from several receptors need to be integrated. Many of these elements are not yet fully characterized. The main goal of this project is to understand BCR selection the germinal center reaction. Particular attention is paid to the B cell cytoskeleton, metabolism, and intracellular transport structures.

Selection and differentiation of B cells in the germinal center
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In specialized structures, so-called germinal centers, the B cell memory and plasma cells secreting high affine antibodies are generated. Both are required to establish a long-lasting, highly specific immunity. The germinal center reaction demends a finely tuned intracellular signal transmission machinery and a flexible adaptation of the metabolism because signals from several receptors are to be integrated. Many of these elements are not yet characterized. The main goal of this project is to understand BCR selection the germinal center reaction. Particular attention is paid to the B cell cytoskeleton, metabolism, and intracellular transport structures. We have shown that B cell speed in germinal centers supports plasma cell generation. This depends on contacts of germinal center B cells with follicular dendritic cells and is mediated by a cytoskeletal protein, EFhd2 (EF hand containing 2). EFhd2 also appears to regulate B cell metabolism via mTOR.

Metabolic control of B cells by mitochondria and autophagy
PI: D. Mielenz
B cells reprogram their metabolism after (pre) BCR activation, but also after activation via TLR4, CD40, and the interleukin-4 receptor in the course of plasma cell differentiation. In this project we investigate how the mitochondrial respiratory chain influences B cell development and plasma cell differentiation. Our results show that the mitochondrial respiratory chain is essential for the development of B cells in the bone marrow at the pre-BCR checkpoint as well as for the development of plasma cells. Mechanistically we show that mitochondrial respiration controls flus of the TCA cycle. This enables synthesis of phosphatidic acid, which drives the mTOR pathway required for plasma cell differentiation. We have furthermore identified a pathway that ensures homeostasis of the endoplasmic reticulum and flux of autophagy in activated B cells. This pathway, mediated by TFG (Trk-fused gene), is essential for plasma cell homeostasis.

Glucose metabolism in plasma cells
PI: H.-H. Jäck, K.Pracht
During the differentiation of mature B cells into antibody-secreting plasma cells their glucose uptake increases constantly. Glucose is an essential factor for the formation and secretion of correctly glycosylated and therefore functional antibodies.

This carbohydrate also seems to be important for the metabolic demands of long-lived plasma cells which are essential players for a longterm immune protection, as they constantly secrete protective antibodies even after the pathogen is cleared. We are using mouse lines with a B cell specific defeciency in glucose uptake to investigate whether nutrients shortage affects the establishment and maintenance of a protective humoral immune response. Furthermore, we are analyzing if differentiating B cells and antibody-secreting cells are able to adjust their metabolic processes in the absence of glucose. Our longterm goal is to understand how the B cell-mediated immune memory is established and maintained, and how altering nutrition or diet can influence these processes.

Teaching

The Division of Molecular Immunology participates in undergraduate and graduate education within the bachelor and master degree programs in biology, life science engineering, and Molecular Medicine, as well as in teaching for medical students.
Students can work on their Bachelor's and Master's theses, as well as medical doctoreal theses embedded in the research focus of the Division of Molecular Immunology. Furthermore, the Division of Molecular Immunology engages in educating and training doctoral students from GK 1660 and the IRTG of the transregio 130 (compare own report) by offering numerous workshops and seminars, like journal clubs or scientific writing and presentation workshops.

Selected publications

Cvetkovic, L., Perisic, S., Titze, J., Jack, H.-M., and Schuh, W. (2019). The Impact of Hyperosmolality on Activation and Differentiation of B Lymphoid Cells. Front Immunol 10, 828.

Reimer, D., Meyer-Hermann, M., Rakhymzhan, A., Steinmetz, T., Tripal, P., Thomas, J., Boettcher, M., Mougiakakos, D., Schulz, S.R., Urbanczyk, S., Niesner, R., Mielenz, D. (2020). B Cell Speed and B-FDC Contacts in Germinal Centers Determine Plasma Cell Output via Swiprosin-1/EFhd2. Cell Rep 32, 108030.

Schuh, W., Mielenz, D., and Jack, H.-M. (2020). Unraveling the mysteries of plasma cells. Adv Immunol 146, 57-107.

Steinmetz, T.D., Schlotzer-Schrehardt, U., Hearne, A., Schuh, W., Wittner, J., Schulz, S.R., Winkler, T.H., Jack, H.-M., and Mielenz, D. (2020). TFG is required for autophagy flux and to prevent endoplasmic reticulum stress in CH12 B lymphoma cells. Autophagy, 1-19.

Pracht, K., Meinzinger, J., Schulz, S.R., Daum, P., Corte-Real, J., Hauke, M., Roth, E., Kindermann, D., Mielenz, D., Schuh, W., et al. (2020). miR-148a controls metabolic programming and survival of mature CD19-negative plasma cells in mice. Eur J Immunol.

International cooperations

Prof. Dr. R.E.M. Toes, Leiden University Medical Center, Rheumatology, Leiden, The Netherlands,

Prof. Dr. Adam Cunningham, University of Birmingham, Birmingham, UK,

Prof. Dr. Marco Herold, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia,

Dr. Rafael Arguello, CNRS, INSERM, and Aix-Marseille University, Marseille, France

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Department of Medicine 4 – Nephrology and Hypertension

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Research focus
- Molecular mechanisms of rare kidney diseases
- Identification and modification of hereditary kidney disease
- Pathophysiological relevance of hypoxia-inducible gene expression
- Pathogenesis of arterial hypertension and hypertensive target organ damage
- Acute and chronic renal allograft failure

Structure of the Department

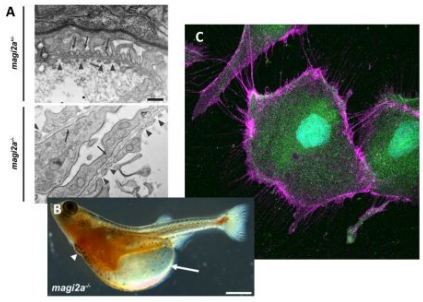
Professorships: 5
Personnel: 244
- Doctors (of Medicine): 34
- Scientists: 18 (thereof funded externally: 16)
- Graduate students: 21

Clinical focus areas
- Diagnosis and treatment of all acute and chronic kidney diseases
- Kidney transplantation including living donor transplantation
- Sepsis and multiorgan failure
- Extracorporeal blood purification
- Refractory arterial hypertension

Research

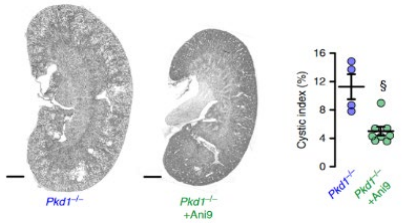
Research at the Department of Nephrology and Hypertension has a strong translational focus. Accordingly, projects encompass experimental and patient-orientated research. Our research aims at better understanding the initiation and course of acute and chronic kidney diseases and the development and complications of arterial hypertension.

Molecular mechanisms of rare kidney diseases
PI: Prof. Dr. J. Müller-Deile, Prof. Dr. M. Schiffer, Dr. Jobst-Schwan
In early 2019 we founded a center for rare disease of the kidney which cared for approximately 75 patients with rare kidney diseases in the most recent quarter. To support research on these rare kidney diseases, we also established a Research Center on Rare Kidney Diseases (RECORD), including a Clinician-Scientist program funded by the Else Kröner Fresenius foundation (www.record.fau.de). The groups working in this area of research employ cell culture models, transgenic zebrafish models, podocyte-specific knockout animals, innovative techniques, interdisciplinary cooperations and work with samples from patients with rare glomerular diseases. The projects are ultimately patient-centered. Communications between different cell types in rare kidney diseases are studied, addressing miRNAs, exosomes, autophagy mechanisms and circulating factors. The ultimate aim of this research is the identification of novel therapeutic approaches for these diseases. Conversely, a better understanding of the pathophysiology can help to prevent the use of futile therapies such as glucocorticoids in some rare, genetic forms of the nephrotic syndrome.



Magi2a knock-out zebrafish develop a primary podocytophaty displaying foot process effacement (A), and generalized edema (B). (C) MAGI2 (green) and ß-catenin (magenta) interact with each other and are colocalized in the podocyte cell membrane.

Identification and modification of hereditary kidney disease
PI: Prof. Dr. M. Schiffer, Prof. Dr. M. Wiesener, PD Dr. B. Buchholz
Recent advances in sequencing technologies permit comprehensive searches for possible genetic causes of kidney diseases, particularly in cases with a family history of the disease. Meticulous assessment of family history, pathological changes, and comorbidities is required. These approaches are brought to bear on individual cases from our outpatient clinic as well as on cases identified in a large national cohort study of patients with chronic kidney disease (GCKD study with approximately 5000 patients). The study center as well as the study's biobank is located in Erlangen. In addition, experimental approaches including cell culture and zebrafish models are used to test for the functional relevance of identified genetic mutations. The ultimate aims are the improvement of diagnostic and therapeutic approaches in these kidney diseases. In one case of a patient with kidney transplant failure we clarified the molecular pathogenesis by examining kidney tubulus cells from the patient's urine: A ciliopathy in the donor's kidney passed to the recipient was the cause of the organ's failure.
One group focuses on autosomal dominant polycystic kidney disease (ADPKD). This disease is characterized by the occurrence and subsequent progressive expansion of fluid-filled cysts in both kidneys. Expansion of the cysts over years and decades (and, consequently, the enlargement of the total volume of the kidneys) proceeds in parallel to the loss of kidney function. Mechanisms leading to cyst expansion are being investigated. Recently, one such mechanism, a chloride channel which drives chloride secretion into the cysts, was identified. Inhibitors of this channel are commercially available (albeit approved only for different diseases) any may serve as a therapeutic approach in the future.



Tubule-specific knockout of Pkd1 (Pkd1$^{-/-}$) leads to the development of polycystic kidneys. Ani9, a specific inhibitor of the calcium-activated chloride channel TMEM16A significantly reduced cyst enlargement.

Pathophysiological relevance of hypoxia-inducible gene expression
PI: Prof. Dr. C. Willam, PD Dr. Dr. J. Schödel, PD Dr. C. Warnecke, Dr. Schley, Dr. Grampp
One pathomechanism, which is highly relevant in acute kidney failure as well as in the development of renal cell carcinoma, concerns hypoxia in kidney tissue. Focus of these studies is the regulation and functional role of the hypoxia inducible transcription factors HIF-1 and HIF-2. Based on studies of the physiological expression of these factors and their regulating enzymes, the activity of the HIF system is being investigated in different types of kidney disease. In addition, experiments are performed to test if kidney disease can be influenced by genetic or pharmacological modulation of the HIF system. The focus of these studies is on the modulation of inflammation which may be either a cause or a consequence of chronic kidney disease. In addition, the epigenetic regulation of HIF transcription is being investigated in renal cell carcinoma. In parallel, the potential long term consequences of hypoxia on renal structure are being analyzed, in particular fibrosis and epithelial to mesenchymal transition of kidney tubule cells.

Pathogenesis of arterial hypertension and hypertensive target organ damage
PI: Prof. Dr. R. Schmieder, Prof. Dr. K. Hilgers, Prof. Dr. R. Veelken, Prof. Dr. J. Titze, PD Dr. A. Dahlmann, PD Dr. A. Bosch, Dr. C. Kopp
A further important research area relates to studies of arterial hypertension. A specific focus in this area lies on the pathogenesis of hypertension as well as on target organ damage induced by hypertension in kidneys, heart, eye, and vasculature. This research includes studies on sodium homeostasis, which test the hypothesis that stores of non-osmotically active sodium exist in the body and that their capacity has an important impact on blood pressure regulation. Together with the department of Radiology, innovative imaging techniques (sodium-MRI) were established and utilized to analyze tissue sodium content in humans.

Additional experimental projects deal with the role of the sympathetic nervous system for the pathogenesis of hypertension and kidney injury and vice versa: an important focus of this research is the role of afferent nerve fibers, which transmit signals from kidney tissue to the brain for the regulation of sympathetic nervous activity. These studies include electrophysiological investigations of ganglion cells, direct recordings of both afferent and efferent fibers in animals, as well as studying the response of patients to renal denervation.
From a patient-centered perspective, target organ damage of the heart, the kidneys and the blood vessels should be considered in conjunction with other risk factors, which often cluster together with hypertension, especially diabetes, hyperlipidemia, and chronic kidney disease. Research on the mechanisms of target organ damage are the focus of experimental as well as clinical studies, the latter taking advantage of data and samples from the aforementioned national cohort study GCKD.

Acute and chronic renal allograft failure
PI: Prof. Dr. M. Schiffer, Prof. Dr. M. Wiesener, Dr. K. Heller, Dr. M. Opgenoorth
In cooperation with the departments of Urology and of Surgery, around 65 kidney and combined kidney-pancreas transplantations are performed per year, including living donor transplantations. Blood group incompatible living donation is a particular focus. The research program in this field aims at optimizing long term graft function. Therefore, our transplant center was included in the innovative follow-up project NTX 360° which aims to improve long-term maintenance care of kidney transplant recipients. In addition, multicenter trials and observational studies are being conducted to evaluate novel immune-suppressive drugs or their combination. To counter severe Virus infections (CMV and BKV) complicating the post-transplant care, we started the generation, amplification and application of autologous or allogenic virus-specific T-cells, together with the department of medicine 5.

Fit on the waiting list – a rehabilitation program for patients on dialysis
PI: Prof. Dr. M. Schiffer, Dr. K. Heller, Dr. M. Opgenoorth
This clinical research program funded by the Bayerisches Staatsministerium für Gesundheit und Pflege is a cooperation between our Department of Medicine 4, the M&I – rehabilitation clinics in Herzogenaurach and Bad Heilbrunn and the Gesundheitsregion PLUS Erlangen-Höchstadt. The aim of the project is a sustained improvement of the care for elderly patients on dialysis who are listed for kidney transplantation. These patients are especially vulnerable to develop a rapid deterioration of their physical and mental health. To alleviate this problem, individual rehabilitation plans targeted to the particular health problems (and scheduling problems) of dialysis patients are provided and implemented. Office-based nephron-logists cooperating with our clinic recruit patients participating in this program. The rehabilitation measures are intended to maintain and improve the patients' health status, and to render the participants viable candidates for transplantation (https://www.fit-für-transplantation.fau.de).

Teaching

The Department of Medicine 4 contributes in many ways to the teaching schedule in internal medicine, including lectures, seminars, bedside teaching in small groups, and internships. We offer electives featuring interdisciplinary teaching, focusing on vascular medicine (together with the Department of Pediatrics and Adolescent Medicine) or intensive care medicine (together with the Department of Anesthesiology).
In 2020, many on-line learning modules were developed as a "replacement" for lectures, seminars and practical courses, which could not be held in presence due to the corona pandemic.
Our faculty members supervises Bachelor's and Master's theses as well as MD and PhD theses.

Selected publications

Müller-Deile J, Schenk H, Schroder P, Schulze K, Bolaños-Palmieri P, Siegerist F, Endlich N, Haller H, Schiffer M. Circulating factors cause proteinuria in parabiotic zebrafish. Kidney Int. 2019; 96:342-349

Jobst-Schwan T, Hoogstraten CA, Kolvenbach CM, Schmidt JM, Kolb A, Eddy K, Schneider R, Ashraf S, Widmeier E, Majmundar AJ, Hildebrandt F. Corticosteroid treatment exacerbates nephrotic syndrome in a zebrafish model of magi2a knockout. Kidney Int. 2019; 95:1079-1090

Schley G, Klanke B, Kalucka J, Schatz V, Daniel C, Mayer M, Goppelt-Struebe M, Herrmann M, Thorsteinsdottir M, Palsson R, Beneke A, Katschinski DM, Burzlaff N, Eckardt KU, Weidemann A, Jantsch J, Willam C. Mononuclear phagocytes orchestrate prolyl hydroxylase inhibition-mediated renoprotection in chronic tubulointerstitial nephritis. Kidney Int. 2019; 96:378-396

Schödel J, Ratcliffe PJ. Mechanisms of hypoxia signalling: new implications for nephrology. Nat Rev Nephrol. 2019; 15:641-659

Tossidou I, Teng B, Worthmann K, Müller-Deile J, Jobst-Schwan T, Kardinal C, Schroder P, Bolanos-Palmieri P, Haller H, Willerding J, Drost DM, de Jonge L, Reubold T, Eschenburg S, Johnson RI, Schiffer M. Tyrosine Phosphorylation of CD2AP Affects Stability of the Slit Diaphragm Complex. J Am Soc Nephrol. 2019; 30:1220-1237

Cabrita I, Kraus A, Scholz JK, Skoczynski K, Schreiber R, Kunzelmann K, Buchholz B: Cyst growth in ADPKD is prevented by pharmacological and genetic inhibition of TMEM16A in vivo. Nat Commun. 2020; 11: 4320

Rodionova K, Veelken R, Hilgers KF, Paulus EM, Linz P, Fischer MJM, Schenker M, Reeh P, Tiegs G, Ott C, Schmieder R, Schiffer M, Amann K, Ditting T. Afferent renal innervation in anti-Thy1.1 nephritis in rats. Am J Physiol Renal Physiol. 2020; 319:F822-F832

Wiesener A, Knaup KX, Büttner-Herold M, Dieterle A, Stoeckert J, Riedl B , Morath C, Wald A, Vondran F, Braun F, Schödel J, Schueler M, Schiffer M, Amann K, Reis A, Kraus C, Wiesener MS. Molecular diagnosis of kidney transplant failure based on urine. Am J Transplant. 2020; 20: 1410 – 1416

International Collaborations
Prof. R. Kleta, University College, London: UK

Prof. P.J. Ratcliffe, University of Oxford, Oxford: UK

Prof. S. Somlo, University of Yale, New Haven: USA

Prof. F. Hildebrandt, Harvard University, Cambridge: USA

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Research focus
- Immune regulation by DN T cells
- Adoptive cell therapy with memory B-lymphocytes for patients after allogeneic stem cell transplantation (alloSCT)
- T cells between immunotherapy and autoimmunity
- Immunometabolism
- Tumor associated macrophages and posttranscriptional regulation by Hoxa9
- Communication of tumor cells and microenvironment
- Molecular immunotherapy
- T cell-based immunotherapy of ocular melanoma
- Tumor microenvironment
- Tumor immune escape
- Cellular immunotherapy
- HLA-laboratory

Structure of the Department

Professorships: 2
Personnel: 127
- Doctors (of Medicine): 37
- Scientists: 12 (thereof funded externally:6)
- Graduate students: 12

Clinical focus areas
- In-patient and out-patient care of patients with leukemia, lymphoma, and non-malignant hematologic diseases
- Allogeneic and autologous stem cell transplantation
- Out-patient stem cell transplant unit
- In-patient and out-patient care of patients with urological tumors, bone and soft tissue sarcoma, head and neck tumors, lung tumors and other solid tumors
- Out-patient unit for urologicial tumors (AURONTE)
- Hematological diagnostics

Research

The main research focus of the Department of Medicine 5 concentrates on tumor immunology. Several research groups examine basic immunological mechanisms of tumor formation, tumor defense, and tumors escape. We have a special research focus on the characterization and blockade of graft-versus-host reactions after allogeneic stem cell transplantation and the improvement of graft-versus-leukemia responses. The long-term goal is to translate these concepts into innovative cell-based therapies.

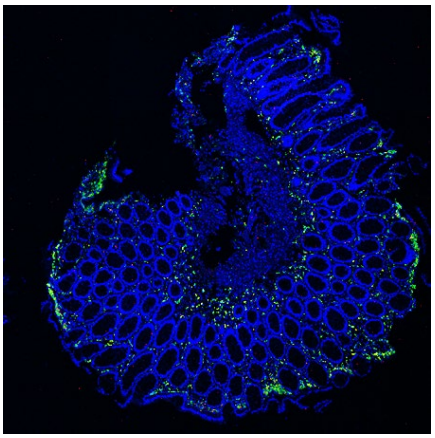

Figure 1. Tissue section from the colon of a GvHD patient. Macrophages were stained by anti-CD68 (green) and anti-PD-L1 (red). Cells were counterstained with DAPI (nucleus, blue).

Immune regulation by DN T cells
PI: Prof. Dr. A. Mackensen, Dr. S. Völkl
The population of human TCRα/β+ CD4-CD8 double-negative (DN) T cells plays a special role in the regulation of immune responses. In this project, the group investigates the immunoregulatory function of human DN T cells. In addition, the role of DN T cells under pathologic conditions as autoimmunity and transplant rejection is currently determined. The long-term goal is to develop a clinical strategy for using DN T cells to treat graft-versus-host disease (GvHD) after allogeneic stem cell transplantation.
Funding: DFG, Forschungsstiftung Medizin

Adoptive cell therapy with memory B-lymphocytes for patients after allogeneic stem cell transplantation (alloSCT)
PI: Dr. J. Winkler, Prof. Dr. T. Winkler, Prof. Dr. M. Mach
The aim of our project is the preclinical development of a new, first-in-man cell based therapy for the improvement of humoral immune responses in patients after alloSCT. We developed a study protocol for a phase I/IIa clinical trial for the adoptive transfer of allogeneic donor B-lymphocytes for patients four months after alloSCT according to GCP. The application of allogeneic B lymphocytes is intended for 15 patients in escalating cell dosages. So far, 13 patients received the B-cell product and no severe adverse events were observed.
Funding: DFG

T cells between immunotherapy and autoimmunity
PI: PD Dr. Dr. A.N. Kremer
The main focus of this group is the separation of beneficial graft-versus-leukemia (GvL) effect after alloSCT from detrimental GvHD by characterization of the intracellular processing pathways of HLA class II restricted antigens as well as the identification of tumor-specific T-cell targets in breast cancer.
Further we analyze the role of these antigens in the pathogenesis of autoimmune diseases and the CD4+ T cell mediated eradication of HLA class II negative tumors via indirect antigen presentation.
Funding: DFG, Else Kröner Fresenius Foundation, Ernst Jung-Foundation, IZKF, Wilhelm-Sander-Stiftung, Bavarian Ministry for Science and Arts

Immunometabolism
PI: Prof. Dr. D. Mougiakakos
We focus on alterations of the metabolism and the immune system in cancer and after stem cell transplantation. An understanding regarding tumor-associated (metabolic) strategies contributing to an immunosuppression will support development of therapeutic strategies. Furthermore, we aim at ”learning” how tumors weaken immune responses in order to translate these findings into potential experimental approaches for the treatment of GvHD following SCT.
Funding: DFG (Einzelanträge, TRR221, TR305, GRK2599, FOR2866), IZKF, Elitenetzwerk Bayern, Industrie

Tumor associated macrophages and therapeutic antibodies
PI: PD Dr. H. Bruns
Macrophages are the main component of the tumor microenvironment in the most malignancies. Although macrophages can, in principle, target neoplastic cells and mediate antibody-dependent cytotoxicity, tumor-associated macrophages (TAM) regularly fail to exert direct cytotoxic functions. However, TAM are thought to be protumorigenic because they promote angiogenesis and metastasis. The underlying mechanisms responsible for this observation remain unclear. Our research is focused on the functional and molecular analysis of the tumor microenvironment and aims at identifying and modulating potential therapeutic target structures.
Funding: DFG, Wilhelm Sander Foundation, Volkswagen Foundation

Communication of tumor cells and microenvironment
PI: Dr. G. Lutzny-Geier
Our group is interested in the communication of tumor cells with their microenvironment. Understanding how different signaling pathways get activated through intrinsic signals of the tumor cell itself and extrinsic signals of the microenvironment is one aim of our studies. Therefore, we investigate how the microenvironment is modulated by tumor cells and if interference with this modulation can be used as new therapeutic approach for lymphoma patients.

Funding: ELAN, Trunk Foundation, industry, DFG

Molecular immunotherapy
PI: Dr. F. Müller
The young research group exploits antibody-targeted recombinant immunotoxins to kill cancer cells specifically. The immunotoxins induce a highly immunogenic cell death which changes the immunosuppressive milieu within a tumor thereby inducing anti-cancer immunity. Central to the group's research are (i) the development of innovative immunotoxins and of (ii) understanding and augmenting the immunotoxin-induced anti-cancer immune response. The mechanism of immune modulation by immunotoxins in combination with checkpoint inhibitors and toll-like receptor agonists is studied in animal models.
Funding: German Cancer Aid (Max-Eder Junior Research Group), DFG, IZKF, Research Foundation of Medicine, industry

T cell-based immunotherapy of ocular melanoma
PI: Dr. J. Bosch
The main focus of our research group is to develop a T cell-based immunotherapy specifically designed for treatment of ocular melanoma. We focus on analysis of immune cell infiltration in the primary tumor originating in the immuneprivileged eye. In addition, we determine if uveal melanoma vaccines or bi-specific antibodies activate different sub-populations of CD4+ T cells and which cytokines activated T cells secrete. Furthermore, we test if chimeric antigen receptor modified (CAR) T cells are reactive and cytotoxic against uveal melanoma cells.
Funding: DFG

Modulation of T cell responses in graft-versus-host disease
PI: PD Dr. S. Spoerl
Our research aims at therapeutically targeting T cell responses after allogeneic stem cell transplantation. In this context, we want to avoid a severe immune reaction mediated by the graft-versus-host effect (GvHD), by at the same time maintaining the graft-versus-leukemia effect in order to prevent a relapse of the underlying disease.
Our studies do not only target GvHD-specific medication but also focus on the involvement of special T cell subtypes as for example T follicular helper cells or regulatory T follicular cells the pathogenesis of GvHD.
Funding: ELAN, Forschungsstiftung Medizin, Manfred-Roth-Stiftung

Tumor immune escape
PI: Prof. Dr. A. Mackensen, Dr. M. Aigner
By modulation of their metabolism, tumors are able to generate advantages for growth and proliferation for themselves. Our group focuses on the functions of 5'-Deoxy-5'methylthioadenosine (MTA) and its degrading enzyme MTAP as it is known that these molecules play a role in many malignancies. The influence of MTA produced by tumors on the activation, proliferation, and various effector functions of cytotoxic cells (T cells, NK cells) are studied.
Funding: DFG

Cellular immunotherapy
PI: Prof. Dr. A. Mackensen, Dr. M. Aigner, Dr. R. Gary,
The focus of this group lies on adoptive T cell therapy. Within the scope of a clinical trial phase I/IIa, CMV- and EBV-specific T cells are manufactured for patients after allogeneic stem cell transplantation to mediate protection against CMV and EBV infection. We are expanding the application of this cellular therapeutics against other viruses like SARS-CoV-2 and BKV
In addition, we have established manufacturing of CARs (chimeric antigen receptor T cells) and TRUCKS (cytokine producing CARs) and their translation to the clinic.
Funding: Deutsche Krebshilfe, Bayerisches Ministerium für Wissenschaft und Kunst, Wilhelm-Sander Stiftung

HLA-laboratory
PI: Prof. Dr. B. Spriewald
In recent years, the laboratory has been interested in new methods for the detection of various subclasses of anti-HLA antibodies in solid organ transplantation. Our immunogenetic studies look into polymorphisms of several cytokines and T cell regulatory genes and their association with rheumatic and malignant disorders. Another focus is on experimental studies for the induction of transplantation tolerance and reduction of chronic rejection. These studies are performed in close collaboration with the working group of experimental heart surgery.

Teaching

The Department of Medicine 5 takes part in the curricular teaching for Medicine and Dentistry. Bachelor's and Master's theses as well as MD and PhD theses are offered and supervised regularly.

Selected publications

Bruns H, Jitschin S, Gamali S, Saul D, Böttcher M, Mackensen A, Jitschin R, Mougiakakos D. A novel immunoregulatory function of beta-2-microglobulin as a promoter of myeloid derived suppressor cell induction. Leukemia. 2019 May;33(5):1282-1287.

Kretschmann S, Herda S, Bruns H, Russ J, van der Meijden ED, Schlötzer-Schrehardt U, Griffioen M, Na IK, Mackensen A, Kremer AN. Chaperone protein HSC70 regulates intercellular transfer of Y chromosome antigen DBY. J Clin Invest. 2019 Jun 17;129(7):2952-2963.

Jitschin R, Böttcher M, Saul D, Lukassen S, Bruns H, Loschinski R, Ekici AB, Reis A, Mackensen A, Mougiakakos D. Inflammation-induced glycolytic switch controls suppressivity of mesenchymal stem cells via STAT1 glycosylation. Leukemia. 2019 Jul;33(7):1783-1796.

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Strobl CD, Schaffer S, Haug T, Völkl S, Peter K, Singer K, Böttcher M, Mougiakakos D, Mackensen A, Aigner M. Selective PRMT5 Inhibitors Suppress Human CD8 + T Cells by Upregulation of p53 and Impairment of the AKT Pathway Similar to the Tumor Metabolite MTA. Mol Cancer Ther. 2020 Feb;19(2):409-419.

International cooperations
M. Miano, MD, Department of Pediatric Haematology-Oncology, IRCCS Istituto Giannina Gaslini, Genoa: Italy

Prof. F. Falkenburg, Leiden University: The Netherlands

Dr. T. Graf, Centre for Genomic Regulation, University of Barcelona: Spain

Dr. I. Pastan, NCI, NIH, Bethesda: USA

Prof. R. Kiessling, Karolinska Institut, Stockholm: Sweden

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Research Focus

- Stroke research – clinical and experimental
- Neurocritical care
- Telemedicine and health services
- Epilepsy
- Neuroimmunology
- Pain and Headache
- Autonomic nervous system
- Neuromuscular diseases
- Dystonia and botulinum toxin therapy
- Neuro-oncology

Structure of the Department

Professorships: 3
Personnel: 312

- Doctors (of Medicine): 75
- Scientists: 12 (thereof funded externally: 9)
- Graduate students: 30

Clinical focus areas

- Emergency care
- Stroke
- Neurocritical care
- Epilepsy Center (EZE)
- Neuroimmunology
- Neuromuscular diseases
- Pain Medicine
- Neuro-oncology
- Autonomic nervous system disorders
- Neurophysiology
- Ultrasound
- Dystonia und botulinum toxin therapy
- Neurocognitive Disorders
- Telemedicine

Research

The Department of Neurology is one of the largest neurological centers in Germany treating 4.000 in-patients and more than 19.000 outpatients each year. The research activities of our clinic are shown in detail below. During the reporting period more than 200, some of them high-ranking publications could be published.

Stroke research – clinical and experimental
PI: Prof. Dr. H. Huttner, PD Dr. B. Kallmünzer, PD Dr. J. Kuramatsu
Each year about 7,000 patients are admitted to our specialized neurological emergency room. After an immediate clinical examination, adequate diagnostic procedures and prompt specific emergency treatment are initiated, if necessary. The Department of Neurology thereby drives the development and improvement of innovative new therapeutic options for acute care and secondary prevention of stroke. It is involved in international, prospective clinical trials, while the screening and inclusion of individuals is managed directly on admission and during the patient´s stay at the stroke unit. Additionally, scientific analysis are based on prospective clinical registries. The participation is offered also to patients, who are being transferred from the North-Bavarian telestroke network STENO. We treat more than 1,400 inpatients on our 14-bed monitored stroke unit. A very high level of medical care (iv-thrombolysis rate > 25%) is combined with advanced research, including clinical studies on thrombolysis, mechanical thrombectomy (annually > 200), and secondary prevention of cardioembolism.

Neurocritical care
PI: PD Dr. J. Kuramatsu, Prof. Dr. H. Huttner
At our dedicated 12-bed neurocritical care unit over 400 patients annually are managed using state-of-the-art neuromonitoring and treatment concepts. For patients with severe stroke, intracranial hemorrhage, meningitis, and status epilepticus the main therapeutic target is prevention of secondary brain injury which is supplemented by progressive clinical and translational research projects. Emerging concepts are validated by collaborative efforts involving multicenter studies and investigator-initiated trials that may and have influenced guidelines. Current research projects involve, large-sized individual participant data meta-analyses, randomized controlled trials, target-trial emulations, and biobanking.

Telemedicine
PI: PD Dr. B. Volbers
Since 2007, the Department of Neurology has been coordinating the Stroke Network using Telemedicine in Northern Bavaria (STENO), which includes 3 stroke centers and 18 regional hospitals. As the only telestroke-network of its kind, it has been certified in 2011 according to DIN EN ISO 9001:2008 for its network-wide quality management system. STENO is part of the medical standard care and ensures comprehensive stroke care for about 12.000 stroke patients per year in North Bavaria and southern Thuringia at the highest level. Scientific research covers diagnostic and therapeutic options in acute ischemic stroke, including thrombolysis, mechanical thrombectomy and secondary prevention, and in intracerebral hemorrhage, including secondary evolution of perihemorrhagic edema, as well as the impact and effects of STENO on stroke management in mainly rural areas.

Epilepsy
PI: Prof. Dr. H.M. Hamer, MHBA
The Erlangen Epilepsy Center ranks among the top five university epilepsy centers in Germany. Scientific hot spots include:
1) Electrophysosiology of higher cortical function, including single units activity;
2) Epilepsy in CNS-malformations;
3) Automatic seizure detection;
4) Magnetoencephalography;
5) Neuropsychology/Cognition and invasive EEG;
6) Quantitative EEG in epilepsy and encephalopathy;
7) Drug monitoring;
8) Historical aspects of epileptology;
9) Socio-economic aspects of epilepsy.
10) Telemedicine
Funding: EU, DFG, Bavarian State Ministry of Health and Care

Neuroimmunology
PI: Prof. Dr. V. Rothhammer
The Neuroimmunology research group focuses on biomarker research and validation in clinical research projects in Multiple Sclerosis and other autoimmune inflammatory disorders of the nervous system. These projects are deeply embedded into preclinical experimental projects aiming at a deeper understanding of the relevance of environmental and microbial factors in their interaction with endogenous metabolism and CNS resident immune cells. Supported by national and international research grants (DFG Heisenberg Grant, ERC Starting Grant HICI, DFG SFB TRR274, IITs, among others), we aim to develop a deeper understanding of the role of glial cells in acute and chronic inflammation and their regulation by transcriptional and epigenetic mechanisms. Ultimately, we seek to develop novel therapeutic and monitoring strategies for hence untreatable forms of autoimmune diseases of the nervous system.

Pain and Headache
PI: Prof. Dr. F. Seifert, MHBA
This group investigates neural mechanisms of sensory, autonomic and cognitive processing in pain disorders (neuropathic pain, headache), stroke and multiple sclerosis. We use psychophysical and autonomic testing combined with functional and structural brain imaging methods (voxel-based lesion symptom mapping (VLSM), functional magnetic resonance imaging (fMRI), repetitive transcranial magnetic stimulation (rTMS).

Autonomic nervous system
PI: PD Dr. J. Köhn
The research group ANS focuses on the investigation of central and peripheral control mechanisms of the autonomic nervous system. By quantitative and qualitative testing of autonomic cardiovascular modulation, we evaluate possible pathologies due to structural CNS defects in patients with ischemic stroke, subarachnoid hemorrhage and epilepsy. In addition, quantitative sensory testing of thermal perception refines the

evaluation of small fiber neuropathies, and the value of automated pupillometry in neuro-ICU patients is being investigated.

Neuromuscular diseases
PI: Dr. M. Türk, Dr. C. Möbius
The Neuromuscular Disease Center is an interdisciplinary center providing a specialized outpatient clinic and a neurohistological laboratory for diagnostic biopsies and for the investigation of neuromuscular diseases. The neuromuscular research at the department of neurology focuses on:
1) ^{1}H and ^{23}Na MRI in muscle diseases
2) 3D-sonography in neuropathies
3) Registry studies and muscle sonography of motor neuron diseases

Dystonia and botulinum toxin therapy
PI: Dr. C. Möbius
Our main aim is to improve the diagnostic and therapeutic process for patients with dystonic movement disorders and spasticity. Other than participating in several multicenter clinical trials, our research focus lies in the early detection and treatment of post stroke spasticity and the identification of specific muscle patterns in cervical dystonia using ultrasound and ultrasound-guided electromyography.

Neurooncology
PI: PD Dr. M. Uhl
The goal of interdisciplinary neuro-oncology is the treatment of patients with brain tumors. Beside the daily routine patients we have the ambition to provide attractive clinical trials for all patients. A focus here are currently translational immune therapy studies of the phases II and III.

Teaching

Between everyday clinical pratice and the teachings segment of our department the interdisciplinary clinical courses „Querschnittsfächer“ for immunology/ infectiology, emergency medicine and pain medicine gained widespread recognition by the students.

Selected publications
Kuramatsu JB et al. Association of Surgical Hematoma Evacuation vs Conservative Treatment With Functional Outcome in Patients With Cerebellar Intracerebral Hemorrhage. JAMA. 2019 Oct 8;322(14):1392-1403.

Diener HC et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. N Engl J Med. 2019 May 16;380(20):1906-1917.

Campbell BCV et al. Extending thrombolysis to 4·5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. Lancet. 2019 Jul 13;394(10193):139-147.

Thomalla G et al. Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. Lancet. 2020 Nov 14;396(10262):1574-1584.

Tsaktanis T, Beyer T, Nirschl L, Linnerbauer M, Grummel V, Bussas M, Tjon E, Mühlau M, Korn T, Hemmer B, Quintana FJ, Rothhammer V. Aryl Hydrocarbon Receptor Plasma Agonist Activity Correlates With Disease Activity in Progressive MS. Neurol Neuroimmunol Neuroinflamm. 2020 Dec 24;8(2):e933.

Walther K, Volbers B, Erdmann L, Dogan Onugoren M, Gollwitzer S, Kasper BS, Kurzbuch K, Lang J, Schwab S, Schwarz M, Hamer HM. Psychological long-term outcome in patients with psychogenic nonepileptic seizures. Epilepsia. 2019 Apr;60(4):669-678.

International Cooperations
Prof. F. J. Quintana, Harvard Medical School, Boston, USA

Prof. Jorge Ivan Alvarez, University of Pennsylvania, Pennsylvania, USA

Prof. Bernhard Staresina, University of Birmingham, Birmingham, UK

Prof. Simon Hanslmayr, University of Glasgow, Glasgow, UK

Prof. M. Grosse-Wentrup, University Vienna, Austria

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Research focus
- Neurodegenerative diseases
- Translational neurosciences
- Clinical research and development

Structure of the Division

Professorships: 2
Personnel: 20
- Doctors (of Medicine): 7
- Scientists: 3 (thereof funded externally: 2)
- Graduate students: 7

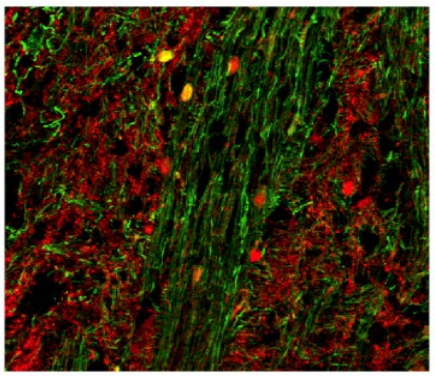
Clinical focus areas
- Outpatient clinical and research center for neurodegenerative movement disorders
- Center of the National Network for Parkinson's disease and European Huntington's disease Center
- Rare genetic movement disorders (Center for rare diseases)
- Atypical Parkinsonian syndromes

Research

The Division of Molecular Neurology focusses on the functional, behavioural, cellular, and pathological alterations in neurodegenerative diseases. The academic outpatient clinic provides state-of-the-art care for patients with neuro-degenerative movement disorders with particular focus on diagnostic work-up and treatment of Parkinsonian Disorders, Huntington's Disease and Motor Neuron Diseases. We participate in numerous national and international clinical studies. Furthermore, by applying medical engineering methods, an objective and opti-mized monitoring of patients with movement disorders is being developed in the framework of interdisciplinary research networks at the University Erlangen. By applying modern stem cell technologies, patient-based insights into cellular and biochemical disease mechanisms are studied.

Neurodegenerative diseases
The scientific focus of the Division of Molecular Neurology emphasizes on stem cell biology and neurodegenerative mechanisms in the context of sporadic Parkinson's disease, Multiple System Atrophy, Huntington's disease, and Hereditary Spastic Paraplegia. Neuroregenerative mechanisms with particular interest in the generation of new neurons and glial cells in the adult brain (adult neuro- and gliogenesis) are analyzed using cell culture systems (induced pluripotent stem cells) and transgenic disease models. In a complementary approach, neuro-degenerative mechanisms underlying the interplay of intra- and extracellular α-synuclein are analyzed in detail in order to better understand the molecular mechanisms underlying the pathogenesis of Parkinson's disease. The interaction between neuro-degenerative and inflammatory pathomechanisms within the central nervous system (CNS) is an additional major focus.

Translational neuroscience
A biobank for patient specific induced pluripotent stem cells (IPSCs) and its progeny is established and further developed in the framework of the Bavarian Network ForIPS and ForInter. Cell culture and molecular techniques have been established to delineate and modify pathological mechanisms associated with neuronal and oligodendroglial protein aggregation, degradation, and extracellular secretion mechanisms of alpha-synuclein in sporadic and atypical Parkinsonian syndromes. Alterations in protein degradation can lead to severe damage in neuronal and glial cells. Therefore, the experimental work focuses on the molecular causes, as well as possible therapeutic approaches that cause increased protein turnover in the lysosome. Moreover, we characterize myelin producing oligodendrocytes, which are affected in Multiple System Atrophy, showing a pronounced demyelination. The comprehensive analysis of cellular and molecular biological processes on patient derived material provides a unique opportunity to better understand molecular pathogenesis in neurodegenerative diseases and to analyze patients on an individual basis.
This translational neuroscience research work is supported in several interdisciplinary projects.
Funding: DFG, BMBF, Bavarian State Ministry of Economic Affairs and Media, Energy and Technology, Bavarian State Ministry of Education, Science, and the Arts, IZKF, Michael J. Fox Foundation.



Alpha-synuclein aggregation (red) in neuronal cells (synapsin: green) in the basal murine forebrain/thalamus region.

Clinical research and development
The Movement Disorders Outpatient Clinic and Center for Rare Movement Disorder, focus on clinical neuroscience research of sporadic Parkinson's disease (PD), rare Parkinsonian syndromes (Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA)) and Huntington's Disease. Another research focus is on Hereditary Spastic Paraplegia. The outpatient clinic, as a university center works in close cooperation with colleagues in private practice to provide continuous care for patients in the region. In particular, we participate in numerous national and international trial registries (e.g. for Huntington's Disease and PSP) and in innovative drug trials (antisense oligo-nucleotides; ASO). Together with the new professorship for stereotactic neurosurgery (Prof. Dr. T. Kinfe), deep brain stimulation was successfully reestablished at the University Hospital.
The outpatient centers scientific work focusses on the investigation of new biomarkers, that allow a better differential diagnosis of movement disorders, and facilitate monitoring of disease progression and therapeutic effects. In addition, the effects of tailored exercise therapy in Parkinson's disease are being investigated. The following projects are in progress:
- Differential diagnosis of MSA by means of 3T and 7T MRI (in close cooperation with the Department of Neuroradiology)
- Progression assessment of idiopathic Parkinson's Disease using non-motor symptoms such as anhedonia and constipation (microbiome; supported by the Adalbert-Raps Foundation)
- Sensor-based gait analysis as an early differential diagnostic biomarker and progression marker of Huntington's disease (funded by the Huntington Foundation of the Deutsche Huntington Hilfe)
- Sensor-based analysis of hyperkinetic movement disorders for differential diagnostic classification
- Sensor-based monitoring of gait impairment in patients with Hereditary Spastic Paraplegia (BMBF project "treatHSP")
- Validation of digital mobility outcomes and measurement methods using wearable sensor devices - the clinical validation study 'Mobilise-D' (EU project, Innovative Medicines Initiative), https://www.mobilise-d.eu/
- MOBILITY APP: Physiotherapy for atypical Parkinsonian syndromes in the clinical setting and in everyday life (D-A-CH project)
- Development of digital signatures of spastic gait patterns: self-learning algorithms for the calculation of clinically relevant gait parameters (funded by the Förderverein für HSP-Forschung e.V., https://hsp-hilfe.de/foer-derprojekt-gaitlab-ganganalyse/)
- Individualized, digital exercise in Parkinson's disease" (funded by the Manfred Roth Foundation and the Medical Research Foundation of the University Hospital Erlangen)
-Gait monitoring in the home environment (project "FallRiskPD", Medical Valley Award)

Motion analysis and therapy projects are carried out in close cooperation with the Machine Learning and Data Analytics Lab (Prof. Bjoern Eskofier, Dr. Felix Kluge), the companies Portabiles GmbH and Portabiles HealthCare Technologies GmbH as well as the German Parkinson Association – Regional Group Erlangen (Christine Enders, Wolf-Jürgen Aßmus). Particularly noteworthy is the EU project Mobilise-D, which aims to measure mobility in a total of 2.400 patients in everyday life using wearable sensor technology. The consortium includes 34 university centers that want to submit a so-called digital biomarker to EMA and FDA for approval in five years (2019-2024) in order to be able to use it as an objective endpoint in clinical studies (project leaders PD Dr. Heiko Gaßner, Prof. Dr. Jürgen Winkler). The concept for digital exercise training developed in the department was awarded with the Hertie Prize for Commitment and Self-Help in 2020 (PD Dr. Heiko Gaßner).

We have studied new MRI sequences in a murine model of MSA, suggesting that these sequences may dramatically facilitate the differential diagnosis of Parkinsonian syndromes, especially MSA (Lambrecht et. al; 2020). Currently, these sequences are being tested in a cross-sectional study in the clinic.

The symptoms anhedonia and constipation are early non-motor symptoms of PD. We analyze these symptoms with respect to disease progression. While the microbiome in PD patients is characterized by deficient probutyrogenic taxa, it may not be a suitable biomarker. We therefore aim to evaluate the therapeutic possibilities of dietary-based microbiome alterations (Cosma-Grigorov et al., 2020).

Sensor-based gait analysis in Huntington's Disease is a technical biomarker in the assessment of disease stage and motor impairment (Gaßner et el., 2020) and will be studied further.

At the Center for Rare Movement Disorders, numerous rare hyperkinetic movement disorders have been causally elucidated (e.g., McLeod syndrome (1:10,000,000), ERCC4-induced chorea) and contributed to national case series to better classify these disorders.

Teaching

The Division of Molecular Neurology participates in the teaching activities of the medical faculty in clinical neurology, the master's program Molecular Medicine, and at the technical faculty (medical technology). The focus on neuroscience in the Interdisciplinary Center of Neuroscience could be supported, a medical-technical project could be included in a research group application, and a neuroscientific research group (GRK 2162: Development and Vulnerability of the Central Nervous System; see separate report) could successfully be funded.

Within the scope of the supervision of scientific-academic work, bachelor's and master's theses as well as medical, physiotherapeutic, sports science, engineering and natural science doctorates are supervised.

Selected publications

Regensburger M, Minakaki G, Kettwig M, Huchzermeyer C, Eisenhut F, Haack TB, Kohl Z, Winkler J (2020), Novel Biallelic CTSD Gene Variants Cause Late-Onset Ataxia and Retinitis Pigmentosa. Mov Disord 35:1280-1282, 10.1002/mds.28106

Cosma-Grigorov A, Meixner H, Mrochen A, Wirtz S, Winkler J and Marxreiter F (2020) Changes in Gastrointestinal Microbiota Com-position in PD—A Pivotal Role of Covariates. Front. Neurol. 11:1041. doi: 10.3389/fneur.2020.01041

Gaßner H, Sanders P, Dietrich A, Marxreiter F, Eskofier BM, Winkler J, Klucken J.J; Clinical Relevance of Standardized Mobile Gait Tests. Reliability Analysis Between Gait Recordings at Hospital and Home in Parkinson's Disease: A Pilot Study. J Parkinsons Dis. 2020;10(4):1763-1773.

Lambrecht V, Hanspach J, Hoffmann A, Seyler L, Mennecke A, Straub S, Marxreiter F, Bäuerle T, Laun FB, Winkler J.; Quantitative susceptibi-lity mapping depicts severe myelin deficit and iron deposition in a transgenic model of mul-tiple system atrophy. Exp Neurol. 2020 Apr 14;329:113314.

Wanner P, Winterholler M, Gaßner H, Winkler J, Klucken J, Pfeifer K, Steib S (2020). Acute exercise following skill practice promotes motor memory consolidation in Parkinson's disease. Neurobiology of Learning and Memory 178; 107366

International cooperations

Prof. Dr. F. H. Gage, Laboratory of Genetics-Gage, The Salk Institute for Biological Studies, La Jolla: USA

Prof. Dr. B. Bloem, Radboud University Medical Center, Nijmegen: The Netherlands

Prof. Dr. E. M. Masliah, Department of Neurosciences, University of California, San Diego, La Jolla: USA

Prof. Dr. G. Wenning, University Hospital of Innsbruck, Innsbruck: Austria

Prof. Dr. R. Krüger, University of Luxemburg, Luxemburg: Luxemburg

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Focus of Research

- Imaging and Physics Research
- Molecular Imaging and Radiochemistry
- Translational Nuclear Medicine

Structure of the Department

Professorships: 2
Personnel: 45

- Doctors (of Medicine): 9
- Scientists: 10 (4 of which funded externally)
- Graduate students: 9

Areas of clinical focus
The Clinic of Nuclear Medicine offers all currently available diagnostic and therapeutic procedures provided by this specialty.

Research

Imaging and physics research
PI: Dr.-Ing. P. Ritt

Nuclear medicine is concerned with the distribution and visualization of radiotracers in the human body. The imaging modalities consist of single-photon emission computed tomography (SPECT) and positron emission tomography (PET) combined with anatomical imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) in one device (SPECT/CT, PET/CT, PET/MRI).

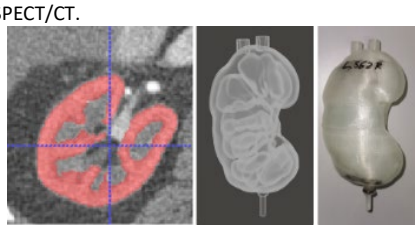
The therapeutic applications of nuclear medicine refer to the selective irradiation of tissues, including malignant tumors, by a radiopharmaceutical. The type of radiopharmaceutical and the dose administered are selected based on the individual patient, a risk-benefit analysis, and an estimation of the radiation dose (dosimetry) absorbed by the target tissue and normal adjacent tissues.

The Imaging and Physics Research Group focuses on improvements in SPECT and PET imaging and in image-based dosimetry. The group collaborates with the Pattern Recognition Lab (FAU), the Institute for Multiscale Simulation (FAU), the Ostbayerische Technische Hochschule Amberg-Weiden, and Siemens Healthineers. Selected research projects were technologically and financially supported by Siemens Healthineers.

The following paragraphs elaborate on the activities of the Imaging and Physics Research Group:

The image quality of SPECT is diminished by the absorption and scattering of photons, the partial volume effect (PVE), and by motion. These problems lead to the reduced accuracy of the quantification of the concentration of radiation in absolute units (for example, kilobecquerel per liter). The Imaging and Physics Research Group implements and validates new methods and applications for quantitative SPECT.

The PVE can be corrected by software-models that use dedicated algorithms. The Imaging and Physics Research Group develops and manufactures CT- and MRI-derived organ phantoms of individual patients in order to validate the algorithms before initiating their use in clinical practice. The phantoms are manufactured by 3-D printing. For validation, the phantoms are filled with a radioactive liquid and imaged by PET/CT or SPECT/CT.



Kidney phantom of an individual patient. First, the region is segmented on a CT image of the patient (left). A phantom model is then generated and post-processed by software (center). Finally, the phantom is manufactured by a 3-D printer (right).

Image-based dosimetry of radiation therapy in Nuclear Medicine is still predominantly carried out for volumes of interest (VOIs) that encompass entire organs or tumors. Consequently, only the mean value of the absorbed radiation dose (Gray [Gy]) of the VOI is available. Dose heterogeneities within a VOI are not evaluable, and thus the standard approaches of conventional radiation therapy such as dose-volume-histograms (DVH) are not applicable. The Imaging and Physics Group develops methods for determining the absorbed dose for each voxel of a patient's SPECT or PET dataset, and thus methods for deriving dose-volume-histograms. The methods are based on advanced algorithms, such as simulation of radiation transport (Monte Carlo).

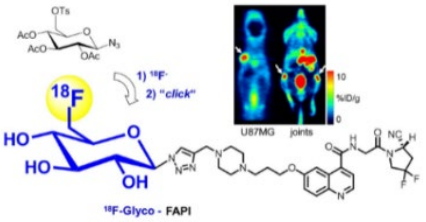
Molecular imaging and radiochemistry
PI: O. Prante

The diagnostic images of nuclear medicine show the distribution of radioactively labeled substances within a patient's body. The distribution reflects the interaction of radiopharmaceuticals with functionally relevant proteins. By visualizing this interaction, nuclear medicine can bridge the gap between molecular biology and clinical imaging, and correlate imaging results with the etiology of a specific disease or metabolic disorder. The use of molecular tracers for functional imaging is now called molecular imaging.

The main foci of research by the Department of Molecular Imaging and Radiochemistry are the development of new radiochemical labeling methods for the production of radiopharmaceuticals, the preclinical in vitro and in vivo evaluation of novel radiopharmaceuticals, and the translation of new radiotracers into the clinic for use in patients. Important recent examples of laboratory products developed at the Translational Research Center (TRC) include new ^{18}F-labeled ligands for the neuropeptide-Y1 receptor (Y1R), which have been studied as tracers for the diagnosis of mammary carcinoma in animals.

Novel radiopharmaceuticals for the diagnosis of prostate carcinoma have also been developed. ^{18}F-labeled glycosyl donors were conjugated to ligands that bind to prostate-specific membrane antigen (PSMA). Investigations of these labeled ligands identified radiopharmaceuticals that enabled improved imaging of tumors near the kidneys.

In 2020, we succeeded with the first synthesis of an ^{18}F-labeled FAP inhibitor. A comparative study of the novel tracer ^{68}Ga-FAPI-04 was performed in animal models (see Figure).



Radiosynthesis of ^{18}F-fluoroglycosylated FAP inhibitor: Click chemistry-based labeling facilitates the first synthesis of an ^{18}F-labeled radiotracer for the diagnosis of fibrotic diseases.

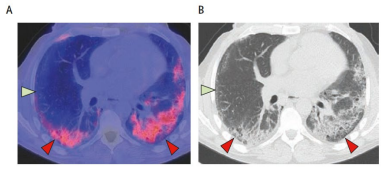
^{18}F-Glyco-FAPI binds to fibrotic tissue and shows increased transport to joints, suggesting that ^{18}F-Glyco-FAPI is effective for the diagnosis of rheumatoid arthritis. The translation of ^{18}F-Glyco-FAPI into clinical practice is currently underway. The development of all new radiotracers has been intensively supported by PET imaging studies of small animals. These radiopharmaceutical projects were supported by the DFG and were performed in close cooperation with the Chair of Pharmaceutical Chemistry (Faculty of Sciences).

Since 2020, the BMBF has supported the joint BICRA research consortium (collaboration with the University of Würzburg and University of Münster). The research consortium has focused on the development of targeted radiotracers with fast biodistribution. Moreover, the radiopharmaceutical research projects are supported by the Emerging Field Initiative of the FAU.

The Professorship of Molecular Imaging and Radiochemistry leads the GMP facility of the nuclear medicine clinic. The facility has the approval to produce radiopharmaceuticals in accordance with the §13 AMG (Medicinal Products Act). Currently, seven different

radiopharmaceuticals, which predominantly address the diagnosis and therapy of different types of cancer, are being produced for use in patients. The translational research efforts have led to the introduction of such new radiopharmaceuticals as ^{68}Ga-FAPI-04 and ^{18}F-PSMA-1007 into the clinic for the diagnosis of fibrotic diseases and prostate cancer, respectively. Our group's various translational research projects have allowed the development of innovative diagnostic and therapeutic radiopharmaceuticals. Our GMP-compliant facility in the Department of Nuclear Medicine can synthesize radiopharmaceuticals and thus enable their fast translation into clinical practice.

Translational nuclear medicine
PI: Christian Schmidkonz
The focus of this research group is the translation of preclinically developed methodology into clinical molecular imaging and radiotherapy. Radioligands that bind to the prostate-specific membrane antigen (PSMA) have revolutionized the diagnosis of prostate cancer and its recurrence. Until now, such ligands have only been available for PET, which is relatively expensive. In cooperation with Progenics (Tarrytown, NY, USA) and ROTOP (Dresden, Germany) our group has made the SPECT/CT-compatible radiopharmaceutical Tc^{99m}-MIP 1404 available to the nuclear medicine FAU clinic. This unlicensed product is being used clinically under the auspices of §13 (2b) AMG. The collected imaging data have provided a large body of evidence that represents an important starting point for the clinical use of Tc^{99m}-MIP 1404 and for the implementation of clinical trials.



^{68}Ga-FAPI-04 uptake in individuals with systemic sclerosis-ILD compared with control individuals. (A) Representative image of a ^{68}Ga-FAPI-04 PET-CT scan from a patient with systemic sclerosis-ILD with selective ^{68}Ga-FAPI-04 uptake in fibrotic areas of the lower left and lower right lung lobes (red arrows), but not in non-fibrotic areas, such as the middle lobe (green arrow). (B) The corresponding CT component confirms that the uptake of the tracer ^{68}Ga-FAPI-04 shown on PET-CT is exclusively present in areas of fibrotic tissue undergoing remodeling.

Current nuclear medical technology predominantly traces acute inflammatory activity in rheumatologic disease. PET tracers that bind to the fibroblast activating protein (FAP) address the stroma of malignant tumors, and thus have great diagnostic potential in the field of oncology. In Erlangen, in a cooperative project between the clinics of nuclear medicine and rheumatology, they are also used to trace active fibrotic lesions in rheumatic diseases, allowing the active lesions to be monitored for response to innovative treatments. This represents a paradigm shift away from a rather nonspecific visualization of inflammation to an imaging method that is oriented to the pathogenesis of fibrosis. A collaboration with the pediatric clinic has investigated the detection of the DNA of Ewing sarcoma in blood samples for the diagnosis of the recurrence of the tumor, in association with FDG-PET imaging. This represents a new diagnostic approach since specific tumor markers for Ewing sarcoma had not been previously available. The combination of molecular imaging and DNA detection shows promise for the early diagnosis of the recurrence of Ewing sarcoma, allowing early initiation of treatment and improving the prognosis of patients. Estimating the radiation dose of radionuclide therapy deposited in tumor tissue is a challenge because of the heterogeneity of tumors and the patient-specific kinetics of the metabolism and excretion of the radionuclides. A collaboration between the Clinic of Nuclear Medicine and the Department of Biophysics of the University of Regensburg has led to the development of artificial intelligence to improve radiation dosimetry in tumors and critical organs such as the kidney. Monte Carlo simulations have been used to obtain patient-specific dose estimations that are quantitatively and spatially more accurate than the previous standard MIRD method.

Teaching

The Department instructs medical students on nuclear medicine, which includes optimization of the medical process, medical physics, and molecular medicine. Furthermore, the Department performs postgraduate teaching for physicians in Middle and Upper Franconia. The Professor for Molecular Imaging and Radiochemistry also provides lectures for the students of molecular sciences in the scientific faculty.

Selected Publications
Schmidkonz C, Rauber S, Atzinger A, Agarwal R, Götz TI, Soare A, Cordes M, Prante O, Bergmann C, Kleyer A, Ritt P, Maschauer S, Hennig P, Toms J, Köhner M, Manger B, Stone JH, Haberkorn U, Baeuerle T, Distler JHW, Agaimy A, Kuwert T, Schett G, Ramming A. Disentangling inflammatory from fibrotic disease activity by fibroblast activation protein imaging. Ann Rheum Dis. 2020 Nov;79(11):1485-1491.

Schmidkonz C, Krumbholz M, Atzinger A, Cordes M, Goetz TI, Prante O, Ritt P, Schaefer C, Agaimy A, Hartmann W, Rössig C, Fröhlich B, Bäuerle T, Dirksen U, Kuwert T, Metzler M. Assessment of treatment responses in children and adolescents with Ewing sarcoma with metabolic tumor parameters derived from ^{18}F-FDG-PET/CT and circulating tumor DNA. Eur J Nucl Med Mol Imaging. 2020 Jun; 47(6):1564-1575.

Toms J, Kogler J, Maschauer S, Daniel C, Schmidkonz C, Kuwert T, Prante O. Targeting Fibroblast Activation Protein: Radiosynthesis and Preclinical Evaluation of an F-18-Labeled FAP Inhibitor. J Nucl Med. 2020, 61(12):1806-1813

Potemkin R, Strauch B, Kuwert T, Prante O, Maschauer S. Development of F-18-Fluoro-glycosylated PSMA-Ligands with Improved Renal Clearance Behavior. Mol Pharm. 2020, 17(3):933-943

International Cooperation
A.H. Vija, PhD, Siemens Molecular Imaging, Hofmann Estates, MI, USA

A. Opanowski, Progenics Pharmaceuticals, New York City, NY, USA

Dr. R. Haubner, Department of Nuclear Medicine, Medizinische Universität Innsbruck, Innsbruck, Tyrol, Austria

Prof. Dr. M. Pomper, Johns Hopkins University, Baltimore, MD, USA

Prof. Dr. P. Riss, University of Oslo, Oslo, Norway

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Main research topics

- Translational/clinical phase I–IV studies, health-care research, genetic studies (Central Research Unit)
- Biomaterials studies (whole blood, serum, tissue, body fluids) (Biobank Unit)
- Genome analyses, digitalization and artificial intelligence (Biostatistics and Informatics Unit)
- Molecular research (Laboratory for Molecular Medicine)
- Cryopreservation, artificial reproductive organs (Laboratory for Reproductive Medicine)

Structure of the department

Professorships: 3
Employees: 320

- Physicians: 50
- Scientists: 10 (8 of whom are externally funded)
- Doctoral candidates: 27

Main focuses of clinical care

- Minimally invasive and reconstructive surgery for genital and breast carcinomas
- Targeted therapies for genital and breast carcinomas
- Counseling for patients with high-risk breast and ovarian cancer
- Pre-, intra- and postpartum care for high-risk obstetric patients
- Prepartum diagnosis and care in cases of fetal malformation
- Conservative and surgical treatment in patients with extensive endometriosis (rASRM IV, deeply infiltrating endometriosis)
- Fertility-preserving therapy in cancer, including ovarian tissue cryopreservation
- Digitalization of care for gynecological/oncological and obstetric patients

Research

Research priorities in the Department of Gynecology are based on the clinical orientation of its seven certified centers (University Breast Center for Franconia, Familial Breast and Ovarian Cancer Center, University Gynecological Oncology Center for Franconia, Continence and Pelvic Center, University Perinatal Center for Franconia, University Endometriosis Center for Franconia, University Reproductive Center for Franconia). Supplementary central infrastructure units are the Biostatistics and Informatics Unit, the Central Research Unit and the Institute for Women's Health, the Translational Biobank Unit, the Laboratory for Molecular Medicine, and the Laboratory for Reproductive Biology.

Biostatistics and Informatics Unit: Digitalization and artificial intelligence in the care of gynecological oncology and obstetrics patients
University Breast Center for Franconia, University Gynecological Oncology Center for Franconia, University Perinatal Center for Franconia
During the COVID-19 pandemic, the digitalization of care was further expanded for our gynecological oncology and obstetrics patients. An app was developed that ensures patient data sovereignty and anonymous data transfers to the Department. Recruitment channels were adapted to the "home care" situation using web-based research study information and eConsent. This is currently being used in the DEfenseCOVID-19 registry study (www.corona-register.de, with a direct link for study participation via https://freeda.one) to collect well-founded data from all cancer patients during the pandemic about their disease and treatment, as well as on mood and vaccination behavior.
Along with other goals, the digitalization of preventive medicine is being addressed using an integrated patient portal in the collaborative projects SMART-Start for pregnancy (a collaborative project along with IT-FAU, funded by the German Federal Ministry of Health, BMG) and in DigiOnko-Brustkrebs (funded by the Bavarian State Ministry of Health and Care).
With proper development and application in medicine, artificial intelligence (AI) has the potential to lead to improvements in prevention, early detection, diagnosis, and identifying novel treatments, and it can thus make a real contribution to personalized medicine. In the smart data project KDI, managed by Siemens and funded by the German Federal Ministry for Economic Affairs and Energy (BMWi), it has been possible to establish an initial basis for supporting tumor conferences using machine-learning algorithms. Further development of this is aimed for in the joint project MIwin, funded by the Germany Federal Ministry of Education and Research (BMBF). The intention is that in the future, AI approaches should facilitate patient–doctor discussions as a documentation aid.

Laboratory for Molecular Medicine:
— Tumor biology and genetics, innate immunity and immunoediting
University Breast Center for Franconia, Familial Breast and Ovarian Cancer Center, University Gynecological Oncology Center for Franconia
Together with the Institutes of Pathology (Prof. A. Hartmann) and Urology (Prof. B. Wullich), the complete endogenous retroviral (ERV) expression and regulation in relation to innate immunity are being analyzed for the three cancer entities bladder, kidney, and fallopian tube. Innate immunity in tumor cells is activated here using double-stranded ERV-RNA via TLR3 and MDA5 receptors, and using ERV proteins via TLR4 receptors. For bladder tumors, a significant correlation has been demonstrated between high levels of ERV expression and inflammation, as well as longer survival. Secondly, kidney tumors were found to be associated with significantly better survival when there was high expression of specific ERV proteins. For fallopian tube carcinomas, the epigenetics of DNA and histones play a major role in ERV expression. This is being analyzed in collaboration with George Washington University (Washington, DC). The improved survival associated with activated inflammation might therefore be due to increased ERV expression. In summary, stimulation of ERV expression using epigenetic regulators might represent a new treatment method.
Using isolated human primary epithelial and mesenchymal breast tumor cells, it was possible to produce so-called spheroids — i.e., multicellular aggregates consisting of several thousand cells. In the process, these were identified as homo-spheroids (with a single cell type) or hetero-spheroids (with several cell types). With the help of 3D analyses (in collaboration with the Institute of Biophysics, Prof. B. Fabry), it has now been shown for proliferation and invasion that these spheroids behave like tumor fragments or biopsies. The complete sequencing of the RNA shows that specific transcription factors are overregulated in the tumor cells. Further experiments with more complex hetero-spheroids, especially with immune cells, as well as normal cell spheroids from healthy breast tissue, are expected to contribute to a better understanding of breast carcinogenesis.
— Genetic basis for pathological pregnancies
University Perinatal Center for Franconia, University Reproductive Center for Franconia
Molecular research in obstetrics is focusing on the detection of molecular causes and biomarkers for pathological changes during pregnancy and placental development. In the Franconian Maternal Health Evaluation Study (FRAMES), genetic variants in the aromatase gene CYP19A1, the progesterone receptor, and the estrogen receptor were analyzed and patients with preeclampsia were compared with healthy control individuals. In the Clinical Gravidity Association Trial and Evaluation (CGATE) program, molecular markers in the blood were investigated for their association with breast volume increases during pregnancy. Markers that are also associated with the occurrence and progression of breast cancer were found to have an influence on breast volume increases during pregnancy. In addition, in collaborative projects with the Erlangen Department of Pediatrics, molecular changes — especially in the retinoic acid signaling pathway and corticosterone metabolism — were analyzed in mouse and rat models of intrauterine growth restriction.

Central Research Unit: Clinical studies in gynecology

University Breast Center for Franconia, Familial Breast and Ovarian Cancer, University Gynecological Oncology Center for Franconia, University Endometriosis Center for Franconia

From 2001 to the end of 2020, more than 260 research projects were carried out in clinical phase I–IV studies, the objective of which is to achieve thorough individualization of therapy, increasing its effectiveness and minimizing side effects. Whole-genome sequencing and the very latest targeted therapies are being used for this purpose. The studies include curative and palliative treatment approaches.

One of the central projects is the Germany-wide PRAEGNANT registry for patients with metastatic breast cancer, which was first established in 2014. Tests for new biomarkers are being carried out. Among other things, these biomarkers provide information about the effectiveness and toxicity of treatment approaches and about the patients' quality of life. Using whole-genome sequencing makes it possible to identify innovative therapy targets, which can then be investigated in the framework of clinical studies or outside of the approval process. The data collected represent potential approval-procedure data — i.e., so-called real-world data.

In collaboration with Department of Medicine 5 — Hematology and Internal-Medical Oncology at Erlangen University Hospital, claudin-6 testing is being carried out on solid tumors as part of the Claudentify-6 Study. If the test result is positive, patients can receive further targeted therapy using chimeric antigen receptor T cells (CAR-T) in the BNT211 study.

In addition to the projects developed by the Central Research Office and the Institute for Women's Health, the local center is taking part in numerous internationally important approval-procedure trials.

Biobank Unit: Collection of biomaterials

University Breast Center for Franconia, University Gynecological Oncology Center for Franconia, University Perinatal Center for Franconia, University Endometriosis Center for Franconia, University Reproductive Center for Franconia

The Biobank in the Department of Gynecology is one of the largest biobanks worldwide in the field of gynecological research. It includes not only patients from the hospital's own Breast Center (approx. 10,000 participants), Genital Cancer Center (approx. 6,400), Endometriosis Center (approx. 2,300), and Perinatal Center (approx. 1,800), but also patients from nationwide multicenter studies. Currently, biomaterials (132,000 blood samples, 16,500 tissue samples, 30,000 urine samples, and 150,000 serum/plasma and stool samples) are available from approximately 63,000 test persons. In a collaborative project with the Institute of Pathology, 10,500 tumor blocks from patients in clinical studies have now been acquired. The blood data can be compared with those from the tumor (for mutation analyses and expression patterns). Within the framework of a project funded by Horizon2020 and EraCoSysMed, markers in the peripheral immune system and in the tumor microenvironment are being analyzed to predict the treatment response and prognosis during immune checkpoint inhibitor therapy. The PRAEGNANT research network for patients with metastatic breast cancer (currently approx. 4,000 patients at 60 centers in Germany) represents an increasingly important component of the biomaterials collection. In this context, the use of the PRAEGNANT registry study for patient selection based on clinical data and central testing of the biomarker heregulin for potential inclusion in a clinical study (SHERBOC) has been investigated, among other topics.

Laboratory for Reproductive Biology: Artificial organs and fertility preservation

University Endometriosis Center for Franconia, University Reproductive Center for Franconia, University Gynecological Oncology Center for Franconia

Although the results of fertility-preserving measures in cancer patients are good, with many pregnancies achieved, there is a group of patients whom it is not yet possible to help due to the nature of their disease. In these patients, there is a risk that the transplantation of preserved ovarian tissue may cause the cancer to recur, since malignant cells are present in the tissue. Helping these patients is an important focus of the research work. One approach is to create an artificial ovary using 3D electrospinning. In this process, follicles free of tumor cells are isolated from the removed ovarian tissue and inserted into artificial support scaffolds — produced by the Chair of Materials Science (Biomaterials) at Friedrich Alexander University (Erlangen–Nuremberg). The follicles are then further cultivated in the scaffolds, since follicles are unable to grow without the 3D structure of the stroma. In addition, the support scaffolds are rendered functional using growth factors.

In order to answer scientific research questions, the Endometriosis Center collects patient-history and clinical data for endometriosis patients, as well as biomaterials, in the framework of the International Endometriosis Evaluation Program (IEEP). The aim is to identify risk factors and predictive markers in relation to the diagnosis and recurrence of the disease, as well as on the effectiveness of treatment, relative to the patients' main symptoms. A sub-study forming part of the program compared different methods of obtaining circulating cell-free DNA.

In addition, a bioassay was set up in which the ingrowth of cells from endometriosis lesions into a collagen scaffold can be measured, allowing conclusions to be drawn regarding the invasiveness of these cells.

The staff of the Endometriosis Center are acting is coordinators for guideline development and for this purpose have carried out a systematic analysis of the literature from 2013 to 2018. This has made it possible to derive recommendations and statements for the diagnosis and treatment of patients with endometriosis.

Teaching

Since the end of 2010, the duty area of teaching in the Department of Gynecology has been one of the first university clinical institutions in Germany to have its own certified quality management system (now DIN EN ISO 9001:2015). This is regularly re-certified. Offering compulsory and elective subjects, the Department of Gynecology takes part in the curricular teaching of medicine and in interdisciplinary teaching in the framework of the cross-disciplinary subjects of general prevention, sexual medicine, and emergency medicine. The Department of Gynecology has its own Skills Lab, specially adapted to the requirements of teaching in obstetrics and gynecology, which is used for training as part of the block internship and the Practical Year. The Department of Gynecology also supervises medical doctorates.

Selected publications

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International collaborations

Prof. D. Easton, MD, Breast Cancer Consortium, Cambridge, United Kingdom

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Prof. D. Slamon, MD, University of California at Los Angeles (UCLA), Los Angeles, California, USA

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Research focus
- Improvements in corneal transplantation
- Pharmakologic modulation of corneal endothelial regeneration
- Corneal stem cells and stem cell-based strategies for ocular surface reconstruction
- Erlangen Glaucoma Registry
- Biomorphometry of the optic nerve
- Minimally invasive glaucoma surgery
- Functional aspects of retinal neurodegeneration
- Retinal physiology
- Non-invasive electrophysiology in humans and animals
- Selective studies of photoreceptor types and postreceptoral pathways
- Autoimmunity and glaucoma
- Autoimmunity and Post-COVID-syndrome
- Pseudoexfoliation syndrome/glaucoma
- Clinico-pathological concepts in diagnosis and management of ocular diseases
- Circulation of the eye and the visual pathway, computer-aided-diagnosis

Structure of the Department

Professorships: 8
Personnel: 176
- Doctors (of Medicine): 43
- Scientists: 13 (thereof funded externally: 7)
- Graduate students: 57

Clinical focus areas
- Surgery of the frontal eye
- Cornea surgery
- Reconstructive surgery of the frontal eye
- Glaucoma seamless transconjunctival retinal vitreal surgery (23-gauge-vitrectomy)
- Minimal invasive glaucoma surgery employing implants
- Refractive surgery with the femtosecond laser
- Cataract surgery with innovative intraocular lenses
- Intraocular injections of compounds to treat age related macular degeneration (AMD)
- Special consultation
- Departments of optometry, fluorescence angiography, and laser
- Outpatients' department
- Cornea bank
- Laboratories

Research

The Department of Ophthalmology belongs to the leading centers in the areas of lamellar corneal transplantation including structural biology of the cornea as well as diagnostics and pathophysiology of glaucomas at a national and international level. An interdisciplinary team of clinician and basic scientists conducts patient-oriented experimental and clinical research into corneal disorders, neurodegenerative diseases, such as glaucoma, and ocular tumors. The broad spectrum of methodologies applied includes molecular and cell biologic experiments, histology and electron microscopy, electrophysiology and visual psychophysics, and state-of-the-art imaging modalities, such as OCT angiography and magnetic resonance imaging. New medical devices for treatment of ocular diseases are being tested as part of multicenter studies. The major goal of the research efforts is to elucidate the pathophysiological causes underlying degenerative and vascular diseases of the eye and visual pathway on a molecular, cellular, and systemic level, to advance the microsurgical techniques, to secure the quality of treatments, and to promote the development of novel therapeutic concepts and treatment strategies.

Development of new methods for lamellar corneal transplantation
PI: Prof. Dr. F.E. Kruse, PD Dr. T. Tourtas, PD Dr. J. Weller
The Department of Ophthalmology has an internationally leading position in the performance and advancement of new minimally invasive techniques of lamellar corneal transplantation, such as DMEK (Descemet Membrane Endothelial Keratoplasty), using grafts consisting of a single cell layer to replace the diseased corneal endothelium. The clinical research group focuses on the further development of pre-, intra-, and postoperative strategies and the analysis of clinical outcomes to continuously improve quality and reproducibility of the new surgical techniques.

Pharmakologic modulation of corneal endothelial regeneration
PI: Prof. Dr. F.E. Kruse, PD Dr. T. Tourtas, PD Dr. J. Weller, Prof. Dr. U. Schlötzer-Schrehardt
Due to a worldwide shortage of donor corneas for transplantation, there is an increasing need for regenerative cell therapies for treatment of corneal endothelial disorders, such as Fuchs' corneal endothelial dystrophy. Rho kinases (ROCK) are involved in the regulation of multiple cell functions. The efficacy of selective ROCK inhibitors for functional regeneration of the corneal endothelium in early stages of disease is evaluated in clinical studies and accompanying experimental trials.

Corneal stem cells and stem cell-based strategies for ocular surface reconstruction
PI: Prof. Dr. U. Schlötzer-Schrehardt, Prof. Dr. F.E. Kruse
Transplantation of cultivated limbal epithelial progenitor cell grafts has been used to restore epithelial defects of the human cornea in patients with limbal stem cell deficiency. This research project explores the molecular characteristics of corneal stem and progenitor cells together with their specific niche microenvironment and their utilization for improved stem cell based therapies on tunable biosynthetic matrices. The applicability of alternative autologous stem cell sources for corneal epithelial tissue engineering strategies is also investigated.

Erlangen Glaucoma Registry
PI: Dr. Dr. B. Hohberger, Prof. Dr. R. Lämmer, Prof. Dr. C. Mardin
Due to the slow progression of glaucoma, a large study population and long-time observations are needed to gain insights into its long-term effects and progression rates. These data have been integrated into a unique patient registry, the Erlangen Glaucoma Registry, founded in 1991. It contains almost all available research data for registered glaucoma patients. This allows for cross-sectional and, in particular, for longitudinal observations and for evaluation of prognostic validity of diagnostic procedures. This database also serves for evaluation and optimization of personalized medical and surgical treatment procedures.

Biomorphometry of the optic nerve
PI: Prof. Dr. C. Mardin, Prof. Dr. R. Lämmer, Dr. Dr. B. Hohberger
The main focus of this research project is the development and application of novel imaging methods for early detection of glaucoma and to quantify disease progression. Next to morphometric tests (e.g. OCT), OCT-angiography is implemented and improved. The findings are also applied to other diseases, like diabetic retinopathy and age-related macular degeneration.

Minimally invasive glaucoma surgery
PI: Prof. Dr. R. Lämmer, Dr. Dr. B. Hohberger
As an alternative to traditional glaucoma surgery, minimally invasive glaucoma surgery (MIGS) has shown promise for the future management of glaucoma patients. It refers not to a single surgery, but rather to a group of distinct procedures and devices that aim to decrease intraocular pressure, the major risk factor of glaucoma. In this clinical study, the efficacy, safety, intraoperative complications and postoperative outcome of different procedures and devices will be comparatively evaluated, providing more reliable data for proper indications and personalized treatment strategies. The overall goal is to record all MIGS procedures in a registry and to identify risk factors for the surgical procedures and

clinical outcome. Individual and molecular targets, defining the clinical success, are investigated.

Functional aspects of retinal neurodegeneration
PI: Prof. Dr. J. Kremers, PD Dr. C. Huchzermeyer
In this research project, new electrophysiological and psychophysical techniques are developed to study the functional aspects of retinal degeneration, especially of glaucoma and hereditary retinal degenerations. Electrophysiological tests are objective and allow a direct assessment of retinal pathophysiology. Psychophysical tests can be very sensitive and give an impression about perceptual changes in patients. Novel methods are developed to accurately study the responses that are elicited by single photoreceptor types or by different retinal pathways. Innovative developments in the multifocal stimulation technique and in perimetry are implemented to allow an early diagnosis of retinal degeneration.

Retinal physiology
PI: Prof. Dr. J. Kremers
The goal of this working group is to study the function of the normal and diseased retina. To reach that goal, we record electrophysiological responses of the retina of rodent models of human diseases. In addition, we perform electrophysiological and psychophysical experiments with normal human test persons and patients to identify different signal pathways in the retina and the changes caused by a disease. The results of the animal and human experiments are related with each other so that the pathophysiological processes can be better understood.

Autoimmunity and glaucoma
PI: Dr. Dr. B. Hohberger, Prof. Dr. C. Mardin
The pathomechanisms of glaucoma are complex and multifactorial. Apart from the most important risk factor, i.e. elevated intraocular pressure, autoimmune processes appear to be involved. In fact, there is increasing evidence from animal and human studies that glaucoma is an autoimmune disease, associated with alterations in autoantibody profiles. Clinical studies specifically investigate the role of agonistic autoantibodies against ß2-adrenergic receptors in glaucoma pathogenesis. The removal of ß2-autoantibodies as a novel therapeutic strategy for lowering intraocular pressure is also evaluated in this project.
Autoimmunity and Post-COVID syndrome
Based on the experience in glaucoma research, studies on microcirulation and autoimmunity were done in patients after COVID-infection.

Pseudoexfoliation syndrome/glaucoma
PI: Prof. Dr. U. Schlötzer-Schrehardt
Pseudoexfoliation (PEX) syndrome is world-wide a leading cause of chronic open-angle glaucoma. The focus of this research project is the molecular analysis of the underlying, genetically determined, fibrotic process through functional characterization of known PEX-associated coding and non-coding risk variants, functional analysis of rare genetic variants as well as the identification of novel PEX-associated genes through transcriptome analyses followed by pathway and gene network analyses.

Clinicopathologic concepts in diagnosis and management of ocular diseases
PI: PD Dr. J. Weller, Dr. R. Meiller, Prof. Dr. A. Bergua, Prof. Dr. G. Gusek-Schneider
Multidisciplinary diagnosis and management of orbital diseases and epibulbar lesions: The purpose of this study is to establish correlations between morphologic, biomicroscopic, histologic, and molecular genetic criteria and the long-term results of surgical excision and plastic reconstruction. Surgical management of periocular malignant tumors using frozen section control and plastic reconstruction: indications, methods, and results.

Circulation of the eye and the visual pathway, computer-aided diagnosis, and virtual education
PI: Prof. Dr. G. Michelson
Ocular circulation of the eye and the visual pathway: The tissues and vessels of the eye reflect systemic diseases and are a perfect system for the visualization of physiologic processes of the body. Immunological processes, diabetes, and arterial hypertension can be evaluated quantitatively in the eye. Computer-aided-diagnosis and virtual education: Ophthalmology needs new methods for medical information processing to optimize diagnosis and therapy. Automated analysis of ophthalmic images combined with automated classification leads to a fast and bias-free evaluation, which is an important prerequisite for screening. Diffusion measurement of the visual pathway based on magnetic resonance images neurodegenerative eye diseases often involve the entire visual system. In some cases, they are induced by a cerebral macro- and microangiopathy with subsequent ischemic changes and degeneration of the visual pathway. The new non-invasive technique based on magnetic-resonance imaging provides information about the integrity and orientation of the visual pathway.

Teaching

Results of research are directly implemented in medical student and postgraduate teaching. Owing to the extensive contacts with colleagues abroad, many foreign students come to the Department of Ophthalmology for at least a part of their study (graduate or post-graduate) and for further education.

Selected publications

Schlötzer-Schrehardt U, Zenkel M, Strunz M, …, Kruse FE. Potential Functional Restoration of Corneal Endothelial Cells in Fuchs Endothelial Corneal Dystrophy by ROCK Inhibitor (Ripasudil). Am J Ophthalmol. 2020; 224:185-199

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Grau E, Horn F, Nixdorff U, Michelson G. OCT and IOP findings in a healthy worker cohort: results from a teleophthalmic study in occupational medicine. Graefes Arch Clin Exp Ophthalmol. 2019 Nov;257(11):2571-2578.

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Michelson G, Forst T. Diabetic Macular Edema in Diabetological Practices. Klin Monbl Augenheilkd. 2020 Nov;237(11):1320-1325.

International cooperations
Prof. Dr. M. Greiner, Department of Ophthalmology and Visual Sciences, University of Iowa Carver College of Medicine, Iowa: USA

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Prof. Dr. N. Koizumi, Department of Biomedical Engineering, Faculty of Life and Medical Sciences, Doshisha University, Kyotanabe: Japan

Prof. Dr. T. Aung, Singapore Eye Research Institute, Singapore National Eye Centre: Singapur

Prof. Dr. S. Deng, Stein Eye Institute, University of California, Los Angeles: USA

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Research focus
- Ultrasound, endoscopy, and salivary glands
- Division of Phoniatrics and Pediatric Audiology
- Experimental Oncology/nanomedicine (SEON)
- Speech perception with hearing aids and Cochlear implants
- Allergology/clinical immunology and rhinology
- Experimental otolaryngology
- Laboratory for sleep disorders/somnology

Structure of the Department

Professorships: 5
Personnel: 355
- Doctors (of Medicine): 43
- Scientists: 34 (thereof funded externally: 18)
- Graduate students: 32

Clinical focus areas
- Minimal invasive surgery of salivary glands
- Lancer surgery
- Cochlear implantat surgery
- Nose/paranasal surgery
- Clinical and surgical treatment of voice disorders
- Pediatric hearing disorders
- Diagnosis and treatment of sleep disorders

Research

The Department of Otorhinolaryngology – Head and Neck Surgery is one of the largest hospitals in Germany and has a comprehensive research repertoire. In the clinical area, the focus is on ultrasound, the diagnosis/treatment of salivary gland diseases, tumor and voice disorders, vestibular and hearing impairments as well as somnology and allergology. These foci are reflected in the basic research area. Nanomedicine, which carries out translational projects as well as extensive basic research, is another highly interdisciplinary focus. Ultrasound, endoscopy, and salivary glands In modern ultrasound systems and endoscopy units, studies on sonographic imaging of head and neck malignancies and salivary gland tumors remain a cornerstone of scientific work. The role of ultrasonography for the diagnosis of sialolithiasis was systematically examined using a large group of patients. Our results show an accuracy of approximately 95% for the diagnosis of sialolithiasis. Gland-conserving surgery for benign salivary gland diseases is one of our priorities. The main topics are currently the long-term results after limited, extracapsular resection especially of cystadenolymphomas and pleomorphic adenomas of the glandula parotis. Minimally invasive interventions of the salivary glands and their excretory ducts are not only applications in daily practice, but have been systematically reviewed and evaluated scientifically. Combined endoscopic and open surgical procedures provide a new way of treating obstructive salivary gland disorders. The application of Pneumatic Intracorporeal Lithotripsy, introduced in 2015, has been expanded in our Department, particularly in the context of the multimodal treatment of the difficult cases of sialolithiasis, which until recently required resection of the affected salivary gland under general anesthesia.

Division of Phoniatrics and Pediatric Audiology
Our clinical research focuses on the development of new methods allowing for quantitative voice diagnostics. The major part is the objective analysis of endoscopic high speed recordings during voice production. Within our basic research we concentrate on physical interactions during voice production. We develop and analyze numerical models (lumped-mass models, finite-volume-models) and experimental models (synthetic silicon vocal folds and ex-vivo animal cadaver larynx models). We expect to gain more insight into the interaction between airflow, vocal fold dynamics and resulting acoustics for physiologic and pathologic voice production. We apply state-of-the-art methods from the scientific area of artificial intelligence. Since 2016, we have been analyzing the vocal fold tissue from the molecular-biological point of view. All these topics have the goal to enhance diagnostics and the treatment of our patients.

Experimental Oncology/nanomedicine (SEON)
PI: Prof. Dr. C. Alexiou
The Section for Experimental Oncology and Nanomedicine (SEON) has successfully expanded the main topics of oncology, cardiovascular diseases, regenerative medicine, imaging and nanotoxicology and has added the area of infection research as a new pillar. The research work here relates to the nanoparticle-based magnetic isolation of specific bacteria and toxins for the therapy and diagnosis of bacterial infectious diseases. Here, we were able to acquire extensive funding from the Doctor Robert Pfleger Foundation. The basic research gained from this grant helped us to scientifically address the challenges in the context of the emerging corona pandemic. For example, with the support of the Manfred Roth Foundation, we were able to acquire the project "Functionalized Superparamagnetic Iron Oxide Nanoparticles (SPIONs) as a Platform Technology for the Diagnosis and Therapy of Enveloped Viruses" (including SARS COV-2) and we are working on developing an antigen test. In the field of regenerative medicine, SEON is successfully funded as a project partner together with the Universities of Würzburg, Bayreuth and partners from FAU in the DFG-SFB/Transregio 225 "From the basics of biofabrication to functional tissue models". A special highlight was the 10th anniversary of SEON on September 18, 2019, which we celebrated with a scientific symposium and numerous visitors. The world's first installation of a robot-controlled magnet for nanoparticle therapy was also presented to the public at this event. This was also extensively reported in the media. In summer 2019, we received the prestigious Medical Valley Award for the project "Safe contrast agents for magnetic resonance imaging (MRI)". As part of the AI competition organized by the Bavarian State Government, we were successful with the complementary joint application Medical-Nano-Micro-Robotics together with the TU-Munich, the University of Applied Sciences Munich and the University of Applied Sciences Ansbach. With this extensive funding, it is now possible to fill a W2 professorship and pending equipment positions. In this reporting period, our work was again honored with numerous scientific awards at various national and international congresses and, among others, Dr. med. dent. Magdalena Alev received the doctoral award of the STAEDTLER Foundation on October 22, 2020 for her doctoral thesis, which was evaluated summa cum laude.

Installation of a TX 200 high-performance 6-arm robot from Stäubli in SEON's animal operating room for precise control and positioning of the magnetic field.

Speech perception with hearing aids and Cochlear implants
Restoring hearing performance with technical devices such as hearing aids or cochlear implant systems is one of the most important challenges in audiological research. The focus of this project

is the prediction of speech comprehension based on audiological characteristics. Based on an existing hearing loss, the attenuation and distortion of the speech signal are estimated and the speech intelligibility is predicted. On the basis of clinical data and special hearing tests, models were developed that can predict hearing and speech understanding with a CI system based on speech understanding with hearing aids, the etiology and anamnestic data.
The data are used to evaluate hearing aid fittings and to substantiate the indication for CI fittings.

Allergology/clinical immunology and rhinology
Endonasal endoscopic sinus surgery and following oral desensitization with ASS come into question as a treatment for NSAID-intolerant patients. The aim of the study is to elaborate and perform a treatment scheme for a treatment with an intravenous desensitization with ASS. The collected data of the intravenous desensitization as an efficient therapy for patients with NSAID-intolerance is going to be evaluated and compared to oral desensitization with ASS.

Experimental otolaryngology
In our group, we investigate among others the development of tinnitus. We developed a new model based on information-theoretical approaches in which tinnitus is a by-product of a mechanism that is able to improve hearing thresholds. Based on the model we developed a new therapy that gave promising results in first pilot studies. In addition, data from animal research support this model. With a new statistical method developed by us, we investigate space-time patterns of cortical activity and are able to describe tinnitus-specific activity in the brain that may be diagnostically used. Additionally, we were able to categorize human sleep stages from EEG data with this method and generate new insight for the sleep medicine. Furthermore, we develop new methods for the determination of sensory thresholds in humans and animals with which it is now possible to determine thresholds, e.g. of auditory brainstem responses, in a completely automatic and objective manner. For all these and other questions, we additionally develop artificial neuronal network models and applications for artificial intelligence

Sleep laboratory / experimental sleep medicine
On the part of the clinic, the sleep medicine department offers a comprehensive spectrum of current diagnostics and therapy of all sleep disorders according to ICSD-3 with a focus on "sleep-related breathing disorders". Within the framework of experimental sleep medicine, a DFG-funded research focus is on the analysis of sleep architecture with respect to the macro- as well as microstructure of sleep. A major goal is the establishment of a novel, fully objectified and thus automatable method of sleep stage analysis by means of a global pattern analysis of the cortical activity distribution. Further goals are the investigation of spatiotemporal developments of cortical activity during sleep stage changes and the investigation of local sleep phenomena in patients with obstructive sleep apnea. With the goal of a deeper understanding in the field of sleep electrophysiology, methods such as non-supervised dimensional reduction (deep autoencoders), time series analysis (Bayesian superstatistics), and statistical cluster analysis (combination of Gaussian mixture models with evidence-based Bayesian model selection) are applied.
Another translational research focus lies on the optimization of diagnostics and the individualization of therapeutic concepts for patients with obstructive sleep apnea. A key objective in this respect is the validation of different circulating biomarkers on a serological basis. The use of biomarkers as a screening tool in primary diagnostics as well as for individual cardiovascular risk stratification and for monitoring of the treatment response will be investigated. The aim of this project is the use of circulating biomarkers in clinical routine in order to enable individualized therapy strategies in the context of personalized medicine in the future.

Teaching

The Department of Otorhinolaryngology - Head and Neck Surgery is involved in the curricular teaching of Medicine, Dentistry and Logopedics with compulsory and elective subjects. Particularly the interdisciplinary teaching concerning medical technology, nano-technology, toxicology and integrated life sciences has to be pronounced.
Bachelor's and Master's theses as well as MD and PhD theses are supervised.

Selected publications
Hoppe U, Hocke T, Hast A, Iro H. Cochlear Implantation in Candidates With Moderate-to-Severe Hearing Loss and Poor Speech Perception. Laryngoscope, 2020.

Karawacka W, Janko C, Unterweger H, Mühlberger M, Lyer S, Taccardi N, Mokhir A, Jira W, Peukert W, Boccaccini AR, Kolot M, Strauss R, Bogdan C, Alexiou C, Tietze R. SPIONs functionalized with small peptides for binding of lipopolysaccharide, a pathophysiologically relevant microbial product. Colloids Surf B Biointerfaces, 2019, 174: 95-102

Friedrich RP, Schreiber E, Tietze R, Yang H, Pilarsky C, Alexiou C. Intracellular Quantification and Localization of Label-Free Iron Oxide Nanoparticles by Holotomographic Microscopy. Nanotechnol Sci Appl, 2020, 13:119-130

P. Gomez, A. M. Kist, P. Schlegel, D. A. Berry, D. K. Chhetri, S. Dürr, M. Echternach, A. M. Johnson, S. Kniesburges, M. Kunduk, Y. Maryn, A. Schützenberger, M. Verguts, M. Döllinger. BAGLS, a multihospital benchmark for automatic glottis segmentation. Scientific Data, 7(1):186; 2020.

P. Schlegel, M. Kunduk, M. Stingl, M. Semmler, M. Döllinger, C. Bohr, A. Schützenberger. Influence of spatial camera resolution in highspeed videoendoscopy on laryngeal parameters. PloS ONE, 14(4):e0215168; 2019.

International cooperations
D.A. Berry, PhD, University of California Los Angeles, Los Angeles: USA

M. Kunduk, PhD, Louisiana State University, Baton Rouge: USA

C. Madell, PhD, The University of Sydney, Sydney: Australia

N. Li-Jessen, PhD, McGill University, Montreal, Kanada

Prof. Dr. M. Kaltenbacher, TU-Graz, Graz: Austria

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Research focus
- Medication safety
- Perinatal programming and early determination of renal and cardiovascular disorders
- Rare endocrine disorders with a focus on growth abnormalities
- Genetic skin diseases of the neonate
- Genomic aberrations in childhood malignancies
- Differentiation pathways during skeletal development
- Experimental and translational imaging
- Perinatal hypoxic brain injury and neuroprotection

Structure of the Chair

Professorships: 5
Personnel: 430
- Doctors (of Medicine): 81
- Scientists: 15 (thereof funded externally: 10)
- Graduate students: 6

Clinical focus areas
- Medical care of preterm and term newborn infants
- Pediatric endocrinology/diabetology
- Pediatric gastroenterology
- Pediatric nephrology
- Neuropediatrics
- Pediatric endocrinology
- Pediatric oncology and hematology

Research

Research at the Department of Pediatrics and Adolescent Medicine is focused on the area of perinatal medicine. This involves disease-oriented experimental, preclinical, and clinical studies. Further main research interests lie in the fields of pediatric endocrinology, oncology, neuropediatrics and pharmacotherapy. The Department has its own clinical trial center which also serves as an accredited institution for professional training in the field of drug information.

Medication safety
PI: Prof. Dr. A. Neubert
We have a long history of research in the area of pediatric pharmacotherapy, focusing on medication safety (AMTS). Our contribution to the "AMTS-Aktionsplan 2013-2015" (item 16: Development of recommendations for the use of drugs in children particularly in the inpatient care) led to current BMG-funded activities of our Department to establish an evidence-based dosing information database for children in Germany. We are also in charge of the country-wide project "KiDSafe" funded by the Innovation Fonds. Within this project the aforementioned dosing database (pediatric formulary) and other measures to increase medication safety are being evaluated in detail. Moreover, we actively participate in several EU-funded projects (e. g. GAPP, EPTRI, c4c) and have coordinated a multicenter phase 3 study to investigate the use of clonidine as sedative agent in pediatric intensive care units (CloSed; compare own report). The aim of most projects is a pediatric-use marketing authorization for the studied drugs.

Perinatal programming and early determination of renal and cardio-vascular disorders
PI: Prof. Dr. A. Hartner, PD Dr. F. Fahlbusch
Our research aims at elucidating the consequences of an early impairment of organ development for the pathogenesis of diseases during adolescence and adult life. To this purpose, the sequelae of a congenital reduction of nephron numbers or disruption of renal development for the kidney and the cardiovascular system are being studied. We have been focusing on the pathogenetic mechanisms of inflammatory renal disease, hypertension, and heart failure. In further studies, we are attempting to clarify which placental alterations may lead to defects in organ systems of the offspring and can expedite the onset of later disease. These studies are being performed in collaboration with the Perinatal Center of Middle Franconia and the Comprehensive Cancer Center Erlangen-EMN.

Genetic skin diseases of the neonate
PI: Prof. Dr. H. Schneider
Our primary research goal is to identify pathogenetic mechanisms underlying geno-dermatoses (hereditary disorders of the skin and its appendages) at the molecular level and to develop appropriate therapeutic approaches. Some of these diseases may be associated with life-threatening complications already in the first weeks after birth. In addition to the skin, other organs, such as eye, ear, and lung, are frequently affected by pathogenetic processes. First systematic natural history studies in patients of different age groups allowed the characterization of genotype-phenotype relationships as a prerequisite for specific therapeutic attempts. In DFG-funded projects, we have been investigating the feasibility of prenatal protein replacement or gene therapy in mouse models of epidermolysis bullosa, lamellar ichthyosis, and hypohidrotic ectodermal dysplasia. We coordinated the first clinical trial in children with hypohidrotic ectodermal dysplasia, a multicenter study to evaluate the safety and efficacy of a recombinant ectodysplasin A1 administered at the earliest stage of postnatal development. Based on promising preclinical data, the results of this clinical trial, and the success of named-patient use case studies, we are currently preparing a phase 3 trial to investigate such protein replacement therapy *in utero*.

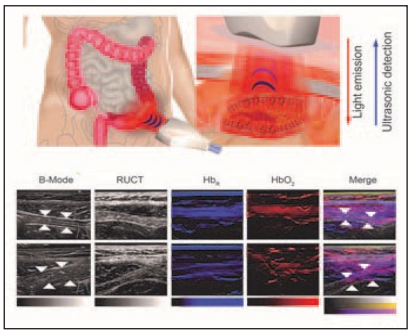
Physiology und Pathophysiology of growth disorders
PI: Prof. Dr. J. Woelfle
Growth is a central phenomenon of childhood, which frequently serves as an indicator of health and disease. Conditions affecting physiological growth conditions can result both in reduced growth velocity, with a subsequent risk of developing short stature, but can also result in excessive growth with an increased risk of gigantism and/or tall stature. Within this area we are interested in genetic and epigenetic mechanisms of growth disorders, in particular in alterations of growth hormone receptor signaling and the transcriptional regulation of members of the growth hormone-IGF-1-axis.

Genomic aberrations in childhood malignancies
PI: Prof. Dr. M. Metzler
Cancer cells show characteristic genetic alterations which are important not only for tumorigenesis and disease progression, but also as molecular markers allowing the detection of specific tumor cells – for diagnostic purposes, monitoring of tumor response to therapy, and for relapse recognition. Besides investigating such molecular markers, we have been analyzing germ-line mutations of selected tumor types that predispose to malignancies early in life. As national study center for chronic myeloid leukemia in childhood and adolescence, we are continuing intense research on clinical and biological aspects of this model disease.

Differentiation pathways during skeletal development
PI: Prof. Dr. M. Rauh, Prof. Dr. H. Schneider
To clarify the role of certain signaling molecules during skeletal development, we have been using a broad spectrum of methods including gene expression assays, immunohistochemistry, models of osteogenesis *in vitro* and *in vivo*, and determination of various enzyme activities by mass spectrometry. A related research project is focused on the controlled differentiation of cord blood-derived mesenchymal stem cells into osteoblasts and chondrocytes. These cells could be used for autografts, e.g. in the treatment of cleft lip and palate (the most frequent congenital malformation) to reduce the number of surgical interventions required.

Experimental and translational imaging
PI: Dr. F. Knieling
Conventional diagnostic imaging methods are often invasive, time-consuming, and harbor risks for complications. These limitations

potentiate in children and adolescents, whose organisms are particularly vulnerable. Light- and sound-based imaging approaches, like multi-spectral optoacoustic tomography (MSOT), offer novel opportunities to perform non-invasive diagnostics. Pulsed laser light in the near-infrared spectrum leads to the generation of ultrasonic waves, which are received by special transducers. Our current projects combine MSOT and other imaging technologies with aspects of basic research and clinical pediatrics to achieve rapid translation of the findings into routine diagnostic procedures.



The principle of multispectral optoacoustic tomography

Neonatal neurology and neuroprotection
PI: Prof. Dr. R. Trollmann
The research of this group is focused on the early detection of perinatally acquired brain lesions and neuroprotection. In an established mouse model of perinatal hypoxia, we have been investigating molecular effector mechanisms of the immature brain after perinatal damage due to hypoxia and excitotoxicity as well as neuroprotective strategies, e.g. administration of erythropoietin and prolyl hydroxylase inhibitors. We are studying the impact of acute hypoxia on early neuronal migration, angiogenesis, astrocytic, and blood-brain barrier function and have been evaluating approaches to pharmacological stabilization of hypoxia-inducible transcription factors (HIF). Moreover, age-specific effects of excitotoxic stimuli on the regulation of excitatory neurotransmitter systems during early development are being characterized in a mouse model of neonatal seizures. The investigation of hypoxia-induced neuroinflammatory mechanisms *in vitro* and in animal models also stimulates the progress of projects on neuroprotective strategies beyond the neonatal period.

Teaching

The Department of Pediatrics and Adolescent Medicine participates with compulsory and elective courses in the degree programs in Medicine and Dentistry. Alongside traditional teaching, special research seminars and interdisciplinary courses are offered. An „emergency care simulator“, adapted to the needs of neonatology and pediatric intensive care, enables the training of emergency medical procedures and team-work analysis of the management strategies applied. This includes regular reviews of real emergency situations experienced in our clinic.
Individual researchers supervise Bachelor’s and Master’s theses as well as MD and PhD theses.

Selected publications
Zahn J, Hoerning A, Trollmann R, Rascher W, Neubert A. Manipulation of Medicinal Products for Oral Administration to Paediatric Patients at a German University Hospital: An Observational Study. Pharmaceutics. 2020 Jun 23;12(6):583.

Eberl S, Ahne G, Toni I, Standing J, Neubert A. Safety of clonidine used for long-term sedation in paediatric intensive care: A systematic review. Br J Clin Pharmacol. 2020 Dec 23. doi: 10.1111/bcp.14552.

Schmidt M, Rauh M, Schmid M, Huebner H, Ruebner M, Wachtveitl R, Cordasic N, Rascher W, Menendez-Castro C, Hartner A, Fahlbusch FB. Influence of Low Protein Diet-Induced Fetal Growth Restriction on the Neuroplacental Corticosterone Axis in the Rat. Front Endocrinol (Lausanne). (2019) 10:124

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

Krieg P, Dick A, Latzko S, Rosenberger S, Meyer J, Crumrine D, Hielscher T, Elias PM, Rauh M, Schneider H. Conditional Alox12b knockout: degradation of the corneocyte lipid envelope in a mouse model of autosomal recessive congenital ichthyoses. J Invest Dermatol 2020, 140:249-253 378:1604-1610

Plamper M, Gohlke B, Schreiner F, Woelfle J. Phenotype-Driven Diagnostic of PTEN Hamartoma Tumor Syndrome: Macrocephaly, But Neither Height nor Weight Development, Is the Important Trait in Children. Cancers (Basel). 2019, 11(7):975.

Schulte S, Gohlke B, Schreiner F, Gruenewald M, Fimmers R, Stoffel-Wagner B, Bartmann P, Woelfle J. Thyroid Function in Monozygotic Twins with Intra-twin Birth Weight Differences: A Prospective Longitudinal Cohort Study. J Pediatr. 2019 Aug;211:164-171

Jung S, Ballheimer YE, Brackmann F, Zoglauer D, Geppert CI, Hartmann A, Trollmann R. Seizure-induced neuronal apoptosis is related to dysregulation of the RNA-edited GluR2 subunit in the developing mouse brain. Brain Res. 2020 May 15;1735:146760. doi: 10.1016/j.brainres.2020.146760.

Jung S, Topf HG, Boie G, Trollmann R. C1 Esterase Inhibitor Reduces BBB Leakage and Apoptosis in the Hypoxic Developing Mouse Brain. Neuromolecular Med. 2020 Mar;22(1):31-44. doi: 10.1007/s12017-019-08560-8.

International cooperations
Prof. Dr. T. Grange, Department of Pediatrics, Washington University School of Medicine, St. Louis: USA

Dr. P. Schneider, Department of Biochemistry, University of Lausanne, Epalinges: Switzerland
Dr. O. Delattre, INSERM U830, Institut Curie, Paris: France

Prof. Dr. D. Reinhardt, Department of Anatomy & Cell Biology, McGill University, Montreal: Canada

Prof. Dr. Catherine Tuleu, University College London, London: UK

Prof. Dr. Dick Tibboel, Erasmus Medical Center, Rotterdam: The Netherlands

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Research focus

- Cardiopulmonary exercise testing and the cardiopulmonary capacity of children
- Influence of elite level athletics on cardiac health
- Myocarditis and sport
- Sports in Fontan patients
- Risk stratification after cardiac surgery
- Pathophysiology of the Fontan circulation
- Congenital Cardiology Cloud
- Echocardiography
- Pathophysiology of congenital heart disease in a rat model
- Multimodality imaging
- Interventional therapy
- Pharmacological studies

Structure of the Division

Professorship: 1
Personnel: 79

- Doctors (of Medicine): 22
- Scientists: 2 (thereof funded externally: 2)
- Graduate students: 20

Clinical focus areas

- Interventional therapy of congenital heart defects in the catheter laboratory
- Surgical therapy of congenital heart defects in close cooperation with the Division of Pediatric Cardiac Surgery
- Intensive care after cardiac surgery
- Specialized ambulatory services: congestive heart failure, transplant, arrhythmias, sports, Fontan-patients

Research

In the Division of Pediatric Cardiology, patient research on treatment techniques and care structures is performed. A particular focus is on different modalities of cardiovascular imaging and pathophysiology in univentricular hearts after Fontan operations. In basic research there are two working groups on the pathophysiology of congenital heart defects in the small animal model and a material biobank on the molecular genetic causes of congenital heart defects.

Cardiopulmonary exercise testing and the cardiopulmonary capacity of children
PI: Dr. Dr. I. Schöffl, Dr. K. Rottermann
Cardiopulmonary exercise testing in very young children and in children with limited cardiopulmonary capacity presents several challenges. The bicycle ergometry as well as the one performed on a treadmill have several limitations when testing children. In a study with 7 – 10 year-old healthy children we were able to implement a field test, using a mobile cardiopulmonary exercise testing device. The children were instructed to perform 4 steps of 2 minutes with increasing speed after each step. The test was conducted in a local park. This way the children were able to run according to their own capabilities. In comparison to a cardiopulmonary exercise test performed on a bicycle the children all reached maximal exertion while enjoying themselves.
In a second study we now want to transfer this protocol onto even younger children (4 – 6 year-olds). At the same time the test protocol is being used in a multicentre study design to develop normal values for children aged 4 – 8 years.

Influence of elite level athletics on cardiac health
PI: Dr. I. Schöffl
Sudden cardiac death is the leading medical cause of death in young athletes. Detailed knowledge about the sport specific, cardiac adaptations are necessary in order to evaluate the influence of sports performed at an elite level on the heart and in order to develop adequate measures to prevent sudden cardiac death. In a first study in which we investigated the Junior German National Team in climbing we were able to show that climbing at an elite level led to characteristic cardiac adaptations, comparable to those observed in elite athletes from contact sports. In a second study we want to investigate the influence of an extreme endurance sport on the heart. The athletes from the German nation team in ski mountaineering, cross country skating and biathlon will be investigated using echocardiography with standard measurements in combination with strain measurements and cardiopulmonary exercise testing.

Myocarditis and sport
PI: Dr. Dr. I. Schöffl, Dr. A. Weigelt
The most common cause for myocarditis is a viral infection of the heart muscle. In Germany myocarditis represents the most common cause for sudden cardiac death in young athletes. The correlation between viral infection and the development of a myocarditis has been shown in animal models but not in humans so far. It is believed that athletes have a higher risk of viral infections and as a consequence of catching viral myocarditis. However, the number of patients is so small that this is mere speculation at this point. After having had myocarditis a rest from physical activity depending on the severity of the disease is recommended by the ESC. The level of evidence for these recommendations however, is poor, due again to the small number of patients. Since 2013 all myocarditis patients from 25 centres across Germany and Austria have been gathered to gain a better insight into this disease. In a common approach with this MYKKE registrar we have now developed a quiestionnaire eliciting the influence of physical activity on the occurrence of myocarditis, the recommendations given by the treating physicians, the compliance to these recommendations as well the outcome after 12 months. In a second, prospective, multicentre approach myocarditis patients are closely followed and monitored over a timeframe of 24 months and provided with clear instructions and training plans when returning to sport.

Sports in Fontan patients
PI: Dr. A. Weigelt, Dr. Dr. I. Schöffl
The cardiopulmonary fitness can be estimated using cardiopulmonary exercise testing. The main parameter is the VO_2peak which also represents the best prognostic value with regards to mortality, transplantation, and liver failure. The VO_2peak can be increased by physical activity. In a study, in which the VO_2peak of Fontan patients was compared to their physical activity during childhood and adolescence using a questionnaire, we hope to prove the positive correlation between sports and VO_2peak. This could imply an improvement of the most important prognostic value through physical activity.
In further studies we plan to implement intervention studies in order to improve the cardiopulmonary fitness and thus the long-term survival of our Fontan patients.

Risk stratification after cardiac surgery
PI: Dr. M. Schöber, Dr. R. Zant
The aim of this study is to identify patients with a high risk of profound shock by defined clinical parameters. Once identified, a structured approach is initiated to provide optimal organ-oxygenation. We use urinary lactate measures, which to the best of our knowledge has not been evaluated as prognostic parameter in critically ill patients so far. However, this method may be superior to serum lactate measurements in this patient collective: Urinary lactate summarizes a greater time period and therefore may be superior by equalizing short, but clinically irrelevant peak values. This study is supported by the Johannes und Frieda Marohn-Stiftung.

Pathophysiology of the Fontan Circulation
PI: Prof. Dr. S. Dittrich, Dr. J. Moosmann
Patients with univentricular heart malformations require several successive cardiac operations resulting in Fontan circulation: the univentricular heart supplies the systemic circulation and pulmonary circulation remains passive. The pathophysiological changes of the Fontan circulation are the focus of our research:
By near-infrared spectroscopy (NIRS) measurements, we demonstrated that Fontan patients, especially with PLE, have alterations in perfusion ratios with low regional oxygen saturation (rSO2). Moreover, by molecular genetic miRNA analysis, we succeeded in identifying altered miRNA-controlled immunological pathways in Fontan patients with PLE. We were able to

demonstrate these immunological changes in terms of altered lymphocyte populations as well as changes in T-cell differentiation corresponding to chronic inflammation. In a large cross-sectional MRI-analysis, we have shown that pathological abdominal and thoracic lymphatic pattern are present in a relevant number of Fontan-patients and that pathologic lymphatic pattern are associated to clinical symptoms after Fontan operations. These observations support the hypothesis, that the lymphatic system may play a crucial role in the Fontan-physiology.

Congenital Cardiology Cloud
PI: Dr. U. Doll, Dr. K. Rottermann
As part of the governmental program "Bayern Innovativ" (PBN-MED-1609-0004) and funding by the Bavarian State ministry for economics and media, energy and technology, a tele-medical platform could be established, meshing inpatient treatment with long-term ambulatory care.
Better use of medical findings, improved documentation and treatment planning and a strong emphasis on patient´s involvement determine the subjects of the intersectoral cloud used in this healthcare research project. Incoming tele-medical consultations and second opinion requests are used for sharing patient related data such as medical reports and echocardiographic or heart catheterization diagnostic imaging. In addition, performing of live tele-medical videoconferences with referring physicians takes place, in order to discuss these diagnostic findings. Clinical data of interest can be shared with our patients via a tele-medical cloud and patients can be supervised by videoconference in their familiar domestic surroundings.

Pathophysiology of congenital heart disease in a rat model
PI: Dr. M. Alkassar
We examine changes in the development of power inside single cardiac muscle cells and tissue in diseased rats. These results are used to optimize a simulation software specifically designed to depict impending cardiac insufficiency at an early stage. The simulation illustrates the power inside the cardiac muscle in four dimensions and shows critical areas.
Funding: Klaus Tschira Foundation

Multimodality imaging
PI: Dr. M. Alkassar
Three-dimensional display of anatomical structures was used for planning of therapy. We established new three-dimensional display options with echocardiography, CT, and MRI which help to develop a realistic idea of heart and vessels. The use of such a display in the field of pediatric cardiology is investigated in various studies. We were able to prove an enormous advantage of 3D-heart models in the context of catheterizations. A following study currently investigates the benefit of 3D-imaging regarding the compensation of respiration and heartbeat. Another study investigates the advantages of 3D-models in the pre-procedural planning of surgical operations. Therefore we project very real-looking three-dimensional images of the heart with the help of a virtual reality glasses (VR) into the room. For a tactile perception, we also create three-dimensional life-sized pressure of the heart of silicone. The Division of Pediatric Cardiology is one of the leading international centers for the establishment and further development of multi-modal methods for the treatment of children with heart disease in Germany.

Interventional therapy
PI: Dr. T. Abu-Tair
To estimate risk and prognosis of patients, who underwent perforation and balloonvalvuloplasty of critical pulmonary valve stenosis and pulmonary valve atresia in infancy between 1996 and 2014, morphologic, hemodynamic und procedural data have been collected in a multicentric study. These data have been evaluated regarding prognostic impact at time of pulmonary valve replacement, surgical manipulation at the RVOT or RVOT-Stenting. Despite these over decades established and successful performed procedure there is still a lack of data regarding mid- and long-term-outcome. In addition, other interventional procedures to preserve ventricular function will be evaluated regarding risk-factors and long-term-outcome.

Pharmacological studies
PI: Prof. Dr. S. Dittrich, Dr. Martin Schöber
We completed the study "Effect and Safety of Treatment with ACE inhibitor enalapril and beta-blocker metoprolol on the onset of Left Ventricular Dysfunction in Duchenne Muscular Dystrophy", a long-going multicentric investigator-initiated pharmacology study in children and adolescents. The use of anti-congestive drugs in patients with Duchenne muscular dystrophy has now been included in the guideline recommendations.
Currently there is an ongoing Phase III study of pharmacotherapy in children: the panoramic study of Novartis for the use of a combination preparation LCZ696 (sacubitril / valsartan) for the treatment of heart failure

Teaching

The Division of Pediatric Cardiology takes part in the general teaching program of the Department of Pediatrics and Adolescent Medicine. Additionally, medical students are taught pediatric cardiology within an elective course on pediatrics. Furthermore, we offer the possibility to perform clinical electives in our Division. MD doctorates are supervised.

Selected publications

Dittrich S, Weise A, Cesnjevar R, et al. Association of Lymphatic Abnormalities with Early Complications after Fontan Operation. The Thoracic and cardiovascular surgeon. 2020

Herrmann H, Cabet E, Chevalier NR, et al. Dual Functional States of R406W-Desmin Assembly Complexes Cause Cardiomyopathy With Severe Intercalated Disc Derangement in Humans and in Knock-In Mice. Circulation 2020 Oct 7. doi: 10.1161 PMID: 33023321

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Söder S, Wällisch W, Dittrich S, et al. Three-Dimensional Rotational Angiography during Catheterization of Congenital Heart Disease A ten Years' experience at a single center. Sci Rep. 2020; 10: 6973.

Schöffl I, Ehrlich B, Stanger S, et al. Exercise Field Testing in Children: A New Approach for Age-Appropriate Evaluation of Cardiopulmonary Function. Pediatr Cardiol 2020.

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UNIVERSITY HOSPITAL

Department of Plastic and Hand Surgery

Chair of Plastic and Hand Surgery

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Research focus
- Biofabrication (SFB TRR225)
- Tissue engineering
- Interaction of regenerative strategies and tumor progression
- New imaging techniques in reconstructive surgery
- Clinical experimental research
- Clinical studies

Structure of the Department

Professorship: 1
Personnel: 29
- Doctors (of Medicine): 17
- Scientists: 7 (thereof funded externally: 7)
- Graduate students: 60

Clinical focus areas
- Reconstructive microsurgery
- Esthetic surgery
- Burn surgery
- Breast surgery
- Hand surgery
- Body contouring
- Lymphedema/lipedema
- Laser
- Hyperhidrosis

Research

Research interests of the Department of Plastic and Hand Surgery are the engineering of bioartificial tissue, tumor biology as well as clinical experimental research and clinical retrospective studies.

Biofabrication (SFB TRR225)
PI: Prof. Dr. R.E. Horch[1,2], Prof. Dr. A. Arkudas[1,2], PD Dr. A. Kengelbach-Weigand[2], Dr. D. Steiner[1]

1) Biofabrication of cellularized and AV loop vascularized tissue containers for the transplantation of drug-producing cells

This DFG funded project (SFB TRR225) targets the generation of a transplantable therapeutic tissue container for the treatment of autoimmune diseases or cancer

2) Using biofabrication, a 3D tumor model will be developed, serving for the investigation of different aspects of tumor progression in a controlled manner both *in vitro* and in the vascularized *in vivo* AV loop model. This project is DFG funded (SFB TRR 225)

Tissue engineering
PI: PI: Prof. Dr. R.E. Horch[1-11], Prof. Dr. A. Arkudas[1-10], PD Dr. A. Kengelbach-Weigand[7,8,11], Dr. D. Steiner[2,3], Dr. A. Cai[1,6], Dr. M. Hessenauer[4], Dr. W. Müller-Seubert[5,9,10]

1) Tissue engineering of skeletal muscle

The final aim of this project is the generation of axially vascularized, innervated skeletal muscle tissue

2) Tissue engineering of axially vascularized bone in a small animal model

The aim of this study is to generate axially vascularized bioartifical bone tissue using bioactive matrices in combination with endothelial cells (EC) and adipose derived stem cells (ADSC).

3) Investigation of the specific cell-cell interactions between ADSC and EC concerning osteogenic differentiation
4) Intravital microscopy in the AV loop model to understand the mechanisms of de novo tissue formation in the AV loop model, we developed a suitable chamber model which allows intravital microscopic evaluation
5) Ischemic tolerance of different tissues

By using the model of rat hindlimb amputation, extracorporeal perfusion, and replantation, we analyze and try to prolong the critical ischemia time of different tissues

6) Transplantation of whole muscle constructs in a novel rat model

A skeletal muscle is transplanted into a rat in an isolation chamber. Perfusion and functional analyses of the isolated muscle will be conducted

7) Differences in functional cell properties of ADSC affected by patient factors
8) Skin tissue engineering by the use of ADSC Current treatment options for chronic wounds will be optimized using growth factors and ADSC
9) Influence of irradiation on perfusion of random pattern flaps
10) Influence of stem cells on irradiated flaps

This project measures the influence of topically applied stem cells on perfusion of irradiated random pattern flaps

11) Therapeutic strategies for the treatment of irradiated skin

Interaction of regenerative strategies and tumor progression
PI: Prof. Dr. R.E. Horch[1-7], Prof. Dr. A. Arkudas[5-7], PD Dr. A. Kengelbach-Weigand[1-7], Dr. T. Hauck[5-7]

1) Effects of tumors on a developing blood vessel network

The goal of the project is the characterization of the influence of tumor cells on the development of a blood vessel network and the role of endothelial progenitor cells (EPC) in tumor associated angiogenesis

2) Tumor angiogenesis and vasculogenesis in breast cancer

This study investigates the effect of mammary carcinoma cells on the angiogenic properties of EPC

3) Paracrine and cell-cell interaction of ADSC and mammary epithelial cells in the focus of development of breast cancer

This study evaluates the influence of ADSC on the behavior of cells in the breast and breast cancer tissue

4) Significance of tumor-associated fat stem cells in breast cancer progression

The surrounding adipose tissue of mammary carcinomas is probably changed by the influence of the tumor and may play a role in tumor progression. This will be investigated by analyzing stem cells from tumor-associated adipose tissue compared to stem cells from healthy adipose tissue

5) Establishment of a novel *in vivo* tumor model for breast cancer

This study aims to develop an *in vivo* 3D tumor model in which individual aspects of tumor progression and tumor therapy can be examined in a controlled manner

6) The autotaxin-LPA axis in breast cancer

This *in vitro* study evaluates the interplay of LPA, Autotaxin, adipose tissue and different breast cancer subtypes and the effect of radiotherapy on ATX-LPA signaling in breast cancer

7) The effect of irradiation on lipotransfer and breast cancer

This study investigates the oncological safety of lipotransfer into irradiated mammary tissue based on *in vitro* experiments with human cell lines

New imaging techniques in reconstructive surgery
PI: Prof. Dr. R.E. Horch[1-6], Prof. Dr. A. Arkudas [2,5,6], PD Dr. I. Ludolph[1-4], Dr. T. Hauck[1]

1) Three dimensional perforator mapping by Cinematic rendering

The aim of this study is to assess the clinical value of Cinematic Rendering in abdominal-based autologous breast reconstruction

2) Intraoperative fluorescence imaging of tissue perfusion in free flap transplantation using the SPY Elite® system

To improve the knowledge of tissue perfusion in free tissue transfer and free flap autonomization in the long term follow-up, intraoperative fluorescence imaging of tissue perfusion using a laser camera was performed

3) Comparison of thermography, hyperspectral analysis and ICG-angiography in the perfusion analysis of free flaps for autologous breast reconstruction
4) Intraoperative perfusion of free flaps from the abdomen for autologous breast reconstruction is assessed by using thermography, hyperspectral analysis and ICG-angiography
5) ICG-angiography for analysis of the zonal perfusion of free flaps from the abdomen for autologous breast reconstruction

By using ICG-angiography intraoperatively, the zonal perfusion of DIEP/ms-TRAM flaps is analyzed to gain further insight in the vascular anatomy and the perforasome theory

6) Impact of CT angiography on perforator mapping in autologous breast reconstruction
7) Perfusion analysis of myocutaneous flaps using ICG-angiography

Clinical experimental research

PI: Prof. Dr. R.E. Horch[1-12], Prof. Dr. A. Arkudas[1-3, 4, 6, 7, 12], PD Dr. I. Ludolph[5, 8-11], Dr. A. Cai[6], Dr. J. Grüner[6,11], Dr. A. Geierlehner[1-3, 8], Dr. D. Steiner[3]

1) Assessment of blood flow characteristics in free flaps using Transit Time Flowmetry and microvascular angiography
2) Flow measurement of the arterial and venous vessels of free and local flaps
3) Blood flow measurement and proteome profiling of arteriovenous loops in free tissue transfer procedures
4) Flow coupler efficacy in DIEP/ms-TRAM flaps for autologous breast reconstruction
5) Impact of negative pressure wound therapy on skin perfusion
6) Perfusion analysis of the skin using thermography and hyperspectral analysis following negative pressure wound therapy in healthy volunteers
7) Prospective analysis of grip force in common hand conditions

This prospective study evaluates the effect of a surgical procedure on hand grip force

8) Evaluation of carpal instability regarding scapholunate ligament injuries

The aim of this study is to evaluate wrist mobility between carpal bones using CT analysis in order to invent new strategies to treat ligament injuries

9) Proteom profiling and immunohistochemical analysis of chronic wound during negative pressure wound therapy
10) Analysis of skin elasticity before and after body countering procedures
11) Influence of different silicone surface textures to prevent capsular fibrosis of the breast Capsular fibrosis represents a significant complication following implantation of silicone breast implants, necessitating further surgical intervention. Experimental in vitro studies are conducted to investigate diverse silicone surface textures and their influence on capsular fibrosis
12) Molecular and histological investigations in periimplant mamma tissue
13) Comparison of shoulder function of patients after muscle-sparing and complete latissimus dorsi harvest

The aim of this study is the evaluation of the relevance of muscle-sparing latissimus dorsi flap harvesting regarding shoulder functionality and strength

Clinical studies

PI: Prof. Dr. R.E. Horch[1-10], Prof. Dr. A. Arkudas[1-3,5], PD Dr. I. Ludolph[2-6], Dr. W. Müller-Seubert[8,9], Dr. T. Hauck[10], Dr. A. Cai[3], Dr. A. Geierlehner[5,6], Dr. M. Stumpfe[2], Dr. J. Grüner[4], N. Fritz[7]

1) Technical innovations to reduce complications rates in free DIEP/ms-TRAM flaps

This retrospective study investigates the application of ICG-angiography, coupler anastomoses, preoperative perforator mapping with CTA, and mesh implantation at the donor site and their influence on complication rates.

2) Investigation of laboratory results in body countering surgery

Analysis of laboratory results and their impact on the postoperative course in body contouring surgery following massive weight loss

3) Analysis of quality of life and physical activity of postbariatric patients

The impact of body contouring procedures on quality of life and physical activity of patients that have undergone massive weight loss is retrospectively analyzed

4) Negative pressure wound therapy (NPWT) in breast implant associated infections

In the study the effect of NPWT on reducing the bacterial load and number in breast implant associated infections is analyzed

5) Limb salvage procedure in immune-compromised patients with therapy resistant leg ulcers – The value of ultra-radical debridement and instillation negative pressure wound therapy
6) Negative pressure wound therapy in the treatment of chronic leg ulcers

Investigation of chronic wounds of the lower leg with regard to the use of negative pressure wound therapy and the defect reconstruction

7) Influence of k-wire transfixation on the proximalization of the first metacarpal after resection suspension interposition arthroplasty
8) Retrospective analysis of surgical therapy in cubital tunnel syndrome

In this study, outcomes and complications after partial medial epicondylectomy in cubital tunnel syndrome are analyzed

9) Dupuytren s disease

Retrospective analysis of severe, advanced and relapsing Dupuytrens disease with actual evaluation by DASH-Score. Evaluation of the Erlangen distraction device

10) The role of the pedicled gastrocnemius flap in covering defects in the knee and proximal lower leg area

This retrospective study evaluates the outcome of pedicled gastrocnemius flaps. The results are evaluated using a self-created and a validated questionnaire (Knee Outcome Survey)

Teaching

With compulsory and elective subjects, the Department of Plastic and Hand Surgery is involved in the curriculum-based teaching in medicine. In this context, besides a preclinical conjoint course together with the Institute of Anatomy, a microsurgical suture course is offered besides theoretical courses.
Furthermore, MD and PhD theses are supervised.

Selected publications

A. Kengelbach-Weigand, K. Tasbihi, P.L. Strissel, R. Schmid, J.M. Marques, J.P. Beier, M.W. Beckmann, R. Strick, R.E. Horch, A.M. Boos, Plasticity of patient-matched normal mammary epithelial cells is dependent on autologous adipose-derived stem cells, Sci Rep 9(1) (2019) 10722.

R. Schmid, S.K. Schmidt, J. Hazur, R. Detsch, E. Maurer, A.R. Boccaccini, J. Hauptstein, J. Tessmar, T. Blunk, S. Schrufer, D.W. Schubert, R.E. Horch, A.K. Bosserhoff, A. Arkudas, A. Kengelbach-Weigand, Comparison of Hydrogels for the Development of Well-Defined 3D Cancer Models of Breast Cancer and Melanoma, Cancers (Basel) 12(8) (2020).

R.E. Horch, I. Ludolph, A. Cai, K. Weber, R. Grutzmann, A. Arkudas, Interdisciplinary Surgical Approaches in Vaginal and Perineal Reconstruction of Advanced Rectal and Anal Female Cancer Patients, Front Oncol 10 (2020) 719.

D. Steiner, R.E. Horch, I. Ludolph, M. Schmitz, J.P. Beier, A. Arkudas, Interdisciplinary Treatment of Breast Cancer After Mastectomy With Autologous Breast Reconstruction Using Abdominal Free Flaps in a University Teaching Hospital-A Standardized and Safe Procedure, Front Oncol 10 (2020) 177.

A. Geierlehner, R.E. Horch, W. Muller-Seubert, A. Arkudas, I. Ludolph, Limb salvage procedure in immunocompromised patients with therapy-resistant leg ulcers-The value of ultra-radical debridement and instillation negative-pressure wound therapy, Int Wound J 17(5) (2020) 1496-1507.

International cooperation

Prof. S. Jiaming, Tongji Medical College, Huazhong University of Science and Technology, Wuhan: China

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Research focus
- Depressions
- Dementias
- Addiction disorders
- Clinical neurochemistry and neurochemical dementia diagnostics
- Health Services Research
- Clinical Sensory Perception
- Sensory perception
- Molecular psychiatry

Structure of the Chair

Professorships: 4
Personnel: 248
- Doctors (of Medicine): 36
- Scientists: 29 (thereof funded externally: 14)
- Graduate students: 83

Clinical focus areas
- Depression
- Memory disorders
- Dementia
- Schizophrenia
- Addiction
- Anxiety disorders

Research

Our research is based on a broad spectrum of methods, ranging from basic clinical research to clinical research and care research.

Depressions
Sphingolipids are essential components of the nerve cell membrane and regulate the flow of signals between neurons. We were able to further investigate the relationship between sphingolipids and affective disorders in translational preclinical and clinical studies.
Funding: DFG, BMBF, and IZKF
In a randomized-controlled multicenter study (StudieKuS) to investigate the efficacy of a Boulder Therapy intervention (BPT) in people with depression, BPT was shown to be significantly superior to the active control group and not inferior to Cognitive Behavioral Therapy, improvements are stable over at least 1 year, digitization of the manual was prepared. Funding: OH-DO-KWAN-Foundation

Dementias
In the context of clinically oriented basic research on dementias, further studies were performed to better understand β-amyloid metabolism and the involvement of systemic immunological processes. Thus, it was shown that astrocytes may not only be involved in the clearance of amyloid beta peptides (Aβ) in Alzheimer's disease (AD), but appear to produce N-terminally truncated Aβ (Aβn-x) independently of BACE1, which generates the N-Terminus of Aβ starting with Asp1 (Aβ1-x). A candidate protease for the generation and degradation of Aβn-x is cathepsin B (CatB), which could explain the opposite roles of astrocytes in AD. Cell culture experiments of our study indicated that non-lysosomal CatB mediated the production of Aβ2-x in astrocytes. However, the degradation of Aβ1-x seemed to be dependent on lysosomal CatB in H4 neuroglioma cells, but not in primary astrocytes. These findings highlight the importance of considering organelle targeting in drug development to promote Aβ degradation.
In another study, we investigated whether microvesicles in CSF reflect AD and thus may be suitable for dementia diagnostics. Flow cytometric analysis showed that the microvesicular content of tau protein and APP was significantly reduced in Alzheimer's patients compared with controls. The total number of microvesicles and the expression of other antigens did not differ between the cohorts.
Another BMBF-funded collaborative project ("NADIM") in cooperation with the companies INVIGATE GmbH, Quantum Analysis GmbH, Immunotools GmbH and Cytecs GmbH is pursuing the development of a diagnostic system based on the identification of phagocytes recirculating from the brain into the blood. It thus pursues a novel cell- and blood-based approach in dementia diagnostics. The core of the project is the detection of phagocytosed, intracellular biomarkers of neurodegeneration.
In the nationwide, multicenter RCT DemWG, the effect of a complex psychosocial intervention on hospital admissions, falls, cognitive abilities, quality of life, and psychological and behavioral problems in people with dementia and MCI in shared-housing arrangements (abWGs) is investigated. Here, the complex intervention consists of the three components A) advanced training of nursing and care staff in abWGs, B) advanced training of the responsible GPs and C) non-pharmacological, multimodal group intervention MAKS-mk+. Collaborating partners: Institute for Public Health and Nursing Research (IPP) at the University of Bremen. Funding: Innovation Fund of the G-BA.
In the five-year "Digital Dementia Registry Bavaria (digiDEM Bavaria), the long-term course of people with MCI and mild to moderate dementia is investigated since 2019. In addition, various digital support services are being provided. The project is a cooperation of several partners of FAU. Funding: Bavarian State Ministry of Health and Care. In the RCT "MAKS-s", the effects of a multimodal psychosocial training program specially developed for people with severe dementia are being investigated. Funding: GKV Spitzenverband.
In the RCT "Stoppt die Demenz", two computerized cognitive training programs for influencing MCI symptoms are being investigated. Cooperation partners: TH Nuremberg, genesis Systems gGmbH. Funding: Reinhard Frank Foundation.
In the observational study "Care4All (Ambient Assisted Living)" the use of a social assistance robot within a multimodal psychosocial group therapy for people with mild to moderate dementia is tested. The involvement of the therapy participants and therapists ensures a continuous expansion of the robot's functional range. Cooperation partners: HTW Dresden, Dresden University Hospital, Carus Consilium Dresden, Cognitec Systems GmbH and Cultus Dresden. Funding: European Regional Development Fund of the European Union.

Addiction disorders
The role of sphingolipids and their regulatory enzymes in the development of alcohol addiction was investigated in translational studies. A central role of ceramides in the brain could be demonstrated. In the emotional centers of the brain, such as the hippocampus and the amygdala, individual ceramides regulate not only alcohol consumption, but also behavior associated with anxiety and depression. Thereby, the local ceramide concentration is controlled by a large number of different enzymes. It could be shown that the activity of acid sphingomyelinase also plays an important role in the development of cocaine addiction in behavioral models in rats and primates. The changes indicate that lipid systems also exhibit a molecular plasticity in the development of addiction, as is typical for normal learning processes. Other enzymes involved in the development of addiction are the neutral and acidic ceramidase. A brain area-specific role in different learning processes could be demonstrated especially for the neutral ceramidase. Furthermore, it could be shown that the neutral ceramidase in the blood is a good predictor for the cognitive performance in rats and primates.
In further studies, the role of 2D: 4D finger lengths, the neuroimmune regulator TANK and the leptin or testosterone levels in the blood as risk factors for alcohol addiction could be confirmed and expanded. In addition, new pharmacotherapies were investigated in preclinical tests. Promising results were found in reducing the amount of alcohol drinking for the FKBP51 inhibitor SAFit2.
Funding: DFG

Clinical neurochemistry and neurochemical dementia diagnostics
The analysis of the cerebrospinal fluid (CSF) offers excellent diagnostic possibilities in a variety of neurological and psychiatric disorders, and the Laboratory for Clinical Neurochemistry and Neurochemically Dementia Diagnostics has been an internationally recognized center for neurochemical diagnostics of neurodegeneration for several years now. In spite of global pandemic issues, the Laboratory was 2020 successfully reaccredited and extended its ISO 15189 certificate for the next five years. The Lab continued its efforts in development and validation of new biomarkers of neurodegeneration, including candidate biomarkers from the blood. The Erlangen Score interpretation algorithm, developed in the

Laboratory and reported in details in the previous Report (2019), was further validated, and finally was included as a routine tool for diagnostic application. To that end, a close cooperation with the MIK-Team resulted in a full automatization of the algorithm on the lab's data processing platform (Swisslab). The Erlangen Score algorithm was also recommended in the official S1 guidelines "Lumbar puncture and Cerebrospinal Fluid Analysis" of the German Neurological Society (AWMF-Nr.: 030/141). Following this development, several centers in Germany decided to adopt the algorithm for their routine use. The head of the Laboratory continues his tasks as a member of the advisory board of the German Society of Clinical Neurochemistry and CSF Analysis (DGLN, e. V.), and the Board of the Society accepted our offer to organize the next Conference of the Society in Erlangen, which will be held in May 2021 (most probably as a virtual event). The Lab continues its coordination tasks in the international inter-center proficiency testing scheme for CSF biomarkers biobanking.

Health Services Research

In cooperation with the Interdisciplinary Pain Center, the care situation of headache patients in the long-term course is examined. The evaluation of the routine data contains courses over a period of 5 years. In cooperation with the MDK Bavaria, a representative study on the situation of informal caregivers was started in order to investigate not only the care needs but also the benefits of home care for the first time. Funding: Leifheit Foundation.

Clinical Sensory Perception

While sensory information such as touch, vision and hearing is normally primarily processed via the thalamus as the "gateway to consciousness", the olfactory system has a special feature: It partially projects directly into the limbic system without thalamic filtering. We make special use of this feature to investigate anhedonia, the inability to feel pleasure, by olfactory means.

Anhedonia can occur as a severe symptom in depression, and it further defines the subtype of melancholic depression. It has been shown that patients with melancholic depression have an altered olfactory experience (Clepce et al. 2010). In depressed patients, the limbic system shows morphological changes and it is thus also a key structure for the genesis of depression. With specific knowledge about the processing of olfactory information, a basis for the design of an odor-based anhedonia test will be formed.

Our completed study of 61 subjects clearly shows that memories can be effectively triggered by presentation of odors, and that these memories can be efficiently assessed in terms of hedonic value and intensity using our testing algorithm. We attributed the correlation of the hedonic value of an odor with the hedonic value of the memory elicited to a learned affective evaluation of an odor: If an odor is already positively occupied by experience, we also perceive it as more pleasant. For further validation, in an ongoing study depressed and anhedonic patients versus healthy control subjects will be tested with our olfactory anhedonia test. Anhedonia represents a cross-diagnosis phenomenon in psychiatric disorders. Thus, the olfactory approach of our test development could be potentially relevant for a variety of disorders.

Sensory perception

One focus of our work are multisensory integration studies with respect to food perception. Currently, we are working on the topic of olfactory-visual integration during food intake in different life stages within the BMBF cluster Enable. Here we investigate the influence of age on sensory integration processes, as well as the influence of a product label on sensory perception using functional imaging.

Olfactory-trigeminal interactions are of particular importance with regard to the masking of unpleasant odor impressions. In an fMRI experiment, we investigated the masking behavior of a eucalyptol-ammonia mixture. The aim was to mask the unpleasant ammonia odor using the fresh eucalyptol odor. It was established that the olfactory component of the ammonia could be masked, but the trigeminal component could not be masked. Trigeminal perception was actually enhanced by the addition of eucalyptol. This enhancement was also reflected in the activation of typical parts of the pain system of the human brain - the insula and the secondary somatosensory cortex.

We are also members of the Global Consortium for Chemosensory Research (GCCR), which is interested in the impact of SARS-CoV-2 infection on the chemical senses. A questionnaire was created to query the subjective assessment of the senses of smell and taste, as well as trigeminal perception during infection. It was found that SARS-CoV-2 infection leads to severe impairment of the senses of smell and taste, and that the loss of the senses of smell and taste during the pandemic should be understood as an alarming symptom of infection.

Molecular psychiatry

Synaptic transmission plays a key role in neuronal function. The release of neurotransmitter from presynapse depends on highly complex and dynamic interplay of proteins and lipids. The breakdown and dismantling of presynapse is the first hallmark in various neurodegenerative and neuropsychiatric conditions, indicating that presynapse represents the neuronal compartment with highest vulnerability to pathological insults. Over the past years, we investigated the molecular mechanism that control neurotransmitter release and contribute to presynapse integrity. In collaboration with M. Heine (Mainz) we demonstrated that naturally expressed splicing variants of presynaptic voltage gated calcium channels that differ in their anchoring to presynaptic scaffolds and lateral mobility within presynapse also decisively shape plasticity of neurotransmitter release. DFG FE1335/3

We discovered new role of presynaptic scaffolding protein CtBP1 in the retrieval of synaptic vesicles during compensatory endocytosis. DFG GRK2162, IZKF J74

We conducted further studies in the frame of the collaborative project GeNeRARe (German Network of RASopathy research). BMBF GeNeRARe

We described new function of scaffold protein Bassoon in the control of presynaptic protein homeostasis. Bassoon interacts with the core proteasome and via this interaction, it inhibits its catalytic activity. In collaboration with M. Friese (Hamburg) we demonstrated that proteasome activation and Bassoon inactivation are neuroprotective in an animal model of amyotrophic lateral sclerosis. DFG 1335/1

Teaching

The Department of Psychiatry and Psychotherapy participates with compulsory and elective subjects in the curricular teaching of Medicine and Logopedics. Particularly noteworthy here is the interdisciplinary teaching within the framework of the cross-sectional subjects EKM, Q9 (clinical pharmacology / pharmacotherapy) and Q10 (prevention and health promotion) and in the context of the compulsory elective subject of sexual medicine. Since 2019, the department offers an interproffessional seminar to teach taking a sexual anamnesis to students of medicine and psychology as well as nurses-to-be. The Department has further expanded the simulation program of patients. Students can practice acting in difficult situations with agitated, affective, rejecting and uncooperative patients. In addition, Objective Structured Clinical Examinations (OSCE) stations were developed to validate communication and investigation skills. Induced by the corona pandemic, the classical lecture has been replaced by online case discussions and blended learning. The bed-side teaching has also been shifted to the internet by replacing face to face examinations by video-calls.

Curricular teaching in Medical Psychology and Medical Sociology in the preclinical study section includes a basic lecture, a course and a seminar. During the reporting period, Erlangen's medical students achieved the rank 1 in the written part of the first section of the Medical Examination compared to all other German universities with the same examination format (multiple choice). Bachelor's and Master's theses as well as MD and PhD theses are supervised.

Selected publications

Baldeiras I, …, Lewczuk P. Erlangen Score as a tool to predict progression from mild cognitive impairment to dementia in Alzheimer's disease. Alzheimers Res Ther, 2019;11(1):2.

Zoicas, I., …, Kornhuber, J., (2020) Ceramides affect alcohol consumption, depressive-like and anxiety-like behavior in a brain region- and ceramide species-specific way in male mice. Addiction Biology 25: e12847.

Parma V et al. (2020) More than smell. COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. Chemical Senses 2020 Oct 9;45(7):609-622.

Kratzer, A., …, Graessel, E. (2020). The DemWG study: reducing the risk of hospitalisation through a complex intervention for people with dementia and mild cognitive impairment (MCI) in German shared-housing arrangements: study protocol of a prospective, mixed-methods, multicentre, cluster-randomised controlled trial. BMJ Open, 10(12), e041891.

Karg N, …, Luttenberger K. (2020) Bouldering psychotherapy is more effective in the treatment of depression than physical exercise alone: results of a multicentre randomised controlled intervention study. BMC Psychiatry. 12;20(1):116.

Ivanova D., …, Fejtova A. (2020). CtBP1-Mediated Membrane Fission Contributes to Effective Recycling of Synaptic Vesicles. Cell Rep 30, 2444-2459 e2447.

International cooperations

Prof. G. Schumann, Institute of Psychiatry Psychology and Neurology, King's College London, London: Großbritannien

Prof. M. Filip, Institute of Pharmacology, Polish Academy of Sciences, Krakow: Poland

Prof. M. Barros, Primate Center, University of Brasilia, Brasilia, Brasilien

Dr. Z. Hassan, Centre for Drug Research, Universiti Sains Malaysia, Penang: Malaysia

Prof. H. Zetterberg, Sahlgrenska Academy, Mölndal: Sweden

UNIVERSITY HOSPITAL

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Research Focus
- Prenatal risk factors for infant, child and adolescent development
- Long-term effects of early cardiac surgery on child and adolescent development
- Evaluation of therapeutic interventions and treatment success in adolescents with Anorexia nervosa
- Parental stress in child and adolescent psychiatric care
- Prenatal trauma and fetal programming in a mouse model

Structure of the Division

Professorships: 1
Personnel: 156
- Doctors (of Medicine): 27
- Scientists: 6 (thereof funded externally: 2)
- Graduate students: 10

Treatment units: 35 inpatient, 23 day patient; 15 day patient (in cooperation with Klinikum Fürth)

Clinical focus areas:
- Attention deficit/hyperactivity disorder (ADHD)
- Tic and obsessive-compulsive disorders
- Anxiety and depressive disorders
- Posttraumatic stress disorders
- Eating disorders
- Autism spectrum disorders
- Reduced intelligence with psychiatric comorbidity
- Regulation, feeding and behavior disorders in early childhood

Research

The aims of the scientific projects of our Division are to contribute to a better understanding of the developmental processes and the neurobiological basis of mental disorders in children and adolescents and to learn more about the underlying mechanisms of therapeutic interventions. The main topics addressed by the research unit (headed by PD Dr. Anna Eichler and Prof. Dr. O. Kratz) are described below.

Prenatal risk factors for infant, child and adolescent development
PI: A. Eichler
In the longitudinal FRANCES (Franconian Cognition and Emotion Studies) study, we are investigating the long-term consequences of prenatal risks (including alcohol, depression, stress) for child adjustment at ages 6-9 (study period 2012-2015) and 12-14 (study period 2019-2021) in cooperation with the Departments of Obstetrics and Gynecology and of Psychiatry and Psychotherapy. Developmental status is measured in a multilevel design in cognitive, emotional, and social outcomes: In addition to neuropsychological (including intelligence testing) and neurophysiological (including event-related brain electrical potentials) developmental measures, the focus is on neurobiological markers (including alcohol metabolites in neonatal meconium, cortisol concentrations in saliva and hair, high sensitive inflammatory markers in blood). Results to date have shown, among other things, that even subliminal 'non-visible' prenatal alcohol consumption affects child development, as evidenced by reduced cognitive performance, altered cortisol secretion, impaired brain electrical activity, and facial features. Child biomarkers of intrauterine alcohol exposure were superior in predictive power to pregnant women's self-reports in this regard. Prenatal depressive symptoms were associated with an irritated cortisol stress system and, in combination with low socioeconomic status and inconsistent parenting behavior with emotional and behavioral child problems. Also in cooperation with the Departments of Obstetrics and Gynecology and of Psychiatry and Psychotherapy, we are investigating the effects of an app- and mindfulness-based program during pregnancy - designed to reduce stress and substance use in the mother - on the one-year-old infant's ability to self-regulate and on broader developmental outcomes in a randomized controlled trial. The study is part of the IMAC-Mind research consortium, which bundles research projects on addiction prevention and addiction therapy in childhood and adolescence throughout Germany.
Funding: Else Kröner-Fresenius-Stiftung, BMBF

Long-term effects of early cardiac surgery on child and adolescent development
PI: A. Eichler
In cooperation with the Department of Pediatric Cardiac Surgery at the University Hospital Erlangen, we study a sample of children who underwent surgery for ventricular septal defect (VSD) before their 3rd birthday and compare them with a non-affected control group. Differences in language development and anxiety symptoms at primary school age (6-9 years) were evident. However, the developmental differences only were present if the mother reported own anxiety symptoms (risk factor) and could be leveled out if the mother showed proactive parenting behavior (protective factor), respectively. Currently, the children are re-surveyed in early adolescence (12-14 years) to answer the question of child developmental trajectories and associated risk and protective factors.
Funding: Deutsche Stiftung für Herzforschung

Multimodal evaluation of therapeutic interventions and treatment success in adolescents with Anorexia nervosa and evaluation of an intervention to reduce body dissatisfaction
PI: S. Horndasch und V. Stonawski
The FRALANA (FRAnconian Longitudinal Study of Anorexia Nervosa in Adolescents) focuses on two aspects to improve the treatment of eating disorders in adolescents: (1) A basic module investigates predictors for successful inpatient treatment of Anorexia nervosa. Somatic, neurobiological, neurophysiological, psychosocial and behavioral parameters will be examined. (2) In the intervention module, an eye tracking based body exposure intervention aimed at the reduction of body dissatisfaction is evaluated. Attentional bias via eye tracking and stress profiles via salivary markers will help to reveal potential underlying mechanisms. Clinical and healthy control groups will be included to investigate disease-specific aspects. The results will help to identify predictors for treatment success and develop novel prevention and intervention programs.

Parental stress in child and adolescent psychiatric care
PI: V. Irlbauer-Müller
Emotional and behavioral problems in children and adolescents are associated with increased parental stress. Parental stress negatively affects parenting behavior, increases the likelihood of dysfunctional parent-child interaction, and thus influences the image the children have of their parents. Our previous research has shown, first, that parents searching for treatment of their children in our clinic exhibit high levels of parental stress and, second, that these levels influence the parental perception and description of child symptomatology. In ongoing studies, we are assessing the effect of parent-centered interventions (including Parent Resource Group and fathers' group) on parental distress and children's parenting perceptions. In a piloted evaluation of our Parent Resource Group developed in 2017, we found evidence of parental stress reduction as well as increased parenting skills in parent-child interactions.

Therapeutic interventions – Clinical effects and underlying mechanisms
PI: O. Kratz
Neurofeedback involves a brain-computer interface which enables to learn self-control over specific aspects of neural (EEG) activity. While our earlier multi-center studies demonstrated the clinical effectiveness of neurofeedback for children with ADHD, our meta-analysis indicated in addition that neurofeedback effects (compared to non-active control treatments) lasted longer after the end of treatment. Our further studies („short-term studies" with less training session) aimed at how to optimize neurofeedback training and learn more about the mechanisms underlying a successful training („neuroplasticity").
Special light concepts are used to stabilize circadian rhythms in mental disorders. In our light

laboratory, increased attentional performance under blue vs. red light was observed in healthy adolescents and first indications of improved sleep quality were obtained (actigraphy measures) after red vs. blue light. Evaluation of the efficacy of light exposure in adolescents with clinically relevant emotional and behavioral symptoms are ongoing.
The question of feasibility and efficacy of the QTRobot therapy robot for the treatment of child and adolescent psychiatric patients compared to healthy controls in two training conditions (therapist vs. robot) is the subject of our QT-Study. Here, we focus on children aged 6-10 years with autism spectrum disorders and social anxiety. In these patient groups, interpersonal contact with adults and peers is challenging. We are investigating how QTRobot can assist in learning emotional and social skills in a playful and simple way.

Prenatal trauma and fetal programming in a mouse model
PI: Dr. A. Plank
We are investigating the molecular, neuroendocrine and behavioral effects of prenatal trauma in a mouse model. Here, we are particularly interested in temporal aspects and underlying mechanisms of action. Prenatally traumatized pups exhibit reduced body weight, increased anxiety behavior, and increased HPA axis activity. Adult prenatally traumatized animals show altered expression and promoter-methylation of Crhr1 and Fkbp5 in the dorsal hippocampus. In summary, our results support the hypothesis that prenatal trauma has long-term effects on neuroendocrine aspects and anxiety behavior through epigenetic mechanisms and altered expression regulation of key stress system genes.

Teaching

The Division of Child and Adolescent Mental Health is involved in compulsory and elective courses in the curriculum of the degree program human medicine, logopedics and psychology. Particularly noteworthy is the creation of patient video recordings - incorporating parent and therapist reports - for student courses (*Hospideo*-Project; funding: BMBF 'QuiS Digitalisierung in der Lehre' & FAU 'Innovationsfonds Lehre').
MD thesis as well as Bachelor's and Master's thesis (mainly in psychology) are supervised.

Selected publications

Eichler, A., Köhler-Jonas, N., Stonawski, V., Purbojo, A., Moll, G. H., Heinrich, H., . . . Kratz, O. (2019). Child neurodevelopment and mental health after surgical ventricular septal defect repair: risk and protective factors. Dev Med Child Neurol, 61(2), 152-160. doi:10.1111/dmcn.13992

Grimm, J., Stemmler, M., Golub, Y., Schwenke, E., Goecke, T. W., Fasching, P. A., . . . Eichler, A. (2020). The association between prenatal alcohol consumption and preschool child stress system disturbance. Dev Psychobiol
doi:10.1002/dev.22038

Horndasch, S., Oschmann, S., Graap, H., Heinrich, H., Moll, G., & Kratz, O. (2020). Attention towards food: Conflicting mechanisms in anorexia nervosa. Appetite, 154, 104800.
doi:10.1016/j.appet.2020.104800

Horndasch S., Roesch, J., Kratz, O., Vogel, A., Heinric,h H., Graap, H., Moll, G.H., Dörfler, A., Forster, C. (2020). Neural mechanisms of perceptive and affective processing of body stimuli in Anorexia nervosa – are there developmental effects? Psychiatry Research: Neuroimaging, 286:112853.
https://doi.org/10.1016/j.psychres.2020.112853.

Stonawski, V., Frey, S., Golub, Y., Rohleder, N., Kriebel, J., Goecke, T. W., . . . Eichler, A. (2019). Associations of prenatal depressive symptoms with DNA methylation of HPA axis-related genes and diurnal cortisol profiles in primary school-aged children. Dev Psychopathol, 31(2), 419-431.
doi:10.1017/s0954579418000056

Studer, P., Brucker, J. M., Haag, C., Van Doren, J., Moll, G. H., Heinrich, H., & Kratz, O. (2019). Effects of blue- and red-enriched light on attention and sleep in typically developing adolescents. Physiol Behav, 199, 11-19.
doi:10.1016/j.physbeh.2018.10.015

International cooperations
Prof. Ciara McCabe, Neuroimaging of Reward Group, University of Reading, School of Psychology and Clinical Language Sciences, Reading, UK,

Dr. Aida Nazarikhorram, LuxAI S.A., Luxemburg, Luxemburg

UNIVERSITY HOSPITAL

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Research focus
- Psycho-oncology
- Migration and mental health
- Transplantation medicine
- Somatoform disorders and the persistent somatoform pain disorder
- Eating disorders, obesity
- Work ability of medical staff
- Early intervention in the workplace
- Biological psychotherapy research

Structure of the Division

Professorship: 1
Personnel: 69
- Doctors (of Medicine): 12
- Scientists: 5 (thereof funded externally: 3)
- Graduate students: 26

Clinical focus areas
- Eating disorders
- Obesity
- Somatoform disorders including persistent pain disorder
- Posttraumatic stress disorders
- Psycho-oncology

Research

The research of the Division of Psychosomatic Medicine and Psychotherapy focuses on psycho-oncology, migration and mental health, transplantation medicine, somatoform disorders (persistent somatoform pain disorders), eating disorders, obesity, work ability of medical staff, early intervention in the workplace, and biological psychotherapy research.

Psycho-oncology
PI: Prof. Dr. Y. Erim, PD Dr. E. Morawa, M.Sc. C. Schug, Dipl.-Psych. M. Lieb
Current research projects:
- Multicentre randomised controlled intervention study on web-based mindfulness and skill-based stress reduction for patients with cancer (REDUCT) Cooperation project with the LVR Clinic Essen; funding: BMBF
- Psycho-oncological care study to examine the potential target group and their satisfaction with the web-based skills and mindfulness training "Make It".
- Risk-adapted aftercare for uveal melanomas Cooperation project with the West German Tumour Centre Essen; Funding: German Cancer Aid
- Disease concepts, coping with illness and unmet needs in oncological patients with special consideration of the migration background Funding: ELAN program
- Resilience and fear of prognosis in female patients seeking a second opinion (in cooperation with the Department of Obstetrics and Gynecology, Prof. Dr. M. Lux)
- Implementation of a regular paper-screening and a taxonomy of psychooncological interventions in the psycho-oncology services.

Furthermore, the doctoral thesis on the construction and validation of a questionnaire on patient competence in coping with cancer was completed and published.

Migration and mental health
PI: Prof. Dr. Y. Erim, PD Dr. E. Morawa, M.Sc. A. Borho
Considering the demographic development in Germany showing a continuous increase of persons with a migrant background (in 2019 26% of the total population), research is indicated not only on specific burdens, but also on resources of this group, and since November especially of people with a refugee background. Prof. Erim has published a special issue on flight and migration in the Journal of Psychosomatic Research. During the reporting period, two doctoral theses on traumatic experiences, complaints and coping with illness among Syrian refugees and the intercultural opening of hospitals and rehabilitation facilities for psychosomatic medicine and psychotherapy in Bavaria were completed and published. The current research projects deal with health services research. These include a study on the effectiveness of (partially) inpatient psychosomatic treatment for patients with and without a migration background and an ELAN-funded study on the mental health and posttraumatic stress disorders of Arabic-speaking asylum seekers. The Department of Psychosomatic Medicine and Psychotherapy is also investigating verbal violence in institutions towards migrants and refugees in a project funded by the Emerging Fields Initiative (EFI) of FAU and the STAEDTLER Foundation in cooperation with the Centre for Area Studies (Prof. D. P. Bendel), the Chair of Romance Language Philology (Prof. Dr. S. Jansen) and the Chair of Health Psychology (Prof. Dr. N. Rohleder).

Transplantation medicine
PI: Prof. Dr. Y. Erim, Dipl.-Psych. M. Lieb
In cooperation with the Department of Medicine 4, the predictors of adherence after renal transplantation were examined. Based on the results of this study which analyzed patient reported outcomes as well as cognitive tests, a training to optimize the adherence and health behavior was developed and manualized. Within the framework of the research group Emerging Fields Initiative (EFI), a follow-up study of living kidney donors was conducted with particular emphasis on the perceived autonomy as well as fatigue complaints. Three doctoral projects were finished and published during the reporting period.

Somatoform disorders and the persistent somatoform pain disorder
PI: Prof. Dr. Y. Erim
In the etiology of persistent somatoform pain disorder, early childhood adversities, an uncertain binding style, and altered cerebral activations (dysfunctional processing of pain and distress) are postulated as important factors and investigated in this study in cooperation with the Department of Neuroradiology (Prof. Dr. A. Dörfler). In addition to psychometric measurements, neuroimaging techniques are used. Two doctoral theses have been published and are nearing completion.

Eating disorders, obesity
PI: Prof. Dr. Y. Erim, Johannes Krehbiel, PD Dr. G. Paslakis
Within the framework of two doctoral theses (one was already completed during the reporting period), the Approach-Avoidance Task (AAT) paradigm was used to investigate the approach-avoidance behaviour towards food in patients with eating disorders in comparison to a healthy and obese control group. In the process, images of high-calorie as well as low-calorie foods are pulled or pushed away. The study aims to create an innovative implicit therapy component. Besides, a study on eating disorders is carried out using a basic research approach. In a prospective, randomized, double-blind, placebo-controlled clinical trial, the effect of substitution with an estrogen-progestin combination in adult women with anorexia nervosa is investigated.

Work ability of medical staff
PI: Prof. Dr. Y. Erim, PD Dr. E. Morawa, PD Dr. C. Rhein, M.Sc. C. Schug, Dipl.-Psych. M. Lieb, M.Sc. A. Borho
The VOICE study, funded by the BMBF as part of the National Research Network University Medicine (NUM) and carried out as a joint project by the university hospitals of Erlangen, Bonn, Ulm, Cologne and Dresden, aims to identify specific stresses and problems in the context of the COVID 19 crisis as well as sources of personal resilience in the structural, social and spiritual spheres among employees in the health sector and to investigate any resulting stress symptoms such as sleep disorders, but also indications of traumatisation, depression, and anxiety disorders. In addition, work conditions as well as aspects of work-life balance and resources will be surveyed. Based on the data, possible connections between stress/resources and

mental health/quality of life as well as possible differences between genders/ specialties/ settings are to be uncovered. Furthermore, protective and risk factors of mental health as well as high-risk groups including their frequency and composition (age, gender, occupational group, etc.) are to be identified and typical courses of coping processes are to be examined. The first two survey waves (T1: April to July 2020, N = 8071 and T2: November 2020 to January 2021, N = approx. 7200) have already taken place in the reporting period. Depending on the further course of the pandemic, additional measurements may also take place.
As an extension of the VOICE study, the STRESS-MONITOR study, funded by the Bavarian State Ministry of Science and Art, is currently being conducted. The study is to develop an early warning system that indicates overload of medical care staff at an early stage and is based on subjective (psychometric recording of potential workplace-related risk factors and resources) and objective parameters (heart rate variability and stress parameters).

Early intervention in the workplace
PI: Prof. Dr. Y. Erim, M.Sc. S. Hondong
The BMBF-funded Germany-wide randomised and controlled study on the effectiveness of psychosomatic consultation hours in the workplace is being conducted in cooperation with the University Hospital Ulm and other partners. The aim of the study is to ensure rapid and professional diagnosis and psychotherapeutic treatment of psychologically stressed employees directly in the company through the psychosomatic consultation hour and to test the effectiveness of the service.

Teaching

The Department of Psychosomatic Medicine and Psychotherapy is intensively involved in curricular teaching in medical studies, e.g. within the framework of the cross-sectional subject Q 14 together with the Department of Anaesthesiology and the Department of Neurology as well as in the course "Introduction to Clinical Medicine (EKM)". The obligatory subject of psychosomatics in medical studies consists of a main lecture and a practical course in small groups, in which simulation patients with standardized practice cases are used. Students can also take part in the elective subjects "Application-oriented introduction to psychosomatic research for medical students" and "Neurobiological basis of stress-induced disorders for medical students". As part of the Medical Process Management course, the Department of Psychosomatic Medicine and Psychotherapy is already represented in the first semester with a seminar on "Communication and Cooperation Aspects in the Health System". The Department offers a teaching export for the Master's program in Psychology. Advanced training for psychological psychotherapists-in-training is also provided. Master's theses and medical doctorates are supervised.

Selected publications
Aderhold C, Morawa E, Paslakis G, Erim Y. Entwicklung und Validierung eines Fragebogens zur Patientenkompetenz im Umgang mit einer Krebserkrankung (PUK). Z Psychosom Med Psychother. 2019 Sep;65(3):239-256.

Kobel F, Morawa E, Erim Y: Effectiveness of inpatient psychotherapy for patients with and without migratory background: Do they benefit equally? Front Psychiatry. 2020; 11:542.

Lieb M, Tagay S, Breidenstein A, Hepp T, Le Guin CHD, Scheel J, Lohmann DR, Bornfeld N, Teufel M, Erim Y. Psychosocial impact of prognostic genetic testing in uveal melanoma patients: a controlled prospective clinical observational study.BMC Psychol. 2020;8(1):8.

Lieb M, Hepp T, Schiffer M, Opgenoorth M, Erim Y. Accuracy and concordance of measurement methods to assess non-adherence after renal transplantation - a prospective study. BMC Nephrol. 2020;21(1):114.

Borho A, Viazminsky A, Morawa E, Schmitt GM, Georgiadou E, Erim Y. The prevalence and risk factors for mental distress among Syrian refugees in Germany: a register-based follow-up study. BMC Psychiatry. 2020;20(1):362.

Meyer E, Morawa E, Nacak Y, Rösch J, Doerfler A, Forster C, Erim Y. Insular Cortical Thickness in Patients With Somato-form Pain Disorder: Are There Associations With Symptom Severity and Childhood Trauma? Front Psychiatry. 2020;11:497100.

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Research focus
- Clinical trials
- Clinical trials office
- Radiation biology
- Physical aspects of radiation oncology
- Radiation immunobiology
- Translational radiobiology

Structure of the Department

Professorships: 2
Personnel: 140
- Doctors (of Medicine): 24
- Scientists: 29 (thereof funded externally: 11)
- Graduate students: 50

Clinical focus areas
- Percutaneous radiotherapy
- Treatment planning
- Image guided radiotherapy (IGRT)
- 3D conformal radiotherapy
- Intensity modulated radiotherapy (IMRT
- Intensity modulated arc therapy (VMAT)
- Stereotactic body radiation therapy (SBRT)
- Whole-skin- and whole-body-irradiation
- Brachytherapy
- Intensity modulated brachytherapy (IMBT)
- Image guided brachytherapy (IGBT)
- Deep regional hyperthermia with MR-Thermometry
- Local hyperthermia for the treatment of superficial tumors
- Radio-chemo-therapy
- Radio-immuno-therapy
- Low dose radiation therapy (LDRT)

Research

Clinical, biological, immunological as well as physical aspects of radiation oncology are scientifically analyzed. Clinical aspects of radiation oncology are predominantly examined within phase I, II, and III trials. This takes place on the ward, in the outpatient department, the therapeutics department (including brachytherapy) as well as the treatment planning department and hyperthermia unit. Coordination of the clinical trials is carried out by the in-house clinical trials office. Translational and basic radio(immune)-biological research is carried out by two groups, the classical radiation biology group and the radiation immune biology group. The Medical Radiation Physics group has the main scientific focus in respiratory and general organ motion during radiation therapy. In addition, the group is responsible for all medical physics duties of clinical radiation therapy (including control of brachytherapy implants).

Clinical trials
PI: Prof. Dr. R. Fietkau, Prof. Dr. U.S. Gaipl, PD Dr. M. Haderlein, PD Dr. M. Hecht, Dr. G. Lahmer, Prof. Dr. O. Ott, PD Dr. S. Semrau, Prof. Dr. V. Strnad
Phase-III multicenter trials:
1. First-line treatment of locally advanced HNSCC with double checkpoint blockade and radiotherapy dependent on intratumoral CD8+ T cell infiltration (CheckRad-CD8) - IIT
Funding: AstraZeneca GmbH
2. Preoperative radiochemotherapy and adjuvant chemotherapy with 5-fluorouracil versus preoperative radio-chemotherapy and adjuvant chemotherapy with 5-fluorouracil combined with oxaliplatin in patients with locally advanced UICC stage II and III rectal cancer (CAO/ARO/AIO-04) Funding: German Cancer Aid
3. Comparison of partial breast interstitial brachytherapy with external whole breast beam radiotherapy in patients with low risk invasive and in situ breast carcinomas (APBI-III)
Funding: German Cancer Aid
4. Salvage Brachytherapy and Hyperthermia for Recurrent H&N-tumors (HyBT-H&N)
5. Pancreatic carcinoma: chemoradiation compared with chemotherapy alone after induction chemotherapy (CONKO-007)
Funding: German Cancer Aid
6. Effects of deep regional hyperthermia in patients with anal carcinoma treated by standard radiochemotherapy (HYCAN)
7. Cetuximab in combination with platinum-based chemotherapy or radiotherapy in patients with recurrent and/or metastatic SSCHN in clinical routine (SOCCER)
Funding: Merck Serono GmbH Phase-II trials:
1. Randomized phase II study of immune stimulation with Pembrolizumab and radiotherapy in second line therapy of metastatic head and neck squamous cell carcinoma (IMPORTANCE), IIT Funding: MSD
2. PDR/HDR interstitial brachytherapy alone in patients with pT1/pT2 pN0 breast carcinomas after breast conserving surgery (APBI-IV)
3. 3D conformal, external partial breast irradiation in patients with pT1/2 pN0 breast carcinomas after breast conserving surgery (APBI-V)
4. Neoadjuvant chemoradiation with 5-FU (or capecitabine) and oxaliplatin combined with deep regional hyperthermia in locally advanced or recurrent rectal cancer (HyRec)
5. Enhancement of neurocognitive functions by hippocampal sparing radiotherapy (HIPPOSPARE 01)
6. Efficacy of dose intensified radiotherapy of spinal metastases by hypofractionated radiation and IGRT hfSRT mediated boost (SPIN-MET)
7. Salvage brachytherapy and interstitial hyperthermia for locally recurrent prostate carcinoma following radiation therapy (Prostata-BT-HT)
8. De-intensification of postoperative radiotherapy in selected patients with head and neck cancer (DIREKHT)
9. Investigation of the timely-coordinated therapy of patients with metastatic cancer by radiotherapy together with immune checkpoint inhibition (ST-ICI)
10. Analysis of CMV infections in patients with brain tumors or brain metastases during and after radio(Chemo)therapy (GLIO-CMV-01)
11. Immunophenotyping from blood of patients with malignant gliomas (IMMO-GLIO-01)
12. Immunophenotyping from blood of patients suffering from chronic degenerating joint diseases and receiving LDRT (IMMO-LDRT-01)
Observational trials:
1. Efficacy and Safety of Fractionated Stereotactic Radiation Therapy versus Single Fraction Stereotactic Radiosurgery for Large Brain Metastases (FSRT-Trial)
The Department of Radiation Oncology is participating in numerous externally led phase-I-III trials around the globe.

Clinical trials office
PI: Dr. S. Rutzner, Dr. A. Kallies, PD Dr. M. Hecht
The clinical-trial office is responsible for centrally coordinating all clinical trials, including:
1. Planning, organizing, leading, and controlling of clinical trials (IIT and as participating center)
2. Organization of meetings and international training courses
3. Scientific research

Radiation biology
PI: Prof. Dr. L. Distel
We analyse the individually different radiation sensitivity of normal tissue is the most important factor for the dose-limiting occurrence of therapy-related side effects. With different institutions the radiosensitivity in rare diseases is studied. Today the importance of tumor infiltrating lymphocytes for the efficacy of radiotherapy is still largely unknown. In a joint project with the Institute of Pathology, the importance of CD4, CD8, B cells, macrophages and the influence of regulatory T cells is studied in patients with head and neck tumors, gastric carcinomas and rectal carcinomas as well as glioblastomas. The non-professional phagocytosis of tumor and normal tissue cells and its mechanism will be studied as well as its prognostic significance in tumor diseases. In addition the interaction of ionizing radiation and kinase inhibitors in tumor and normal tissue cells will be studied.

Physical aspects of radiation oncology
PI: Prof. Dr. C. Bert
1. Verification of interstitial brachytherapy by an electromagnetic tracking system, EMT-based CT estimation. Funding: Elekta
2. MR-based treatment planning – optimization of sequence parameters, establishing MR-scans in the patient specific immobilization device (mask), quality assurance
3. Development of a digital twin for the medical devices network of radiation oncology. Funding: StMWi, Bayern
4. Optimization of the medical physics quality assurance methods for 4DCT, total skin irradiation, surface guided radiation therapy, risk management

Interdisciplinary workgroup Radiomics and Artificial Intelligence
PI: Dr. F. Putz, Prof. Dr. C. Bert, PD Dr.-Ing. B. Frey
The main emphasis of the Working group Radiomics and Artificial Intelligence in Radiooncology is to gain novel insights into the spatiotemporal dissemination of malignant tumors and to enable spatial predictions by large-scale analyses of imaging studies in order to improve and individualize radiotherapy target volume design and prescription dose distribution. The group uses radiomics and deep learning-based methods to enable imaging-based predictions and integration of imaging with non-imaging biomarkers to guide optimal treatment selection in radiotherapy. Moreover, the working group evaluates novel image informatics methods, like deep learning-based auto-segmentation, in their potential to improve and evolve current Radiooncologic treatment concepts.

Translational Radiobiology
PI: Prof. Dr. U. Gaipl, PD Dr.-Ing. B. Frey
Connections between local and systemic, immune-mediated effects of ionizing radiation alone and in combination with immunotherapy (vaccination, immune checkpoint blockade and clinical hyperthermia) and the underlying immune mechanisms are examined. A further research aim is the analysis of osteoimmunlogical effects of low dose radiation (X-Ray and radon radiation). Moreover, detailed immunomonitoring of radiation-exposed patients is performed in the framework of clinical trials (IMPORTANCE, CheckRadCD8, IMMO-LDRT, IMMO-GLIO, CONKO, GLIO-CMV, DI-REKHT, ST-ICI, RAD-ON02) and respective biomaterial is stored in the in-house biobank.
The following third-party supported projects are currently handled:
1. Modulation of inflammation and genetic risks of dense ionizing radiation
Funding: BMBF, GREWISalpha network
2. Impact and mechanisms of PD-L1, PD-L2 and EGF-R expression on glioma cells following radiochemotherapy and its consequences for combination with vaccination and PD-1 inhibition Funding: DFG
3. Multi-scale-analyses of deep regional hyperthermia as a novel and additive tumor treatment – Microthermia
Funding: Bavarian Research Foundation
4. RAD-ON02 trial: Determination of immunologic and pain relieving effects of radon spa therapy in patients with musculoskeletal disorders Funding: Bavarian State Ministry of Health and Care
5. Creation of advanced cancer treatment planning to boost the effect of radiotherapy by combining with hyperthermia, heating the tumor, Hyperboost Funding: European Commision, ITN-ETN
6. Fine-tuners of the adaptive immune response, FAIR GRK 2599, Funding: DFG

Physicists of our Department together with colleagues from HNO discuss together the treatment regime of patients and common clinical investigative trials. The translational and interdisciplinary examination of the therapy plays a major role in the scientific actions of the Department.

Translational Immunoncology
PI: PD Dr. M. Hecht
The research group investigates immunemodulatory effects of radiotherapy in combination with immune checkpoint inhibitors. Both local and systemic immunological effects of radiotherapy are investigated, which may improve the therapeutic response to immune checkpoint inhibitors. In addition, prognostic and predictive markers will be identified to enable patient selection for future clinical radio-immunological trial designs. Another focus of the group is on direct radiosensitizing effects of targeted tumor therapeutics that can enhance the efficacy of radiation treatment and the underlying mechanisms in DNA damage repair.

Teaching

Radiation Clinic organizes the cross-sectional course 11, Imaging Techniques, Radiation Treatment and Radiation Protection. In the practical course, the new online course Conrad was introduced. In cross-sectional course 6, the Radiation Clinic organizes the interdisciplinary lecture series. As part of this course, students work on an online module, which was partly developed by employees of the Radiation Clinic for the Virtual University of Bavaria. Here, patient examples are used to demonstrate the interdisciplinary approach in oncology. A radiation protection course with practical training for PJ students under recognition of the Bavarian Medical Association is held twice a year. An accompanying teaching concept is offered for PJ students. The lecture series "Prevention, Diagnosis, Therapy and Aftercare of Malignant Diseases" is offered for students of the Medical Process Management program. The practical and theoretical training of Bachelor and Master students takes place within the basic training ”Infections Immunology” and the specialization module ”Immunobiology”. In addition, the department offers interdisciplinary courses for students of physics, medical technology, molecular medicine, medicine, and natural sciences. Students have the opportunity to work on the Bachelor’s or Master’s theses and graduates are supervised during their PhD and MD projects, all embedded in the research focus of our department. Laboratory rotations are offered for students of GK 2599 (compare own report). In addition, the department offers interdisciplinary courses for students of physics, medical technology, molecular medicine, medicine, and natural sciences.

Selected publications

Sun R, Sundahl N, Hecht M, …, Deutsch E. Radiomics to predict outcomes and abscopal response of patients with cancer treated with immunotherapy combined with radiotherapy using a validated signature of CD8 cells. J Immunother Cancer. 2020 Nov;8(2):e001429.

Goerig NL, Frey B, Korn K, …, Gaipl US*, Fietkau R* (*equal contribution). Early Mortality of Brain Cancer Patients and its Connection to Cytomegalovirus Reactivation During Radiochemotherapy. Clin Cancer Res. 2020 Jul 1;26(13):3259-3270

Fietkau R, Hecht M, Hofner B, …, Balermpas P; PacCis-Study Group. Randomized phase-III-trial of concurrent chemoradiation for locally advanced head and neck cancer comparing dose reduced radiotherapy with paclitaxel/ cisplatin to standard radiotherapy with fluorouracil/cisplatin: The PacCis-trial. Radiother Oncol. 2020 Mar;144:209-217. doi: 10.1016/j.radonc.2020.01.016.

Schnellhardt S, Erber R, Büttner-Herold M, …, Distel L. Accelerated Partial Breast Irradiation: Macrophage Polarisation Shift Classification Identifies High-Risk Tumours in Early Hormone Receptor-Positive Breast Cancer. Cancers (Basel). 2020 Feb 14;12(2):446. doi: 10.3390/cancers12020446. PMID: 32075091; PMCID: PMC7072550.

International cooperations
Dr. K. Luminczky, Prof. G. Safrany, Frédéric Joliot-Curie National Research Institute for Radiobiology and Radiohygiene (NRIRR), Budapest: Hungary,

Prof. Dr. C. Polgár, Center of Radiotherapy, National Institute of Oncology, Budapest: Hungary,

Prof. Dr. Eric Deutsch, Department Radiotherapy, Gustave Roussy Cancer Campus, Villejuif Cedex: France,

Dr. C. Badie, Public Health England, Centre for Radiation, Chemical & Environmental Hazards Didcot: UK

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Chair of Surgery

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Research focus
- Evaluation of prognosis of gastrointestinal tumors
- Randomized trials for gastrointestinal tumors
- Outcomes research of complex surgery with hospital discharge data
- Pathophysiologic role of vascular effects of IFN-γ in gastrointestinal diseases
- Tumor-micromilieu induced plasticity of tumor endothelial cells in colorectal carcinoma
- Genome editing of pancreatic tumor models
- Organoid models in pancreatic cancer
- Immunepathophysiology of acute (sepsis) and chronic (colitis) inflammation
- Immunephenotyping and liquid biopsy analysis of gastrointestinal tumors

Structure of the Chair

Professorships: 4
Personnel: 308
- Doctors (of Medicine): 38
- Scientists: 10 (thereof funded externally: 6)
- Graduate students: 44

Clinical focus areas
- Oncological surgery
- Surgery of the gastrointestinal tract
- Metabolic and bariatric surgery
- Endocrinological surgery
- Minimally invasive surgery
- Transplantation
- Outpatient surgery
- Surgical emergency

Research

Clinical research at the Department of Surgery mainly consists of the clinical cancer registry, randomized trials of gastrointestinal tumors and evaluation of nationwide hospital discharge data. The translational research is focused on colorectal cancers/inflammatory bowel diseases and pancreatic cancer. Groups of investigators focusing on tumor micromilieu and sepsis are connecting the main research topics.

Evaluation of prognosis of gastrointestinal tumors
PI: Prof. Dr. R. Grützmann, Prof. Dr. S. Merkel
Since 1978, a clinical cancer registry has been prospectively maintained for organ specific tumor documentation. At present, more than 30,000 patients are registered. Main foci are on colorectal cancer with over 13,000 and pancreatic cancer with over 2,700 documented cases. Patients are followed for life with only 1% of patients lost to follow-up. The scientific evaluation of this data focuses on health services research, quality management, the improvement of tumor classification, the identification of prognostic factors, the definition of quality indicators, and quality of life research. The documentation of specific diagnostics and multimodal treatment strategies results from an interdisciplinary cooperation of numerous departments and institutes at the Faculty of Medicine.

Randomized trials for gastrointestinal tumors
PI: Prof. Dr. R. Grützmann, Dr. H. Golcher
The Department of Surgery respectively the interdisciplinary Colorectal Cancer Center/ Modul Pancreas Cancer took part in different multicenter trials about gastrointestinal tumors, inter alia " Pancreatoduodenectomy with or without pro- phylactic Ligamentum teres hepatis wrap around the gastroduodenal artery stump for prevention of pancreatectomy hemorrhage" or "International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (T-REX)". The "Prospective trial for comparison of hepaticojejunostomy as interrupted versus continuous suture" was initiated the department of surgery. Patients were screened during the interdisciplinary tumor board for gastrointestinal tumors, assigned to the studies and further attended. The surgical second opinion ("panel of surgeons") for the CONKO-007-trial (patients with non resectable pancreatic carcinoma) is organized by the study team, too, and evaluation takes place in the daily tumor conference.

Outcomes research of complex surgery with hospital discharge data
PI: PD Dr. C. Krautz
A variety of surgical procedures in general surgery are associated with varying perioperative outcomes due to their complexity. Analyses of nationwide hospital discharge data provide the possibility to examine the underlying causes. Currently, we are assessing the effects of volume-based referral on perioperative outcomes in complex surgery in order to give recommendations for the future hospital market structure in Germany.

The interferon-γ pathway in the immune evasion of colorectal cancer
PI: PD Dr. N. Britzen-Laurent, Prof. Dr. Dr. M. Stürzl
Interferon-γ (IFN-γ) is a pleiotropic cytokine, which plays an important role in the immunosurveillance of colorectal cancer (CRC). Here we investigated the impact of IFN-γ-resistance in tumor cell lines on tumor progression. Colon tumorigenesis increased in mice with an inactivated IFN-γ pathway in intestinal cells. In human CRC, a decreased expression of the IFN-γ receptor (IFNγRα) correlated with reduced cancer-related survival and increased metastasis. At the molecular level, IFN-γ-resistance was due to a decreased stability of IFNγRα, which was attributed to a defective N-glycosylation. Expression of the glycosyl-tranferase MGAT3 could reinstate IFNγRα expression and signaling activity. These data suggest that IFN-γ resistance is a common evasion mechanism of CRC tumor cells that is regulated by protein N-glycosylation.

The role of vascular plasticity in gastrointestinal diseases
PI: Prof. Dr. E. Naschberger, PD. Dr. N. Britzen-Laurent, Prof. Dr. Dr. M. Stürzl.
The importance of vascular plasticity for the development of gastrointestinal diseases is investigated in colorectal carcinoma and inflammatory bowel disease. An important finding of these studies was that tumor vessels in colorectal carcinoma release soluble mediators that counteract tumor development in prognostically favorable tumors. In addition, we found that interferon-induced vascular permeability is a critical driver in the development of inflammatory bowel disease. Both findings open up new approaches for the treatment of gastrointestinal diseases and are currently being validated in different experimental models and tested with regard to their translational applicability for the treatment of the diseases.

Cellular memory processes in the pathogenesis of colorectal carcinoma
PI: Prof. Dr. Dr. M. Stürzl, Prof. Dr. E. Naschberger
The tumor microenvironment is established by the interplay of tumor cells with stromal cells (e.g. endothelial cells, fibroblasts) and immune cells and controls the course of the disease. The hypothesis of this research area is that stromal cells in colorectal carcinoma are shaped by different microenvironments and retain certain "memory functions" to the environment in the tumor also in culture. Cellular memory processes are exploited to gain new insights into the pathogenesis. To this end, we established novel methods for isolating fibroblasts and endothelial cells from colorectal carcinomas with different microenvironments and identified via the differential characterization of the isolated cells at the genome, transcriptome, and epigenome levels novel mediators that control metastasis. The approach confirms that cultured stromal cells can serve as cell spies for the intra-tumoral microenvironment and it provides new approaches to treat the disease.

Genome editing of pancreatic tumor models
PI: Prof. Dr. C. Pilarsky
Pancreatic cancer is the fourth most frequent cause of cancer in the western world with a five

year survival rate of 10%. This is caused by late detection and chemoresistance of the tumor. In this project we are trying to understand more precisely which mechanisms influence tumor development. Based on the well-known changes in the tumor genome, we are targeting specific genes, especially gene involved in DNA repair, with CRISPR/Cas9 technology and are testing whether our tumor models become more sensitive to the application of chemotherapeutic agents. This allows an adaptation of chemotherapeutic regimens to the mutation pattern of the individual tumor within the framework of modern precision medicine. In the second part of this approach we identify genes associated with metastasis and invasion to identify metastasis associated targets for pharmacological intervention.

Organoid models in pancreatic cancer
PI: Prof. Dr. C. Pilarsky
In this project we will test the influence of the culture conditions on the chemosensitivity of pancreatic carcinomas. For this purpose, pancreas tumor cells are grown as a special tissue culture, the organoid culture, and treated with chemotherapeutic agents. This allows us to examine how the individual models can be treated in a tissue. This allows a better understanding of the necessary dosage of chemotherapeutic agents and a possible better preclinical testing of new chemotherapies.

Immunepathophysiology of acute (sepsis) and chronic (colitis) inflammation
PI: PD Dr. G. Weber, Dr. A. Bénard
The immune system consists of innate and adaptive components that operate in close proximity to protect the host against infections. During infection the host can be at risk due to imbalanced immune responses. A major therapeutic goal, then, is to establish an equilibrium between controlling infection and controlling inflammation. One promising strategy is to harness the endogenous immune system to augment processes that are beneficial and curb processes that cause harm. Such strategies, however, require understanding of the diseases pathophysiology. Currently, we are focusing on the role of interleukin-3 as central regulator for acute and chronic inflammation.

Immunephenotyping and liquid biopsy analysis of gastrointestinal tumors
PI: PD Dr. G. Weber
Successful treatment of cancer disease is based on the in-depth understanding of the involved mechanisms leading to cancer development and progression. Thus, precise knowledge of the immunogenicity of the individual tumor as well as early and precise diagnosis is required. Within this project, we will develop non-invasive alternative techniques – so called liquid biopsies - to diagnose cancer disease, predict and monitor disease progression, and finally to improve patient selection for established treatment strategies. In addition, we are immunologically phenotyping the individual cancer disease to evaluate immune therapeutic strategies.

Teaching

The Department of Surgery is offering courses for students of Medicine, Dentistry, Molecular Medicine, and biology. The Dr. House colloquium is an interdisciplinary lecture with the internal medicine. By the implementation of a surgical skills lab, surgical residents as well as medical students benefit from learning different surgical approaches and may acquire basic surgical skills using modern laparoscopic simulators. MD and PhD theses are supervised.

Selected publications

Merkel S, Weber K, Brunner M, Baecker J, Agaimy A, Göhl J, Hohenberger W, Schellerer V, Grützmann R. Prognostic subdivision of pT2 rectal carcinomas. Int J Colorectal Dis. 2019 Mar;34(3):409-415.

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Mlecnik B, Bifulco C, Bindea G, Marliot F, Lugli A, Lee JJ, Zlobec I, Rau TT, Berger MD, Nagtegaal ID, Vink-Börger E, Hartmann A, Geppert C, Kolwelter J, Merkel S, Grützmann R, Van den Eynde M, Jouret-Mourin A, Kartheuser A, Léonard D, Remue C, Wang JY, Bavi P, Roehrl MHA, Ohashi PS, Nguyen LT, Han S, MacGregor HL, Hafezi-Bakhtiari S, Wouters BG, Masucci GV, Andersson EK, Zavadova E, Vocka M, Spacek J, Petruzelka L, Konopasek B, Dundr P, Skalova H, Nemejcova K, Botti G, Tatangelo F, Delrio P, Ciliberto G, Maio M, Laghi L, Grizzi F, Fredriksen T, Buttard B, Lafontaine L, Bruni D, Lanzi A, El Sissy C, Haicheur N, Kirilovsky A, Berger A, Lagorce C, Paustian C, Ballesteros-Merino C, Dijkstra J, van de Water C, van Lent-van Vliet S, Knijn N, Muşină AM, Scripcariu DV, Popivanova B, Xu M, Fujita T, Hazama S, Suzuki N, Nagano H, Okuno K, Torigoe T, Sato N, Furuhata T, Takemasa I, Itoh K, Patel PS, Vora HH, Shah B, Patel JB, Rajvik KN, Pandya SJ, Shukla SN, Wang Y, Zhang G, Kawakami Y, Marincola FM, Ascierto PA, Fox BA, Pagès F, Galon J. Multicenter International Society for Immunotherapy of Cancer Study of the Consensus Immunoscore for the Prediction of Survival and Response to Chemotherapy in Stage III Colon Cancer. J Clin Oncol. 2020 Nov 1;38(31):3638-3651.

Langer V, Vivi E, Regensburger D, Winkler TH, Waldner MJ, Rath T, Schmid B, Skottke L, Lee S, Jeon NL, Wohlfahrt T, Kramer V, Tripal P, Schumann M, Kersting S, Handtrack C, Geppert CI, Suchowski K, Adams RH, Becker C, Ramming A, Naschberger E, Britzen-Laurent N, Stürzl M. IFN-γ drives inflammatory bowel disease pathogenesis through VE-cadherin-directed vascular barrier disruption. J Clin Invest. 2019 Nov 1;129(11):4691-4707. doi: 10.1172/JCI124884.

Wohlfahrt T, Rauber S, Uebe S, Luber M, Soare A, Ekici A, Weber S, Matei AE, Chen CW, Maier C, Karouzakis E, Kiener HP, Pachera E, Dees C, Beyer C, Daniel C, Gelse K, Kremer AE, Naschberger E, Stürzl M, Butter F, Sticherling M, Finotto S, Kreuter A, Kaplan MH, Jüngel A, Gay S, Nutt SL, Boykin DW, Poon GMK, Distler O, Schett G, Distler JHW, Ramming A. PU.1 controls fibroblast polarization and tissue fibrosis. Nature 2019 Feb;566(7744):344-349. doi: 10.1038/s41586-019-0896-x.

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Bardenbacher M, Ruder B, Britzen-Laurent N, Schmid B, Waldner M, Naschberger E, Scharl M, Müller W, Günther C, Becker C, Stürzl M, Tripal P. Permeability analyses and three dimensional imaging of interferon gamma-induced barrier disintegration in intestinal organoids. Stem Cell Res. 2019 Mar;35:101383.

Sistemich L, Kutsch M, Hämisch B, Zhang P, Shydlovskyi S, Britzen-Laurent N, Stürzl M, Huber K, Herrmann C. The Molecular Mechanism of Polymer Formation of Farnesylated Human Guanylate-binding Protein 1. J Mol Biol. 2020 Mar 27;432(7):2164-2185. doi: 10.1016/j.jmb.2020.02.009. Epub 2020 Feb 19. PMID: 32087202.

Bardenbacher M, Ruder B, Britzen-Laurent N, Naschberger E, Becker C, Palmisano R, Stürzl M, Tripal P. Investigating Intestinal Barrier Breakdown in Living Organoids. J Vis Exp. 2020 Mar 26;(157).

International cooperations
Prof. M. Gack, Department of Microbiology, The University of Chicago, Chicago: USA

Prof. R.D. Kamm, Massachusetts Institutes of Technology - MIT, Cambridge: USA

Prof. M. Kelly/Prof. D.C. Winter, Department of Surgery, St. Vincent's University Hospital Dublin, Dublin: Ireland

Prof. F.K. Swirski, Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston: USA

Prof. D. Tuveson, Cold Spring Harbor Laboratory, Cold Spring Harbor: USA

Prof. O. Sansom/Dr. R. Jackstadt, Beatson Institute, Glasgow, Cancer Research, UK and DKFZ Heidelberg.

Prof. M. Scharl, University Hospital Zürich, Switzerland

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Research focus

- Surgical treatment of congenital malformations, especially in the thoracic, abdominal, skeletal, and integumental areas in newborn and children
- Surgical treatment of chest deformities (pectus excavatum and carinatum)
- Special techniques to resolve recurrences after chest wall repair
- Minimally invasive pediatric surgery (laparoscopy, thoracoscopy, rendezvous procedures)

Structure of the Division

Professorship: 0
Personnel: 10

- Doctors (of Medicine): 7
- Graduate students: 6

Research

Sacral neuromodulation for treatment of chronic constipation disorders in childhood and adolescence
PI: Dr. M. Besendörfer
The neuromodulation project focuses on the clinical implementation and adaptation of sacral nerve stimulation for children with chronic enteric transport disorders, which has already been established in adults. Based on the methodology (E. Tanagho (Urology, San Francisco) / Prof. Dr. K. Matzel (Coloproctology, Erlangen)), the classical invasive sacral nerve stimulation via S3/4 is applied. In collaboration with the company Medtronic, we are evaluating the implantation technique in children and the optimization of the smallest rechargeable pacemaker system (Interstim Micro). Previously, we were able to develop and establish a child-friendly, non-invasive version in which the enteric nervous system is electrically stimulated by adhesive electrodes. In the first clinical evaluation, efficacy was confirmed in 71% by an improvement in stool consistency and bowel movement frequency, as well as a reduction in encopresis with minimal complication rate. In half of the patients, a sustained effect of symptom control was achieved even after cessation of therapy.
After evaluation of the pilot data, two clinical trials are conducted: the first trail evaluates the efficacy of non-invasive sacral neuromodulation compared to conventional therapy (drug and behavioral therapy) in a case-control design. In the second trail, the effect of invasive and non-invasive sacral nerve stimulation will be recorded and compared. In both studies, prospective patient recruitment is performed. Interim results confirm the efficacy of sacral nerve stimulation and a therapeutic superiority over conventional approaches.

Neonatal research
Duodenal atresia
PI: S. Seitz
One of the classic congenital malformations in neonatal surgery is duodenal atresia and stenosis. Like many other procedures in pediatric surgery, it is currently undergoing a process of developing and optimizing minimally invasive surgical techniques. This change is also taking place in the pediatric surgery department of the University Hospital Erlangen.
With the perspective of accompanying this development, the data of patients who have been treated with open surgery during the last 15 years are analyzed. This is a cohort of 50 neonates with congenital duodenal atresia operated on in the first days of life. The aim is to provide a basis for comparison for further prospective studies in this patient population.

Evaluation of biological patches in pediatric surgery and in direct comparison of Tutopatch and SurgiMend
PI: Dr. A. Füldner
In pediatric patients, numerous congenital and acquired conditions require body wall reconstruction by prosthesis, many of them in a contaminated situs. Synthetic, non-absorbable materials have been increasingly replaced in recent years by biological materials of biological origin, which are designed first to provide mechanical stability and then to serve as a scaffold for the migration of autologous cells. Two different products - SurgiMend© (11 patients) and Tutopatch© (17 patients) - were used in our clinic from 2016-2020. This study evaluates the use of both products in pediatric surgical patients and compares both products in terms of safety and ease of use. For this purpose, clinical and demographic data, including length of ICU stay, mortality and patch-associated complications, and costs are collected and compared. Overall, patch-associated complications occurred with similar frequency in both groups, but SurgiMend© was implanted more often in the open abdomen with a contaminated situs (63% vs. 30%), fittingly, patch infections occurred more often here. Patch failure and severe enteric adhesions at the time of explantation occurred more frequently with Tutopatch©. Overall, the data favor SurgiMend© over Tutopatch©, which confirms previous results in the experimental setup.

Necrotizing enterocolitis
PI: Dr. S. Diez
The occurrence of necrotizing enterocolitis (NEC) is mainly determined by the immaturity of children. Impaired interaction between bacteria and immature enterocytes and immune cells has been postulated as the central mechanism of this acute intestinal inflammation. In addition, congenital cardiac malformations predispose to NEC through the impaired hemodynamic impact on the intestinal perfusion. The differentiation of pathophysiology is the center of current research. We have been able to confirm differences in clinical factors and outcome of NEC in preterm infants and in patients with cardiogenic NEC within our own cohort. These differences hint an influence on treatment decisions in the different patient subgroups. Pathophysiology continues to be investigated in collaboration with the Institute of Pathology of the University Hospital and the Tissue Bank of the National Center for Tumor Diseases (NCT) Heidelberg. Hereby, the role of DMBT1 (Deleted in Malignant Brain Tumor 1), a protein of innate immune defense and cell differentiation, is also being investigated with regard to patient subgroups.

Esophageal atresia
PI: Dr. S. Diez
Congenital esophageal atresia is a common malformation of the gastrointestinal tract. Concomitant malformations often occur, especially in the context of the VACTERL syndrome. The success of the surgical repair is significantly influenced by these concomitant malformations. In this project, postoperative complications after esophageal reconstruction were evaluated in the patient collective of the last 10 years (n=50). Hereby, the association of postoperative pneumothorax with a worse outcome could be elaborated. In addition, effects of postoperative continuous muscle relaxation for protected healing of the anastomosis were evaluated, which failed to achieve a significant impact. A prospective patient registry and regular follow-up surveys are being established to detect and treat early potential long-term complications.

Negative pressure wound therapy as a treatment of deep sternal wound infections after cardiac surgery in neonates and small infants
PI: Dr. J. Syed
The correction of congenital heart defects contains multiple risk factors for the development of a deep sternal wound infection, which significantly worsens the patient's outcome. In adults, vacuum-assisted wound closure is an established procedure for treating surgical site infections after heart

surgery. Current data show an advantage over traditional treatment strategies, particularly regarding sternal and thoracic stability such as length of hospital stay. Data about the adequate use of vacuum therapy in neonates and small infants are rare. In cooperation with the department of Congenital Heart Surgery, we compare the data from our own clinic with those reported in the literature. The aim is to define a gold standard in the treatment of deep sternal wound infections after cardiac surgery in neonates and small infants.

Elastic stable chest repair (ESCR) in the treatment of congenital chest wall deformities

PI: Dr. J. Syed

Elastic stable chest repair is a surgical technique for the open correction of chest wall deformities such as pectus excavatum, pectus carinatum and mixed deformities. The procedure allows preserving and reconstructing the sternocostal unit and the thoracic stability. Therefore, it is also an appropriate technique for the correction of recurrent deformities with sternocostal pseudarthrosis and thoracic instability. In a 10-year follow-up, we evaluate the surgical technique in regard of patient´s satisfaction, clinical and cardiorespiratory parameters.

ChildOrg: Establishment of in vitro organoids from pediatric tumors

PI: PD Dr. Vera Schellerer, Prof. Dr. E. Naschberger, Prof. Dr. M. Metzler, PD Dr. C. Günther and Dr. M. Kunz

ChildOrg is an interdisciplinary project of the Department of Pediatric Surgery (Schellerer), the Department of Molecular and Experimental Surgery (Naschberger), Pediatric Oncology (Metzler), Gastroenterology (Günther) and Bioinformatics (Kunz). In this project, in silico models and patient-specific established organoid cultures are used to search for optimal drug combinations in childhood tumors. For this purpose, individualized organoid cultures are established from biopsies, which are systematically subjected to omics analyses. Based on this, in silico models will be developed that reflect the in vivo and in vitro situation including metabolic profiling and allow combination therapies to be systematically tested in silico. The most promising drug combinations with low predicted toxicity will be experimentally validated in organoids with respect to their efficacy and subsequently used in the clinic for targeted therapy decisions. This will lead to optimized therapeutic strategies and better clinical management of childhood tumors, while at the same time making a significant contribution to the reduction or even replacement of animal experiments in oncology research, especially with regard to the toxicology of combination therapies.

Teaching

The Division of Pediatric Surgery engages in the curricular teaching according to IMPP (general guidelines for medical studies in Germany). Academic events take place in cooperation with vocational schools at FAU (pediatric nursing, pediatric intensive care medicine, school for operational and technical assistants, physio-therapy, massage), as interdisciplinary lectures and seminars, and in form of practical education in phantom-courses for minimally invasive pediatric surgery in skills lab and hands-on courses. The Division of Pediatric Surgery supervises PhD theses.

Selected publications

Clinical Characteristics of Necrotizing Enterocolitis in Preterm Patients With and Without Persistent Ductus Arteriosus and in Patients With Congenital Heart Disease.
Diez S, Tielesch L, Weiss C, Halbfass J, Müller H, Besendörfer M. Front Pediatr. 2020 Jun 5;8:257

A Pilot Study of Non-invasive Sacral Nerve Stimulation in Treatment of Constipation in Childhood and Adolescence.
Besendörfer M, Kohl M, Schellerer V, Carbon R, Diez S, Front Pediatr. 2020 Apr 16;8:169. doi: 10.3389/fped.2020.00169. eCollection 2020.Front Pediatr. 2020. PMID: 32373563

From pullout-techniques to modular elastic stable chest repair: the evolution of an open technique in the correction of pectus excavatum.
Schulz-Drost S, Syed J, Luber AM, Carbon RT, Besendörfer M. J Thorac Dis. 2019 Jul;11(7):2846-2860. doi: 10.21037/jtd.2019.07.01.J Thorac Dis. 2019. PMID: 31463114

Computed Tomography-Guided Wire-Marking for Thoracoscopic Resection of Small Lung Nodules in Children.
Seitz ST, Schellerer VS, Schmid A, Metzler M, Besendörfer M. J Laparoendosc Adv Surg Tech A. 2019 May;29(5):688-693. doi: 10.1089/lap.2018.0184. Epub 2019 Apr 4.J Laparoendosc Adv Surg Tech A. 2019. PMID: 30946003

International cooperations

Prof. Dr. A. Fisher, Biochemical Center of Research, Weizman Institue of Science, Rehovot: Israel

Prof. Dr. G. Berci, Endoscopic Research, Cedars-Sinai Medical Center, Los Angeles: USA

AO Foundation. TK Thoracic Surgery Expert Group, Davos: Schweiz

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Research focus

- Surgical therapy of hyperhidrosis – a prospective quality control study
- Surgical management of pulmonary metastases from colorectal cancer
- Deep intrathoracic vacuum therapy in septic thoracic surgery
- Imunological and molecular characterization of malignant lung tumors
- Neoadjuvant therapy of locally advanced non-small cell lung carcinoma IIIA; simultaneous radiochemotherapy followed by surgery
- The impact of patho-histologic response following neo-adjuvant radiochemotherapy in locally advanced non-small cell lung cancer
- Prognostic effect of „Salvage"-resection in locally advanced non-small cell lung cancer
- The value of the systematic extensive lymph node dissection in the operative treatment in non-small cell lung cancer
- Pulmonary resection with parietal pleurectomy (WRPP) versus parietal pleurectomy (PP) for the treatment of primary pneumothorax
- Functional analysis of human dendritic cell subpopulations

Structure of the Division

Professorship: 1
Personnel: 11

- Doctors (of Medicine): 7
- Scientists: 7 (therof funded externally: 0)
- Graduate students: 3

Clinical focus areas

- Gentle surgical techniques for lung cancer, lung tumors
- Successful treatment of pathological sweating (hyperhidrosis)
- Video-assisted correction of chest deformations, e.g. pectus excavatum

Research

The research focus of the Division of Thoracic Surgery is to research innovative therapies for operative pulmonary and thoracic diseases to develop new clinical treatment concepts. Furthermore, experimental immunological projects with samples from the lung and human lymphoid organs are carried out within the framework of the cooperation with other divisions and departments.

Surgical therapy of hyperhidrosis – a prospective quality control study
PI: Dr. D. Trufa, Prof. Dr. H. Sirbu, M. Haj Khalaf
Videoscopic assisted thoracic sympathectomy is a widely accepted approach in the therapy of palmar and axillary hyperhidrosis. Long term postoperative results are very heterogeneous. In this trial, we analyze the long term patient satisfaction with a questionnaire specially designed by the Division of Psychosomatics and Psychotherapy.

Surgical management of pulmonary metastases from colorectal cancer
PI: Prof. Dr. H. Sirbu, Dr. W. Dudek
Although resection of solitary lung metastases is widely accepted, pulmonary resection for multiple or bilateral metastases is still under discussion. This monocentric, retrospective study analyzes clinical data, prognostic factors, and long term follow-ups after surgical treatment of pulmonary metastases from colorectal cancer.

Deep intrathoracic vacuum therapy in septic thoracic surgery
PI: Dr. W. Dudek, Prof. Dr. H. Sirbu
Vacuum therapy leads to a significant improvement in the local therapy of infected wounds. The aim of this study is to examine the clinical short and long time results of this therapeutic method in deep infected wounds, e.g. pleural empyema.

Immunological and molecular characterization of malignant lung tumors
PI: Prof. Dr. S. Finotto (Division of Molecular Pneumology), Dr. D. Trufa, Prof. Dr. H. Sirbu
The aim of this research project is to investigate the immunological and molecular basis. The focus within this project are the malignancies that become visible in the lung, especially non-small cell lung cancer (NSCLC). These parameters are then correlated with the clinical findings. Before the surgery, the clinical data (age, height, weight, sex, nutritional status, smoking and occupational history, family history, etc.) are acquired. After the surgery, some samples from resected lung tissue and from removed lymph nodes are analyzed in the laboratory. From the single cell suspension, various cell sub-populations, such as isolated CD4 + or CD8 + T cells, are taken in culture. The cultured cells are then analyzed in different ways (e.g. FACS analysis, ELISA, PCR, etc.). RNA and DNA are isolated, too, which can then be used for epigenetic studies, microarray analysis, and RNA expression analysis. Finally, the proteins can be isolated and analyzed.

Neoadjuvant therapy of locally advanced non-small cell lung carcinoma IIIA; simultaneous radiochemotherapy followed by surgery
PI: Prof. Dr. H. Sirbu, Dr. D. Trufa, Prof. Dr. R. Fietkau (Department of Radiation Oncology)
In this trial, we compare the therapy concept of neoadjuvant radiochemotherapy (45Gy/Cis-platin, Etoposide), followed by surgery, with the concept of definitive radiochemotherapy in patients with locally advanced, non-small cell lung carcinoma stadium IIIA.

The impact of patho-histologic response following neo-adjuvant radiochemotherapy in locally advanced non-small cell lung cancer
PI: Prof. Dr. H. Sirbu, Prof. Dr. R. J. Rieker (Institute of Pathology)
The purpose of the study is the analysis of patho-histologic response of the primary tumor following neo-adjuvant chemoradiation therapy and the long-term impact on survival in order to identify the predisposing factors for survival improvement in patients with locally advanced non-small cell lung cancer.

Prognostic effect of „Salvage"- resection in locally advanced non-small cell lung cancer
PI: Prof. Dr. H. Sirbu, Prof. R. Fietkau (Department of Radiation Oncology) The study purpose is the prognostic effect and impact on local tumor control due to the „Salvage"-surgery for local recurrence and/or persisted primary tumor despite definitive radiochemotherapy in patients with primary inoperable locally advanced non-small cell lung cancer.

The value of the systematic extensive lymph node dissection in the operative treatment in non-small cell lung cancer
PI: Prof. Dr. H. Sirbu, Dr. D. Trufa
The purpose of the study is the investigation of the extensive lymph node dissection under consideration of the lymphatic metastasis pathways and the improvement of the lymph node staging.

Pulmonary resection with parietal pleurectomy (WRPP) versus parietal pleurectomy (PP) for the treatment of primary pneumothorax
PI: Prof. Dr. H. Sirbu, Dr. W. Dudek
Prospective randomized multicenter clinical trial which compares two established surgical procedures (WOPP-study). The aim of the study is to analyze the pneumothorax recurrence rate within the first 24 months after surgical procedure: Parietal pleurectomy with apical lung resection (WRPP) or parietal pleurectomy (PP).
Funding: DFG

Functional analysis of human dendritic cell subpopulations
PI: Prof. Dr. D. Dudziak (Department of Dermatology), Prof. Dr. H. Sirbu
The main scientific focus of the research group of Prof. Dr. D. Dudziak is the characterization of Dendritic cells (DCs) and the initiation of specific T cell immune responses. These studies are being conducted both in the murine and the human setting. First detailed phenotypic and functional analyses of DC subpopulations have been

performed with various human lymphoid tissues (spleen, blood, thymus, bone marrow, cord blood, tonsils) and were recently published). In a collaborative research project with Prof. Dr. H. Sirbu, comparative analyses of the development of different immune cells were extended to other human organs, such as lymph nodes, blood, lungs, and adult thymus. The latter shows residual activity of T cell development, despite a progressed thymic involution. Of note, the analysis of the phenotype and function of the DC subpopulations in various human tissues of the very same donor is of high value, in order to account for the high degree of inter-individual variance.

Teaching

For medical students, the Division of Thoracic Surgery offers current lectures on relevant topics (malignant pulmonary disease, pneumothorax, pulmonary emphysema, pleural empyema, trauma, etc.), an interactive EKM course (introduction into clinical medicine) and offers the possibility of hospitalization on the ward, in the ambulance, and in the operation room of thoracic surgery. The applicants for the practical year in thoracic surgery are given special knowledge (participation to medical thoracic conferences/boards, conduct an interview, preparation of a treatment plan and discussion with the tutor, learning of special aspects of risk medical informing, presentation of the patient during the medical visit, active participation in the operating room). Furthermore, in the Division of Thoracic Surgery supervises Bachelor's, Master's as well as MD theses.

Selected publications

Dudek W, Schreiner W, Mykoliuk I, Higaze M, Sirbu H. Pulmonary metastasectomy for sarcoma-survival and prognostic analysis. J Thorac Dis. 2019 Aug;11(8):3369-3376. doi: 10.21037/jtd.2019.08.10.

Schreiner W, Ludolph I, Dudek W, Horch RE, Sirbu H. Negative Pressure Wound Therapy Combined With Instillation for Sternoclavicular Joint Infection. Ann Thorac Surg. 2020 Nov;110(5):1722-1725. doi:10.1016/j.athoracsur.2020.04.037.

Dudek W, Al Moussa E, Schreiner W, Mantsopoulos K, Sirbu H. Survival and Prognostic Analysis after Pulmonary Metastasectomy for Head and Neck Cancer. Thorac Cardiovasc Surg. 2020 Jun 19. doi: 10.1055/s-0040-1713112

Schreiner W, Mykoliuk I, Dudek W, Sirbu Impact of Selective Quality of Life Analysis in Patients with Local Hyperhidrosis after Sympathicus Clipping. Zentralbl Chir. 2019 Apr;144(2):139-145. doi: 10.1055/a-0808-5003.

Heim L, Kachler K, Siegmund R, Trufa DI, Mittler S, Geppert CI, Friedrich J, Rieker RJ, Sirbu H, Finotto Increased expression of the immunosuppressive interleukin-35 in patients with non-small cell lung cancer. Br J Cancer. 2019 Apr;120(9):903-912. doi: 10.1038/s41416-019-0444-3.

Schreiner W, Dudek W, Rieker RJ, Lettmaier S, Fietkau R, Sirbu H. Major Pathologic Response after Induction Therapy Has a Long-Term Impact on Survival and Tumor Recurrence in Stage IIIA/B Locally Advanced NSCLC. Cardiovasc Surg. 2020 Oct;68(7):639-645. doi: 10.1055/s-0039-1679884.

UNIVERSITY HOSPITAL

Department of Surgery

Division of Transfusion Medicine and Hemostaseology

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Research focus
- Development of new minimally invasive photopheresis methods
- Functional modulation of dendritic cells
- Collection of monocytes for the generation of dendritic cells (DC)
- Clinical research related to hemostaseology
- Clinical research related to hemotherapy
- Mesenchymal stromal cells (MSC)
- Optimization of collection procedures to get regulatory T cells (Tregs)
- Legislation of transfusion

Structure of the Division

Professorships: 1
Personnel: 76
- Doctors (of Medicine): 6
- Scientists: 6 (thereof funded externally: 0)
- Graduate students: 10

Clinical focus areas
- Clinical transfusion medicine
- Blood component supply
- Immunohematological and hemostaseological diagnostics
- Outpatient and inpatient coagulation counseling
- Production and storage of stem cell preparations
- Minimally invasive photopheresis methods

Research

Research in the Division of Transfusion Medicine and Hemostaseology focuses on the characterization of specific blood components, stem cell concentrates, and new experimental cellular preparations. Clinical problems with respect to hemotherapy and coagulation management are also investigated. In the GMP laboratory of the Division, interdisciplinary experimental preparations for innovative clinical trials are produced and tested (Advanced Therapy Medicinal Products, ATMP).

COVID-19 Immunotherapy
PI: Prof. Dr. H. Hackstein
In the course of the SARS-COV-2 pandemic, the department received in April 2020 as one of the first institutions in Germany the permission to produce Covid-19 immune plasma. COVID-19 immune plasma is produced from convalescents in accordance with the German Drug Law and contains virus-specific antibodies. To test the clinical efficacy, the department has initiated a randomized phase II study together with Med. Klinik IV (Prof. Dr. Mario Schiffer): Assessment of Efficacy and Safety of Therapy With COVID-19 Convalescent Plasma in Subjects With Severe COVID-19 (IPCO).

Development of new minimally invasive photopheresis methods
PI: Prof. Dr. H. Hackstein
Current standard photopheresis methods are only able to treat small children to a limited extent. The project group has modified the clinical photopheresis methods and is developing new minimally invasive treatment methods so that critically ill infants can also be successfully treated with a graft versus host disease after bone marrow transplantation. This new mini-photopheresis procedure is characterized by the fact that only very small amounts of blood (100-200 ml whole blood) are required and thus even very small children or vital unstable, critically ill adult patients with contraindications to classical apheresis can be treated.

Functional modulation of dendritic cells
PI: Prof. Dr. H. Hackstein
The project group is investigating pharmacological substances that control or block key functions of dendritic cells with the aim of activating or blocking antigen-specific immune responses. The immunosuppressant rapamycin, for example, is the first clinically used drug that inhibits both, antigen uptake and mobilization of dendritic cells *in vitro* and *in vivo*. Current research projects investigate the role of RNA-editing enzymes in the hematopoietic differentiation of dendritic cells and translational protocols for the accelerated differentiation of monocytes in dendritic cells.

Collection of monocytes for the generation of dendritic cells (DC)
PI: Prof. Dr. E. Strasser
Circulating monocytes are precursors of DC, which play a key role in the immune system's function by presenting antigens to specific lymphocytes. The collection and cultivation of these cells enables the development of new strategies in the treatment of malignant diseases. Members of the Division of Transfusion Medicine and Hemostaseology cooperate with colleagues from the Department of Dermatology to adjust the collection procedures optimally to the specific clinical and experimental demands of procedures aimed at the cultivation, expansion, and priming of DC.

Clinical research related to hemostaseology
PI: Prof. Dr. R. Zimmermann, Prof. Dr. E. Strasser
Other research interests include thrombophilia, traveller's thrombosis, and hemostasis dysfunctions resulting in bleeding disorders. Other current study objectives are preanalytical determinants of fibrinolysis tests, hemostasis tests in systemic lupus erythematodes, and other currently relevant topics.

Clinical research related to hemotherapy
PI: Prof. Dr. V. Weisbach, Prof. Dr. R. Zimmermann, Prof. Dr. E. Strasser
We examine antibodies against red cell antigens, characterize factors influencing the quality of stored red cell concentrates, and study the complex dysfunctions of the coagulation system.

Mesenchymal stromal cells (MSC)
PI: Prof. Dr. V. Weisbach
Mesenchymal stromal cells (MSC) are the predecessors of osteoblasts, chondrocytes, and adipocytes. The term "MSC" especially covers cells cultivated and expanded ex vivo. These cells are a mixture of stem and progenitor cells up to mature stroma cells and are named MSC according to a definition of the International Society of Cellular Therapy. It is expected that MSC will play a major role in future applications of regenerative medicine. The main focus of the working group is the preparation, characterization, and expansion of MSC especially from placentar tissues.

Optimization of collection procedures to get regulatory T cells (Tregs)
PI: Prof. Dr. E. Strasser, PD Dr. J. Strobel
T cells play an important role in adoptive immune response in many diseases (infectious and inflammatory diseases, tumors). DC act as antigen presenting cells for specific T cells activation. The collection of circulating T cells as well as the culture and expansion of T cells, especially regulatory T cells (Tregs), enables the development of new strategies for the anti-inflammatory and immunosuppressive therapies. Members of the Division of Transfusion Medicine and Hemostaseology cooperate with colleagues from the departments of Medicine 1, Dermatology, and Medicine 5 to optimally adjust the collection procedures to the specific clinical and experimental demands of procedures aimed at the cultivation and expansion of Tregs. In the context of cell preparation, analysis of factors responsible for cell damage (cell apoptosis and necrosis) is relevant to optimize the quality of leukocyte products.

Legislation of transfusion
PI: Prof. Dr. R. Zimmermann
Under the auspices of the Legal Counsel and Managing Director of the UK Erlangen, Dr. A.W. Bender, the Division of Transfusion Medicine and Hemostaseology is involved in publications on the legislation and law of blood transfusion in Germany. In the center of attention is the book "Transfusion Law", published by the Wissenschaftliche Verlagsgesellschaft Stuttgart, that has become the benchmark in this field of law and has found its way into the jurisdiction of the German Federal High Court of Justice. Alongside, book contributions and articles on different aspects of the legislation and law of blood transfusion are published.

Teaching

The Division of Transfusion Medicine and Hemostaseology is involved in compulsory and optional courses in the curricular teaching of Medicine and Dentistry. Particularly noteworthy is the interdisciplinary teaching of laboratory diagnostics and clinical pathology together with the Department of Medicine 5 and the Clinical Chemistry Laboratory and the participation in the block training in surgery. We supervise MD and PhD theses.

Selected publications

Buchele V, Hackstein H. A simplified extracorporeal photopheresis procedure based on single high-dose ultraviolet A light irradiation shows similar in vitro efficacy. Transfusion. 2021 Mar;61(3):883-893.

Strasser EF, Steininger PA, Korn K, Achenbach S, Tenbusch M, Cunningham S, Zimmermann R, Überla K, Hackstein H. Validation of a SARS-CoV-2 RNA RT-PCR assay for high-throughput testing in blood of COVID-19 convalescent plasma donors and patients. Transfusion. 2021 Feb;61(2):368-374.

Hackstein H, Kalina A, Dorn B, Keil IS, Baal N, Michel G, Brendel C, Neubauer A, Jakob T, Bein G. CD11c+ dendritic cells mediate antigen-specific suppression in extracorporeal photopheresis. Clin Exp Immunol. 2021 Feb;203(2):329-339.

Kausche LE, Adler W, Zimmermann R, Hackstein H, Strasser EF. Thrombin Generation in Fresh and Frozen-Thawed Platelet Poor Plasma - Is there a Difference? Clin Lab. 2020 Jun 1;66(6).

Cunningham S, Buchele V, Brox R, Strasser E, Hackstein H. Thrombocyte apheresis cassettes as a novel source of viable peripheral blood mononuclear cells. Transfusion. 2020 Jul;60(7):1500-1507.

Schwab L, Michel G, Bein G, Hackstein H. CD71 surface analysis of T cells: a simple alternative for extracorporeal photopheresis quality control. Vox Sang. 2020 Jan;115(1):81-93.

University Hospital

Department of Trauma and Orthopedic Surgery

Chair of Trauma and Orthopedic Surgery

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Research Focus
- 3-D-Imaging, Navigation, Robotics
- Immune Response after Trauma and during Sepsis
- Geriatric Trauma Surgery
- Cartilage Research/ Regeneration
- Biomechanics
- Healthcare Research/ Clinical Studies

Structure of the Department

Professorships: 3
Personnel: 47
- MD: 30
- Graduate Students: 10

Clinical Focus Areas
- Acute Trauma
- Geriatric Trauma Surgery
- Arthroscopic Surgery
- Pelvic Surgery
- Berufsgenossenschaftliches Heilverfahren
- Endoprosthetics
- Pediatric Trauma Surgery
- Septic Surgery
- Spine surgery

Research

The research activities of the Department of Trauma and Orthopedic Surgery are wide-ranging and include both clinical and experimental studies. The focus lies on the diagnosis and therapy of diseases of the musculoskeletal system. The following areas represent the focal points of our scientific commitment.

3-D-Imaging, Navigation, Robotics
PI: Dr. Keil, Prof. Perl
Computer-assisted surgery offers solutions to assist the surgeon pre- or intraoperatively in planning and performing surgery. This includes innovative approaches to intraoperative imaging, especially 3D imaging, as well as automated analysis of the acquired image data. Based on these image data, radiation-free visualization of implants and instruments can be realized with surgical navigation. These data can also be used for robotically assisted surgery, in which individual steps of operations are automated. The research group is concerned with the analysis of these techniques with regard to objectifiable advantages for the patient and the surgical team, as well as with further development in close cooperation with industry.

Immune Response after Trauma and during Sepsis
PI: Prof. Kalbitz, Dr. Lackner, Prof. Perl
The immune response after trauma is being investigated in several clinical studies in the Department of Trauma and Orthopedic Surgery. Close immune monitoring is performed on site in polytraumatized patients. This is closely linked to preclinical research.
The Department of Trauma and Orthopedic Surgery also participates in the stocking of the national serum bank as part of the Trauma Research Network (NTF). In which serum and clinical data of polytrauma patients are collected at different time points. Due to the distribution of study centers throughout Germany, a large number of serum samples can thus be collected and evaluated decentrally on the basis of a wide variety of questions. In another collaborative research project of the Department of Trauma and Orthopedic Surgery biomarkers for the follow-up of immune dysfunction and therapy after blast injuries or pulmonary contusion are being investigated. This is a particularly relevant field of research, since almost half of all severely injured patients have chest trauma.
With the appointment of Professor Kalbitz to the W2 professorship in Traumaimmunology, research of systemic inflammation after trauma and during sepsis and its effects on various organs and organ systems will be further expanded. One focus here lies on post-traumatic and septic cardiac dysfunction.

Geriatric Trauma Surgery
PI: Prof. Palm, Dr. Kopschina
Geriatric traumatology is one focus in the daily routine of the Department of Trauma and Orthopedic Surgery. The clinic is involved in two multicenter studies, including research of the treatment of pertrochanteric femur fractures. We expect that the clinical care of geriatric patients can be further improved by the new gained knowledge and the establishment of specialized interdisciplinary multi-professional therapy concepts.

Cartilage Research/ Regeneration
PI: Dr. Söllner, Dr. Schmidt, Prof. Gelse
In the clinical field of trauma surgery and orthopedics, patients present with a wide variety of joint problems. A large part of the symptoms can often be attributed back to wear and tear of the articular cartilage substance. Clinical and experimental research on cartilage cells and endogenous regeneration processes of the body's own cartilage are the basis for a promising alternative therapy to artificial joint replacement or other invasive interventions.

Biomechanics
PI: Dr. Schmidt, Prof. Palm
Through basic and application-oriented research in the field of (trauma)orthopedic biomechanics, the Department of Trauma and Orthopedic Surgery aims to ensure the best possible care for our patients. The research of movement sequences and the associated mechanical forces, taking into account the anatomical conditions, enables patient-oriented, individual therapy from sports injuries to joint replacement.

Healthcare Research/ Clinical Studies
PI: Prof. Perl, Prof. Palm, U. Perl, Dr. Pressmar
As a supraregional trauma center of the German Society for Trauma Surgery and SAV Clinic of the German Social Accident Insurance Institutions, the Department of Trauma and Orthopedic Surgery attaches great importance to health care research. Therefore, we conduct - concertedly via our clinical study center - various clinical studies to achieve an optimal, state-of-the-art quality of care for our patients.
In the future, pediatric traumatology will also be integrated into health services research with various projects.

Teaching

The Department of Trauma and Orthopedic Surgery participates in curricular teaching and offers numerous required and elective courses in human and dental medicine and medical technology. Particularly noteworthy is the interdisciplinary teaching in the context of the exam preparation courses. In recent years, the digitization of teaching in particular has been advanced. For example, the block practicum and EKM course as well as the lecture are provided in online format. In addition, various examination videos are available online.
Of course, numerous medical doctorates are constantly supervised.

Selected Publications
1. Wenzel L, von Rüden C, Thannheimer A, Becker J, Brand A, Augat P, Perl M. The Pararectus Approach in Acetabular Surgery: Radiological and Clinical Outcome. J Orthop Trauma. 2020 Feb; 34(2): 82–88.

2. Graul I, Marintschev I, Hackenbroch C, Palm HG, Friemert B, Lang P. Modified therapy concepts for fragility fractures of the pelvis after additional MRI. PLoS One. 2020; 15(10): e0238773.

3. Keil H, Luxenhofer M, Vetter Y, Beisemann N, Grützner PA, Franke J. Evaluation of image quality and assessability of a new flat-panel 3D C-arm compared to mobile and fixed computed tomography in posterior spinal fixation. Int J Med Robot. 2020 Oct 13;e2181.

4. Culemann S, Grüneboom A, Nicolás-Ávila JA, Weidner D, Lämmle KF, Rothe T, Quintana JA, Kirchner P, Krljanac B, Eberhardt M, Ferrazzi F, Kretzschmar E, Schicht M, Fischer K, Gelse K, Faas

M, Pfeifle R, Ackermann JA, Pachowsky M, Renner N, Simon D, Haseloff RF, Ekici AB, Bäuerle T, Blasig IE, Vera J, Voehringer D, Kleyer A, Paulsen F, Schett G, Hidalgo A, Krönke G. Locally renewing resident synovial macrophages provide a protective barrier for the joint. Nature. 2019 Aug 1; 572(7771): 670–675.

5. Halbgebauer R, Kellermann S, Schäfer F, Weckbach S, Weiss M, Barth E, Bracht H, Kalbitz M, Gebhard F, Huber-Lang MS, Perl M. Functional immune monitoring in severely injured patients-A pilot study. Scand J Immunol. 2020 Feb;91(2):e12837.

UNIVERSITY HOSPITAL

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Structure of the Department

Professorships: 2
Personnel: 49

- Doctors (of Medicine): 19
- Scientists: 4 (thereof funded externally: 0)
- Graduate students: 1 (Dr. rer. nat.), 14 (Dr. med.)

Clinical focus of care

- University outpatient clinic of Urology and Paediatric Urology at the Universitätsklinikum Erlangen (DIN EN ISO 9001-certified)
- Minimal invasive urology including robotics (DIN EN ISO 9001-certified)
- Kidney transplantation unit; Certified Transplant Center Erlangen-Nürnberg at the Universitätsklinikum Erlangen (DIN EN ISO 9001-certified)
- Kidney transplantation unit focused on children; Certified Paediatric Kidney Center (DIN EN ISO 9001-certified)
- Ambulant Uro-Oncologic Therapy Unit Erlangen (AURONTE)
- Adult's urologic ward, therapy center for private insurance patients at the Malteser Waldkrankenhaus St. Marien
- Trial documentation center at the Malteser Waldkrankenhaus St. Marien
- Certified Urologic Oncology Center (certified by the German Cancer Society)
- Part of the Oncolocy Center (certified by the German Cancer Society) at the Universitätsklinikum Erlangen
- Part of the Comprehensive Cancer Center (CCC) Erlangen-EMN
- Certified Continence and Pelvic Floor Center
- Training Program Center and Supervisor in Sexual Medicine (TPSM)
- EBPU board-certified Paediatric Urology training progamme

Research

The research topics in the Department of Urology and Pediatric Urology cover the areas of basic as well as translational urologic research, also with a particular focus on high-quality statistical assessment. Substantial parts of our research rely on a well-maintained, high quality repository of tissue sample and other biosamples that allows the active participation even in European, multicenter, EU-funded studies in patients with urologic tumors.

Continuous extension of an annotated tumor tissue repository containing urologic tumors
Project manager: Prof. Dr. B. Wullich
New insights into the occurrence of malignant tumors and the identification of new and reliable prognostic biomarkers depend upon the molecular characterization of rather large cohorts of tissue samples since the currently used morphologic criteria only poorly reflect the progression behavior of one patient's specific tumor. To facilitate this research, the collection of tissue samples originating from tumors and corresponding non-tumor tissue as well as blood, serum, and various body fluids, e.g. urine, is of vital importance for translational research projects. A high quality tissue sample repository demands a standardized logistics for the sample transportation from the operating theater to the Institute of Pathology, as well as the careful and standardized preparation of the sample carried out by an experienced pathologist. In close cooperation with the Institute of Pathology, a repository of urologic tissue samples has been established in which tissue samples of all surgically treated malignant urologic tumors are introduced. This tissue repository is part of the CCC biobank. For the application of the required Standard Operating Procedures (SOP), we have established a close cooperation with the German Prostate Carcinoma Consortium (DPKK) e.V. and could furthermore introduce a web-based tissue database system that relies on the established clinical information system within the Department of Urology. All incorporated procedures are consistent with the legal, ethical, technical, and organizational regulations of tissue repositories and databases (patients' informed consent, data security, SOPs, and quality management). In order to meet future challenges of biobanking, we actively support the establishment of a general biobank infrastructure, Central Biobank Erlangen (CeBE). By introducing a broad consent document in conjunction with a digital consent management system, hosted by the Institute for Medical Informatics (MIK), a listing in the German Biobank Registry and a membership in the German Biobank Node, the CeBE will be established as a recognized biobank.

Biomarker patterns from the plasma of prostate cancer patients
Project manager: Prof. Dr. B. Wullich
As co-applicant of the BMBF-Project „Diagnostik mit Biomarker Mustern aus Plasma extra-zellulären Vesikeln (pEV) mit Methoden der künstlichen Intelligenz (KI)" (KI-VesD; PI Prof. A. Baur), we contribute with our clinical study center to the analysis of plasma samples of prostate cancer patients from our Department of Urology and Paediatric Urology. Extra-cellular vesicles that may originate as well from the tumor as from the host immune system, transport nucleic acids and proteins, that are specific for the tumor-host-tumor response. The aim of this project is to detect protein patterns by artificial intelligence techniques (Prof. J. Vera) that can be used in diagnostics and possibly also in prediction of therapy response.

Systemic tumor therapy, clinical trials
Project manager: Prof. Dr. P. J. Goebell
The medical care and treatment of patients with uro-oncologic diseases represents an integral part of our urologic expertise. Systemic therapy forms, besides the provision of surgical treatment, are among the fundamental sources of competence in urology. For this purpose, the outpatient center for uro-oncologic diseases (AURONTE) was founded together with the Department of Medicine 5 to draw therapeutic decisions based on a common interdisciplinary conference.
Thus, it can be assured that all currently activated and planned clinical trials are open to all common patients. Currently open clinical trials mainly focus on new therapeutic options for patients with bladder or prostate cancer. An overview of all currently active clinical trials can be found at: http://www.urologie.uk-erlangen.de/universitaetsmedizin/studienzentrale/aktuelle-studien/

- Sunniforcast: papillary and chromophob renal cell carcinoma: Nivolumab + Ipilimumab vs. Sunitinib
- Cabopoint (F-FR-60000-023): Renal cell carcinoma: Cabozantinib after immunotherapy
- CARAT: Epidemiologisches Register zur Darstellung der Behandlungsrealität und der Therapiemodalitäten beim behandlungsbedürftigen metastasierten oder lokal fortgeschrittenen Nierenzellkarzinom
- PCO: Prostate cancer: all patients with prostatectomy + active surveillance
- RhoVac-002: Prostate cancer: biochemical relapse without metastases after local curative therapy, rPE or RT.
- Talapro-2: Metastasized castration resistent prostate carcinoma (mCRPC): Talazoparib and Enzalutamid.
- Keynote 010: Metastasized castration resistent prostate carcinoma (mCRPC): Pembrolizumab + Olaparib after Docetaxel and AR-targeted therapy
- ARASENS: Metastatic Hormone Sensitive prostate Cancer (mHSPC): A randomized, double-blind, placebo-controlled Phase III study of ODM-201 vs. placebo in addition to standard androgen deprivation therapy and docetaxel.
- Keynote 866: Muscle-invasive bladder cancer patients: perioperative Pembrolizumab + neoadjuvant chemotherapy vs. Placebo + neoadjuvant chemotherapy
- CA 045-009: Muscle-invasive bladder cancer

patients: neoadjuvant and adjuvant Nivolumab + NKTR-214 vs. Nivolumab alone vs. Standard of care
- Niagara: Muscle-invasive bladder cancer patients: Durvalumab + Gemcitabine/Cisplatin neoadjuvant followed by Darvalumab adjuvant
- Titan: Muscle-invasive bladder cancer patients: after platinum-based chemotherapy Nivolumab with possible Ipilimumab Boost.
- Thor: Muscle-invasive bladder cancer patients: after platinum-based chemotherapy Erdafitinib vs. Vinflunin or Docetaxel or Pembrolizumab at detection of a FGFR gene mutation.
- Keynote 361: A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab with or without Platinum-Based Combination Chemotherapy vs. Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma
- STRONG: An Open-Label, Multi-Centre, Safety Study of Fixed-Dose Durvalumab + Tremelimumab Combination Therapy or Durvalumab Monotherapy in Advanced Solid Malignancies
- UroFollow: Marker-based follow-up care of patients with non muscle-invasive low//intermediate-risk bladder cancer

Evidence-based medicine
Project manager: PD Dr. F. Kunath
Evidence-based medicine is the focus of the research projects. It is the aim to use the current best evidence from clinical research to the care of individual patients. There is a close cooperation with the UroEvidence Group of the German Society of Urology and Cochrane Urology of the Cochrane Collaboration to develop high-quality systematic reviews and German language summaries.

Tumor genetic research with focus on identification of biomarkers
Project manager: PD Dr. S. Wach
The identification and characterization of specific biological properties of the prostate carcinoma as well as other malignant tumors, like kidney carcinoma, is the main focus of the research projects. By extensive research using primary tissue samples retrieved from the CCC Biobank, we were able to identify a collection of proteins and RNAs that have the potential for being valuable clinical biomarkers. This knowledge is now being transferred to an experimental diagnostic setting. This will be combined with the advantages of non-invasive biomaterial sampling by investigating protein- and RNA-based biomarkers in blood serum. Besides open surgery, all prostate cancer patients that are eligible for a curative prostatectomy are being offered to be treated by robot-assisted surgery using the da Vinci® surgical system. Here, patient's treatment is supported and supplemented by experimental therapy monitoring. Tumor-associated biomarkers are assessed prior to surgery as well as during the regular follow-up examinations in blood serum. A few selected biomarkers were already successfully validated as targets in experimental therapeutic trials in animal models.

Multifactorial models in uro-tumorpathology
Project manager: Prof. Dr. H. Taubert
In cooperation with the Institute of Pathology and the Tumor Center at the FAU, we collect and assign different clinico-pathological (e.g. TNM-stage, age, gender), tumor biological (e.g. hypoxia, cell lineage) and molecular parameters on RNA and protein level (e.g. stem cell-associated factors, new biomarkers) and analyze them in multifactorial models for their relevance in tumorigenesis, disease progress and survival of the urological tumor patients. We aim at supporting our physicians in identifying urological tumor patients and finding the right therapy stratification and therapy monitoring and in further expanding the basic, molecular knowledge for urological cancers.

Micro-RNA associated regulation of gene expressions in urologic cancers
Project manager: Prof. Dr. H. Taubert
In our ongoing DFG-Project „MicroRNA mediated regulation of key components of the Mediator Complex (MED) and its functional role in CRPC" (TA 145/17-1) we analyze, which microRNAs affect the transcriptional regulation through the Mediator Complex (MED) and which functional role these microRNAs play in castration resistant prostate cancer (CRPC). This is a DFG-cooperation project with partners from the University of Leipzig (Prof. A. Aigner) and the University of Innsbruck (Prof. Z. Culig). In *in vitro* (cell lines) and *in vivo* experiments (mouse and PDX-models) the identified microRNAs will be studied for their effect on tumor(cell)growth and the sensitization for anti-androgen therapies. Furthermore, in cooperation with the Institute of Pathology Erlangen (Prof. A. Hartmann/Dr. M. Eckstein) at applying immunohistochemistry, the clinical relevance of the microRNAs and the components of the MED complex will be determined for prognosis of prostate cancer patients.

Teaching

Medical students are taught in the lecture series of emergency medicine and in general and specialized urological lectures. Students also conduct a block practical in the Department of Urology or one of the associated teaching hospitals. The Department also allows additional education for achievement of the title medical specialist for urology. Additionally, specialized training courses are offered for Systemic Drug Tumor Therapy and the qualification 'Urologic Diagnostic Radiology'. For acquisition and improvement of specialized surgical techniques, the Department of Urology uses patient simulators. These include models for practicing sterile placement of catheters or laparoscopic methods including a simulator at the da Vinci® robotic surgery system for minimally invasive surgery. In addition, practical trainings for basic and advanced techniques in molecular urology are offered.

Selected Publications

Wach S, Taubert H, Cronauer M. Role of androgen receptor splice variants, their clinical relevance and treatment options. World J Urol. 2020 Mar;38(3):647-656.

König P, Eckstein M, Jung R, Abdulrahman A, Guzman J, Weigelt K, Serrero G, Hayashi J, Geppert C, Stöhr R, Hartmann A, Wullich B, Wach S, Taubert H, Lieb V. Expression of AR-V7 (Androgen Receptor Variant 7) Protein in Granular Cytoplasmic Structures Is an Independent Prognostic Factor in Prostate Cancer Patients. Cancers. 2020 Sep 16;12(9):2639.

Wach S, Brandl M, Borchardt H, Weigelt K, Lukat S, Nolte E, Al-Janabi O, Hart M, Graesser F, Giedl J, Jung R, Stoehr R, Hartmann A, Lieb V, Hoebel S, Peters A, Staeubert C, Wullich B, Taubert H, Aigner A. Exploring the MIR143-UPAR Axis for the Inhibition of Human Prostate Cancer Cells In Vitro and In Vivo
Mol. Ther. Nucl. Acids. 2019 Jun 7;16: 272-283

Goebell PJ, Ivanyi P, Bedke J, Bergmann L, Berthold D, Boegemann M, Busch J, Doehn C, Krege S, Retz M, Amsberg GV, Grimm MO, Gruenwald V. Consensus paper: current state of first- and second-line therapy in advanced clear-cell renal cell carcinoma. Future Oncol. 2020 Oct;16(29):2307-2328.

Kahlmeyer A, Stöhr CG, Hartmann A, Goebell PJ, Wullich B, Wach S, Taubert H, Erlmeier F. Expression of PD-1 and CTLA-4 Are Negative Prognostic Markers in Renal Cell Carcinoma. J Clin Med. 2019 May 24;8(5):743.

Sathianathen NJ, Oestreich MC, Brown SJ, Gupta S, Konety BR, Dahm P, Kunath F. Abiraterone acetate in combination with androgen deprivation therapy compared to androgen deprivation therapy only for metastatic hormone-sensitive prostate cancer. Cochrane Database Syst Rev. 2020 Dec 12;12:CD013245.

Kunath F, Jensen K, Pinart M, Kahlmeyer A, Schmidt S, Price CL, Lieb V, Dahm P. Early versus deferred standard androgen suppression therapy for advanced hormone-sensitive prostate cancer. Cochrane Database Syst Rev. 2019 Jun 11;6(6):CD003506.

Sikic D, Eckstein M, Wirtz RM, Jarczyk J, Worst TS, Porubsky S, Keck B, Kunath F, Weyerer V, Breyer J, Otto W, Rinaldetti S, Bolenz C, Hartmann A, Wullich B, Erben P. FOXA1 Gene Expression for Defining Molecular Subtypes of Muscle-Invasive Bladder Cancer after Radical Cystectomy. J Clin Med. 2020 Apr 2;9(4):994.

International Cooperations
Prof. Dr. Henrik Grönberg, Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden,

Prof. Dr. Lars Dyrskjot, Department of Molecular Medicine, Århus University Hospital, Århus, Denmark,

Dr. Boje Nielsen, Molecular Histology, Bioneer A/S, Hørsholm, Denmark,

Prof. Dr. Zoran Culig, Universitätsklinik für Urologie, Medizinische Universität Innsbruck, Innsbruck, Austria

UNIVERSITY HOSPITAL

Department of Operative Dentistry and Periodontology

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Research focus
- Clinical fractography on dental ceramic restorations
- Characterization of lithium silicate glass-ceramics
- Evaluation of new translucent zirconia
- Tailored mechanical test procedures to predict clinical failure mechanisms
- Amalgam alternative restoration materials
- Hydrolysis and fatigue of modern CAD/CAM restoration materials
- Novel materials and techniques for adhesive luting of glass-ceramic restorations
- Wear behavior of dental restoratives against zirconia

Structure of the Department

Professorship: 1
Personnel: 55
- Doctors (of Medicine): 22
- Scientists: 3
- Graduate students: 30

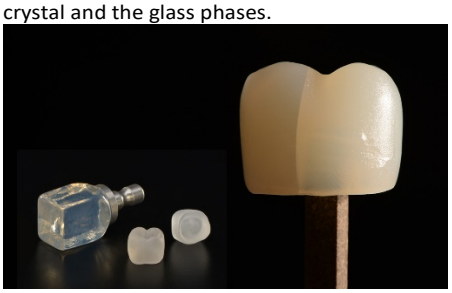
Clinical focus areas
- Operative Dentistry
- Endodontic treatment
- Systematic periodontal treatment
- Pediatric dentistry

Research

The main focus is on dental materials research with fields of expertise in basic science of operative and endodontic treatment procedures and correlation of experimental findings with clinical outcome. Independent, pre-clinical assessment and material development is a further area of interest of the research laboratory.

Clinical fractography on dental ceramic restorations
PI: R. Belli, U. Lohbauer
After the commercial launch of new dental ceramic materials, an increased incidence of intra- oral fractures or chippings has been observed. The method of fractography is intended to clinically analyze failed dental restorations in order to identify relevant fracture mechanisms. In principle, fracture surfaces are intraorally replicated and macroscopically or microscopically investigated, using light or scanning electron microscopy. Specific fracture patterns thus provide information of involved failure mechanisms and respective reasons for failure. In a joint project with a German CAD/CAM milling center, approximately 1,000 failed restorations were fractographically examined and relevant reasons for failure were assessed. Based on the results originating from the Department of Operative Dentistry and Periodontology, a new nonprofit organization (Fracto Forum International e.V.) was founded. An international hands-on workshop on dental fractography was organized in 2019 in Erlangen with support from the Institutes of Pathology (Prof. Hartmann) and Palaeontology (Prof. Munnecke).

Characterization of Lithium Silicate glass-ceramics
PI: R. Belli, U. Lohbauer
Restoratives based on Lithium Silicate glass-ceramics are relatively new, but a popular dental material. However, some intrinsic problems of these systems have been recognized both in the laboratory and clinic, namely, the susceptibility to thermal shock cracks and incompatibilities between the crystal and the glass phases.

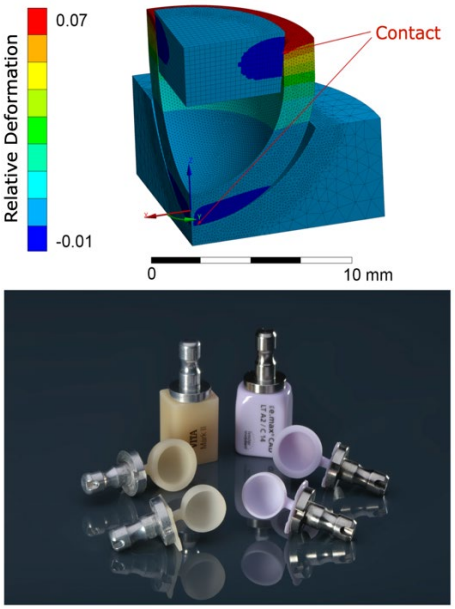


Spontaneously fractured dental crown due to thermal incompatibilities in the ceramic.

We investigate these phenomena in collaboration with the Department of Materials Science (Prof. deLigny) by studying the kinetics of nucleation and crystallization of commercial and experimentally synthesized formulations, especially the effect of zirconia addition, in order to gain insight into the thermal and mechanical behavior of these system, to ultimately improve their clinical performance.

Evaluation of new translucent zirconia materials
PI: R. Belli, U. Lohbauer
Modern zirconia dental restoratives have expanded their clinical indication towards improved optical properties. The compositional modifications in zirconia induce changes in the microstructure thereby reducing their mechanical properties significantly. We took these new zirconia materials under scrutiny by investigating their crystallographic polymorphs in collaboration with the Institute of Applied Mineralogy (Prof. Götz-Neunhoeffer). High-precision mechanical testing aided in establishing reliable structure-property relationships.

Tailored mechanical test procedures to predict clinical failure mechanisms
PI: R. Belli, U. Lohbauer
Our experience with fractographic evaluation of clinically fractured prosthetic components has shed light on the most common types of failure that happen during service in the oral environment. In order to fully comprehend the mechanical aspects of such failures, it is necessary to transfer the geometric and loading conditions to an experimental set-up. We developed model geometries such as that of dental crowns, digitally produced and machined them out of commercially available materials, and subjected this experimental setting to simulate the stress distribution in the mouth. In collaboration with the Department of Engineering Design (Prof. Wartzack) we reinforced our tests with computer simulations using the Finite Element method, which help identifying locations of stress concentrations that are used for the validation of the fracture test.



Simulation (above) of a model sphero-cylindrical model crown geometry, with ceramic test specimens (below).

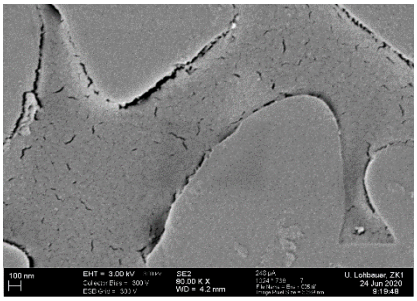
Amalgam alternative restoration materials
PI: R. Belli, U. Lohbauer
Amalgam has been used in the past for treatment of small, carious defects in a wide, permanent, and insurance-covered manner. Adhesive polymer based materials are not sufficiently economical, while glass ionomer based materials do not provide sufficient strength potential for permanent supply. In the research laboratory, new materials are being

investigated that meet the requirements of mechanical strength as well as cost-effectiveness without adhesive bonding and without light polymerization.

Hydrolysis and fatigue of modern CAD/CAM restoration materials
PI: R. Belli, U. Lohbauer
The amount of water taken up by an indirect restorative resin composite material is essential for the assessment of resistance against cyclic fatigue loading and dimensional expansion. We investigated the kinetics of water diffusion into polymer networks by employing a new technique – the Karl-Fischer Titration. We aimed to correlate the water uptake with mechanical fatigue degradation by correlating with dimensional changes of the restoration material upon hydrolysis.

Novel materials and techniques for adhesive luting of glass-ceramic restorations
PI: J.I. Zorzin, U. Lohbauer
One of the most important therapies in dentistry is the restoration of tooth structure defects with glass-ceramic restorative materials. The objective of the research work is to investigate novel materials and techniques for the adhesive luting of indirect glass-ceramic restorations - such as self-adhesive luting resins, universal adhesives and self-etching glass-ceramic primers - with regard to their mechanical load-bearing capacity. Investigations on self-adhesive luting resins showed that swelling and expansion stress of these materials are significantly influenced by their pH neutralization. Materials with low pH neutralization resulted in swelling and failure of ceramic restorations by fracture in vitro. For universal adhesives, sufficient adhesion to glass-ceramic restorative materials was only achieved when they were processed like conventional adhesives using hydrofluoric acid and silane. With self-etching glass-ceramic primers, adhesion was sufficient even without additional application of other materials.

Wear behavior of dental restoratives against zirconia
PI: E. Maier, U. Lohbauer



Wear mechanisms on the nanoscale using high-resolution SEM imaging.

The behavior of human enamel, as well as restorative materials, in the oral occlusion is a focus of clinical interest due to an increasing number of patients with stress-related craniomandibular dysfunction. The resistance of nanohybride composites and advanced ceramic materials to these mechanical fatigue stresses can be evaluated in preclinical settings.
Two-body wear - using an artificial chewing simulator in direct occlusal contact - versus three-body wear - employing a millet seed suspension to mimic food comminution – are used to simulate the direct contact of two antagonists. Increasingly popular Zirconia restoratives seem problematic in this aspect due to their diamond-like hardness. Micro-morphological investigations under the scanning electron microscope are used to analyze the causes of differences in abrasion behavior. The aim of our wear investigations is to enable preclinical predictability of the resistance and longevity of different restorative materials and thus to tailor clinical indications.

Teaching

The Department of Operative Dentistry and Periodontology is involved in the curricular teaching within the frame of the dental students' degree program. Interdisciplinary lectures are held at the institute of Biomaterials (Prof. Boccaccini). In 2018, the Department of Operative Dentistry and Periodontology released a comprehensive text book for dental students entitled „Werkstoffkunde in der Zahnmedizin – Moderne Materialien und Technologien". The Department offers supervision of Bachelor's and Master's theses as well as MD and PhD theses in conjunction with the Departments of Medical Technology, Biomaterials, Engineering Design, and Materials Science and Engineering.

Selected publications

Belli R, Zorzin JI, Petschelt A, Lohbauer U, Rocca GT. Crack growth behavior of a biomedical polymer-ceramic interpenetrating scaffolds composite in the subcritical regimen. Eng Fract Mech 2020;231:107014.

Belli R, Völkl H, Csato S, Tremmel S, Wartzack S, Lohbauer U. Development of a hoop-strength test for model sphero-cylindrical dental ceramic crowns: FEA and fractography. J Eur Ceram Soc 2020;40:4753-4764.

Belli R, Loher C, Petschelt A, Cicconi MR, de Ligny D, Anglada M, Lohbauer U. Low-temperature degradation increases the cyclic fatigue resistance of 3Y-TZP in bending. Dent Mater 2020;36:1086-1095.

Tiu J, Belli R, Lohbauer U. Rising R-curves in particulate/fiber-reinforced resin composite layered systems. J Mech Behav Biomed Mater 2020;103:103537.

Kirsten J, Belli R, Wendler M, Petschelt A, Hurle K, Lohbauer U. Crack growth rates in lithium disilicates with bulk (mis)alignment of the $Li_2Si_2O_5$ phase in the [001] direction. J Non-Cryst Solids 2020;532:119877.

Werbach K, Hummel S, Ebner C, Lohbauer U, Peterlik H. Pitfalls of determining the elastic properties of stabilized zirconia with indentation methods. Ceram Int 2019;47(B):9491-9496.

Lohbauer U, Wendler M, Rapp D, Belli R. Fractographic analysis of lithium silicate crown failures during sintering. SAGE Open Medical Reports. 2019;7:1-8.

Wendler M, Belli R, Lohbauer U. Factors influencing the development of residual stresses during crystallization firing in a novel lithium silicate glass-ceramic. Dent Mater 2019;35:871-882.

Maier EB, V.; Belli, R.; Taschner, M.; Petschelt, A.; Lohbauer, U.; Zorzin, J. New approaches in bonding to glass-ceramic: Self-etch glass ceramic primer and universal adhesives. J Adhes Dent. 2019;21:209-217.

Zorzin J, Beck S, Belli R, Petschelt A, Boccaccini AR, Lohbauer U. Adhesion and interfacial characterization of biomimetically texturized lithium disilicate. Int J Adhes Adhes. 2019;91:131-41.

International cooperations
Prof. H. Peterlik, Institut für Physik, Universität Wien, Vienna: Austria

Prof. T. Lube, Institut für Struktur- und Funktionskeramik, Montan Universität Leoben, Leoben: Austria

Prof. S. Scherrer, University of Geneva, Geneva: Switzerland

Prof. Y. Zhang, Penn State University, Pennsylvania, USA

Prof. J. Ferracane, Oregon Health & Science University, Portland, USA

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Research focus
- Tumor research
- Regeneration processes in inflamed and weakly replaced tissue
- Oral medicine
- Biomedical technology

Structure of the Department

Professorships: 2
Employees: 100
- Doctors: 18
- Scientists: 1
- Graduate students: 20

Clinical focus of care
- Tumor surgery and reconstructive surgery of the oral cavity and face
- Traumatology of the facial skull
- Surgery of malformations of the facial skull and orthognathic surgery
- Surgery of inflammatory diseases of the jaw bone
- dentoalveolar surgery
- Surgery of congenital cleft malformations

Research

The scientific focus in the Department of OCMFS lies on the field of tumor research, as well as on the further development of reconstructive surgery. Oral manifestations as symptoms of systemic diseases are studied as a bridge between dentistry and medicine. One working group works on digitalization projects in research and teaching. In addition, biomedical research is an established scientific aspect of the clinic.

Tumor Research
- Reconstruction and regeneration of weak tissues

In oral and maxillofacial reconstruction using microvascular grafts in irradiated tissue, postoperative thromboembolic complications and wound healing disorders occur in 3 - 20% of cases. Pathomorphologically, media fibrosis and endothelial damage and an over-expression of proliferative cytokines in the transition area between graft and bed are found. Since current fibrosis models describe this as a misguided recourse of embryonic tissue regeneration, this research focus consists of the analysis of highly conserved transcription factors of fibro-genesis in irradiated tissue.

- Tumor immunology

Carcinogenesis and tumor progression can be understood as immunologically mediated processes in the sense of tolerance induction to the tumor. We could demonstrate that there is a correlation between increased malignancy and enhanced M2 macrophage polarization. Regulatory mechanisms of macrophage polarization were also analyzed. In addition, a special focus has been laid on the investigation of prognostic and patho-physiological significance of checkpoint expression; which is investigated in the framework of a DFG-funded project. Here, an increased expression of the immune checkpoints PD-L1 and PD-L2 in oral carcinomas and an association between tumor progression and checkpoint mediated systemic immune tolerance could be shown. Furthermore, an association between local immunosuppression and malignant trans-formation of precursor lesions of oral cancer has been demonstrated. Further investigation has been processed in a prospective multicenter study (PREDICT-OLP).
In a project funded by Tumor Center Erlangen (D) NanoString analysis technology has been applied to investigate the expression of immune checkpoints in tissue samples and peripheral blood from patients with oral cancer.
In addition, we have been working on the establishment of an immunoscore for improved prognostic assessment of oral cancer and neoplasms of the facial skin. As part of this project, a Next-Generation Tissue Microarray is established. The goal is to add immunological parameters to the TNM score and to identify patient subgroups that may particularly benefit from adjuvant immunotherapy.
Additionally, it has been investigated whether a "liquid-immuno-biopsy" of tumor-specific mRNA and miRNA in peripheral blood is suitable as a diagnostic marker for tumor recurrence and as a predictive marker for the response to tumor therapy with checkpoint inhibitors. The long-term vision is to evaluate neoadjuvant low-dose radioimmunotherapy as an induction therapy prior to definitive surgical tumor therapy in the context of a prospective therapy study for patients with oral cancer.
We have also been working on the development of a multiple marker system for the early diagnosis and the degeneration potential of oral leukoplakias. For this purpose, genes and miRNAs directly involved in the malignant transformation of leukoplakia are to be identified by means of next generation sequencing.

Regenerative processes in inflamed and replacement-weak tissue
Since teeth and parts of the jaw bone are derivatives of the neuroectoderm (cranial neural crest), osteoblast progenitors of this region have specific cellular properties, e. g. a particular plasticity. Based on the model disease MRONJ, osteobiological and osteoimmunological characteristics and underlying signaling pathways are comparatively investigated with extracranial tissues in order to understand the exclusivity of these diseases in the maxillofacial region and to exploit the special cellular plasticity for regenerative medical approaches.

Oral Medicine
Chronic inflammatory diseases, such as inflammatory bowel disease, scleroderma or multiple sclerosis, are associated with a disturbed immune response. Due to the increasing incidence of these diseases, their investigation, especially with regard to interdisciplinary cooperation, is becoming more and more important. Current scientific studies show a clear association between chronic inflammatory diseases and periodontitis. However, their mutual influence with possible correlation of disease episodes to specific germ expressions has hardly been studied. In the future, characteristic mediators of inflammation will be investigated to demonstrate a possible link between oral biofilm and inflammatory responses of systemic diseases.

Biomedical technology
The research area of biomedical technology includes research projects on hard and soft tissue regeneration, healing processes of dental implants and laser applications. One research project focuses on the modulation and optimization of peri-implant tissues in the context of masticatory rehabilitation using implant-supported tooth replacements. This relates to the preclinical and clinical investigation of new techniques and materials for the regeneration of jaw defects and long-term stability of hard and soft tissues after jaw augmentation, as well as the regeneration of peri-implant soft tissues and their influence on the health of peri-implant structures. In a third-party funded study, we are currently evaluating the use of pluripotent stem cells from umbilical cord tissue in combination with tMP to optimize peri-implant hard tissue supply. Furthermore, we are investigating the time course of reperfusion and vascularization of free mucosal grafts and collagen matrices in the context of guided soft tissue regeneration. In collaboration with the Bavarian Laser Center (BLZ), we are also investigating tissue-specific laser surgery. We focus on saving specific tissue through non-contact tissue differentiation in soft and hard tissue surgery. In cooperation with the BLZ, we are working on the design of a sensor and process control concept that regulates the laser output in a tissue-selective manner.

Teaching

The Department of Oral and Cranio-Maxillofacial Surgery participates in the curricular teaching of medicine and dentistry with compulsory and elective courses. The elective courses "Skills Lab Facial Surgery" and "Microsurgical skills lab" have been designed for medical students. In this course, they learn the basics of local flap plastic surgery using a porcine model. In addition, theoretical and practical knowledge of microsurgical techniques is taught. The curricular teaching of dentistry also includes digital courses, which were conceived in cooperation with the Department of Hand Plastic Surgery at Erlangen-Nuremberg University Hospital and the Department of Oral and Maxillofacial Surgery of the Klinikum rechts der Isar in Munich. The course "eReconstruction", funded by the Virtual University of Bavaria (VHB), enables interested participants to learn aspects of plastic-reconstructive surgery free of charge. The development of the VHB courses eRadiology and eOral Surgery even before the pandemic enabled a transition-free change from present teaching to a complete mapping of teaching content in virtual space as part of curricular teaching. Medical students also have the option of taking clinical electives. For medical students, there is also the possibility of taking clinical traineeships, as well as the elective subject „Oral and Maxillofacial Surgery“ in the final year of medical school.
Furthermore, (dental) medical and scientific doctorates are supervised.

Selected publications

Nobis CP, Kesting MR, Wolff KD, Frohwitter G, Rau A, Weitz J Development of a template tool for facilitating fibula osteotomy in reconstruction of mandibular defects by digital analysis of the human mandible. Clin Oral Investig 2020; 24(9): 3077-3083

Weber M, Söder S, Sander J, Ries J, Geppert C, Kesting M, Wehrhan F Craniofacial Osteosarcoma-Pilot Study on the Expression of Osteobiologic Characteristics and Hypothesis on Metastasis. Front Oncol 2020; 10 :745.

Weber M, Wehrhan F, Baran C, Agaimy A, Büttner-Herold M, Öztürk H, Neubauer K, Wickenhauser C, Kesting M, Ries J Malignant transformation of oral leukoplakia is associated with macrophage polarization. J Transl Med 2020; 18(1):11

Ries J, Wehrhan F, Baran C, Agaimy A, Danzer E, Bolzel S, Buettner-Herold M, Kesting M, Weber M xpression of the Immune Modulators of the PD-1: PD-L1 Axis in oral Leukoplakia Oncology Research and Treatment 2020; 43: 99-100

Weber M, Amann K, Homm A, Mueller S, Ries J, Geppert C, Preidl R, Kesting M, Wehrhan F Zoledronate Shifts Macrophage Polarization towards M1 in Vivo - An Animal Study on Wistar Rats Oncology Research and Treatment 2020; 43: 100-100

Poon KK, Wurm MC, Evans DM, Einarsrud MA, Lutz R, Glaum J Biocompatibility of (Ba,Ca)(Zr,Ti)O3 piezoelectric ceramics for bone replacement materials. J Biomed Mater Res B Appl Biomater 2020; 108(4): 1295-1303

Rode C, Wyrwa R, Weisser J, Schnabelrauch M, Vučak M, Grom S, Reinauer F, Stetter A, Schlegel KA, Lutz R. Novel Resorbable Composite Material Containing Poly(ester-co-urethane) and Precipitated Calcium Carbonate Spherulites for Bone Augmentation-Development and Preclinical Pilot Trials. Molecules. 2020 Dec 28;26(1):102.

International cooperation

Prof. Glaum Department of Materials Science and Engineering Faculty of Natural Sciences NTNU, Trondheim

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Department of Orthodontics and Orofacial Orthopedics

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Research focus
- Influence of different regulators on orofacial cleft development
- Identification of genetic risk variants by molecular genetics
- Oral symbiosis and dysbiosis
- Histological and histomorphometric investigation of the midpalatal suture
- MRI for cephalometric analysis in orthodonic diagnosis
- In vitro simulation of orthodontic processes
- Material scientific examinations of orthodontic materials

Structure of the Department

Professorship: 1
Personnel: 23
- Doctors (of Medicine): 10
- Scientist: 1
- Graduate students: 11

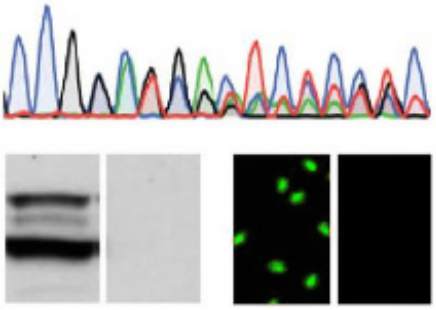
Clinical focus areas
- Treatment of newborn babies with cleft lip and/or palate
- Orthodontic treatment of cleft lip and/or palate
- Orthodontic treatment of dysgnathia / malformations of the upper and/or lower jaw
- Orthodontic treatment of craniofacial anomalies and syndromes
- Orthodontic treatment of tooth displacement
- Orthodontic treatment of tooth agenesis (hypo- or oligodontia)
- Evidence-based orthodontics
- Adult orthodontic treatment

Research

Research of the Department of Orthodontics and Orofacial Orthopedics addresses molecular causes for many of our patients' conditions: cleft lip and/or palate (CL/P), craniofacial dysgnathia, tooth agenesis (hypo- or oligodontia) as well as molar incisor hypomineralization and periodontitis. Other research areas are the composition of the oral microbiome, the histomorphometric analysis of the *Sutura palatina*, the implementation of three-dimensional diagnosis in orthodontics, *in vitro* analyses of molecular processes during orthodontic treatment and material scientific examinations of orthodontic materials.

Influence of different regulators on orofacial cleft development

Cleft lip and/or palate are frequent congenital malformations. Etiology is complex, poorly understood and involves environmental and genetic factors. In order to achieve a better understanding of genetic causes for CL/P we analyze the function of several regulators of palate development in a joint IZKF-funded project with the Chair of Biochemistry and Pathobiochemistry.



Analysis of a gene knockout via DNA sequencing (upper row), western blot (lower left) and immunocytochemistry (lower right)

Identification of genetic risk variants by molecular genetics

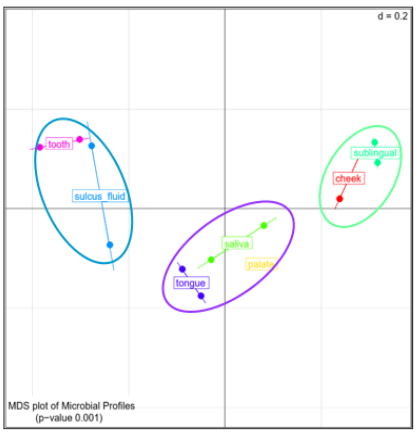
In order to identify risk factors for CL/P, we examine DNA samples from a broad range of patients and, if applicable, their relatives and compare them to data from control groups. In cooperation with the Institutes of Human Genetics of the university hospital of Bonn and of UK Erlangen, we perform next generation sequencing analyses enabling us to analyze large regions of DNA up to whole genomes. Our aim is always to pinpoint (possibly inherited) changes in the patient's DNA sequence that lead to the manifestation of the disease. Chromosomal regions identified in this way serve to find and characterize responsible genes. Those genes are examined in detail with regard to their biological function and how it might cause the cleft. Using the described molecular genetic methods, we also seek to identify relevant genetic loci for craniofacial dysgnathia, tooth agenesis (hypo- or oligodontia).

In further molecular genetic analyses, we seekto identify gene variants contributing to formation and progression of periodontitis. Although the impact of a genetic component is estimably 33 – 50 %, only a few risk variants have been identified up to now. In order to identify unknown genetic variants causing a higher risk for periodontitis, we perform expression quantitative trait locus (eQTL) analyses. By this innovative method, we can identify changes in the transcriptome of immune cells stimulated with periodontal virulence factors and attribute them to certain gene variants. With the same technique, we investigate on genetic factors influencing atherosclerosis and allergies against metals. For these comprehensive analyses, we cooperate with the Institute of Human Genetics and the Institute of Medical Microbiology, Immunology and Parasitology of the university hospital of Bonn and with the Department of Cardiology, Angiology and Pneumonology of the university hospital of Heidelberg and Center of Human Genetics of the university hospital of Marburg.

At best, our molecular genetic analyses lead to new diagnostic possibilities that could direct appropriate therapeutic measures in the sense of personalized medicine. The acquired knowledge might also help to develop new medication and preventive measures.

Oral symbiosis and dysbiosis

In order to identify patients at risk and to define prognostic factors for oral dysbiosis and disease, we analyze the oral microbiome and local cytokine concentrations in cooperation with the Institute of Clinical Microbiology, Immunology and Hygiene using 16S rDNA sequencing and multiplex immuno assay in different patient cohorts. Thereby, we analyze microbiome composition and cytokine concentrations in specific oral niches (palate, tongue, cheek, sublingual, plaque, sulcus fluid and saliva).



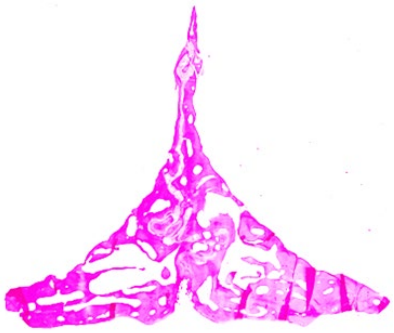
MDS plot to depict microbial diversity within specific oral niches of two different probands.

Histological and histomorphometric investigation of the midpalatal suture

The hard palate and the mid-palatal suture are of pivotal importance in orthodontics. By

means of palatal expansion in cases of transverse maxillary deficiency, the upper jaw can be widened while simultaneously improving nasal breathing, which is also of general medical relevance. Depending on patients´ age, different orthodontic appliances are employed from ordinary braces to surgical assisted procedures, which involve a subtotal Le Fort I osteotomy in adults.

The aim of the present study, which is conducted in collaboration with the Institute of Functional and Clinical Anatomy, is to gain further insight into the morphology and metabolism of the midpalatal suture in different age groups. Histologic and histomorphometric analysis are employed to enhance the understanding of the midpalatal suture.



HE-staining of the mid-palatal suture

MRI for cephalometric analysis in orthodontic diagnosis

For several years, our department has examined the potential and possibilities of three-dimensional imaging for different orthodontic questions. Currently, lateral cephalometric radiographs (LCR) are still routinely used for cephalometric analysis in regards to orthodontic diagnosis and treatment planning. However, this two-dimensional method has several disadvantages such as structure impositions, the dependence of the correct head positioning and last but not least the radiation exposure. Therefore, we are working on using magnetic resonance imaging (MRI) for three-dimensional cephalometric analysis in order to overcome these limitations. However, this technology was originally introduced for soft tissue imaging. In recent years, the representation of hard tissue became more and more popular by new developments. In collaboration with the Fraunhofer Institute for Integrated Circuits IIS in Würzburg and the Institute of Radiology of UK Erlangen, we developed special MRI sequences with ultra-short echo times in order to enable hard tissue imaging (as teeth and bone) according to our requirements. Following, we established a reliable method for implementation of cephalometric analysis in the three-dimensional MRI dataset. With a series of studies, we want to proof the clinical comparability of the MRI and LCR-based cephalometric results. The long-term aim of our project series is to introduce MRI-based cephalometric analysis as an available diagnostic tool in orthodontics and as consequence to reduce radiation exposure especially of children and adolescents caused by orthodontic reasons.

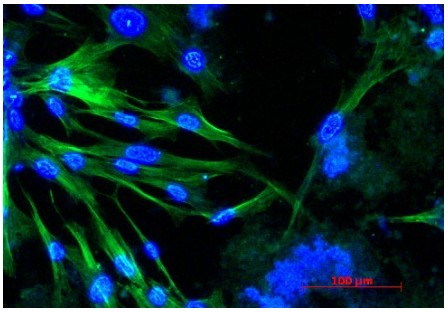
***In vitro* simulation of orthodontic processes**

During orthodontic treatment, tensile strain and pressure load lead to formation and degradation of alveolar bone, respectively. We want to shed light on the molecular processes during these processes and to improve our understanding of bone remodeling. To this aim, we use different cell culture-based *in vitro* models such as the simulation of orthodontic pressure load by applying glass disks of defined weight onto human periodontal ligament fibroblasts.

Material scientific examinations of orthodontic material

Further research fields are material scientific examinations of orthodontic materials and the development of antibacterial material for orthodontic applications. For instance, by using these materials as bonding material for brackets in the long term, we want to reduce number and size of demineralized areas after removal of fixed multibracket appliances, thus minimizing risk of caries for patients.

Additionally, investigations concerning the biocompatibility as well as cyto- and genotoxicity of orthodontic materials are conducted in our department. By means of the γH2AX assay, the genotoxic potential of e.g. orthodontic meth-acrylate-based adhesives is investigated *in vitro*. Moreover, EC-50 curves of clinical relevance are established.



Calcein-staining (green) and DAPI counterstain (blue) of human gingival fibroblasts in order to detect living cells

Teaching

The Chair of Dental, Oral, and Maxillofacial Medicine – especially Orofacial Orthopedics is engaged in dental medicine. Within the scope of orthodontic analysis and treatment, the curriculum comprises comprehensive clinically based material. Skills lab work enables the students to collect and evaluate diagnostic data and to control the clinical application of orthodontic devices.

In addition, MD and PhD theses are supervised, and residents are further trained to become specialized orthodontists according to the Bavarian Curriculum.

Selected recent publications

Safi S, Frommholz D, Reimann S, Götz W, Bourauel C, Neumann AL, Hoerauf A, Ilges H, Safi AF, Jäger A, Hübner MP, Gölz L (2019) Comparative study on serum-induced arthritis in the temporomandibular and limb joint of mice. Int J Rheum Dis DOI 10.1111/1756-185x.13486

Buerfent BC, Gölz L, Hofmann A, Ruhl H, Stamminger W, Fricker N, Hess T, Oldenburg J, Nöthen MM, Schumacher J, Hübner MP, Hoerauf A (2019) Transcriptome-wide analysis of filarial extract-primed human monocytes reveal changes in LPS-induced PTX3 expression levels. Sci Rep 9(1):2562. DOI 10.1038/s41598-019-38985-x

Taubmann A, Willershausen I, Walter C, Al-Maawi S, Kaina B, Gölz L (2020) Genotoxic and cytotoxic potential of methacrylate-based orthodontic adhesives. Clinical Oral Investigations DOI 10.1007/s00784-020-03569-x

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Seidel CL, Gerlach RG, Wiedemann P, Weider M, Rodrian G, Hader M, Frey B, Gaipl US, Bozec A, Cieplik F, Kirschneck C, Bogdan C, Gölz L (2020) Defining Metaniches in the Oral Cavity According to Their Microbial Composition and Cytokine Profile. International journal of molecular sciences 21(21) DOI 10.3390/ijms21218218

Seidel A*, Seidel CL*, Weider M, Junker R, Gölz L, Schmetzer H (2020) Influence of Natural Killer Cells and Natural Killer T Cells on Periodontal Disease: A Systematic Review of the Current Literature. International journal of molecular sciences 21(24) DOI 10.3390/ijms21249766; *contributed equally

UNIVERSITY HOSPITAL

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Research Focus
• Dental biomechanics
• Psychogenic influence/quality of life and complementary medical procedures in dental questions
• Optical 3D-measurement technique in dentistry
• CAD/CAM research laboratories
• Prosthodontics and Implant therapy based on 3 dimensional Imaging

Structure of the Department

Professorships: 2
Personnel: 45

- Doctors (of Medicine): 17
- Scientists: 11 (thereof funded externally: 0)
- Graduate students: 10

Clinical focus areas

- Implant prosthetics
- Fixed and removable prosthetic
- Diagnosis and treatment of temporomandibular joint Dysfunction (TMJD)
- Hypnosis and acupuncture treatment
- Esthetic Dentistry
- Prosthetic rehabilitation with epithesis
- Prosthetic rehabilitation of children

Research

Due to the high demands and quality standards of research projects, synergistic effects of highly qualified specialists are mandatory. This is reflected in the general orientation and a focus on future demands as well as in extensive cooperation with other fields of research. One key focus of research is the aging population and the resulting demographic changes and the investigation of the relationship between oral and general health.

Dental biomechanics
Project manager: PD Dr. R. Matta, Dr. C. Motel
Due to the lack of suitable metrological methods, it has so far been possible only to a very limited extent and in individual cases with very complex experimental set-ups to represent and quantitatively determine biomechanical influences in the oral cavity. A large number of theories on a wide variety of questions have so far neither been clearly confirmed nor refuted scientifically. The aim of the research area is to optimize a renewed, non-contact 3D optical deformation measurement system for clinical in vivo application on patients in order to enable quantitative measurements of biomechanical influences in the oral cavity in real time in future studies and to initiate innovative questions through in vitro investigations. In ongoing and completed in vitro investigations in the fields of material science and biomechanics, the previously existing system has proven its worth. In addition, the first in vivo pilot studies on force-correlated tooth movements have demonstrated a corresponding clinical application. An innovation introduced in the reporting period was the investigation of deformations of implants, superstructures and bone under simulated chewing force, which allows dynamic changes on surfaces to be represented with high precision. For this purpose, the current version of the ARAMIS system from GOM GmbH, which is innovative in dental research, was purchased and already established through its presentation at a specialist congress. The first goal here was to demonstrate the advantages in the field of dental biomechanics over the conventional measuring methods currently used in this field, such as strain gauges. This method opens up a wide range of scientific applications for the future.

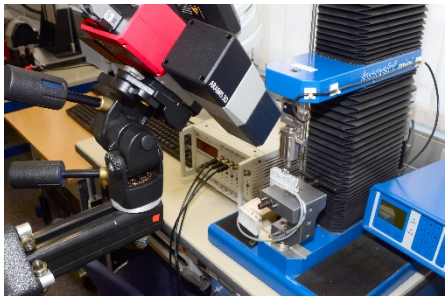

Fig. 1: A new optical 3D measurement technology for biomechanical implant deformation.

Psychogenic impact/quality of life and complementary medical procedures in dental questions
Project manager: Prof. Dr. S. Eitner
This area of research is divided in two main focal points. The first focal point evaluates psychogenic influence on treatment planning and outcome of dental disease patterns with a psychogenic background. Among other factors, the subject's appraisal of his own body can influence dental questions. Besides, the etiological correlation of gag reflexes during dental treatment, the influence of stress and clinical pictures on fear, depressive states, and social parameters are evaluated, too. The second focal point concerns the therapeutic intervention with medical hypnosis and acupuncture in dental treatment and their influence on psycho-social factors as well as pain in above mentioned dental problems.

Optical 3D-measurement technique in digital dentistry
Project managers: PD Dr. R. Matta, Dr. C. Motel, Dr. J. Ries
There is currently a change in technology in the field of dental impression taking. Digital impressions are becoming more established and their indication has been expanded to include multi-unit bridges, extensive implant restorations and bite registration as a result of constant technological progress from single-tooth crowns.
This research area evaluates the accuracy of digital impressions taken by intraoral scanners - also in comparison with conventional methods. This involves investigating which scan protocols, i.e. which sequence of work steps, can lead to the best possible digital imaging of the oral situation. In addition, various parameters of digital impression taking are considered, such as the geometry of the scan bodies required for digital implant impression taking and the various intraoral scanners available on the market, in order to assess the quality and reproducibility of this technology.

CAD/CAM research laboratories
Project managers: PD Dr. R. Matta, Dr. L. Berger
Industrial CAD/CAM manufacturing technologies have gained significant market share in producing dental restorations in recent years, primarily due to standardized product quality and precision as well as economic processing routine in dental laboratories. To achieve high quality and precision, product aligned process routes are a mandatory prerequisite. The research group focuses on segmenting CAD/CAM processes and assessment of the impact on the overall quality. In addition to recently developed methodologies for 3D-display and analysis of microgaps in conventional dental restorations, new protocols are in development for a clinical assessment of fit of implant retained superstructures. The research laboratories are equipped with state-of-the-art industrial non-contact scanners and necessary analytical software programs. As high strength oxide ceramics are applied more frequently as framework materials in dentistry, several research projects assess the clinical application and factors influencing longterm success.

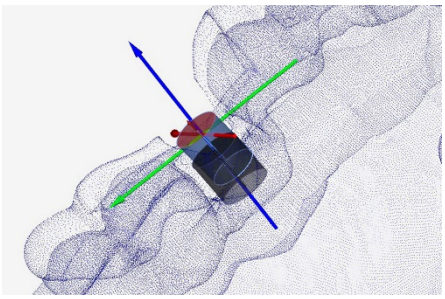

Fig. 2: Comparison of the accuracy of CAD/CAM implant tem- plate to virtual planning.

Prosthodontics and Implant therapy based on 3 dimensional Imaging
Project managers: PD Dr. R. Matta, Dr. A. Seidel, ZÄ S. Knapp
The three dimensional imaging becomes more and

more important for the modern implant and prosthodontic therapy plan. This includes the Computer Tomography (CT), the Cone Bean Computer Tomography (CBCT) and the intraoral digital impression. The focus is on the three dimensional accuracy of the X-ray imaging. In addition, the impact of different dental implant materials on the appearance of artifacts in the 3-dimensional virtual model is investigated. In this context a new method for the 3-dimensional evaluation of CT and CBCT images has been developed. The research in this area is of great importance and interest because the long-term clinical success of prosthodontic and implant restorations depends on the accuracy of the three dimensional transfer of oral structures in “virtual” illustrations.

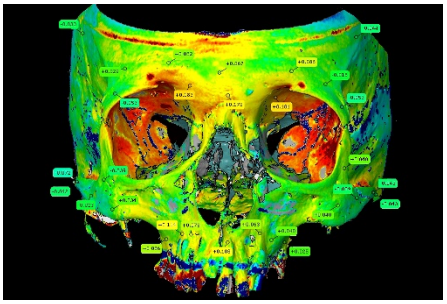

Fig. 3: Illustration of 3 D deviation of CBCT in comparison to optical reference scan.

Functional diagnostics

Project managers: PD Dr. R. Matta, Dr. C. Loibl

The specialty of functional diagnostics is becoming increasingly important and is related to numerous factors, both physical and environmental. Craniomandibular dysfunction, or CMD, is a collective term for a heterogeneous group of disorders that can affect the temporomandibular joint, the masticatory muscles and/or other adjacent structures in the head and neck region. Because the etiology of craniomandibular dysfunction is not yet fully understood, a multifaceted and reversible approach to treatment is recommended. This includes splint therapy, but also manual therapy by specialized physiotherapists. This research area investigates the effects of the different forms of therapy. On the one hand, a back scanner and 3D raster stereography are used to investigate whether and to what extent the various forms of therapy cause changes in posture and individual parameters such as lordosis and kyphosis angles or pelvic rotation. On the other hand, the research area will use scans of the bite situation of patients at different points in time during treatment to examine the extent to which, for example, splint or manual therapy influences the occlusion of the dentition. The aim is to be able to draw conclusions about the extent of the treatment results and their implications for everyday practice.

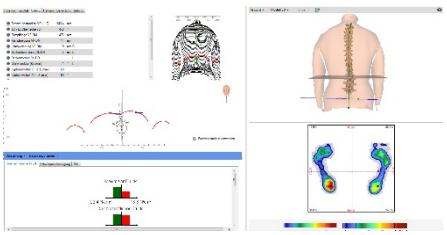

Fig. 4: 3D illustration examples of the spinal reconstruction and foot pressure measurement using the Diers Formetric 4D.

Teaching

The main focus of traditional prosthodontic education has shifted from a technically oriented towards an interdisciplinary treatment approach. Prophylaxis and biology are in the focus as well as minimally invasive treatment concepts. Clinically relevant topics are introduced into the preclinical curriculum, focusing on biologic interactions and material properties. While theoretical knowledge remains integral part of dental education, manual manufacture of dental restoration will be taught only exemplarily. Two new extra-curricular courses have been introduced, through which the new treatment options and theoretical principles of digital dentistry are made available to students of clinical treatment courses in dentistry I and II on a voluntary basis in one-week courses. Doctoral projects are offered at the Chair of Dental Prosthetics within the various research areas and supervised by the scientific staff.

Selected Publications

Motel C, Kirchner E, Adler W, Wichmann M, Matta RE. Impact of Different Scan Bodies and Scan Strategies on the Accuracy of Digital Implant Impressions Assessed with an Intraoral Scanner: An In Vitro Study. J Prosthodont. 2020 Apr;29(4):309-314.

Wolf L, Bergauer B, Adler W, Wichmann M, Matta RE. Three-dimensional evaluation of mandibular deformation during mouth opening. Int J Comput Dent. 2019;22(1):21-27.

Matta RE, Motel C, Kirchner E, Stelzer SP, Adler W, Wichmann M, Berger L. Wear of feldspathic-ceramic-veneered zirconia posterior FPDs after 10 years. BMC Oral Health. 2020 Nov 30;20(1):345.

Schmitt CM, Brückbauer P, Schlegel KA, Buchbender M, Adler W, Matta RE. Volumetric soft tissue alterations in the early healing phase after peri-implant soft tissue contour augmentation with a porcine collagen matrix versus the autologous connective tissue graft: A controlled clinical trial. J Clin Periodontol. 2021 Jan;48(1):145-162.

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Institute of General Practice

Chair of General Practice

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Research focus
- ACE – Adverse Cascade Effects
- ICF – International Classification of Functioning, Disability, and Health
- ICE – Ideas, Concerns, Expectations
- Clinical governance
- GAP – Good doctor –patient communication
- WirtMed
- BayFoNet - Bayerisches Forschungsnetz Allgemeinmedizin
- PRICOV-19
- Development of classifications to describe the content of primary care
- BeLa (Beste Landpartie) for general practice
- Competence center vocational training for general practice Bavaria (KWAB)

Structure of the Institute

Institute of General Practice: Professorship: 1
Personnel: 16
- Doctors (of Medicine): 5
- Scientists: 7
  (thereof funded externally: 5)
- Graduate students: 18 MVZ Eckental:
- Personnel: 10
- Physicians (general practitioners): 4

Clinical focus area
General practice in the medical care center (MVZ) Eckental and Igensdorf

Research

The Institute of General Practice focuses on health services research with a particular emphasis on medical overuse and underuse in ambulatory care. These topics have been the focus of the research network PRO PRICARE. The funding of PRO PRICARE research by the BMBF ended in 2020 after three years of work. Overuse is not only a problem in the context of limited financial resources in an aging society, but also in a situation of a lack of future GPs. The main challenge is how to identify and reduce overuse and underuse. In PRO PRICARE, we have established a broad and long-term cooperation network together with chairs and institutes of the FAU, the UK Erlangen, practice networks in the region of Northern Bavaria, the Association of Statutory Health Insurance Physicians of Bavaria (KVB) and the GWQ ServicePlus AG (representing the company health insurance funds). Within the network, three research projects are being carried out:

ACE – Adverse Cascade Effects
Analysis of pathways of healthcare for patients with thyroid problems with a focus on cascade effects initiated by non-indicated ultrasound examinations. Three studies are conducted:
1) Routine data analysis: comparison of different groups of patients regarding morbidity, health care utilization and costs.
2) Medical record analysis and qualitative interviews: Describing individual treatment pathways.
3) Multi Criteria Decision Analysis: Exploration of motives and attitudes that influence the decision making of patients and physicians.

ICF – International Classification of Functioning, Disability, and Health
Development of a core set of the ICF to assess the functional health of old and very old people. For this purpose, a systematic review, qualitative interviews with elderly patients, an expert survey and a quantitative survey of the health status of elderly people were conducted and published. We are currently working on integrating the four preliminary core sets into a final core set. The core set will then be the basis for the development of a self-report questionnaire for patients. In the future application of the ICF in primary care practice, the effects on patient-related outcomes will be examined with the aim of being able to distinguish useful from useless interventions.

ICE – Ideas, Concerns, Expectations
The project aims to examine whether strengthening patient-centered communication according to the ICE technique can reduce unnecessary diagnostic and therapeutic measures in patients with acute uncomplicated low back pain. Quantitative and qualitative surveys are used to evaluate the importance of patient-centeredness in consultations with primary care physicians.

Clinical governance
The upcoming shortage of primary care physicians in combination with an increasingly aging and chronically ill population calls for solutions to ensure a high level of primary care in the long term. With clinical governance, workflows within a group practice should be harmonized through the development of electronic tools (macros/text modules), documentation quality should be improved and treatment should be adapted to the recommendations of current guidelines.

GAP – Good Doctor – Patient Communication
The GAP study is providing primary care physicians and patients with low back pain with the highly navigable and easy-to-understand internet portal "tala-med". The information is intended to support joint decision-making for diagnostics and therapy.The quality of consultations using the portal will be tested in a prospective, multicenter, cluster-randomized parallel group design. Funding: Innovation Fund of the G-BA.

WirtMed
In WirtMed, new tools are being developed and tested that will enable the associations of statutory health insurance physicians and health insurance funds to review and meaningfully control the cost-effectiveness and quality of drug prescriptions in the future. WirtMed is a consortium project of various universities, KVs and health insurance companies under the leadership of the Department of General Medicine at the Philipps University of Marburg (Prof. Dr. N. Donner-Banzhoff). Our institute is conducting qualitative studies to explore the experiences of GPs and specialists with the Bavarian Agreement on Active Pharmaceutical Ingredients (Bayerische Wirkstoffvereinbarung). Funding: Innovation Fund of the G-BA

BayFoNet - Bavarian Research Network General Practice
BayFoNet is a Bavarian-wide research network established by the Institutes of General Practice in Würzburg, Munich (LMU and TUM) and Erlangen. BayFoNet is funded by the BMBF with about 2 million Euros. The aim is to strengthen research on relevant questions of daily care in general practice. The aim is to recruit 240 practices as research partners. A comprehensive training program is being developed to promote the research skills of primary care physicians. It is intended to enable participants to carry out research projects at a high level and to develop their own project ideas.

PRICOV-19 Study - Primary Care in times of Covid-19
The COVID-19 pandemic has brought unpredictable challenges to the delivery of care in primary care practices. The PRICOV-19 study is an international survey in more than 35 countries that examines the impact of the COVID-19 pandemic on the organization of care in primary care practices. The focus of this ongoing online survey is to determine access to and assurance of patient care in the primary care physician sector

Development of classifications to describe the content of primary care
Since 2006, Prof. Dr. T. Kühlein is a member of the WONCA International Classification Committee (WICC). Furthermore, he has been a member of the Executive Committee since 2012 and was head of the latter until 2020. The WICC is occupied, among other things, with the actualization and further development of the International Classification of Primary Care (ICPC). WONCA is the international organization for general practitioners. Since October 2014, Prof. Dr. T. Kühlein is the

delegate of WONCA to the "Family of International Classifications Council" of WHO. Joint research and development projects are conducted in cooperation with the universities of Gent (Belgium) and Nijmegen (The Netherlands) on the coding of ICE and concerning the use of the ICF in primary care.

BeLa (Beste Landpartie) for general practice
Due to a lack of young GPs, primary care especially in rural areas is in jeopardy. BeLa is a strategy to secure the recruitment of GP trainees by teaching students the advantages of a rural career track. The BeLa program examines whether financial and contentual support of students during the clinical part of the studies combined with a practical training in rural areas enhances the willingness to a subsequent vocational training and settlement these regions. Individual and motivational factors for a settlement in rural areas are identified in a qualitative process evaluation.

Competence center vocational training for general practice Bavaria (KWAB)
The offers issued by the competence center aim at improving the contentual and didactical quality of vocational training in general practice to secure high quality primary care in Bavaria. Additionally, the undertaken measures will be reviewed and evaluated with regard to their effect. Under the umbrella of the competence center, seminars that accompany vocational training are offered regularly for future general practitioners. Furthermore, an experienced GP mentor is assigned to every young colleague in training. The competence center additionally offers Train-the-Trainer seminars for doctors that are licensed for vocational training in order to strengthen their didactic competence and hence optimize the quality of vocational training in practices. The Institute of General Practice has taken on the lead and coordination of the KWAB.

Teaching

In the light of the COVID 19 pandemic, the Institute of General Practice has revised its entire teaching content to a digital format. Since summer 2020, the curricular lectures "General Practice" and selected preclinical and clinical electives are available purely digitally and asynchronously. This ensures that students can work on the course independent of time and location. In addition to the curricular lecture General Practice, the institute offers specific general practice electives on "Anamesetraining", "Problem-oriented learning on clinical cases" as well as the elective "Smart decisions in everyday clinical practice" certified by the German Network of Evidence-Based Medicine DNEbM e.V.. The newest member of the elective family is "Medical On-Call Service". In this elective, students are introduced to typical primary care emergencies. As soon as the pandemic situation will allow it again, students can also participate as observers in the driving service of the medical on-call service. We are pleased to have been able to recruit the experienced general practitioner and leading emergency physician Dr. Thomas Ruppert as a lecturer for this elective. The teaching program of the Institute of General Practice is rounded off by the interprofessional teaching project "Ohne Sorge in die Niederlassung" ("Without Worry into Establishing a Practice"), which offers a business game on how to take over a practice and establish a contract physician. The Institute of General Practice cooperates closely with the Association of Statutory Health Insurance Physicians in Bavaria, the Aktivsenioren e.V. and experts from the fields of law and finance. With this offer, the fears of young physicians about the economic responsibility of the practicing physician are specifically prevented.
Teaching research is primarily concerned with the implementation of digital teaching in medical studies, as well as the integration, analysis and evaluation of scientific competence and the critical handling of medical information in medical studies against the backdrop of the upcoming changes brought about by the Master Plan 2020.
Bachelor's and master's theses as well as medical and scientific promotions are supervised.

Selected publications

Heinmüller, S., Schaubroeck, E., Frank, L., Höfle, A., Langer, M., Saggau, K., Kuehlein, T. (2020). The quality of COPD care in German general practice-A cross-sectional study. Chron Respir Dis, 17, doi:10.1177/1479973120964814

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Tomandl J, Book S, Hoefle A, Graessel E, Sieber C, Freiberger E, Kuehlein T, Susann Hueber, Gotthardt S. (2020) Laying the foundation for a primary care core set of the International Classification of Functioning, disability and health (ICF) for community-dwelling older adults: a qualitative study. J Rehabil Med; 52: jrm00150

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van der Keylen, P., Maun, A., Hoyer, S., Roos, M., Beier, M., Voigt-Radloff, S., & Frank, L. (2019). "Mind the gap" - Verzahnung von Wissenschaft und hausärztlicher Praxis. Zeitschrift für Allgemeinmedizin, 179-184. doi:10.3238/zfa.2019.0179-0184

Voigt-Radloff, S., C. Schöpf, A., Boeker, M., Frank, L., Farin, E., Kaier, K., Maun, A. (2019). Well informed physician-patient communication in consultations on back pain – study protocol of the cluster randomized GAP trial. BMC Fam Pract, 20. doi:10.1186/s12875-019-0925-8

International cooperations
Prof. Dr. J. de Maeseneer, Department of Family Medicine and Primary Health Care, Ghent University, Ghent: Belgium

Dr. I. Heath, London: UK

Prof. Dr. G. Stucki, Department of Health Sciences and Health Policy, University of Lucerne, Luzern: Switzerland

Prof. Dr. J. Brodersen, Centre of Research & Education in General Practice, Department of Public Health, University of Copenhagen: Denmark

UNIVERSITY HOSPITAL

Institute of Radiology

Chair of Diagnostic and Interventional Radiology

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Research focus
- Cardiovascular imaging
- Artificial intelligence and Big data
- Translational imaging in tumor and inflammation
- .Medical engineering
- Breast imaging and gynecological radiology
- Musculoskeletal imaging research
- MR-physics

Structure of the Chair

Professorships: 4
Personnel: 162
- Doctors (of Medicine): 52
- Scientists: 5 (thereof funded externally: 5)
- Graduate students: 11

Clinical focus areas
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Angiography (including therapies)
- Conventional radiography
- Imaging
- Ultrasound
- Mammography
- Biopsies with imaging guidance

Special structural feature
Four locations (departments of Internal Medicine, Surgery, Gynecology and Obstetrics, Pediatrics and Adolescent Medicine)

Research

Scientific focus of the Institute of Radiology is clinical and translational research. Within different study groups and research projects, the clinical impact of various imaging procedures or novel technical developments is evaluated. Furthermore, the Imaging Science Institute (ISI; compare own report) is operated in cooperation with Siemens Healthcare to integrate new developments in diagnostic imaging and novel IT- solutions into the clinical routine and the academic research. Finally, experimental and preclinical studies are well-established in our scientific activities.

Cardiovascular imaging
PI: PD Dr. A. Schmid, PD Dr. M. May, Dr. R. Heiss, Dr. K. Hellwig, Dr. C. Treutlein, Dr. M. Wiesmüller, Dr. M. Zeilinger

One of the main limitations of cardiac MRI are long examination times. Especially for older, ill patients an examination with multiple breathholds is very demanding. In the last couple of years, real time sequences were developed to speed up the examination time. Focus of studies in children and adults is the reproducibility and comparability to the standard sequence. Real time imaging not only shortens examination times, but also gives the opportunity to examine patients with arrhythmia to improve image quality compared to the standard sequence. Another development in the last couple of years are sequences for quantitatively characterization of cardiac tissue. One of the main drawbacks of this new technique is that published values are highly dependent on scanner and sequence type, thus leading to low comparability. Up to now, published values cannot be compared to each other and further studies are mandatory to increase the clinical acceptance of this new technique.

Artificial intelligence and Big data
PI: PD Dr. S. Ellmann, PD Dr. S. Bickelhaupt, Prof. Dr. M. Dietzel, Dr. K. Hellwig, Dr. L. Kapsner
As a result of technological progress, artificial intelligence (AI) and machine learning methods are increasingly being used in diagnostic medical imaging. These methods facilitate the extraction of patterns and correlations in multisectional medical data sources and thereby derive new translational approaches for improving radiological diagnostics as well as for personalizing medical clinical care. Ongoing development and research of these digital health technologies is therefore one of the central tasks of translational clinical research in the 21st century. The working group "Artificial Intelligence and Big Data" designs and develops new research projects in close interdisciplinary cooperation with the medical theoretical subjects and computer science. The aim is to use machine learning and artificial intelligence methods to further improve diagnosis, therapy control and prognosis for patients and to further support the development of personalized precision medicine. The potential of the technology has been demonstrated in studies addressing breast and prostate imaging (see publication list), and is also being evaluated in other medical applications such as rheumatological diseases in interdisciplinary research projects.

Translational imaging in tumor and inflammation
PI: Prof. Dr. T. Bäuerle, PD Dr. S. Ellmann, Dr. K. Hellwig, Dr. V. Popp, Dr. C. Treutlein
Focus of this research group is the establishment and optimization of innovative multimodal imaging techniques (MRI, CT, PET, SPECT, ultrasound, and optical imaging), particularly within interdisciplinary research consortia (e.g. projects within DFG funded programs CRC 1181 Checkpoint of resolution and SPP 2084 µbone). Thereby information on the molecular, functional, and morphologic level are acquired noninvasively and correlated with the underlying pathology or pathophysiology. In cooperation with the Chair of Pattern Recognition, we apply automatic segmentation solutions to determine quantitative image parameters. These parameters are integrated in machine learning algorithms for increasing diagnostic accuracy within larger collectives (radiomics). Examples include the investigation of experimental bone metastases, murine inflammation models (arthritis, asthma, and colitis). Major aim is the translation of these methods into clinical application, e.g. the discrimination of unclear breast and prostate lesions.

Medical engineering
PI: PD Dr. M. May, Dr. M. Wiesmüller, Dr. M. Kopp, Dr. R. Heiss, Dr. M. Wetzl, Dr. M. Schöniger, F. Geissler, S. Daniel, T. Rüttinger, M. Bachl
Computed tomography (CT) is a widespread, accessible diagnostic method. Contemporary scanner technology is capable to provide three-dimensional data with high image resolution. Such images are often crucial to make a clinical diagnosis. However, the concomitant radiation dose must be monitored as the „linear-no-threshold“ model of radiadion induced cancerogenes implies that even minor radiation exposure lead to increased stochastic cancer risk. Consequently, in the past few years we focused our efforts on optimized and personalized examination protocols as well as increased dose efficiency. For each scan protocol the image quality is supposed to remain optimal under consideration of the individual CT indication. Future projects will focus on the clinical evaulation of innovative, articial intelligence-based algorithms (e.g. automated intracranial hemorrhage detection) and intelligent examination protocols.

Breast imaging and gynecological radiology
PI: Prof. Dr. E. Wenkel, PD Dr. S. Bickelhaupt, Prof. Dr. M. Dietzel, Prof. Dr. R. Janka, Prof. Dr. F. Laun, Dr. L. Kapsner, Dr. S. Ohlmeyer, Prof. Dr. R. Schulz-Wendtland, Dr. M. Wetzl
Breast cancer is the most common malignancy in women and imaging plays a central role at all stages of its therapy and prevention. The primary objective of our work is early, minimally invasive, and highly accurate diagnosis. In addition, we investigate imaging biosignatures of breast cancers applying radiomics, artificial intelligence and functional imaging techniques. We collaborate across all relevant disciplines with our local, national and international partners. We drive technical developments in collaboration with leading medical technology companies. Here, the technical optimization of established (digital mammography, tomosynthesis, magnetic resonance imaging, ultrasound) and the evaluation of new methods (dedicated breast computed tomography, microwave imaging etc.) are within the main focus of our activities. A comprehensive research infrastructure including six MRI scanners from 0.55T to 7T field strength and a dedicated breast computed tomography scanner is at our disposal.

Musculoskeletal imaging research
PI: Prof. Dr. F. Roemer, Prof. Dr. T. Bäuerle, Dr. R. Heiss

The focus of musculo-skeletal research at the Department of Radiology is the characterization of osteoarthritis, muscle pathologies and sports-related disorders by MRI. This includes tissue evaluation in osteoarthritis through comprehensive joint assessment and the development and validation of quantitative and semiquantitative evaluation tools for application in cross-sectional and longitudinal fashion. Further, the role of post-traumatic changes and later osteoarthritis development has been a topic of on-going research, which includes multi-dimensional assessment of anterior cruciate ligament injury and its sequelae. The group has been involved in large analyses of imaging data of the Rio 2016 Olympics focusing on joint injuries. A close collaboration with the Department of Radiology at Boston University School of Medicine is on-going where Prof. Roemer holds a position as Adjunct Professor of Radiology and as Co-Director of the Quantitative Imaging Center (QIC), a research group addressing complementary research questions. The department is partner of the APPROACH consortium, which received a 14 million Euro grant from the European Commission's Innovative Medicines Initiative (IMI). An additional focus of the group is MRI of muscle pathologies and interventions including application of advanced metabolic imaging at 7T MRI. Currently the group is leading a multi-center effort applying 7T MRI for assessment of wrist disorders using morphologic and compositional imaging funded by the German Roentgen Society (DRG). Dr. Roemer is Editor-in-Chief of Osteoarthritis Imaging, The official Journal of the International Society of Osteoarthritis Imaging (ISOAI).

MR-physics

PI: Prof. Dr. A. Nagel, Prof. Dr. F. Laun

The focus of this group is on the development of new image acquisition, image reconstruction, and post-processing techniques for MRI. These techniques are evaluated in close collaboration by physicists and clinicians. The aim is to provide improved clinical radiological diagnostics. Among others, techniques are developed to acquire in vivo images of the sodium (23Na)- and potassium (39K)-distribution. These nuclei play an important role in many physiological processes. For example, the 23Na- and 39K- concentrations are closely related to the physiological status of the cells. An additional focus is on the development of new methods to measure susceptibility and diffusion of water molecules in vivo. The measurement of diffusion coefficients provides information about the tissue structure and integrity. Clinical applications of diffusion-weighted imaging are, for example, the diagnostics of ischemic stroke and breast cancer. In addition, new methods are developed to make 7 T MRI applicable in a broad clinical setting. In or-der to enable a quantitative evaluation, suitable validation and reference objects, so-called phantoms, are also being developed. There are numerous national (e.g. German ultra-high field imaging (GUFI) network, DKFZ Heidelberg, MDC Berlin) and international collaborations (including Institute of Cancer Research, London, University of Glasgow, University of Minnesota and Institute of Myology, Paris). In addition, various projects involve a very close cooperation with Siemens Healthineers.

Teaching

Besides the standard lectures and practical courses, innovative clinically orientated courses are regularly offered including interactive discussions of clinical cases. In these courses the students are taught a much more analytic and clinical rather than a systematic approach towards the interpretation of radiologic images. A new online course was established for students to prepare effectively for the state examination. Students of the degree program Medicine can always perform clinical electives or internships at our Institute. Students striving for a doctor's degree are supervised closely when writing their experimental or clinical thesis. Furthermore, the Institute of Radiology participates in degree programs Medical Process Management and Molecular Medicine (Faculty of Medicine) as well as Medical Technology (Faculty of Engineering). In addition, a joint seminar „Physics in Medicine" is offered in cooperation with the Department of Physics (Faculty of Sciences).

Selected publications

Ellmann S, Schlicht M, Dietzel M, Janka R, Hammon M, Saake M, Ganslandt T, Hartmann A, Kunath F, Wullich B, Uder M, Bäuerle T (2020) Computer-Aided Diagnosis in Multiparametric MRI of the Prostate: An Open-Access Online Tool for Lesion Classification with High Accuracy. Cancers 12(9):2366.

Geissler F, Heiß R, Kopp M, Wiesmüller M, Saake M, Wuest W, Wimmer A, Prell V, Uder M, May MS (2020) Personalized computed tomography - Automated estimation of height and weight of a simulated digital twin using a 3D camera and artificial intelligence. Rofo. 2020 Nov 3. doi: 10.1055/a-1253-8558.

Heiss R, Guermazi A, Jarraya M, Engebretsen L, Hotfiel T, Parva P, Roemer FW (2019) Prevalence of MRI-Detected Ankle Injuries in Athletes in the Rio de Janeiro 2016 Summer Olympics. Acad Radiol 26(12):1605-1617.

Kopp M, Loewe T, Wuest W, Brand M, Wetzl M, Nitsch W, Schmidt D, Beck M, Schmidt B, Uder M, May M (2020) Individual Calculation of Effective Dose and Risk of Malignancy Based on Monte Carlo Simulations after Whole Body Computed Tomography. Sci Rep. 10(1):9475. doi: 10.1038/s41598-020-66366-2.

Ohlmeyer S, Laun FB, Palm T, Janka R, Weiland E, Uder M, Wenkel E (2019) Simultaneous Multislice Echo Planar Imaging for Accelerated Diffusion-Weighted Imaging of Malignant and Benign Breast Lesions. Investigative Radiology 54: 524–530.

Saake M, Schmidle A, Kopp M, Hanspach J, Hepp T, Laun FB, Nagel AM, Dörfler, A, Uder M, Bäuerle T (2019) MRI brain signal intensity and relaxation times in individuals with prior exposure to gadobutrol. Radiology 290 (3): 659-668.

Treutlein C, Bäuerle T, Nagel AM, Guermazi A, Kleyer A, Simon D, Schett G, Hepp T, Uder M, Roemer FW (2020) Comprehensive assessment of knee joint synovitis at 7 T MRI using contrast-enhanced and non-enhanced sequences. BMC Musculoskelet Disord. 21(1):116.

International cooperations

Prof. Pascal Baltzer, Medical University of Vienna, Austria

Prof. Ali Guermazi, Boston University School of Medicine, Boston, MA, USA

Prof. Guillaume Madelin, New York University School of Medicine, New York, USA

Prof. Greg Metzger, University of Minnesota, USA

Prof. David Porter, University of Glasgow, Scotland

Prof. Jens Titze, Duke National University of Singapore, Singapore

Prof. Siegfried Trattnig, Medical University of Vienna, Austria

Prof. Maxim Zaitsev, Medical University of Vienna, Austria

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Research focus
- 7 Tesla ultrahigh-field-MR tomography
- functional and metabolic MR-imaging
- neuroimmunology and multiple sclerosis
- Parkinson's disease and multisystem atrophy
- diagnostic imaging of epilepsy
- multiparametric diagnosis of brain tumors
- multimodal imaging of cerebrovascular diseases
- experimental and clinical validation of flat-panel-volume-CT
- holistic assessment of the visual system in glaucoma
- artificial intelligence in neuroradiology

Structure of the Division

Professorship: 4
Personnel: 46
- Doctors (of Medicine): 15
- Scientists: 6 (thereof funded externally: 6)
- doctoral students: 6

Clinical focus areas
- full spectrum of diagnostic and interventional neuroradiology
- multimodal diagnostics in cerebrovascular diseases, brain tumors, neurodegenerative and neuroimmunological diseases and epilepsy
- functional and metabolic high filed neuroimaging
- spinal pain management

Research

The scientific focus of the Department of Neuroradiology is on multimodal imaging, especially in stroke, inflammatory and neurodegenerative CNS diseases, brain tumors and focal epilepsy. Hereby, a paramount scientific focus is on the evaluation of new imaging modalities, in particular „interventional imaging" in ischemic stroke or subarachnoid hemorrhage. In cooperation with our clinical und industry partners, validation and optimization of intravenous and intraarterial flat-panel angiography and flat-detector volume CT is performed. Another focus is on translational research in functional and metabolic highfield MRI in neurodegenerative and neuroimmunological diseases, brain tumors and epilepsy. Moreover, there are several externally third-party funded research cooperations.

7 Tesla high-field neuroimaging
As part of a research collaboration with Siemens Healthineers, various research projects are carried out in close cooperation with the Department of Radiology and the Department of Neurology to validate and optimize clinical ultrahigh-field MRI. The focus of multiparametric and metabolic imaging has been strengthened by the appointment of Professor Moritz Zaiss in 2019, who established a distinct research unit with a focus on CEST-imaging that is closely connected to clinical ultrahigh-field MR scientists.

Functional and metabolic MR-imaging
There are several ongoing research projects in cooperation with departments and institutes at the Faculty of Medicine (Department of Psychiatry and Psychotherapy, Division of Child and Adolescent Mental Health, Division of Psychosomatics and Psychotherapy, Department of Medicine 3, Department of Neurology, Institute of Physiology and Pathophysiology, Institute of Experimental and Clinical Pharmacology and Toxicology) and at the Faculty of Business, Economics, and Marketing involving functional and metabolic MR-imaging (e.g. patients with major depressive disorders, anxiety, and eating disorders, chronic pain syndromes, and rheumatoid arthritis). Together with the Department of Neurosurgery and funded by the DFG, we evaluate and optimize multimodal imaging protocols to evaluate diffuse tumor cell spread in glioma patients.

Neuroimmunology & multiple sclerosis
In patients with multiple sclerosis (MS), 7 Tesla imaging is used to validate reproducible, independent, and sensitive imaging markers that will allow clinical trials of progressive MS to be completed in less time and with fewer resources, and that can be promptly brought into clinical routine for follow-up and therapy monitoring. By use of ultrahigh-field MRI, surrogate parameters (QSM, CEST, myelin-water imaging, Na-imaging, K-imaging) are validated in multiple sclerosis in correlation to the clinical course (outcome measures). Sodium and potassium MRI-measurements are funded by the German MS Society.

Parkinson's disease and multisystem atrophy
Idiopathic Parkinson's syndrome (IPS) can be differentiated from atypical parkinson syndromes. The atypical parkinson syndromes are characterized by a rapidly progressive course and a worse prognosis. Clinically, reliable imaging diagnostics for the early detection and differentiation of these entities is desirable. Hereby, ultrahigh-field MRI with high-resolution morphological sequences and new image contrasts for the direct visualization of the substantia nigra can improve early differential diagnosis.
Additionally, we evaluate QSM (quantitative susceptibility mapping) in patients with IPS and atypical parkinson syndromes to identify functional surrogate parameters of iron metabolism and demyelination for early diagnosis and differential diagnosis.

Epilepsy
In cooperation with the Epilepsy Center, we evaluate different multiparametric imaging strategies in the preoperative workup of patients with focal seizures refractory to medical treatment. Hereby, a major focus is set on correlation of high-resolution 3T and 7T morphologic and functional MR imaging (MR spectroscopy, diffusion tensor imaging, functional MRI, perfusion- and diffusion-weighted MRI, MR volumetry/voxel- based morphometry) with physiological parameters (EEG, MEG, WADA test, SPECT, PET).

Neurooncology
In close cooperation with our clinical partners, the department of radiooncology, the departments of neurosurgery and neurology and the clinical medical physics, the overall goal of our neurooncological research is to conceive the tumorbiology of brain tumors on an imaging basis and to use the results for better diagnostics, differential diagnostics and therapy monitoring in a translational approach. Implemented directly from clinical research into routine reporting, multiparametric imaging including dedicated diffusion, perfusion and quantitative (susceptibility-weighted) imaging for evaluation of tumor microvasculature and oxygen metabolism enables "state-of-art" care of our patients regarding initial diagnosis (differential diagnosis) and especially the reliable follow-up of brain tumors. The combination and analysis of quantitative imaging features (radiomics), allows for reliable imaging-based characterization (diagnosis and grading) of brain tumors; e.g. the differentiation of therapy associated changes from true tumor progression with 94% accuracy.

Multimodal imaging of cerebrovascular diseases
In cooperation with the Department of Neurology, we participate in several studies on acute ischemic stroke. Using multimodal imaging algorithms, including perfusion and diffusion weighted imaging, diffusion tensor imaging, susceptibility-weighted imaging, arterial spin labeling, and contrast-enhanced angiographic imaging, we evaluate the individual indication for acute stroke therapies, such as intravenous thrombolysis, intraarterial thrombectomy, and/ or other neuroprotective therapies. Main focus is the

CT- and MR-derived patient selection for mechanical thrombectomy. Another clinical and scientific focus is the evaluation and validation of new devices for mechanical thrombectomy in acute cerebral stroke. As part of the Stroke Research Consortium in Northern Bavaria (STAMINA), multiple clinical parameters of consecutive patients with acute cerebral ischemia are recorded and correlated interdisciplinary with clinical endpoints to improve treatment.

Experimental and clinical validation of flat-panel volume CT

In close cooperation with Siemens Healthineers, the Pattern Recognition Lab, and our clinical partners we further evaluate intravenous and intraarterial flat-panel volume CT, angiographic techniques, and postprocessing algorithms in cerebrovascular disease. Hereby, a focus is set on the optimized visualization of cerebral microimplants, such as stents, coils, clips, new perfusion techniques, and advanced 3D visualization. A dedicated focus is on the multimodal (one-stop) imaging and work-flow optimization in stroke patients.

Holistic assessment of the optic system in glaucoma

In cooperation with the Department of Ophthalmology we evaluate diffusion tensor imaging (DTI) using 3 and 7 Tesla MRI to assess quantitative and qualitative changes within the optical fiber tracts in glaucoma patients at a very early stage. Disorders in optical fiber tracts result in reduced fractional anisotropy (FA) and atrophy of the tracts which can be used for non-invasive and fast screening, staging and to evaluate therapeutic strategies in glaucoma. Moreover, DTI can be used to distinguish between different forms of glaucoma that require diverse treatment. Further aim is to detect pathological protein deposits in the brain tissue in patients with pseudoexfoliation glaucoma (PEXG), using highfield molecular CEST MRI, to measure the effect of these proteins on neuronal and axonal integrity and resulting cell death by means of Na-imaging, and to measure the damage along the intracranial visual pathway. Hereby, molecular CEST and Na-MRI signatures as well as structural DTI patterns are used to characterize PEX glaucoma subtypes and imaging markers will be correlated with ophthalmologic measurements and location of damage to the visual pathway in a holistic approach.

Artificial Intelligence in Neuroradiology

Neuroradiology gathers support in postprocessing acquired data through artificial intelligence and computer aided diagnosis (CAD) methods. In acute stroke, CAD can help in the estimation of prognosis. By means of automated detection and evaluation of damaged parenchyma, as well as static and dynamic brain perfusion, an individualized therapy can be initiated. AI empowers the machine-readable processing and quantification of imaging data for further treatment.

In interventional neuroradiology, AI can also help to reduce radiation dose for both, patients and physicians. We develop and evaluate new AI-algorithms, that allow 3D imaging of the brain vasculature in higher quality than previous methods by simultaneously cutting the dose by 50%.

In cooperation with our partners we evaluate AI in imaging of neurodegenerative diseases, e.g. an innovative approach for automated segmentation and quantification of brain atrophy in dementia and multiple sclerosis. Detection and monitoring of inflammatory brain lesion volume is also a promising application of AI based algorithms.

Teaching

The Department of Neuroradiology is widely involved in the training of medical students. We train residents in neuroradiology and general radiology and radiological technicians. In addition to the training of medical students in accordance with ÄAppO, the Division of Neuroradiology also conducts courses for the degree program in Medical Technology (Biological and Technical Vision) and the Chair for Pattern Recognition and the School of radiological technicians. In addition, the Department of Neuroradiology offers the lecture „Clinical Neuroimaging“ since 2014.

Together with the Institute of Diagnostic Radiology, the education of physician specialized in Diagnostic Radiology is carried out. For neuroradiology, there is full training authorization.

Selected publications

Lachner S, Ruck L, Niesporek SC, Utzschneider M, Lott J, Hensel B, Dörfler A, Uder M, Nagel AM: (2020) Comparison of optimized intensity correction methods for 23Na MRI of the human brain using a 32-channel phased array coil at 7 Tesla. Z Med Phys. 2020;30(2): 104-115

Rösch J, Mennecke A, Knott M, Hamer HM, Doerfler A, Engelhorn T:(2020) T2-sequence with contrast inversion: diagnostic value in the investigation of gray matter heterotopias. Neuroreport. 2020;31(9): 686-690

Luecking H, Doerfler A, Goelitz P, Hoelter P, Engelhorn T, Lang S: (2020)Two- to five-year follow-up of 78 patients after treatment with the Flow Redirection Endoluminal Device. Interv Neuroradiol. 2020;26(1): 38-44

Schmidt MA, Knott M, Hoelter P, Engelhorn T, Larsson EM, Nguyen T, Essig M, Doerfler A: (2020) Standardized acquisition and post-processing of dynamic susceptibility contrast perfusion in patients with brain tumors, cerebrovascular disease and dementia: comparability of post-processing software. Br J Radiol. 2020;93(1105):

Eisenhut F, Taha L, Kleibe I, Hornung J, Iro H, Doerfler A, Lang S: (2020)Fusion of Preoperative MRI and Postoperative FD-CT for Direct Evaluation of Cochlear Implants : An Analysis at 1.5 T and 3 T. Clin Neuroradiol. 2020;30(4): 729-737

Hoelter P, Muehlen I, Goelitz P, Beuscher V, Schwab S, Doerfler A: (2020)Automated ASPECT scoring in acute ischemic stroke: comparison of three software tools. Neuroradiology. 2020;62(10): 1231-1238

Macha K, Hoelter P, Siedler G, Knott M, Schwab S, Doerfler A, Kallmünzer B, Engelhorn T. Multimodal CT or MRI for IV thrombolysis in ischemic stroke with unknown time of onset. Neurology. 2020 Dec 1;95 (22)

International cooperations

Massachusetts General Hospital, Harvard, USA, Professor Chris Farrar

UCL Queen Square Institute of Neurology, London, Großbritannien, Professor Xavier Golay

Inselspital Bern, Schweiz, Professor Roland Wiest

Technische Universität Graz, Österreich, Professor Rudolf Stollberger,

Institute of Biostructures and Bioimaging (IBB), Turin, Italien, Dr. Dario Longo