FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG

FACULTY OF MEDICINE

# Research Report 2015

## Faculty of Medicine


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# Research Report 2015

# Faculty of Medicine

## PRECLINICAL INSTITUTES



## CLINICAL THEORETICAL INSTITUTES



## CLINICAL CHAIRS

## UNIVERSITY HOSPITAL

## RESEARCH UNITS



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## ACADEMIC SOCIETY



## APPENDIX

The Faculty of Medicine of the FAU launches for the eighth time a research report which outlines the scientific and research achievements of its members. It gives a consistent overview about the research priorities and projects within the Faculty of Medicine in the years 2013 – 2014. The innovative and competitive research of the institutes and departments belonging to the Faculty of Medicine is illustrated – a research that forms the basis for an outstanding education of our students, for patient care at the highest level, and skilled training of the scientific and professional junior staff.

A crucial milestone was achieved by the opening of the Translational Research Center (TRC) in 2014 which represents physically the "bench-to-bedside" research performed within the Faculty of Medicine. In a unique way, scientists from different areas of expertise work together and try to find new and better treatment and therapy options by innovative procedures. Thus, the TRC represents in an exemplary manner the close connection between the theoretical institutes and the clinical disciplines which is one distinguished feature of the Faculty of Medicine at the FAU.

This unique facility will soon be complemented congenially by the Max-Planck-Center for Physics and Medicine. This center reflects the realization of an extraordinary idea, aiming at gaining new knowledge and progressing medicine by connecting physicists from the Max Planck Institute for the Science of Light with physicians from the UK Erlangen involved in research and with scientists focusing on molecular medicine as well as with further scientists from the Faculties of Sciences and Engineering. We are very grateful that the State of Bavaria provides an impressive investment for the realization of this center. To ensure a productive future of this singular facility, all institutions partnered in this center need to care for the operating costs.

The Faculty of Medicine continues to have a special focus on supporting the concentration on focal research areas that combine different disciplines and involve several faculties. These focal research areas are

- Infection research and immunology
- Renal and vascular research
- Neurosciences
- Tumor research and
- Medical technology.

Competitive research structures, purposeful calls of professorships, and a joint strategic orientation with the UK Erlangen shall be further expanded, thus facilitating the realization of our research aims. Contentual foci are defined by interdisciplinary research associations, supported by extramural funds, like SFB, GK, DFG research groups, and BMBF networks, like the leading edge cluster Medical Valley for excellence in medical technology.

Another important target of the Faculty of Medicine is the support of the junior scientific staff. Structured graduate programs and numerous research training groups contribute to reach this aim.

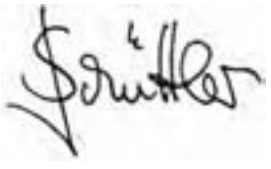
The appointment of Mrs. Nora Anton, M.A./M.Sc., as international affairs coordinator was an important step to professionalize the internationalization of the university medicine. She coordinates the realization and further development of the internationalization policy within the Faculty of Medicine and is the contact person for most diverse questions, as visiting scientists and/or physicians, a welcoming culture, support of international research and mobility, as well as international visibility.

The initiation of the network TRENAL (Translational kidney research – from physiology to clinical application) together with the Yale University (USA) and the University College London (GB) was a big step towards the realization of the internalization policy. TRENAL will be supported by the DAAD (German Academic Exchange Service) from 2015 onwards for four years within the program "Strategic partnerships and thematic networks". This network enables young as well as established scientists to enlarge and deepen international contacts, to gain experiences in different health and research systems, and to improve their career chances. Thus, university medicine in Erlangen deepens already existing contacts to leading research universities and institutes a cooperation model that is based up on one research focus.

Within the reporting period (2013 – 2014), several remarkable achievements could be reached either in already existing programs or by support of individual projects through the DFG, BMBF, and EU as well as private foundations and industrial partners that are very important when it comes to support academics. Exemplary for this support are the successful re-evaluation of clinical research group 257 (CEDER) as well as the foundation of the Bavarian Research Alliance ForIPS.

I would like to thank you all as well as the Bavarian taxpayers. I would further like to thank the numerous experts for our (research) project proposals and publications, thus helping us to ensure the quality of our research. Without the support of sponsors and experts, we were not able to sow the seeds for the distinctive characteristic of our Faculty of Medicine, i.e. the thrilling synthesis of innovative research combined with an optimal patient care and a problem-centered education and training. Thus, the Faculty of Medicine is facing the international competition for the most qualified heads and ideas to further research for the humans.

Erlangen, July 2015



Prof. Dr. med. Dr. h.c. Jürgen Schüttler
The Dean of the Faculty of Medicine

Photo: glasow, fotografie, Erlangen

# Abbreviations

- B.Sc.: Bachelor of Science
- BMBF: Federal Ministry of Education and Research
- DFG: German Research Foundation
- FAU: Friedrich-Alexander-Universität Erlangen-Nürnberg
- GK: Research Training Group
- IZKF: Interdisciplinary Center for Clinical Research
- M.Sc.: Master of Science
- NFZ: Nikolaus-Fiebiger-Center of Molecular Medicine
- SFB: Collaborative Research Center
- UK Erlangen: Universitätsklinikum Erlangen

# Institute of Anatomy

## Chair of Anatomy I

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**Research Focus**
- Innervation of the gastrointestinal tract
- Nervous system, inflammation, and pain
- Cell biology of the NF2 tumor suppressor protein

## Structure of the Institute

Together with the Chair of Anatomy II, the Chair of Anatomy I composes the Institute of Anatomy. Altogether, 16 persons are employed, five of them on an external funding basis. Research is conducted by six scientists (chairman, senior scientists, postdoctoral fellows), eight doctoral thesis students (both, MD and Ph.D.), and six technicians. The Chair of Anatomy I provides the facilities and logistics for gross anatomy, including body donation. This is essential not only for teaching, but also for applied clinical research and postgraduate training.
Most of the teams investigate various aspects of autonomic innervation, in particular of the gastrointestinal tract; one group studies cell biology of tumor suppressor genes. A broad spectrum of conventional histology, histochemistry, and immunohistochemistry, light-, confocal, and electron microscopy, electrophysiology (in collaboration with the Institute of Physiology and Pathophysiology) and in vitro preparations of isolated organs as well as molecular biology is applied. Equipment and laboratory facilities are available also for other groups both, within and outside the Faculty of Medicine.

## Research

### Innervation of the gastrointestinal tract

Project managers: Prof. Dr. W. Neuhuber, Prof. Dr. J. Woerl, Prof. Dr. M. Raab, Prof. Dr. A. Brehmer
Studies on the esophagus focused on novel mediators of enteric co-innervation, e.g. tachykinins and dopamine.
Afferent vagal terminals around myenteric ganglia, so-called intraganglionic laminar endings (IGLEs), are putative mechanosensors probably exerting also additional purposes in the enteric neuronal circuitry. They were further characterized with respect to their equipment with muscarinic acetycholine and CGRP receptors. In addition, pre- and postsynaptic proteins, e.g. synaptotagmin1, bassoon and homer1, were detected in IGLEs, further supporting the idea of their synaptic influence onto enteric neurons.
Morpho-chemical phenotyping of enteric neurons in healthy human intestines was continued. In addition, morphological and immunohistochemical characterization of enteric neurons in Chagas-induced megacolon was initiated in collaboration with Prof. Dr. A. da Silveira (Brazil). This line of research is serving as a paradigm for forthcoming investigations on the enteric nervous system in other gastrointestinal disorders.

### Nervous system, inflammation, and pain

Project manager: Prof. Dr. W. Neuhuber
In collaboration with colleagues of the Department of Medicine 4 – Nephrology and Hypertension, nerve fiber populations relevant for nephritis pathophysiology were studied. In collaboration with the Institute of Physiology and Pathophysiology, studies on innervation of the cranial dura and neuronal modulation in experimental colitis were continued.

### Cell biology of the NF2 tumor suppressor protein

Project manager: PD Dr. M. Kressel
The neurofibromatosis type 2 (NF2) protein merlin is a classical tumor suppressor protein. Disturbed function or loss of function, e.g. through inherited NF2 gene mutation, typically results in neurinomas of the VIII$^{th}$ cranial nerve. However, the NF2 protein not only regulates the proliferation of peripheral glial cells and the genesis of the largest commissural tract in the brain, but acts in a yet unknown way as a common cellular mechanosensor which controls cell density dependent the proliferation of precursor cells by inhibiting the ubiquitous Hippo pathway for organ size control.
We focused on subcellular localization of merlin, since one isoform turned out to be a nucleo-cytoplasmic shuttle protein. This extended the classical view of merlin from a purely plasma membrane associated protein towards a nuclear regulator of proliferation. The protein domains essential for the respective subcellular localization were tracked down and the effects on the function of the protein were studied. The protein was observed in living cells in high resolution microscopy in close cooperation with other groups and correlated to the migratory behavior of the cells.

## Teaching

Both anatomical chairs collaborate in teaching anatomy. In particular, the Chair of Anatomy I is concerned with courses in gross anatomy and parts of interdisciplinary clinical-anatomical seminars and courses of neuroanatomy. The dissection course with its small group format with correlated main lecture is of pivotal importance. Seminars, partly in PBL (problem-based learning) format and using electronic media, provide opportunity for students to train practical application of knowledge they have acquired in the dissection room (seminars of imaging methods, surface anatomy, clinical anatomy). Members of the Institute of Anatomy provide lectures and courses also for other faculties.

### Selected Publications

Jabari S, da Silveira AB, de Oliveira EC, Quint K, Wirries A, Neuhuber W, Brehmer A. Interstitial cells of Cajal: crucial for the development of megacolon in human Chagas' disease? Colorectal Dis 2013, 15: e592-e598

Hübsch M, Neuhuber WL, Raab K. Muscarinic acetylcholine receptors in the mouse esophagus: focus on intraganglionic laminar endings (IGLEs). Neurogastroenterol Motil 2013, 25: e560-e573

Jabari S, da Silveira AB, de Oliveira EC, Quint K, Wirries A, Neuhuber W, Brehmer A. Mucosal layers and related nerve fibres in non-chagasic and chagasic human colon – a quantitative immunohistochemical study. Cell Tissue Res 2014, 358: 75-83

Schueler M, Neuhuber WL, De Col R, Messlinger K. Innervation of rat and human dura mater and pericranial tisssues in the parieto-temporal region by meningeal afferents. Headache 2014, 54: 996-1009

Beuscher N, Jabari S, Strehl J, Neuhuber W, Brehmer A. What neurons hide behind calretinin immune oreactivity in the human gut? Histochem Cell Biol 2014, 141: 393-405

Horling L, Bunnett NW, Messlinger K, Neuhuber WL, Raab M. Localization of receptors for calcitonin gene-related peptide to intraganglionic laminar endings of the mouse esophagus: peripheral interaction between vagal and spinal afferents? Histochem Cell Biol 2014, 141: 321-335

### International Cooperations

Prof. Dr. H.-R. Berthoud, University of Louisiana, Baton Rouge: USA

Prof. C. Chiang, Department of Cell and Developmental Biology, University Medical Center, Nashville: USA

Dr. M. Giovannini, Institut Curie, INSERM, Paris: France

Prof. S. Pulst, Neurogenetics Lab and Division of Neurology, Cedars-Sinai Medical Center, Los Angeles: USA

Prof. F. Schrödl, Augenklinik SALK, University of Salzburg, Salzburg: Austria

Prof. Dr. A. da Silveira, Department of Anatomy, University of Uberlandia, Uberlandia: Brazil

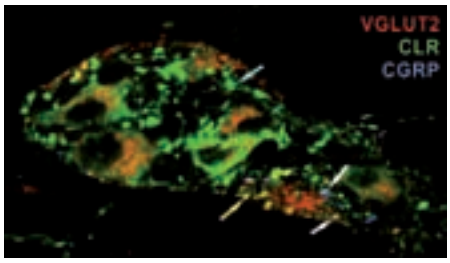
Prof. Y. Shimizu, Department of Basic Veterinary Science, Gifu University, Gifu: Japan

Prof. J.-P. Timmermans, Institute of Histology and Cell Biology, University of Antwerp, Antwerp: Belgium

## Meetings and International Training Courses

16. – 19.04.2013: 12th International Erlangen Course in Facial Plastic Surgery (in collaboration with the Department of Otorhinolaryngology)

10. – 11.10.2014: 5th Erlangen Seminar for Practical Foot Surgery (in collaboration with the Society for Foot and Ankle Surgery)




*A myenteric ganglion in the mouse esophagus. The vagal mechanosensors IGLEs (red, VGLUT2 positive) are equipped with the CGRP receptor (green, CLR; overlay resulting in yellow). CGRP positive spinal sensory fibers (blue) contact the vagal sensors at the site of the receptor, indicated by the mixed color white. This suggests a peripheral influence of spinal afferents on vagal mechanosensor (compare also Horling et al. 2014). CLR is also expressed by myenteric neuronal cell bodies.*

# Institute of Anatomy

## Chair of Anatomy II

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**Research Focus**
- Temperature sensitive Transient Receptor Potential (TRP) channels at the ocular surface
- Influence of osteopontin (OPN) to neurodegenerative processes in the eye
- The wide range of surfactant proteins
- Influencing factors with regard to learning related behavior of medical students
- Ocular surface wound healing
- Corneal Collagen Cross-linking (CXL)

## Structure of the Institute

The Institute of Anatomy consists of the Chair of Anatomy I and the Chair of Anatomy II. Since the inauguration of Prof. Dr. F. Paulsen in 2010 as new director, the Institute has been in a continuous restructuring and renovation which is expected to be completed in late 2015. In the past two years, most of the laboratory space was renovated, newly furnished, and equipped. Currently, 27 staff members are employed at the Institute. In the period from 2013 to 2014, nine employees were funded by grants at least partly. Nine Ph.D. students as well as two Master students and four Bachelorands of molecular medicine were involved in scientific work. The functional anatomy of the body, including embryology, the entire microscopic anatomy, and parts of neuroanatomy were represented in teaching. In addition, members of the Chair of Anatomy II participated in the lessons of the macroscopic anatomy given by the Chair of Anatomy I. There were collaborations with other projects, particularly with regard to the SFB initiative "hoarseness" and several long-time international collaborations. Since 2011, Prof. Dr. L. Bräuer has been holding the W2 professorship located at the Chair of Anatomy II. His former position as W1 Professor was upgraded to a W2 professorship via tenure track at the end of 2014. The teaching staff is currently supported by a FAU guest professorship hold by PD Dr. E. Eppler (Zurich, Switzerland).

## Research

### Temperature sensitive Transient Receptor Potential (TRP) channels at the ocular surface

Project managers: Dr. F. Garreis, Prof. Dr. F. Paulsen

The Transient Receptor Potential (TRP) proteins belong to the group of membrane-bound, ligand-gated cation channels. They serve as i.a. sensors for temperature, pain, pheromones, and pH-value changes. A functional subgroup of the TRP family are the temperature-sensitive TRP channels (thermo TRPs). They primarily serve the perception of temperature changes, but are also activated by different physical stimuli (pH-value, mechanical stimuli) and by a number of different plant constituents for example capsaicin (chillies) and many more. Here, the expression of thermo-TRPs is not limited to neurons (fibers), but is also common in non-neuronal cells. TRP channels play a significant role in maintaining the intracellular calcium homeostasis as well as in different physiological and pathophysiological cellular processes. In cooperation with Dr. S. Mergler (Elektrophysiologisches Labor der Augenklinik, Charité, Berlin), we were able for the first time to demonstrate the functional expression of individual thermo-TRP subtypes in the epithelial and endothelial cells of the cornea as well as in the conjunctiva epithelial cells at the healthy ocular surface. Furthermore, we were able to demonstrate a thermo-TRP-induced change of the intracellular calcium concentration in the uveal melanoma cells and in retinoblastoma cells. Current research projects are examining the functional expression and regulation of the thermo-TRP channels and their interaction with growth factors and their receptors in different inflammatory and non-inflammatory diseases at the ocular surface.

### Influence of osteopontin (OPN) to neurodegenerative processes in the eye

Project managers: Prof. Dr. M. Scholz, Prof. Dr. F. Paulsen

In close cooperation with the Department of Ophthalmology (Prof. Dr. J. Kremers), we performed morphological, molecular, and electrophysiological studies on the structure and function of the retina of the osteopontin knockout (OPN$^{-/-}$) mouse. Retinal ganglion cells (RGCs) are the only neuronal cell type of the retina which are able to express OPN under physiological conditions. In initial studies, our group was able to demonstrate a significant correlation between the age-dependent increased OPN expression and the also age-related damage within the retina and optic nerve in the glaucoma model of the DBA/2J mouse by analysis of the protein composition of the aqueous humor. In different experimental approaches, the morphological and physiological characterization of OPN$^{-/-}$ mouse was performed. The results of validated inducible light damage setups will give evidence about the effects due to the absence (OPN$^{-/-}$) or overexpression (DBA/2J) of OPN with regard to neurodegenerative processes within the retina.

### The wide range of surfactant proteins

Project managers: Dr. M. Schicht, Prof. Dr. L. Bräuer, Prof. Dr. F. Paulsen

The ongoing and continuous characterization of surfactant proteins (in particular surfactant associated 3 (SFTA3), recently described by us) shows the immense spectrum of activity of these proteins in the human organism. Within recent experiments, we were able to demonstrate that SFTA3 has stimulating effects on the activity of alveolar macrophages and in addition leads to an increased phagocytic activity. These and other studies suggest that SFTA3 may play an important role during inflammatory processes within the lung. The previously described properties make SFTA3 a potential candidate for the diagnosis, prevention, and possibly treatment of lung diseases.

### Influencing factors with regard to learning related behavior of medical students

Project managers: Prof. Dr. M. Scholz, Prof. Dr. F. Paulsen

Theories about learning styles and types of learning are an integral part for several decades of discussions about teaching basics. The learning typology divides learners into different groups which differ both, in terms of their learning behavior as well as their personality and preferences. We studied the context of the present types of learning with the sense of coherence and burnout symptoms in medical students of the preclinical terms at the FAU. A total of 530 students were interviewed in the winter term 2012/13 with standardized psychometric questionnaires for this purpose. Our students showed a significant correlation between the respective learning style and the expression of the sense of coherence as well as cognitive

and emotional burnout symptoms. Hereby, the learning styles of students differed significantly in the same parameters. We could also show that learning styles and types of learning do not only affect the study performance, there also exist relationships with sense of coherence and psychological ailments. A more forward looking integration of the theory of types of learning in the medical education curriculum could affect positively both, the performance as well as the psychological well-being of the students.

### Ocular surface wound healing

Project managers: Dr. U. Hampel, Prof. Dr. F. Paulsen

Aim of this project is to investigate the impact of Relaxin 2 (RLN2) on corneal stromal scar formation. Using specific receptors, RLN2 increases migration and proliferation and regulates expression of matrix metalloproteinases in human corneal and conjunctival epithelial cells in vitro. In vivo experiments in a murine corneal epithelial wound healing model demonstrated an accelerated defect closure under recombinant RLN2 treatment. These results clearly indicate the positive effect of RLN2 on corneal epithelial wound healing. However, corneal wounds often do not only affect the epithelial layer, but in most cases also involve the corneal stroma leading frequently to stromal scar formation as a complication. Such corneal scars are a major cause for blindness world-wide. Although there are possible approaches to treat corneal opacity, there is still a lack of non-invasive options. Besides RLN2, other prospective substances are tested for their ability to induce corneal wound healing.

### Corneal Collagen Cross-linking (CXL)

Project managers: Dr. C.M. Hammer, Prof. Dr. F. Paulsen

In keratokonus patients, a biomechanically weak - ened central cornea gives rise to corneal ectasia. Clinically, the biomechanical strength of the cornea is increased by collagen cross-linking (CXL). Here, the corneal stroma is imbibed with riboflavin and exposed to UVA light. This increases the number of collagen cross-links which augments structural stability and counteracts keratokonus progression. In collaboration with WaveLight GmbH, we used a femtosecond laser to create a stromal pocket in which riboflavin was injected while the epithelium remained intact (pocket-CXL). The efficiency of pocket-CXL was only half as pronounced as that of the standard method, as revealed by stress-strain measurements. In cooperation with the Department of Applied Physics, Tübingen, we were able to use atomic force microscopy to examine the depth-dependent distribution of standard CXL efficiency. Current research focuses on corneal stiffness profiles after pocket-CXL.

## Teaching

The Chair of Anatomy II has performed the lectures on the functional aspects of human anatomy with accompanying demonstration courses and the general and specific histology (including embryology) in combination with the courses of microscopic anatomy and associated seminars. In the seminar on functional and clinical anatomy of the musculoskeletal system, the students were increasingly taught wet specimens, and new lecture notes for the course were developed. The microscopic anatomy is conceptually transformed into a model of the future that makes use of the virtual histology. In this context, in collaboration with the Institute of Anatomy at the University of Regensburg (Prof. Dr. R. Witzgall) and in close cooperation with the Fraunhofer Institute for Integrated Circuits and the Virtual University of Bavaria (vhb), a first online course "General anatomy with clinical implications" can be booked at the which is free for all students at Bavarian universities. In addition, most of the histological specimens used in the courses in Erlangen and Regensburg can be viewed online with high resolution. All courses are attended by students of medicine, dentistry, and molecular medicine. A course about special histology will be available together with a course about embryology as of summer term 2015. In addition, students of the study course Medical Process Management were taught anatomy. Prof. Dr. M. Eichhorn and Prof. Dr. F. Paulsen are included in teaching courses of MAOT (Master Program in Advanced Optical Technologies) and SAOT (Erlangen Graduate School in Advanced Optical Technologies) graduate schools and organize lectures and demonstration courses for interested students of the study course medical engineering.

### Selected Publications


Hampel U, Sesselmann S, Iserovich P, Sel S, Paulsen F, Sack R. Chemokine and cytokine levels in osteoarthritis and rheumatoid arthritis synovial fluid. J Immunol Methods 2013, 396(1-2): 134-9

Schicht M, Rausch F, Finotto S, Mathews M, Mattil A, Schubert M, Koch B, Traxdorf M, Bohr C, Worlitzsch D, Brandt W, Garreis F, Sel S, Paulsen F, Bräuer L. SFTA3, a novel protein of the lung: three-dimensional structure, characterisation and immune activation. Eur Respir J 2014, 44(2): 447-56

Neumann C, Garreis F, Paulsen F, Hammer CM, Birke MT, Scholz M. Osteopontin is induced by TGF-β2 and regulates metabolic cell activity in cultured human optic nerve head astrocytes. PLoS One 2014, 9(4): e92762

Wild K, Scholz M, Ropohl A, Bräuer L, Paulsen F, Burger PH. Strategies against Burnout and Anxiety in Medical Education – Implementation and Evaluation of a New Course on Relaxation Techniques (Relacs) for Medical Students. PLoS One 2014, 9(12): e114967

Seifert J, Hammer CM, Rheinlaender J, Sel S, Scholz M, Paulsen F, Schäffer TE. Distribution of Young's Modulus in Porcine Corneas after Riboflavin/UVA-Induced Collagen Cross-Linking as Measured by Atomic Force Microscopy. PLoS One 2014, 9(1): e88186

Rausch F, Schicht M, Bräuer L, Paulsen F, Brandt W. Protein modeling and molecular dynamics simulation of the two novel surfactant proteins SP-G and SP-H. J Mol Model 2014, 20(11): 2513


### International Cooperations

Prof. Dr. E. Cuerda, Universidad Rey Juan Carlos, Madrid: Spain

Prof. M. Willcox, Ph.D., University of New South Wales, Sydney: Australia

Prof. Y. Diebold, Universidad de Valladolid: Spain

Y. Asano, Santen Pharmaceutical Co. Ltd., Nara: Japan

D. Overby, University of London: UK

Prof. D. Sullivan, Ph.D., Schepens Eye Research Institute: USA

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**Research Focus**

- Molecular mechanisms of development and progression of malignant melanoma
- Chondrocytic differentiation and pathophysiological processes in cartilage
- Molecular basis of regeneration and fibrosis in liver and skin
- In vivo functions of glycine transporters
- The role of oxidative stress-induced posttranslational modifications in α synuclein pathology
- Structure and function of synaptic signaling complexes in the central nervous system

## Structure of the Institute

The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry. In addition, the Professorships of Bioinformatics and of Biochemistry and Molecular Imaging are integrated in the Institute. The Institute of Biochemistry constitutes the interdisciplinary Emil-Fischer-Center (EFI, see own report) together with the Institute of Experimental and Clinical Pharmacology and Toxicology (Faculty of Medicine) and the Institute of Pharmaceutical Chemistry (Faculty of Sciences).
The Chair has a total of 34 employees (more than half of them funded by grants), including eight scientists, 12 Ph.D. students, and eight technicians.

## Research

### Molecular mechanisms of development and progression of malignant melanoma

Project managers: Prof. Dr. A.K. Bosserhoff, PD Dr. S. Kuphal, Dr. P. Dietrich
Malignant melanoma, also called black skin cancer, shows a drastic increase in incidence and unchanged high mortality in recent decades. Melanoma is a clinically relevant tumor, characterized by gradual progression, metastatic dissemination, rapid and pronounced resistance to therapy. In particular, for metastatic melanoma curative therapy approaches are still lacking, resulting in a 10-year survival rate 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. Our group is 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 the mature microRNAs as key post-transcriptional regulatory elements, their processing in melanoma is in the center of our current research.

### Chondrocytic differentiation and pathophysiological processes in cartilage

Project managers: Prof. Dr. A.K. Bosserhoff, Dr. S. Niebler
Cartilage is a tissue comprising of only a single cell type, namely chondrocytes. In the development, cartilage further forms the Anlage of the bony skeleton. In the adult organism cartilage covers, for example, the articular surfaces of our bones and is characterized, among other things, by high pressure elasticity. Damage to the cartilage is not curable today. By better understanding the molecular processes in the chondrogenic differentiation, we are trying to develop new therapeutic options. As part of our research, we are focusing on different molecular groups. We study molecules of the repellent factor family and transcriptional regulators, such as AP2Epsilon. A further focus is on the molecule MIA which plays an important role in cartilage differentiation and homeostasis.

### Molecular basis of regeneration and fibrosis in liver and skin

Project managers: Prof. Dr. A. Bosserhoff, Dr. S. Arndt, Dr. P. Dietrich
The liver is the central organ of the whole metabolism. Nutrients are supplied 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 fats. Another important function of the liver is detoxification. Intoxication with chemicals and environmental toxins, drug or alcohol abuse, obesity, metabolic disorders (e.g. hemochromatosis), and viral infections (hepatitis B and C), among other factors, are common causes of liver damage. The damage is associated with a marked hepatocellular apoptosis/necrosis. This, in turn, may result in an inflammatory reaction which further worsens the situation. As a result of liver inflammation (hepatitis), fibrosis frequently develops which can lead to liver cirrhosis. Cirrhosis is the most important risk factor for the development of hepatocellular carcinoma (HCC). Until today, there are hardly any treatment options to restore the homeostasis of the liver after acute or chronic 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 almost the same, 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 the growth factor family of BMP molecules. Also we could characterize BMP6 as an essential regulator of iron metabolism in recent years.

### In vivo functions of glycine transporters

Project manager: Dr. V. Eulenburg
Neurotransmission with high temporal and spatial resolution requires the rapid termination of synaptic transmission. At glycinergic synapses, this is achieved by rapid uptake of the presynaptically released glycine into the nerve terminal and the surrounding glial cells by high affinity transporters, the so called GlyTs. By complex genetical, biochemical, and behavioral approaches, we have shown that at least in neonatal animals glial expressed GlyT1 is in control of the extracellular glycine concentration, whereas in older animals this function can partially be compensated by neuronal expressed GlyTs. Moreover, we could show in animal models that a partial inhibition of the GlyT1 mediated uptake activity is beneficial for the treatment of chronic pain conditions. In conclusion, our research has contributed to a better understanding of how glial and neuronal expressed trans-

porters influence synaptic transmission under physiological and pathophysiological conditions. Additionally, our results demonstrate that inhibition of GlyT1 might constitute a new treatment strategy for the treatment of chronic pain conditions.

### The role of oxidative stress-induced posttranslational modifications in α synuclein pathology

Project manager: PD Dr. W. Xiang

Parkinson disease (PD) is one of the most common neurodegenerative diseases. Aggregation of α synuclein protein (αSyn) and oxidative stress are known to play an important role in the pathogenesis of PD. In our project, we want to verify the hypothesis that elevated levels of free radicals under oxidative stress induce posttranslational modifications (PTM) of proteins. Altered proteins via PTM in turn can trigger damage to cells, particular to neuronal cells. Our studies demonstrate that oxidative stress does evoke PTMs in proteins. Such oxidative PTMs can significantly change the structural and functional features of αSyn which promote the formation of aggregated αSyn species. Interestingly, several PTM-induced αSyn species lead to neuronal death. Besides PTM, we are also interested in cellular effects of oxidative stress which are characterized by the accumulation of reactive oxygen/nitrogen species and reduced cellular antioxidative capacity. Furthermore, we develop mass spectrometry-based methods for analysis of pathological modifications of DNA and proteins.

### Structure and function of synaptic signaling complexes in the central nervous system

Project managers: Prof. Dr. R. Enz, Dr. R. Dahlhaus

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. Synthesis of many synaptic proteins is regulated by the Fragile X Mental Retardation Protein FMRP. Malfunction may cause diseases, including epilepsy und autism. Thus, synaptic proteins represent interesting targets for therapeutic intervention.

To investigate molecular mechanisms of synaptic signal transduction, we analyze structure, expression, and function of synaptically localized macromolecular signal complexes that are associated with metabotropic glutamate receptors (mGluRs) and GABAc receptors (GABAcR). We compare the expression of interacting proteins in the retina, map binding regions, and analyze their 3D-structure. With Simiate we discovered a new synaptic protein regulated by FRMP that functions as a molecular link between nuclear gene expression and dendritogenesis.

## 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.

### Selected Publications


Kappelmann M, Kuphal S, Meister G, Vardimon L, Bosserhoff AK. MicroRNA miR-125b controls melanoma progression by direct regulation of c-Jun protein expression. Oncogene 2013, 32(24):2984-91

Braig S, Bosserhoff AK. Death inducer-obliterator 1 (Dido1) is a BMP target gene and promotes BMP-induced melanoma progression. Oncogene 2013, 32(7):837-48

Xiang W, Schlachestzki JCM, Helling S, Bussmann JC, Berlinghof M, Schäffer TM, Marcus K, Winkler J, Klucken J, Becker CM. Oxidative stress-induced posttranlational modifications of alpha-synuclein: Specific modification of alpha-synuclein by 4-hydroxy-2-nonenal increases dopaminergic toxicity. Mol and Cell Neurosci 2013, 54:71-83

Derlig K, Gießl A, Brandstätter JH, Enz R, Dahlhaus R. Identification and Characterisation of Simiate, a Novel Protein Linked to the Fragile X Syndrome. PLoS One 2013, 8:e83007

Arndt S, Wacker E, Dorn C, Koch A, Saugspier M, Thasler WE, Hartmann A, Bosserhoff AK, Hellerbrand C. Enhanced expression of BMP6 inhibits hepatic fibrosis in non-alcoholic fatty liver disease. Gut 2014, Jul 10: pii: gutjnl-2014-306968

de Jel MM, Engelmann JC, Kunz M, Schiffner S, Kuphal S, Bosserhoff AK. Transcriptome sequencing of melanocytic nevi and melanomas from Grm1 transgenic mice to determine melanoma driver mutations. Pigment Cell Melanoma Res 2014, 27(4):678-80


### International Cooperations

Prof. Dr. M. Herlyn, Wistar Institute, Philadelphia, USA

T. F. Outeiro, Ph.D., H. Vicente Miranda, University Lisbon, Lisbon: Portugal

Prof. C. Aragón, Prof. B. López-Córcuera, Universidad Au tonoma de Madrid, Madrid Spain

Prof. H. Qian, University of Illinois at Chicago, Chicago: USA

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

### Research Equipment

Bruker Daltonik, Esquire 6000 ESI-IT MS

Bruker Daltonik, Autoflex 1 MALDI-TOF MS

### Meetings and International Training Courses

04. – 05.06.2013: „Trends in Melanoma research", Bonn (Congress president: Prof. Dr. A.K. Bosserhoff)

13. – 16.11.2014: 2014 Internationaler Kongress der Society for Melanoma Research, Zürich

11. – 13.12.2014: „Trends in Melanoma research", Regensburg (Congress president: Prof. Dr. A.K. Bosserhoff)

# Institute of Biochemistry – Emil-Fischer-Center

## Chair of Biochemistry and Pathobiochemistry

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**Research Focus**

- Transcription factors and chromatin-modifying complexes as regulators of neural development
- SoxC proteins
- SoxD proteins
- SoxE proteins
- Impaired signal transduction in mitochondrial and neuromuscular myopathies
- β-thymosins, substrates of transglutaminases during blood coagulation, angiogenesis, wound healing, and apoptosis

## Structure of the Institute

The Chair of Biochemistry and Pathobiochemistry, the Chair of Biochemistry and Molecular Medicine, the Professorship of Bioinformatics, and the Professorship for Molecular Imaging constitute the Institute of Biochemistry. They are furthermore part of the Emil-Fischer-Center (EFI, see own report) which in addition harbors the Institute of Experimental and Clinical Pharmacology and Toxicology (Faculty of Medicine), the Chair of Medicinal Chemistry, and the Chair of Food Chemistry (both Faculty of Sciences). Several groups study transcription and posttranscriptional processes as well as β-thymosins with regard to molecular mechanisms and physiological roles in development, disease, and regeneration of the nervous system and other organ systems. The technological spectrum is broad and ranges from biochemical and molecular methods to the generation and characterization of transgenic mice.

## Research

### Transcription factors as regulators of neural development

Several groups are interested in the characterization of transcriptional regulators and chromatin-modifying complexes that participate during development of the mammalian nervous system in determination and differentiation of neural stem cells to glia and neurons. Work on transcription factors is mainly focused on members of the Sox protein family and their interacting partners. Analysis of these transcription factors will lead to a better understanding of developmental defects, tumor formation, and regenerative processes in the nervous system. Among chromatin-modifying complexes, Brg1-dependent BAF complexes have been analyzed for their role in the specification and terminal differentiation of myelin-forming glia.

### SoxC proteins

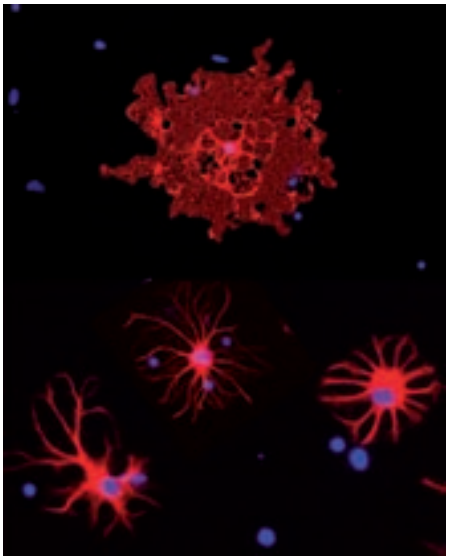
Project manager: PD Dr. E. Sock
All SoxC proteins occur in many tissues and organs during embryogenesis. Whereas loss of Sox4 or Sox11 leads to severe developmental defects (such as heart and outflow tract malformations, B-cell maturation defects, asplenia, skeletal malformations, and hypoplasias of several organs), Sox12 deletion remains without obvious phenotypic consequences in the mouse. Despite strong expression of all three SoxC proteins in the developing nervous system, neural defects become visible only upon combined deletion of more than one SoxC protein. Nervous system defects are predominantly caused by changes in proliferation and apoptosis. Overexpression studies in the mouse have, however, also pointed to an influence of SoxC proteins on neural maturation.

### SoxD proteins

Project manager: Prof. Dr. C. Stolt
The three closely related SoxD proteins Sox5, Sox6, and Sox13 participate as regulatory proteins in the development of several neuronal subpopulations and glial cells of the nervous system. Own studies indicate that SoxD proteins function as modulators of SoxE function in glia. Both, Sox5 and Sox6, antagonize Sox9 and Sox10 during embryonic development in oligodendrocytes and thereby prevent precocious specification and terminal differentiation within this cell lineage. A similar mode of action has also been determined for SoxD proteins in neural crest derivatives such as melanocytes. Here, SoxD proteins recruit transcriptional co-repressors to the regulatory regions of those genes that would otherwise be activated by SoxE proteins in a cell-specific manner.

### SoxE proteins

Project manager: Prof. Dr. M. Wegner
Transgenic mouse models have shown that the three closely related group E Sox proteins, Sox8, Sox9, and Sox10, have numerous functions during nervous system development. Sox9 and Sox10 are essential for survival and pluripotency of neural crest stem cells, the source for most cells of the peripheral nervous system. Sox9 and Sox10 furthermore determine which derivatives develop from neural crest stem cells. In Sox10-deficient mice, glial cells are missing from the peripheral nervous system. The enteric nervous system is completely absent.
In the central nervous system, Sox9 and Sox10 regulate several steps in gliogenesis. Sox9 is responsible for the specification of neural stem cells into oligodendrocytes, whereas Sox10 guides terminal differentiation and myelination in oligodendrocytes as a direct activator of myelin genes in cooperation with transcription factor Myrf. During the period between specification and terminal differentiation, oligodendrocyte development is jointly regulated by Sox9 and Sox10. Functional support comes from the related Sox8 which is co-expressed at lower levels. Their mode of action includes recruitment of the basal transcription machinery in a mediator-dependent manner as well as interactions with chromatin-remodeling complexes such as the Brg1-containing BAF complex.
Functions of group E Sox proteins were not only obvious in transgenic mouse models, but are equally 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.



*Cultured CNS glial cells (nuclei in blue) stained with oligodendroglial (top) and astroglial (bottom) markers (red).*

### Impaired signal transduction in mitochondrial and neuromuscular myopathies

Project manager: Prof. Dr. S. Hashemolhosseini
Muscle-specific MuSK acts as main switch for synaptogenesis at the postsynaptic apparatus of the neuromuscular junction. Own work identified protein kinase CK2 as MuSK binding partner. CK2 binds MuSK via its β subunit, phosphorylates it and thus regulates the stability of acetylcholine receptor clusters. Moreover, CK2β-deficient mutant mice are affected by mitochondrial myopathy. In these mice mitochondrial import is impaired due to lack of CK2-dependent phosphorylation of subunits of the mitochondrial protein translocase. As a consequence, mitochondria are removed by Pink1 and Parkin-mediated mitophagy. Behavioral tests and electrophysiological studies demonstrated muscle weakness, and substantial changes of the transcriptome were determined. It is the aim to unravel the molecular causes of neuromuscular pathologies in humans and to establish the basis for new therapeutic interventions.

### β-thymosins, substrates of transglutminases during blood coagulation, angiogenesis, wound healing, and apoptosis

Project manager: Prof. Dr. E. Hannappel
Thymosins were originally isolated from thymus, but do not represent thymic hormones. Thymosin β-4 (Tß4) is a main intracellular G-actin sequestering peptide in most mammalian cells. Apart from this intracellular function, Tß4 seems to be a player in wound healing and inflammation. Tß4 is a substrate of transglutaminases. Glutaminyl residues of Tß4 can be cross-linked to amino groups of other molecules. Blood platelets contain high concentrations of Tß4. During aggregation Tß4 is cross-linked by factor XIIIa to the fibrin clot and thus limited in its activity to the immediate surroundings despite being a small and highly soluble peptide. Tß4 can be labeled by photo-activatable derivatives of cadaverine without loss of function and is then a useful tool to study interaction with other proteins. Tß4 prevents the PDGF-BB induced activation of hepatic stellate cells and the formation of fibrotic tissue. This antifibrotic effect is likely caused by direct interaction between Tß4 and PDGF-BB, arguing that Tß4 could be used as an antifibrotic drug for treatment of liver fibrosis.

## Teaching

The Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry jointly organize and carry out all curricular activities (lectures, seminars, practical courses) in biochemistry and molecular biology for students of medicine and dentistry during the preclinical phase of their studies. Similarly, all teaching in biochemistry and molecular biology for students of molecular medicine is performed by the two chairs. The Chair of Biochemistry and Pathobiochemistry furthermore contributes significantly to teaching activities in neurobiology, cell biology, and developmental biology for students of molecular medicine. Together with the Chair of Biochemistry and Molecular Medicine, it ensures the biochemical training of students from the Department of Medicinal Chemistry and from the program in Medical Engineering.

### Selected Publications


Wegner M. Mighty Bugs: Leprosy Bacteria Turn Schwann Cells into Stem Cells. Cell 2013, 152: 15-16

Vogl MR, Reiprich R, Küspert M, Kosian T, Schrewe H, Nave KA, Wegner M. Sox10 cooperates with the Mediator subunit 12 during terminal differentiation of myelinating glia. J Neurosci 2013, 33: 6679-6690

Hornig J, Fröb F, Vogl M, Hermans-Borgmeyer I, Tamm ER, Wegner M. The transcription factors Sox10 and Myrf define an essential regulatory network module in differentiating oligodendrocytes. PLoS Genetics 2013, 9: e1003907

Glasgow S, Zhu W, Stolt CC, Huang TE, Chen F, LoTurco JJ, Neul JL, Wegner M, Mohila C, Deneen B. Mutual Antagonism Between Sox10 and NFIA Regulates Diversification of Glial Lineages and Glioma Sub-Types. Nat. Neurosci 2014, 17: 1322-1329

Paul MH, Harvey RP, Wegne, M, Sock E. Cardiac outflow tract development relies on the complex function of Sox4 and Sox11 in multiple cell types. Cell Mol Life Sci 2014, 71: 2931–2945

Atreya R, Neumann H, Neufert C, Waldner MJ, Billmeier U, Zopf Y, Willma M, App C, Munster T, Kessler H, Maas S, Gebhardt B, Heimke-Brinck R, Reuter E, Dorje F, Rau TT, Uter W, Wang TD, Kiesslich R, Vieth M, Hannappel E, Neurath MF. In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease. Nat Medicine 2014, 20: 313-318


### International Cooperations

Dr. M. Castagnola, Universita' Cattolica, Roma: Italy

Dr. P. Charnay, IBENS, École normale supérieure, Paris: France

Dr. B. Deneen, Baylor College of Medicine, Houston, Texas: USA

Dr. G. Faa, University of Cagliari, Cagliari: Italy

Dr. R. Harvey, University of New South Wales, Kensington: Australia

Dr. D. Meijer, University of Edinburgh, Edinburgh: UK

Dr. D. Metzger, IGBMC, University Strasbourg, Strasbourg: France

Dr. V. Lefebvre, Cleveland Clinic, Cleveland: USA

Dr. W. Pavan, National Human Genome Institute, NIH, Bethesda: USA

Dr. L. Sommer, University Zurich, Zurich: Switzerland

Dr. U. Suter, ETH Zurich, Zurich: Switzerland

Dr. A. Schedl, University Nice, Nice: France

# Institute of Biochemistry – Emil-Fischer-Center

## Professorship of Bioinformatics

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**Research Focus**
- Bioinformatics of biomolecular interactions
- Computational analysis of host-pathogen interactions
- Design of novel Alzheimer drugs via computer simulations of protein aggregation
- Application of information-theoretic methods in protein-docking analysis
- Molecular mechanisms of drug resistance of HIV-1 protease

## Structure of the Division

The Professorship of Bioinformatics builds together with the Chair of Biochemistry and Molecular Medicine, the Chair of Biochemistry and Pathobiochemistry, and the Professorship for Molecular Imaging the Institute of Biochemistry. The Institute of Biochemistry constitutes the interdisciplinary Emil-Fischer-Center together with the Institute of Experimental and Clinical Pharmacology and Toxicology (Faculty of Medicine) and the Institute of Pharmaceutical Chemistry (Faculty of Sciences). The Professorship has eight employees (seven of them are funded by grants), including three scientists and five graduate students.

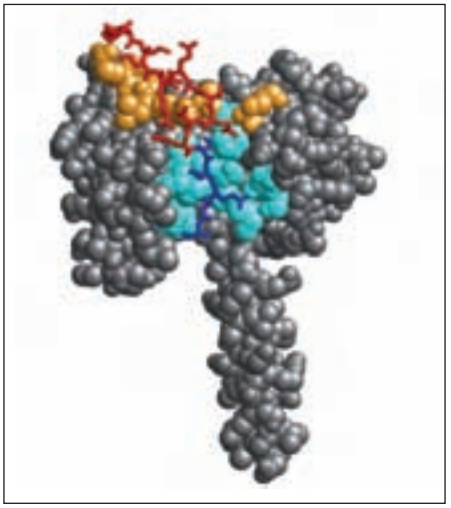
## Research

### Bioinformatics of biomolecular interactions

Protein-protein interactions play a crucial role for the transduction of information in biological signaling pathways. 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 is primarily interested in investigating molecular interactions by a variety of computational tools (e.g. sequence data analysis, molecular modeling, and molecular dynamics).
Molecular dynamics simulations are used to study the dynamics of viral proteins (e.g. HIV protease), the conformational transitions of human proteins (e.g. Alzheimer Aβ-amyloid), or the effect of covalent modifications on molecular recognition processes. Molecular modeling is used to generate the structure of isolated proteins or biomolecular complexes and provides the basis for a molecular understanding of mutational effects on protein stability and binding properties. In addition, sequence based methods are developed that allow an improved detection of functional linear interaction motifs. Such motifs play an important role for the interactions of numerous pathogens with the target molecules of their host.

### 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 that bind 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 problem 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 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. In order to further increase the reliability of the predictions, modeling of sequence motifs in complex with the respective adapter domains is performed, thus allowing to judge the likelihood of an interaction based on a three-dimensional structure.
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 Tio protein from Herpesvirus ateles (stick presentation) in complex with human TRAF3 (space-filled presentation).*

### Design of novel Alzheimer drugs via computer simulations of protein aggregation

Protein conformational diseases are unique since a change in the three-dimensional structure of a protein leads to a biological loss and/or gain of function. Most often, a stable 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(1-42) 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 are capable of preventing 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 fibrillar Aβ42 oligo-

mers and thermodynamic analyses of the aggregation interfaces. In addition, we investigate the effect of different solvent environments on the conformational stability of such Aβ42 oligomers.

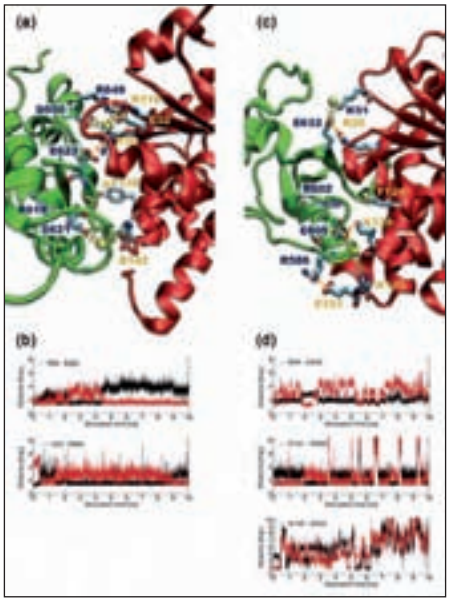
Another aspect of the project focuses on the molecular modeling of Aβ in complex with different ligands. These ligands which are experimentally characterized by our collaboration partners were shown to block Aβ aggregation by binding to small Aβ oligomers. Computational tools were employed to identify the binding site of these known ligands and also for the design of novel, more affine ligands.

*Tetrameric structure of the region 17-42 from the human amyloid-β peptide.*

### Application of information-theoretic methods in protein-docking analysis

Molecular docking represents a versatile computational method for determining the structure of protein-protein complexes. Despite considerable efforts to enhance the accuracy of docking predictions during the past years, a general solution to this problem is not yet within reach. One major challenge is the definition of suitable criteria for a scoring function that allows the identification of a good docking solution among many false arrangements.

In our group, we have adapted the concepts from information theory to treat the biological problem of protein-protein docking. We have developed a formalism based on the concept of mutual information (MI) to investigate different features with respect to their information content in protein docking. We have also shown that the MI-values of these features can successfully be converted into a scoring function. Current work includes the analysis of larger datasets and more sophisticated structural features to obtain a robust and widely applicable approach.



*Relevant interactions in the complex structure of the Dual-Specificity Phosphatase VHR (red) with the SH2 domain of the STAT factor 5a (green) predicted by docking.*

### Molecular mechanisms of drug resistance of HIV-1 protease

The Human Immunodeficiency Virus (HIV) is a member of the retrovirus family. The HIV-protease is essential for replication and assembly of the virus and therefore has become an important target for the design of antiviral agents. These drugs bind to the active site of the protease, thus blocking access of the substrate resulting in a catalytically inactive enzyme. A major problem, however, is the rapid development of resistance to antiretroviral drugs resulting from mutations of amino acids in the protease. Mutations can occur at a large variety of locations in HIV-protease and can also confer different levels of resistance for distinct inhibitors. The mechanism of most of these mutations cannot fully be explained on the basis of the static three-dimensional structures available. Using molecular dynamics simulations, we were able to show that several mutations in HIV-protease affect the dynamics of the protein, thus decreasing the affinity of inhibitor binding. Moreover, these simulations reveal novel target sites within the protease and should therefore facilitate the design of novel and more effective drugs.

*Model of the antigen-binding fragment of the neutralizing SM5-1 antibody (pink and purple) bound to Domain-II (green) of the HCMV gB homotrimer. One protomer is colored according to its five domains.*

## Teaching

The Professorship of Bioinformatics organizes lectures, seminars, and practical courses in the course program of Molecular Medicine and computer sciences.

### Selected Publications


Jardin C, Stefani A.G, Eberhardt M, Juber JB, Sticht, H. An Information-Theoretic Classification of Amino Acids for the Assessment of Interfaces in Protein-Protein Docking, J Mol Model 2013, 19: 3901-10

Kassler K, Sticht H. Molecular Mechanism of HIV-1 gp120 Mutations That Reduce CD4 Binding Affinity, J. Biomol. Str Dyn 2014, 32: 52-64

Socher E, Sticht H. Horn AH. The Conformational Stability of Nonfibrillar Amyloid-β Peptide Oligomers Critically Depends on the C-Terminal Peptide Length. ACS Chem Neurosci 2014, 5: 161-167

Stump JD, Sticht H. Mutations in herpes simplex virus gD protein affect receptor binding by different molecular mechanisms, J Mol Model 2014, 20: 2192

Spindler N, Diestel U, Stump JD, Wiegers AK, Winkler TH, Sticht H, Mach M, Muller YA. Structural Basis for the Recognition of Human Cytomegalovirus Glycoprotein B by a Neutralizing Human Antibody, PLoS Pathogens 2014, 10: e1004377

Scherer M, Klingl S, Sevvana M, Otto V, Schilling EM, Stump JD, Müller R, Reuter N, Sticht H, Muller YA, Stamminger T. Crystal structure of cytomegalovirus IE1 protein reveals targeting of TRIM family member PML via coiled-coil interactions, PLoS Pathogens 2014, 10: e1004512

# Institute of Biochemistry – Emil-Fischer-Center

## Professorship of Molecular Medicine with focus on Molecular Imaging

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**Research Focus**
- Transcriptional programs in the regulation of adult neurogenesis
- Metabolic control of stem cell development and adult neurogenesis
- Functional characterization of intellectual disability factors

## Structure of the Division

The Professorship of Molecular Medicine with focus on Molecular Imaging builds together with the Chair of Biochemistry and Molecular Medicine, the Chair of Biochemistry and Pathobiochemistry, and the Professorship of Bioinformatics the Institute of Biochemistry. The Institute of Biochemistry constitutes the interdisciplinary Emil-Fischer-Center (EFI, see own report) together with the Institute of Experimental and Clinical Pharmacology and Toxicology (Faculty of Medicine) and the Institute of Pharmaceutical Chemistry (Faculty of Sciences). The Professorship has six employees (three of them are funded by grants), including three scientists and three graduate students.

## Research

### Transcriptional programs in the regulation of adult neurogenesis

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 now strong evidence that adult neurogenesis significantly contributes to hippocampus-dependent learning and memory processes. Analysis of preclinical models indicates that impaired adult hippocampal neurogenesis contributes to the pathophysiology of cognitive and affective symptoms during ageing and in neurodegenerative and neuropsychiatric diseases. Thus, understanding of the mechanisms regulating adult neurogenesis is of major basic neuroscientific and clinical interest.

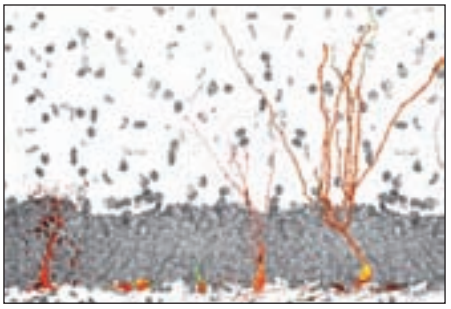
The generation of new functional neurons from stem cells is a complex multistep process. Current data indicates that each developmental step is controlled by stage-specific transcription factors. In collaboration with the research group of Prof. Dr. M. Wegner (Chair of Biochemistry and Pathobiochemistry), we discovered the SoxC group transcription factors Sox4 and Sox11 as key regulators of neuronal fate determination of adult neural stem cells. Intriguingly, we could also demonstrate that Sox4 and Sox11 represent essential factors for neuronal reprogramming of somatic cells.

We have now developed a method that allows analyzing the transcriptome of adult-born neurons during distinct developmental stages. Bioinformatical analyses of the stage specific transcriptome raised the hypothesis that SoxC proteins may not only control neuronal fate determination in the adult neurogenic lineage, but may also regulate the timing of synaptic integration of adult-born neurons. Indeed, genetic, histological and electrophysiological analyses revealed that SoxC proteins negatively regulate the functional integration of adult-born neurons.

To further delineate the transcription factor networks controlling adult hippocampal neurogenesis we performed a proteomic screen for SoxC interacting transcription factors. We are presently validating candidate interactors and are analyzing their function in adult hippocampal neurogenesis. Moreover, ongoing projects are focusing on the identification of transcriptional downstream targets and regulators of SoxC proteins in adult neurogenesis. This project is conducted in close collaboration with the research group of Prof. Dr. J. Winkler (Division of Molecular Neurology, Department of Neurology) and is funded by the IZKF Erlangen.

### Metabolic control of stem cell development and adult neurogenesis

In contrast to adult neural stem cells, neurons are postmitotic, have a highly complex morphology and communicate with each other via high-energy consuming mechanisms. It is assumed that the generation of a functional neuron from stem cell is accompanied by profound changes in cellular metabolism. We found strong evidence that increased mitochondrial biogenesis and activity of mitochondria-dependent metabolic pathways parallel neuronal development. Most intriguingly, impairing mitochondrial transport resulted in profound alterations of neuronal development. We are now analyzing the impact of impaired mitochondrial biogenesis and mitophagy on hippocampal neurogenesis in adult mice. Preliminary results indicate that such manipulations result in a premature ageing-phenotype which raises the interesting possibility that impaired mitochondrial function may significantly contribute to the age-associated impairment of adult neurogenesis-dependent plasticity.



*Neural stem cells give rise to functional neurons through a complex developmental sequence. This process is accompanied by extensive remodeling of the mitochondrial compartment.*

### Functional characterization of intellectual disability factors

Sox11 mutations were recently identified in a subset of patients suffering from Coffin-Siris Syndrome, a developmental disorder associated with intellectual disability. Proteomic analysis of the Sox11 interactome and of Sox11 target genes revealed that Sox11 interacts with a number of intellectual disability-related transcription factors and regulates the expression of intellectual disability (ID) genes. These data suggest that a subset of ID causing genes is connected via a SOX11-dependent transcriptional network and that perturbation of this network contributes to the pathophysiology of intellectual disability. We will combine human genetics, mouse genetics, transcriptomics, and bioinformatics to determine the developmental function and targets of such hypothesized network and to probe network components as novel etiological genes in ID. This project is conducted in close collaboration with Prof. Dr. A. Reis (Institute of Human Genetics) and is funded by the IZKF Erlangen.

## Teaching

The Professorship of Molecular Medicine with focus on Molecular Imaging organizes lectures, seminars, and practical courses in the course program of molecular medicine and participates in all curricular activities (lectures, seminars,

practical courses) in biochemistry and molecular biology for students of medicine and dentistry during the preclinical phase of their studies.

### Selected Publications


Ortega F, Gascón S, Masserdotti G, Deshpande A, Simon C, Fischer J, Dimou L, Chichung Lie D, Schroeder T, Berninger B. Oligodendrogliogenic and neurogenic adult subependymal zone neural stem cells constitute distinct lineages and exhibit differential responsiveness to Wnt signalling. Nat Cell Biol 2013 Jun;15(6): 602-13

Merz K, Lie DC. Evidence that Doublecortin is dispensable for the development of adult born neurons in mice. PLoS One 2013 May 7;8(5): e62693

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### International Cooperations

Prof. Dr. S. Jessberger, Institut für Hirnforschung, University Zurich, Zurich: Switzerland

Prof. A. Muotri, Ph.D., Cellular and Molecular Medicine, University of California San Diego, La Jolla: USA

Dr. N. Nagarajan, Systems Biology, Genome Institute Singapore: Singapore

Dr. A. Schinder, Instituto Leloir, Buenos Aires: Argentina

Dr. V. Lefebvre, Department of Cell Biology, Cleveland Clinic, Cleveland: USA

# Institute of Cellular and Molecular Physiology

## Chair of Physiology (Systems Physiology)

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**Research Focus**
- Renal epithelial ion channels
- Cardiac ion channels

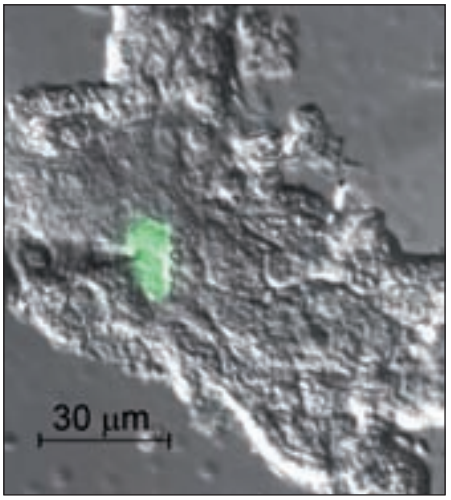
## Structure of the Institute

The Institute of Cellular and Molecular Physiology (Chair of Physiology (Systems Physiology) is housed in a teaching and research building located centrally in Erlangen. In addition to modern research laboratories, the building offers a lecture hall with a capacity for 200 students as well as seminar rooms for small group teaching and practical classes. The Institute makes a substantial contribution to the physiology teaching of preclinical medical and dental students and is also involved in the molecular medicine course.
The renal physiology research group in the Institute is headed by the Director, Prof. Dr. C. Korbmacher, the additional cardiac physiology research group is headed by an associate professor, Prof. Dr. T. Volk.
The research focus of the Institute is the study of renal and cardiac ion channels. This research area is of pathophysiological relevance since an inappropriate regulation of renal and cardiac ion channels may cause arterial hypertension or cardiac arrhythmias, respectively.
The analysis of ion channels involves studies at the level of the cell membrane, but also includes aspects of cellular physiology, such as protein trafficking, endocytosis/exocytosis, protein-protein interactions between transport and regulatory proteins as well as interactions with elements of the cytoskeleton. The experimental investigation of these complex topics requires a range of sophisticated electrophysiological, cellular, molecular, and biological methods. In addition to cellular model systems (cell culture, heterologous expression systems), transgenic and knock-out mice are used to study the function and regulation of ion transport processes in native tissues and in the whole animal. This integrated approach provides fascinating opportunities to gain novel insights into physiological and pathophysiological mechanisms and may lead to a better understanding of disease processes.

## Research

### Renal epithelial ion channels

Project manager: Prof. Dr. C. Korbmacher
In the kidney and other epithelial tissues, ion channels are involved in the highly selective and regulated control of ion fluxes across apical and basolateral membranes of epithelial cells. These ion channels are important for intracellular ion homeostasis and transepithelial electrolyte transport. The delicate regulation of these ion channels is pivotal for the maintenance of a healthy 'milieu interieur' as evidenced by severe disease states that result from abnormal ion channel function. Indeed, the study of molecular mechanisms involved in epithelial ion channel regulation is likely to be relevant to understand a range of diseases.
In this context, the group investigates in particular the complex mechanisms involved in the regulation of the epithelial sodium channel (ENaC). Ion flux through ENaC is the rate limiting step for sodium absorption in the aldosterone sensitive distal nephron. The appropriate regulation of ENaC activity is critical for the maintenance of body sodium balance and hence for the long term control of arterial blood pressure. This is evidenced by 'gain of function' mutations of ENaC which cause a hereditary form of severe salt-sensitive arterial hypertension (Liddle's syndrome).
The molecular mechanisms involved in ENaC regulation are still incompletely understood and involve a complex network of regulatory proteins, kinases, and proteases. Proteolytic activation of ENaC may be pathophysiologically relevant in the context of inflammatory kidney disease and may contribute to sodium retention in nephrotic syndrome. Proteases may also indirectly modulate ion channels. Recently, it has been demonstrated that an activation of the non-selective cation channel TPRV4 (transient receptor potential vanilloid 4) can be mediated by the protease-activated receptor 2 (PAR2). TRPV4 is highly expressed in the distal nephron and collecting duct, but its function is largely unknown. TRPV4 belongs to the same gene family as the polycystins (PKD1 and PKD2) mutated in autosomal dominant polycystic kidney disease (ADPKD). One aim of the group is to characterize the function and regulation of TRPV4 and to explore its possible role in tubular ion transport and renal cyst growth. The group uses a combination of electrophysiological and molecular biological techniques to characterize the functional interaction of ion channels with various receptors, agonists, and regulatory proteins and to identify molecular regions relevant for channel function and regulation.
A better understanding of the molecular mechanisms involved in the regulation of epithelial ion channels will hopefully provide novel insights into their pathophysiological role. This ultimately may lead to new diagnostic and therapeutic concepts.

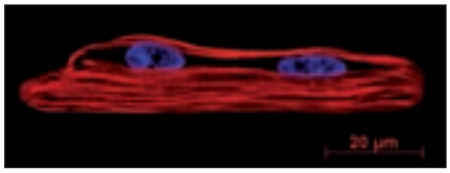



*Microdissected collecting duct of a mouse kidney. One principal cell was stained with fluorescein via a patch pipette.*

### Cardiac ion channels

Project manager: Prof. Dr. T. Volk
The key interest of this group is to identify cellular and molecular mechanisms that regulate the function and expression of cardiac ion channels and thereby lead to differences in action potential duration (APD) and contractility in the heart.
It is well established that regional differences in APD in different areas of the heart are of great importance for a normal course of repolarization. Within the left ventricular free wall, for example, 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.




*Isolated cardiomyocyte from a rat heart. Fluorescence dyes were used to stain nuclei in blue and actin fibers in red.*

In order to further understand the underlying mechanisms, this group investigates the regulation and pharmacology of ion channels ($Na^+$, $K^+$ and $Ca2^+$ 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 which participates in the regulation of cardiac $Ca2^+$ 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.

## Teaching

Both chairs of physiology (Institute of Physiology and Pathophysiology and Institute of Cellular and Molecular Physiology) jointly organize all curricular teaching of physiology (lectures, seminars, and practical classes) for medical and dental students and for students following the course of Molecular Medicine. The Institute of Cellular and Molecular Physiology contributes to the teaching of cellular physiology and is responsible for teaching the physiology of organ systems (e.g. heart, circulation, kidney, salt and water homeostasis, respiration, acid-base homeostasis, gastrointestinal physiology, hormones). In addition, the Institute contributes to a course entitled Molecular Pathomechanisms for Molecular Medicine students and also offers advanced practicals and thesis projects for these students. An overview of the subject and its theoretical foundation is presented in traditional lectures which are supplemented by interactive small group seminars. These seminars reinforce the topics of the lectures and emphasize relevant clinical aspects. In practical classes, theoretical concepts are illustrated by experiments and the students have the opportunity to acquire practical skills. They cover topics such as cardiac and circulatory physiology, ECG, blood, kidney, metabolism, respiration, and spiroergometry.

### Selected Publications

Rauh R, Soell D, Haerteis S, Diakov A, Nesterov V, Krueger B, Sticht H, Korbmacher C. A mutation in the beta-subunit of ENaC identified in a patient with cystic fibrosis-like symptoms has a gain-of-function effect. Am J Physiol Lung Cell Mol Physiol 2013, 304: L43-55

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### International Cooperations

Prof. N. Bunnett, Ph.D., Monash University (MIPS), Melbourne: Australia

Prof. M.J. Caplan, Yale University, New Haven: USA

Prof. D. Cook, University of Sydney, Sydney: Australia

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

Prof. J.M. Edwardson, University of Cambridge, Cambridge: UK

Prof. M.D. Hollenberg, University of Calgary, Calgary: Canada

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

Prof. P. McIntyre, RMIT, Bundoora, Victoria: Australia

Prof. R.J. Parmer, University of California (UCSD), San Diego: USA

Prof. B.C. Rossier, Prof. E. Hummler, University of Lausanne, Lausanne: Switzerland

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**Research Focus**

- Neurophysiologic substrates of higher brain functions: Biophysics and functions of voltage-dependent ion channels
- Transduction, integration, plasticity in primary nociceptive neurons
- Trigeminal nociception and headache generation
- Properties of peripheral human C-fibers
- Functional imaging of brain activity by fMRI

## Structure of the Institute

The Institute of Physiology and Pathophysiology comprises one chair and two professorships of physiology with their work groups and two further groups led by an academic director and a professor emeritus. In addition, the Institute houses collaborating work groups from the Departments of Medicine I, IV, Anesthesiology, and Neurology of the UK Erlangen. In the context of long-standing scientific collaborations, the Institute regularly welcomes guest scientists from the USA, South Korea, Czech Republic, Hungary, and Romania who often stay for extended research periods.

A total of 84 persons works at the Institute, 26 of them are funded by grants. The research is conducted by 19 Ph.D./MD scientists, 39 doctoral students, and 19 technical assistants. In the reporting period, one scientist was appointed as W2-professor for physiology at the University Hospital Aachen (Prof. Dr. A. Lampert), another scientist was awarded a Heisenberg-Professorship of the DFG (Prof. Dr. K. Zimmermann).

The overall research spectrum ranges from cellular and molecular biological topics and the microphysiology of neuronal networks to behavioral physiology and human studies, the latter including microneurography, functional imaging, and psychophysics in healthy volunteers and chronic pain patients.

## Research

### Neurophysiologic substrates of higher brain functions: Biophysics and functions of voltage-dependent ion channels

Project manager: Prof. Dr. C. Alzheimer

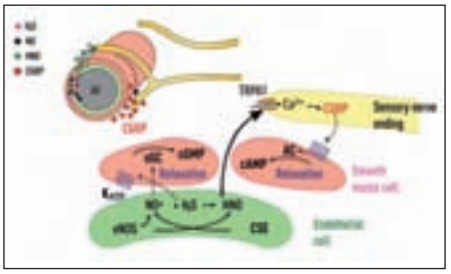
Our research focuses on the electric behavior of CNS neurons under normal and pathological conditions. Using high resolution neurophysiological and optical techniques, we investigate function and regulation of ion channels and synapses. Our aim is to understand fundamental neural processes which are essential for cognitive and motor 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 β 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.

### Transduction, integration, plasticity in primary nociceptive neurons

Project manager: 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, toxins and gaso - transmitters 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, Kv7.2/7.3, HCN) came in focus, because only few subtypes decide on excitability, i.e. on generation, frequency, and propaga - tion of action potentials to the central nervous system. Neuroimmunology is a rapidly growing field that, for example, studies the interaction of substance P with the immune system which may essentially contribute to chronic inflammatory, including autoimmune diseases.



*HNO-TRPA1-CGRP pathway in neurovascular regulation. TRPA1/CGRP expressing sensory nerve endings communicate with smooth muscle cells surrounding the endothelium of arterial vessels (AV). Endothelial cells produce NO (through eNOS) and H2S which react to nitroxyl (HNO). HNO is freely diffusing and activates TRPA1 receptors of perivascular nerve endings leading to CGRP release upon Ca2+ inflow. CGRP activates smooth muscular CGRP receptors causing arterial relaxation through cAMP elevation. Besides, NO can directly activate sGC to increase cGMP and H2S can activate ATP-sensitive $K^+$ channels (KATP), classical vasodilatory principles.*

### Trigeminal nociception and headache generation

Project manager: 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 which 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.

### Properties of peripheral human C-fibers

Project manager: PD Dr. B. Namer

Morphological and electrical properties of peripheral unmyelinated neurons (C-fibers) are studied directly in healthy subjects and patients with painful and painless neuropathies. Especially patients with defined mutations of ion channels that change the excitability of peripheral C-fibers are of interest. The focus lies on nociceptors and mechanisms which contribute to genesis of pain, in particular spontaneous neuro-

pathic pain. The methods to examine C-fibers in awake humans include non-invasive assessment of axon reflexes and psychophysical studies as well as microneurography. The main topics are:

1) Effects of pharmacological modulation of voltage-gated sodium channels on biophysical properties of human C-fibers (microneurography und axon-reflexes), epidermal nerve fiber density, and altered pain sensation of humans (psychophysics);
2) Microneurographic and psychophysical assessment of C-fiber properties of patients with erythromelalgia with and without mutations in voltage-gated sodium channels;
3) Microneurography of C-fibers in patients with painful and painless neuropathies, especially with small fiber neuropathy.

### Functional imaging of brain activity by fMRI

Project manager: 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 Psychiatry and Psychotherapy analyze the central changes induced by psychogenic or emotional stress or by addiction.

## Teaching

In the preclinical curricula of medicine and dentistry, the Institute contributes to the teaching of the basics of cellular physiology and provides the complete education in neurophysiology. Besides the traditional teaching methods including lectures, practical courses, and seminars, the Institute also offers internet-based seminars. Half of the practical courses are held in a contiguous time block which is highly appreciated by the students. The positive evaluation of the practical courses is also due to the continuous upgrade of the experimental setups thanks to funds provided by the students' fees. To bridge the gap between preclinical education and clinical work, elective seminars on the neurobiological principles of neuropsychiatric diseases are offered on a regular basis. Furthermore, presentations by clinical experts from the UK Erlangen are integrated into the lecture series in neurophysiology to promote translational thinking.

The Institute participates with lectures, seminars, and practical courses in the bachelor and master degree program Molecular Medicine. In addition, interdisciplinary lectures are given to students of natural and technical sciences, to pharmacists, and to students of psychology who select medicine as a subsidiary subject or a main focus. For them, not only neurophysiology, but all topics of physiology are covered.

### Selected Publications


Sachse CC, Kim YH, Agsten M, Huth T, Alzheimer C, Kovacs DM, Kim DY. BACE1 and presenilin/-secretase regulate proteolytic processing of KCNE1 and 2, auxiliary subunits of voltage-gated potassium channels. FASEB J 2013, 27: 2458-2467

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Eberhardt M, Dux M, Namer B, Miljkovic J, Cordasic N, Will C, Kichko TI, de la Roche J, Fischer M, Suárez SA, Bikiel D, Dorsch K, Leffler A, Babes A, Lampert A, Lennerz JK, Schueler M, Messlinger K, Dux M, Neuhuber WL, De Col R. Extracranial projections of meningeal afferents and their impact on meningeal nociception and headache. Pain 2013, 154: 1622-1631

Namer B, Pfeffer S, Handwerker HO, Schmelz M, Bickel A. Axon reflex flare and quantitative sudomotor axon reflex contribute in the diagnosis of small fiber neuropathy. Muscle Nerve 2013, 47: 357-363

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### International Cooperations

Prof. Dr. S. Bevan, Dr. D. Andersson, King´s College, London: UK

Prof. Dr. J. Olesen, Glostrup Hospita, Copenhagen: Denmark

Prof. Dr. P. Kemppainen, University of Turku, Turku: Finland

Prof. Dr. G. Kobal, ALTRIA CS, Richmond: USA

Prof. Dr. E. Jørum, University of Oslo, Oslo: Norway

Prof. Dr. A. Babes, University of Bucharest, Bucharest: Romania

Prof. Dr. S. Werner, ETH Zurich, Zurich: Switzerland

Prof. Dr. P. Zygmunt, Lund University: Sweden

Prof. Dr. H. van Brederode, University of Washington, Seattle: USA

Prof. Dr. C. Woolf, Prof. Dr. B. Bean, Harvard University, Boston: USA

Prof Dr. B. Turnquist; Bethel University, St Paul, Minnesota: USA

Prof. Dr. A. Korngreen, Bar Ilan University, Tel Aviv: Israel

Prof. Dr. B. Wallace, Birckbeck College, London: UK

Prof. Dr. E. Fransén, KTH Royal Institute of Technology, Stockholm: Sweden

# 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

The Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine (IPASUM) belongs to the clinical-theoretical institutes of the FAU. The Institute has 45 employees (21 of them are financed by third-party funds). Research is carried out by twelve Ph.D. scientist, five Ph.D. students, and eleven technical assistants. IPASUM houses a W2-professorship for biomarkers in the field of occupational medicine next to a C4-professorship for occupational and social medicine.
Different working groups develop molecular markers of exposure to hazardous substances as well as procedures to quantify skin penetration of these substances. They also standardize diagnostic premedical findings. Furthermore, IPASUM examines work-related exposure of employees and of the general population within the framework of population studies.
The office for occupational medical care of the FAU is affiliated to IPASUM. Its physicians carry out the preventive medical checkups of all employees and students at the FAU. They also advice the heads of FAU and UK Erlangen in terms of occupational health protection and offer measures for health promotion.
IPASUM coordinates the working groups „Biological limit values" and „Analysis in biological materials" of the Commission of the Investigation of Health Hazards of Chemical Compounds in the Work Area of the DFG and houses the scientific offices of these working groups.
Next to this, IPASUM is in charge of a quality assessment scheme for analysis in biological material (G-EQUAS). The laboratories of IPASUM serve as reference laboratories for G-EQUAS and other quality assessment schemes worldwide.

## Research

### 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 which 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 analyse not only the exposure, but also the data of ambient monitoring (inhalative and dermal exposure). These studies are generally promoted by the Gesetzliche Unfallversicherungsträger (German Social Insurance), the German State Ministries or the German 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 schools, phthalates in pharmaceuticals/toys, or aromatic amines in clothes. These studies are often supported by the local authorities, the Bavarian State Ministry of the Environment and Public Health, and the German Federal Environment Agency.

### Biomarker in Occupational Medicine

Project manager: Prof. Dr. S. Schmitz-Spanke
This working group examines the cellular response to exposure to hazardous substances in the low dose range. In cell 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 analysed and the time of failure characterised. Next to a wide spectrum of molecular biological methods, the working group applies different techniques of the "top-down" protein analysis, the enrichment of phosphoproteins and the separation of proteins and metabolites, respectively. One research focus at the FAU, established in cooperation with the excellence cluster EAM (Engineering of Advanced Materials), is laid on the interaction between nanoparticles and proteins and its possible toxic effects.

### Dermatotoxicology

Several projects which 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). These projects are supported by the DFG and the German employer's liability insurance association. Furthermore one working group of IPASUM deals with the assessment of hazardous substances in the area of skin penetration for the Commission of Investigation of Health Hazards of Chemical Compounds in the Work Area of the DFG. 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).

*HEROS – Investigation of the intra-observer variability of the **H**and **E**czema Sco**R**e for **O**ccupational **S**creening as part of a field study.*

### Molecular markers of exposure to hazardous substances

This research area develops and validates procedures for the quantitative assessment of molecular markers of individual exposure to hazard-

ous 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 which give information about the specificity, sensitivity, and toxicokinetic behavior.

### 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 54th round robin test of G-EQUAS was finished within the report period. At the moment G-EQUAS comprises 151 analysis parameters; about 200 laboratories worldwide (two-thirds of it 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 which support the health resources and wellbeing of the employees. IPASUM 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.

### Healthcare research

This research area develops, among others, concepts and their effectiveness for interventions after psychic traumatization caused by extreme situations at work. This concerns not only disaster relief forces, but also employees of the police-, bank-, retail-, healthcare-, and the public transport sector. Important and necessary elements of preventive concepts are the immediate and fast acute care of those affected, in order to help them cope with psychic traumatization and to avoid manifest diseases.

Once research project of IPASUM investigates how far these concepts are scientifically evident by examining the psycho-social acute care (first aid) of employees from the public transport sector after accidents, suicides, and attacks.
A second area of the healthcare research is the project "Healthcare in Bavarian schools". The project's aim is to develop the need for occupational care in Bavarian schools and to establish a model for a decentralized support system in German schools. The project is run in cooperation with the Institute and Outpatient Clinic of Occupational-, Social- and Environmental Medicine of the LMU Munich.

## Teaching

Since 2006, Prof. Dr. H. Drexler has been Dean for Student Affairs. The science of occupational, social, and environmental medicine (lecture, field work, and E-learning) is based on the Medical Licensure Act. There is a cross section coordination of Q3 and Q10.

### Selected Publications


Dennerlein K, Schneider D, Göen T, Schaller KH, Drexler H, Korinth G. Studies on percutaneous penetration of chemicals – Impact of storage conditions for excised human skin. Toxicol In Vitro 2013, 27: 708-713

Eckert E, Leng G, Gries W, Göen T. Excretion of mercapturic acids in human urine after occupational exposure to 2-chloroprene. Arch Toxicol 2013, 87: 1095-1102

Jäger T, Drexler H, Göen T. Ion pairing and ion exchange chromatography coupled to ICP-MS to determine selenium species in human urine. J Anal At Spectrom 2013, 28: 1402-1409

Fromme H, Lahrz T, Kraft M, Fernbacher L, Mach C, Dietrich S, Burkardt R, Völkel W, Göen T. Organophosphate flame retardants and plasticizers in the air and dust in German daycare centers and human biomonitoring in visiting children (LUPE 3). Environ Int 2014, 71: 158-163

Göen T, Schramm A, Baumeister T, Uter W, Drexler H. Current and historical individual data about exposure of workers in the rayon industry to carbon disulfide and their validity in calculating the cumulative dose. Int Arch Occup Environ Health 2014, 87: 675-683

Pink M, Verma N, Rettenmeier AW, Schmitz-Spanke S. Integrated proteomic and metabolomic analysis to assess the effects of pure and benzo[a]pyrene-loaded carbon black particles on energy metabolism and motility in the human endothelial cell line EA.hy926. Arch Toxicol 2014, 88: 913-934


### International Cooperations

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

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

Dr. J. Cocker, Health and Safety Laboratory (HSL), Buxton: UK

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

Prof. P. Jacobsen, Bispebjerg University Hospital, Copenhagen: Denmark

Dr. J. Mráz, National Institute of Public Health, Prague: Czech Republic

### Research Equipment

Sciex API 2000, LC-MS/MS-System

Agilent, GC-MS/MS System 7000

Agilent, ICP-MS System 7500 cx

# Institute of Clinical and Molecular Virology

## Chair of Clinical Virology

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**Research Focus**
- Retroviruses
- β-herpesviruses
- DNA Tumor Viruses

## Structure of the Institute

During the past two years, ten independent research groups worked at the Institute of Clinical and Molecular Virology. Main research activities focus on (1) the role of retroviruses in immunodeficiency and oncogenesis, (2) the pathogenesis of β-herpesviruses, such as the human cytomegalovirus, and (3) DNA tumor virology. Thereby, issues of infection biology, tumor virology, vector development, therapy research, native and adaptive immunity, signaling, and epigenetics are investigated. With the appointment of Prof. Dr. K. Überla as Director of the Institute there will be an additional research focus on the development of viral vaccines.

The majority of the staff members are third-party funded Ph.D. students and postdocs of biology, molecular medicine, biochemistry, and medicine.

The Clinical Diagnostics Section offers a broad range of state-of-the-art serological and molecular methods for the detection of virus infections, including genotyping as well as antiviral drug resistance testing for immunodeficiency, herpes, and hepatitis viruses. Major activities target on retrovirus diagnostics, where the Institute of Clinical and Molecular Virology performs assistance in the explanation of doubtful HIV and HTLV diagnostic results and in antiviral drug resistance testing for laboratories all over Germany. During the last two years, the range of molecular diagnostic tests was clearly expanded, e.g. by the introduction of real-time PCRs for the detection of Hepatitis E virus and enteroviruses, and the development of protocols for the detection of nucleic acids of tropical viruses (Dengue virus, Chikungunya virus, West Nile virus).

## Research

### Retroviruses

Project managers: Prof. Dr. U. Schubert[1], Prof. Dr. T. Gramberg[2], Dr. A. Thoma-Kreß[3]

Two HIV research groups and one HTLV research group are working at the Institute. The first research group studies the interaction of host and virus proteins on the molecular level in order to define interface regions of binding partners that can be used as target structures for anti-viral strategies. A major focus of their research encompasses general aspects of HIV-1 biology, including the role of cellular factors in retrovirus assembly. Those studies are focused on the role of the ubiquitin-proteasome-system in late processes of the HIV replication cycle.

The second research group investigates innate and intrinsic immunity in retroviral infection. It focuses on the cell biology and molecular mechanisms of intracellular restriction factors, such as the proteins of the TRIM family or the recently discovered protein SAMHD1 which can inhibit reverse transcription of retroviruses.

The third research group focuses within the SFB796 (see own report) on the molecular mechanisms of cell-to-cell transmission of the retrovirus Human T-cell leukemia virus Type 1 (HTLV-1) with a special interest on modulation of the cytoskeleton by viral proteins. In addition, it analyzes new functions of the viral oncoprotein Tax which could contribute to the development of the aggressive neoplasia adult T-cell leukemia.

### β-herpesviruses

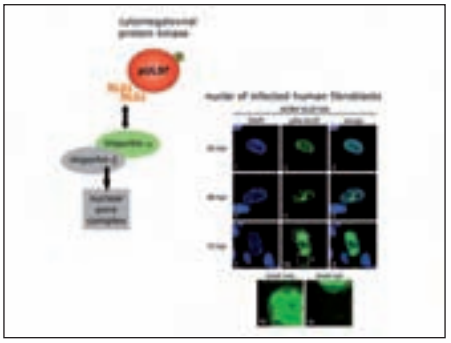
Project managers: Prof. Dr. M. Mach[1], Prof. Dr. T. Stamminger[2], Prof. Dr. M. Marschall[3], Prof. Dr. A. Ensser[4]

The characterization of molecular mechanisms of human cytomegalovirus (HCMV) replication and the immune defense against HCMV is an - other key focus of the Institute of Clinical and Mo - lecular Virology. The first research group defines in collaboration with Prof. Dr. T. Winkler (Chair of Genetics, Faculty of Engineering) the key factors providing protective humoral immunity following HCMV infection. In the murine CMV model, the protective mechanisms of antibodies in immunosuppressed host organisms are investigated. For human CMV, antigens which are involved in the induction of neutralizing antibodies are characterized. Their results clearly disprove the so far commonly-received opinion that antibodies do not play any role in the protection from CMV infections in risk groups.

The second research group analyzes the mechanism of viral regulatory proteins that exert essential functions for efficient replication and are thus attractive novel target molecules for antiviral therapy. It identified a novel intrinsic immune mechanism against herpesviruses that appears to be critical for the switch between latency and lytic replication. Importantly, in collaboration with Prof. Dr. Y. Muller (Chair of Biotechnology, Faculty of Engineering), the crystal structure of a viral antagonistic protein of intrinsic immunity could recently be solved. Thus, this work paved the way for insights into the molecular mechanism of antagonization as well as for the rational design of interfering drugs.

The third research group investigates the role of protein kinases which play an important regulatory role in herpesviral replication and pathogenicity. Specific focus is on the crosstalk between viral and cellular protein kinases involved in complex regulatory processes of herpesviral replication cycles. This area of research aims at developing a new generation of antiviral drugs on the basis of protein kinase inhibitors.

In a translational project, the forth research group develops chimeric immunoreceptors for antiviral adoptive immunotherapy of CMV infection.



*Nuclear Translocation of Protein Kinase pUL97 of Human Cytomegalovirus. The viral protein kinase pUL97 is translocated to the nucleus of virus infected cells through two nuclear localization sequences, NLS1 and NLS2. This transport is mediated by the direct binding to a prominent transporter of the cellular nuclear import machinery, namely importin alpha. The intranuclear localization of pUL97 comprises the entire lumen of the nucleus, with an accumulation in viral replication centers (see inset nuc) and at lower intensity at the nuclear envelope.*

### DNA Tumor Viruses

Project managers: PD Dr. F. Neipel[1], PD Dr. B. Biesinger[2], Prof. Dr. A. Ensser[3], Prof. Dr. W. Doerfler[4]

This research focus aims at elucidating the mechanisms of cellular growth transformation by

DNA tumor viruses. The Kaposi's sarcoma-associated human herpesvirus type 8 (HHV-8) is associated with certain B-cell lymphomas and Kaposi's sarcoma. The first group focuses on the identification of genes which are involved in tumor development. They identified a new receptor for HHV-8, the ephrin receptor tyrosine kinase A2 (EphA2). EphA2 is bound to the glycoproteins H and L (gH/gL) of HHV-8. The binding of these viral glycoproteins not only mediates entry of the virus into host cells, but also induces signal transduction pathways known to be involved in the tumorigenic process by vascularization. Thus, HHV-8 encounters and activates cellular genes contributing to oncogenesis at the earliest stages of infection.

The second group studies T-cellular signaling pathways regulated by the viral oncoproteins StpC and Tip from Herpesvirus saimiri C488 as well as Tio from Herpesvirus ateles. These investigations address signaling cascades, activating the transcription factor NF-κB or regulated by tyrosine kinases of the Src family, and their target genes.

Analyzing the cell-differentiating proliferative signaling pathways that are stimulated by Tip is also a main focus of the third group within the SFB 796 (see own report). Furthermore, this group investigates the chromatin structure and replication of latent herpesvirus genomes in T and B cells. Novel mechanisms of intrinsic immunity against gamma herpesviruses were revealed in cooperation with Prof. Dr. T. Stamminger. DNA methylation and/or histone modification have been documented to affect many biomedical processes via the regulation of gene expression.

The forth group characterizes different aspects of DNA-methylation in HIV-1 proviral genomes, in transgenic cells, and in the human genome.

## Teaching

In cooperation with the colleagues from the Institute of Clinical Microbiology, Immunology, and Hygiene, the Institute of Clinical and Molecular Virology offers curricular lectures and practical courses in infectiology and immunology to medical students. These general infectiology courses have been expanded to dental students, students of the degree programs Medical Process Management and Life Science Engineering as well as to pharmaceutical students. Within the Bachelor's degree program of Molecular Medicine, the lectures impart basics of general virology. Viral education is complemented with F1 practical courses offered to groups of two or three students including an accompanying methods seminar or offered individually. The students work under the direct instruction of the team leaders on current research projects in the lab. In the advanced seminar of the Master's degree program of Molecular Medicine, the students are introduced to original scientific publications. A three-week F2 practical course aims at improving the students' knowledge of laboratory techniques and at imparting skills on how to design scientific projects. In the six week F3 practical course, the students work on their own project under the supervision of a group leader. For the Bachelor's and Master's degree programs Biology, Integrated Life Sciences, and Cell and Molecular Biology, the Institute of Clinical and Molecular Virology provides specialization modules to the students. Special lectures conveying background knowledge of the research areas are offered to students of all degree programs. Moreover, the members of the Institute of Clinical and Molecular Virology were essentially involved in the weekly seminars, periodic workshops, and annual retreats of the GK 1071 (see own report).

### Selected Publications


de Jong SJ, Albrecht JC, Giehler F, Kieser A, Sticht H, Biesinger B. Noncanonical NF-B activation by the oncoprotein Tio occurs through a nonconserved TRAF3-binding motif. Sci Signal 2013, *6*(272): ra27

Bolduan S, Hubel P, Reif T, Lodermeyer V, Höhne K, Fritz JV, Sauter D, Kirchhoff F, Fackler OT, Schindler M, Schubert U. HIV-1 Vpu affects the anterograde transport and the glycosylation pattern of NTB-A. Virology 2013, 440(2): 190-203

Mohr CF, Kalmer M, Gross C, Mann MC, Sterz KR, Kieser A, Fleckenstein B, Kress AK. The tumor marker Fascin is induced by the EBV-encoded oncoprotein LMP1 via NF-kB signals in lymphocytes and contributes to their invasive migration. Cell Commun Signal 2014, 12: 46

Scherer M, Klingl S, Sevvana M, Otto V, Schilling EM, Stump JD, Müller R, Reuter N, Sticht H, Muller YA, Stamminger T. Crystal structure of cytomegalovirus IE1 protein reveals targeting of TRIM family member PML via coiled-coil interactions. PLoS Pathog 2014, 10(11): e1004512

Milbradt J, Kraut A, Hutterer C, Sonntag E, Schmeiser C, Ferro M, Wagner S, Lenac T, Claus C, Pinkert S, Hamilton ST, Rawlinson WD, Sticht H, Couté Y, Marschall M. Proteomic analysis of the multimeric nuclear egress complex of human cytomegalovirus. Mol Cell Proteomics 2014, 13(8): 2132-46

Full F, Jungnickl D, Reuter N, Bogner E, Brulois K, Scholz B, Stürzl M, Myoung J, Jung JU, Stamminger T, Ensser A. Kaposi's sarcoma associated herpesvirus tegument protein ORF75 is essential for viral lytic replication and plays a critical role in the antagonization of ND10-instituted intrinsic immunity. PLoS Pathog 2014, 10(1): e1003863


### International Cooperations

Prof. A. Balasubramanyam, Baylor College of Medicine, Houston: USA

Prof. W. Britt, University of Alabama at Birmingham, Birmingham: USA

Prof. J. Chen, Vanderbilt University Medical Center, Nashville: USA

Prof. S. Chou, Oregon Health and Science University, Portland: USA

Dr. Y. Couté, INSERM U1038/UJF, CEA, Grenoble: France

Prof. T. Fossen, University of Bergen: Norway

Prof. S. Jonjic, Dr. T. Lenac, University of Rijeka: Croatia

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

Dr. J.-M. Péloponèse, CNRS- UMR5236, Montpellier: France

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

Prof. B. Ray, University of Burdwan, West Bengal: India

Dr. Y. Reissand, Dr. I. Alroy, Proteologics Ltd., Rehovot: Israel

Prof. K. Strebel, National Institutes of Health (NIH), Bethesda: USA

Prof. Y. Yarden, The Weizmann Institute of Science, Rehovot: Israel

### Meetings and International Training Courses

12.03.2014: Technologien für zellbasierte Therapien, Erlangen

### Research Equipment

ABI, Prism 3100 Genetic Analyzer and Data Bank (bis 2014)

BD Biosciences, Flow Cytometer LSR II

Illumina, MiSeq Desktop Next Generation Sequencer

Leica, TCS SP5 Confocal Microscope

# Institute of Clinical and Molecular Virology

## Division of Experimental Therapeutics

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**Research Focus**

- Comprehenisve phenotyping and therapy-studies in animal models of human neurodegenerative disorders (Morbus Alzheimer (AD), Chorea Huntington (HD), Morbus Parkinson, Schizophrenia, stress-induced disorders, Attention deficit hyperactivity disorder)

### Structure of the Division

The Division of Experimental Therapeutics is located in the Preclinical Experimental Animal Center (PETZ; see own report) within the Franz-Penzoldt-Center (FPZ) and contributes to essential responsibilities of the FPZ. The FPZ is an interdisciplinary facility, responsible for fundamental and preclinical animal research in Erlangen. In this context, the Division of Experimental Therapeutics offers highly standardized methods for the characterization of transgenic animals during preclinical studies in the context of neurodegenerative disorders and immunological research.
The use of transgenic animal models supports our research focus: Morbus Alzheimer (McGill-R-Thy1-APP rats), Chorea Huntington (BACHD mice, tgHD rats), Morbus Parkinson (PD mice), Schizophrenia (Sca17 rats), Attention deficit hyperactivity disorder (ADD) (SHR rats), Dipeptidylpeptidase 4 (DPP4) as a new pharmaceutical target for post traumatic stress disorders (DA Wildtype-, DA DPP4mut-rats).

### Research

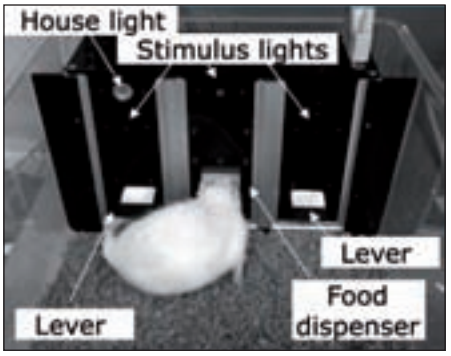
Comprehenisve phenotyping and therapy-studies in animal models of human neurodegenerative disorders (Morbus Alzheimer (AD), Chorea Huntington (HD), Morbus Parkinson, Schizophrenia, stress-induced disorders, Attention deficit hyperactivity disorder).

The Division of Experimental Therapeutics deals with comprehensive phenotyping and translational preclinical experimental therapeutic approaches in primarily transgenic rodent models for human neurodegenerative disorders. A present focus is on neurodegenerative processes induced by protein aggregational diseases (polyglutamine disorders, Parkinson´s and Alzheimer´s disease). One goal is to provide models with a high predictivity for the human condition. Presently, drugs are tested for their therapeutic efficiency in AD or HD (e.g. QC-inhibitors, cholinesterase-inhibitors). Various behavioral, neurological, immunological, molecular, and histological techniques are applied to char - acterize the pathophysiology and to develop new therapies. The presented methods allow a precise characterization of mouse- and rat transgenic animal models of human neurodegenerative disorders.
1. Analysis of motoric function and coordination (Accelerod test procedure, Catwalk-test, Open Field)
CatWalk XT (compare figure) is a highly sensitive tool to assess gait and locomotion. The rat or mouse traverses a glass plate voluntarily (towards a goal box), and its footprints are captured. CatWalk XT visualizes the prints and calculates statistics related to print dimensions and the time and distance relationships between footfalls.

*Catwalk XT system (Noldus)*

2. Analysis of sensory-motoric gating (Startle Response, Prepulse Inhibition (PPI))
3. Analysis of emotionality and fear (Social Interaction Test, Elevated Plus-Maze)
4. Analysis of learning and memory (Radial-Maze Test, Novel Object Recognition Test, operant conditioning)

The operant conditioning units (OBS, compare figure) used in this study consist of two retractable levers positioned on either side of a central food crib, covered with a clear Perspex panel hinged at the top, so that the animal could push it open to retrieve the food delivered upon completion of a successful trial.




*Rat in front of an operant wall (TSE Systems)*

5. Behavioral phenotyping with the PhenoMaster (PhenoTyper, IntelliCage, und PhenoMaster (PM))
6. Telemetry for the analysis of physiological parameters
Furthermore, the analyses of animal bevavioral phenotyping experiments are supported by general molecular- (RealTime-PCR), biochemical- (western-Blot, co-immunoprecipitation) and histological studies (immunohistochemistry, immunofluorescence).

### Teaching

Seminars contribute to the curricula in clinical and experimental biomedicine, including anatomy, pharmacology, reproductive biology, and laboratory animals sciences. We employ modern educational technologies in several seminars and practical courses which also have been evaluated repeatedly. The seminars are part of the B.Sc./M.Sc. of Molecular Medicine at the FAU and they are integrated in postgraduate research programs.
The following seminars are offered to the students of the degree programm Molecular Medicine:
"Seminar experimental animals and knowledge of their reproduction" and „System-interactions and neuroendocrine-immunology: From anatomy to pathology".
These seminars impart deep knowledge of the structure and function of the nervous, neuroendocrine and immune system. Afterwards the students will have a comprehensive knowledge about the involved physiological pathways, e.g. the classical symptom "fever" as an adaption of the immune system to pathophysiological processes. These seminars represent a compendium of different medical domains and basic principles to allow a broad understanding on the complexity of somatic processes.

The seminars "Generation of transgenic mice and rats as animal models of human diseases" and „Dealing with Experimental animals" (animal protection law, experimental design, and methods) together with laboratory training are also offered to students of the degree program Molecular Medicine (M.Sc.).
A further seminar and practical training ("Pathophysiological animal models: Pathophysiology and genetic studies" and „Practical training on experimental animals") during the degree program Molecular Medicine is offered to the students. It imparts knowledge on the phenotyping of experimental animal models. During the practical training, the student will take part in ongoing and routine methods in the context of experimental animal phenotyping together with frequently used methods. Here, the contents and acquired knowledge depend on the teaching and scientific topic of the involved scientists.

### Selected Publications


Tasic T, Stephan M, von Hörsten S, Pabst R, Schmiedl A. Differential OVA-induced pulmonary inflammation and unspecific reaction in Dark Agouti (DA) rats contingent on CD26/DPPIV deficiency. Immunobiology, 2014, 219(11): 888-900

Dimitrijević M, Aleksić I, Vujić V, Stanojević S, Pilipović I, von Hörsten S, Leposavić G. Peritoneal exudate cells from long-lived rats exhibit increased IL-10/IL-1β expression ratio and preserved NO/urea ratio following LPS-stimulation in vitro. Age (Dordr) 2014, 36(4): 9696

Schmiedl A, Grützner D, Hoffmann T, von Hörsten S, Stephan M. DPP4 inhibitors increase differentially the expression of surfactant proteins in Fischer 344 rats. Acta Physiol (Oxf) 2014, 212(3): 248-61

Urbach YK, Raber KA, Canneva F, Plank AC, Andreasson T, Ponten H, Kullingsjö J, Nguyen HP, Riess O, von Hörsten S. Automated phenotyping and advanced data mining exemplified in rats transgenic for Huntington's disease. J Neurosci Methods 2014, 234: 38-53

Wang Z, Grigo C, Steinbeck J, von Hörsten S, Amann K, Daniel C. Soluble DPP4 originates in part from bone marrow cells and not from the kidney. Peptides 2014, 57: 109-17

Hupa KL, Schmiedl A, Pabst R, Von Hörsten S, Stephan M. Maternal deprivation decelerates postnatal morphological lung development of F344 rats. Anat Rec (Hoboken) 2014, 297(2): 317-26.


### International Cooperations

Prof. A. Petersen, University of Lund, Lund: Sweden

Prof. H.-P. Lipp, ETH Zurich, Zurich: Switzerland

A.P. Osmand, Ph.D., University of Tennessee, Knoxville: USA

Prof. O. Stiedl, Ph.D., Neuroscience Campus Amsterdam, Amsterdam: The Netherlands

Prof. Dr. C. Cuello, MD, McGill University, Montreal: Canada

### Research Equipment

TSE Systems GmbH, PhenoMaster

New Behavior AG, IntelliCage

# Institute of Clinical Microbiology, Immunology, and Hygiene

## Chair of Microbiology and Immunology of Infection

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**Research Focus**
- Pathogenesis of Q-fever
- Microbial phosphatases
- Molecular mycology
- NK cells and therapy in leishmaniasis
- Arginase and NO synthase in antimicrobial defense
- Regulation of innate immunity in infection and inflammation
- Innate immunity, granulocytes, and mast cells
- Tissue milieu and the immune response
- Genetic and bacterial factors in chronic inflammation

## Structure of the Institute

The Institute of Clinical Microbiology, Immunology, and Hygiene is active in research, teaching, and clinical diagnostics. The Institute houses the Chair of Microbiology and Immunology and, since November 2008, the independent Division of Infection Biology (see own report). 97 employees are working at the Institute, 34 thereof are paid by extramural funds. The research is carried out by twelve scientists with a MD or Ph.D. degree, 25 Ph.D. students, and ten technical assistants.

The different research groups of the Institute 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 Coxiella, Listeria, Mycobacteria, Salmonella, Leishmania, and Aspergillus. The Institute is fully equipped with laboratories (BSL2, BSL3), hypoxia chambers for in vitro and in vivo analyses, fluorescence and confocal laser scanning microscopes, real-time PCR machines, analytical fluorescence activated cell sorters (FACS), sequencing and imaging systems.

The clinical work of the Institute is focused on the diagnostics of bacterial, fungal, and parasitic infectious diseases, on hospital hygiene, and the prevention of infectious diseases by immunization. The Institute runs the university outpatients' clinic for vaccination and travel medicine. The diagnostic section of the Institute (head: Dr. C. Schoerner) is accredited by the DAKKS and functions as reference center for the nationwide quality control and proficiency tests in bacteriological, serological, and mycological diagnostic procedures.

## Research

### Pathogenesis of Q-fever

Project manager: Dr. A. Lührmann

The obligate intracellular bacterium *Coxiella burnetii* causes 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 at clarifying how *C. burnetii* infection develops into chronic inflammation. To obtain insights into the pathogenicity of *C. burnetii,* we are analyzing host cell and bacterial factors that are necessary for the establishment of the replicative *C. burnetii*-containing vacuole. Additionally, we are investigating the molecular mechanisms of action of bacterial virulence factors, in particular those with anti-apoptotic activities.

### Microbial phosphatases

Project manager: 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 studies phosphatases from two human pathogens: (a) a PIP and tyrosine phosphatase named LipA from the bacterium *Listeria monocytogenes* and (b) tyrosine phosphatases secreted by the protozoon *Leishmania major.*

### Molecular mycology

Project manager: Prof. Dr. S. Krappmann

Molds of the genus *Aspergillus* (e.g. A. *fumigatus*) represent an increasing threat for immunocompromised patients. The pathogenicity of *A. fumigatus* is presumably a multi-factorial trait. Major efforts in this research group aim at identifying and characterizing the fungal-specific virulence determinants, such as its versatile metabolism that allows for propagation inside a susceptible host. Furthermore, the recently discovered sexual cycle of *A. fumigatus* is investigated. These analyses are accompanied by studies to expand and improve the molecular toolbox of *Aspergillus* molecular biology.

*Assessing the antibiotic susceptibility of a recombinant, fluoride-sensitive A. fumigatus strain towards an established antifungal substance.*

### NK cells and therapy in leishmaniasis

Project manager: PD Dr. U. Schleicher

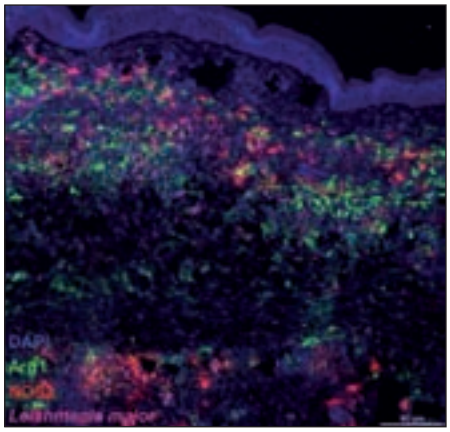
The activation of NK (natural killer) cells is part of the early immune response against Leishmania parasites. The group investigates the signals that lead to the stimulation or inhibition of NK cells in cutaneous or visceral leishmaniasis, the mechanisms by which NK cells contribute to parasite control, and the modulation of the NK cell response for therapeutic purposes. The relevance of the human NK cell response is studied *in vitro* and in humanized mice. In another project, the group analyzes the anti-parasitic, immunoregulatory, and/or wound healing-promoting effects of pharmaceutical sodium chlorite which showed promising therapeutic effects in cutaneous leishmaniasis in two clinical trials.

### Arginase and NO synthase in antimicrobial defense

Project manager: Prof. Dr. C. Bogdan

Nitric oxide (NO) which is synthesized from L-arginine by the inducible NO synthase (iNOS) in macrophages and other cells is essential for the defense against intracellular pathogens and a central immunoregulator. In macrophages, the mechanism will be investigated that underlies the suppression of iNOS translation by arginine-deficiency which occurs during infections following the induction of the arginine-metabolizing enzyme arginase. Both, the host cell arginase 1 and the parasite arginase, will be analyzed. The long-term aim is to define the role of

host or parasite arginase for the lifelong survival of *Leishmania in vivo.* Finally, the group studies whether the antimicrobial effect of NO is due to iron-deprivation of the pathogen.




*Confocal microscopy analysis of skin lesions of C57BL/6 tumor necrosis factor-deficient mice infected with 3 x $10^6$ Leishmania major promastigotes. Green: Arginase 1 (Arg1); red: iNOS; magenta: Leishmania; blue: nuclei. The overlap of green and red fluorescence (colocalization of Arg1 and iNOS) yields the color yellow.*

### Regulation of innate immunity in infection and inflammation

Project manager: Prof. Dr. R. Lang

Our research aims at elucidating how the immune system generates resistance to infection without causing excessive inflammation. The group discovered that the cord factor, a mycobacterial cell wall glycolipid, is a ligand of the C-type lectin receptor Mincle. We have characterized the activation of macrophages and the induction of Th1/Th17 responses by Mincle. In ongoing work, we are addressing macrophage reprogramming by the cord factor as a mycobacterial evasion strategy. To avoid tissue damage, the innate immune response requires control by endogenous "brakes" (e.g. IL-10). We have identified several IL-10-induced genes (e.g. Socs3, Dusp1) which inhibit the signaling by pattern recognition and cytokine receptors. These results may be useful for the design of vaccines or for the modulation of immune responses in inflammatory diseases.

### Innate immunity, granulocytes, and mast cells

Project manager: Prof. Dr. H.U. Beuscher

The group investigates the survival strategies, the immunoregulatory functions, and the production of inflammatory mediators by neutrophils from patients with rheumatoid arthritis. The work aims at characterizing an anti-apoptotic factor and its mechanism of action as well as possible therapeutic applications. A second project investigates phagocytosis and killing of bacteria by mast cells and its contribution to antibacterial host defense.

### Tissue milieu and the immune response

Project manager: Dr. J. Jantsch

Under physiological conditions (e.g. in certain layers of the skin and in the gastrointestinal tract) and in inflamed tissues, the oxygen levels may be very low ($pO2 < 0.5$ %). Under high-salt diet, sodium will accumulate in the skin without simultaneous water retention resulting in interstitial hypertonicity. The group explores whether the immune system orchestrates the homeostasis of peripheral milieu factors (i.e. oxygen availability and interstitial tonicity) and whether, in turn, an altered milieu (e.g. hypoxia, interstitial hypertonicity) will regulate the immune response and defense against infectious pathogens via the respective transcription factors.

### Genetic and bacterial factors in chronic inflammation

Project manager: Prof. Dr. J. Mattner

Autoimmune responses and inflammatory processes in the intestine and the liver result from a combination 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. The group investigates the genetic and immunological factors that govern the immune responses in the intestine and liver. Furthermore, we analyze the role of bacterial antigens in the development of autoimmune responses by applying gene deletion strategies.

## Teaching

The employees of the Institute teach students of medicine, dentistry, molecular medicine, biology, and pharmaceutical sciences in medical microbiology, immunology, and hygiene, in infectious disease research, and in the area of clinical microbiological diagnostics and tropical infectious diseases. The training takes place in form of seminars, practical courses, lectures, laboratory rotations, as well as bachelor, master, MD, and Ph.D. theses. Together with the Institute of Clinical and Molecular Virology, the Institute organizes a continuous medical education series on infectious diseases for medical doctors in the region.

### Selected publications

Amich J, Schafferer L, Haas H, Krappmann S. Regulation of sulphur assimilation is essential for virulence and affects iron homeostasis of the human-pathogenic mould Aspergillus fumigatus. PLoS Pathog 2013, 9: e1003573

Soulat D, del Fresno C, Roth S, Blazek K, Udalova I, Sancho D, Ruland J, Ardavin C. Interferon-beta production via Dectin-1-Syk-IRF5 signaling in dendritic cells is crucial for immunity to C. albicans. Immunity 2013, 38: 1176-1186

Eckart RA, Schulze-Luehrmann J, Bisle S, Wittmann I, Jantsch J, Schmid B, Berens C, Lührmann A. The anti-apoptotic activity of the Coxiella burnetii effector protein AnkG is controlled by p32-dependent trafficking. Infect Immun 2014, 82: 2763-2771

Jebran AF, Schleicher U, Steiner R, Wentker P, Mahfuz F, Stahl HC, Amin FM, Bogdan C, Stahl KW. Rapid healing of cutaneous leishmaniasis by high-frequency electrocauterization and hydrogel wound care with or without DAC N-055: a randomized controlled phase IIa trial in Kabul. PLoS Negl Trop Dis 2014, 8 (2): e2694

Mahnke A, Meier RJ, Schatz V, Hofmann J, Castiglione K, Schleicher U, Wolfbeis OS, Bogdan C, Jantsch J. Hypoxia in Leishmania major skin lesions impairs the NO-dependent leishmanicidal activity of macrophages. J Invest Dermatol 2014, 134: 2339-2346

Schoenen H, Huber A, Sonda N, Zimmermann S, Jantsch J, Lepenies B, Bronte V, Lang R. Differential control of Mincle-dependent cord factor recognition and macrophage responses by the transcription factors C/EBPbeta and HIF1alpha. J Immunol 2014, 193: 3664-75

### International cooperations

Prof. P. Andersen, Statens Serum Institut (SSI), Copenhagen: Denmark

J. P. Gomes, Ph.D., National Institute of Health, Lisbon: Portugal

H. Haas, Ph.D., Innsbruck Medical University, Innsbruck: Austria

K. Hoebe, Ph.D., Cincinnati Children's Hospital Medical Center, Cincinnati: USA

Prof. H. Körner, Menzies Research Institute, Tasmania: Australia

L.J. Mota, Ph.D., Instituto de Tecnologia Química e Biológica, Lisbon: Portugal

P. Murray, Ph.D., St. Jude Children´s Research Hospital, Memphis: USA

Prof. J. Titze, Vanderbilt University, Nashville: USA

Prof. L. Wicker, University of Cambridge, Cambridge: UK

# Institute of Clinical Microbiology, Immunology, and Hygiene

## 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

The Division of Infection Biology was founded in 2008 as an independent division at the Institute of Clinical Microbiology, Immunology, and Hygiene. The Division is headed by Prof. Dr. D. Vöhringer who was recruited in October 2010 as W2 professor by the FAU. The Division employs three scientists with Ph.D. degree, five Ph.D. students, and two technicians.

## Research

### 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, 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 Biol - ogy 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 hapten-specific 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.

### Functionality and plasticity of memory-like T cells

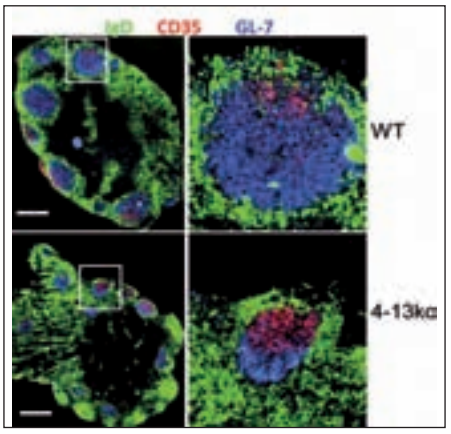
Memory-like T cells (TML) develop by homeostatic proliferation from naive T cells and constitute a substantial population of T cells in the elderly population. Whether these cells maintain their functionality remains unclear. Furthermore, it is not known whether they compete with normal memory T cells for survival. We generated a mouse model to address these questions. The mice generate large numbers of TML cells so that we can characterize their functions in infection models with helminths or viruses.

### Role of dendritic cells for maintenance of immunological tolerance

Dendritic cells (DC) play an important role as antigen-presenting cells for activation of naive T cells. They can further promote immunological tolerance by deletion of autoreactive T cells from the thymus or by inhibiting the activation of peripheral T cells. We generated mice that constitutively lack DC and noticed that these mice develop spontaneous systemic autoimmune inflammation. The pathology is characterized by increased levels of activated T cells, high serum immunoglobulin levels, formation of autoantibodies, weight loss, and infiltration of leukocytes into various tissues. Using this model, we studied whether regulatory T cells are affected by the absence of DCs, whether autoantibodies are causative for the disease, and whether impaired negative selection of autoreactive T cells could account for the loss of immunological tolerance in these mice.

### IgE response and germinal center reaction

Funded by the ERC starting grant PAS_241506, we studied the regulation of the IgE response against helminths and allergens. We first compared the IgE response in wild-type mice, IL-4/IL-13-deficient mice, and mice that lack IL-4/IL-13 expression only in T cells. The results clearly showed that the IgE response requires IL-4/IL-13 from T cells. To our surprise, we further observed that the germinal center response was dependent on IL-4/IL-13 production from T cells. This requirement was also observed in mice immunized with ovalbumin or sheep red blood cells, but not after infection with lymphocytic choriomeningitis virus or mouse cytomegalovirus. This indicates that IL-4/IL-13 is only required for the germinal center response during type 2 immune responses. Furthermore, we could show by deep sequencing in collaboration with Prof. Dr. O. Pabst from the Hannover Medical School that the repertoire of IgE and IgG1 sequences is largely overlapping. This indicates that affinity maturation may take place at the level of IgG1-expressing B cells which then undergo a secondary class switch recombination event to IgE. In case these results can be confirmed in human allergic individuals, one could think about new therapeutic options that interfere with generation of allergen-specific antibodies at the level of IgG1-expressing B cells.




*Germinal center reaction in helminth-infected mice. Histological stainings of cryosections from tracheal lymph nodes isolated from wild-type (WT) or IL-4/IL-13-deficient (4-13ko) mice that had been infected with the helminths Nippostrongylus brasiliensis ten days before analysis. Germinal centers are shown in blue, B cells are green, and follicular dendritic cells appear red.*

## Teaching

The Division of Infection Biology is closely associated to the Institute of Clinical Microbiology, Immunology, and Hygiene. Both institutions offer joined lectures, seminars, and practical courses for students. The teaching activities are dedicated to microbiology and immunology with a special focus on host-pathogen interac-

tions. Scientists of the Division also supervise students that perform their Bachelor- or Masterthesis.

## Selected Publications


Voehringer D. Protective and pathological roles of mast cells and basophils. Nat Rev Immunol 2013, 13: 362-375

Mchedlidze T, Waldner M, Zopf S, Walker J, Rankin AL, Schuchmann M, Voehringer D, McKenzie ANJ, Neurath MF, Pflanz S, Wirtz S. IL-33-dependent innate lymphoid cells mediate hepatic fibrosis. Immunity 2013, 39: 357-371

Turqueti-Neves A, Otte M, Prazeres da Costa O, Höpken UE, Lipp M, Buch T, Voehringer D. B-cell-intrinsic STAT6 controls germinal center formation. Eur J Immunol 2014, 44: 2130-2138

Schwartz C, Oeser K, Prazeres da Costa C, Layland LE, Voehringer D. T cell-derived IL-4/IL-13 Protects Mice against Fatal Schistosoma mansoni Infection Independently of Basophils. J Immunol 2014, 193: 3590-3599

Oeser K, Voehringer D. Conditional IL-4/IL-13-deficient mice reveal a critical role of innate immune cells for protective immunity against gastrointestinal helminths. Mucosal Immunol 2014 Oct 22. doi: 10.1038/mi.2014.101

Schwartz C, Turqueti-Neves A, Hartmann S, Yu P, Nimmerjahn F, Voehringer D. Basophil-mediated Protection against Gastrointestinal Helminths Requires IgE-induced Cytokine Secretion. PNAS 2014, 111: E5169-77


## International Cooperations

Prof. R. Locksley, MD, University of California San Francisco, San Francisco: USA

Dr. D. Artis, Weill Cornell Medical College, New York: USA

Prof. R. Maizels, University of Edinburgh, Edinburgh: United Kingdom

Prof. P. Fallon, Trinity College Dublin, Dublin: Ireland

## Research Equipment

Bio-Rad Cell Sorter S3

# Institute of Experimental and Clinical Pharmacology and Toxicology

## Chair of Clinical Pharmacology and Clinical Toxicology

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**Research Focus**
- Molecular characterization of drug transporters
- Transporter-mediated drug-drug interactions
- Personalized drug therapy
- Molecular and clinical characterization of therapeutic targets in the L-arginine-NO-nitrate pathway
- Analysis of drugs and endogenous substances
- Safety in drug therapy

## Structure of the Institute

The Chair of Clinical Pharmacology and Clinical Toxicology constitutes together with the Chair of Pharmacology and Toxicology and the Doerenkamp-Chair for Innovations in Animal and Consumer Protection (which expired on 30.06.2013) the Institute of Experimental and Clinical Pharmacology and Toxicology. The position of the executive director of the Institute rotates between the Chair of Pharmacology and Toxicology (Prof. Dr. A. Ludwig) and the Chair of Clinical Pharmacology and Clinical Toxicology (Prof. Dr. M.F. Fromm) on a biennial basis. 29 persons are working at the Chair of Clinical Pharmacology and Clinical Toxicology with six of them being funded by extramural sources. Research is conducted by six scientists, two of them being specialists in clinical pharmacology, twelve MD or Ph.D. students, and five technicians. The working 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 Chair has excellent opportunities for drug analytics and a clinical trial unit. In addition, a drug information service is available for the physicians of the UK Erlangen and for external physicians. The following topics, funded e.g. by the DFG, the German Cancer Aid, the German Federal Ministry of Health (BMG), and the BMBF, are in the focus of our studies: Uptake and efflux transporters for drugs, mechanismsm underlying drug-drug interactions, genetic determinants of drug effects (pharmacogenomics), transporter expression and regulation in tumors, cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism, and safety in drug therapy.

## Research

### Molecular characterization of drug transporters

Project managers: Prof. Dr. J. König, Prof. Dr. M.F. Fromm

Transport proteins located in distinct membrane domains are important for the uptake, distribution, and excretion of drugs and drug metabolites. Therefore, the molecular characterization of drug transporters is in the focus of our research.

We could demonstrate that the transport of HMG-CoA-reductase inhibitors (statins) can be allosterically modified by non-steroidal anti-inflammatory (NSAIDs) or oral antidiabetic drugs in addition to the competitive transport inhibition by these drugs. Structure-function relationship studies currently investigate which amino acids or protein regions within the drug uptake transporters OATP1B1 and OATP1B3 are responsible for substrate recognition and allosteric transport modulation. Furthermore, the expression and epigenetic regulation of drug transporters in human head and neck squamous cell carcinoma samples was investigated in a cooperation with the Department of Otorhinolaryngology – Head and Neck Surgery. For the investigation of transcellular transport processes and for the analysis of transporter-metabolism interplay, several multiple-transfected cell lines were established recombinantly overexpressing transport proteins or transporters together with metabolizing enzymes. In cooperation with Prof. Dr. A. Birkenfeld (University Hospital Carl Gustav Carus, Dresden), we characterized the human sodium-coupled citrate transporter NaCT which is now under further investigation regarding its possible role as target for drug therapy.

### Transporter-mediated drug-drug interactions

Project managers: Prof. Dr. J. König, Prof. Dr. M.F. Fromm

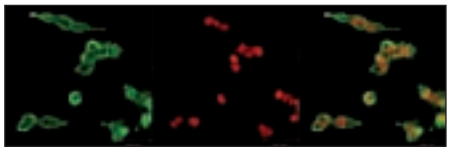
Simultaneously administered drugs or food constituents can inhibit transporter-mediated uptake or elimination of victim drugs. This leads to altered plasma concentrations of the victim drug and to altered drug effects or an increased risk of adverse drug reactions. In collaboration with colleagues from Fukushima Medical University (Japan), we could show by in vitro studies and a clinical study in healthy volunteers that green tea markedly reduces the plasma concentrations of the ß-blocker nadolol and that this is likely due to inhibition of transporter (OATP2A1)-mediated uptake of nadolol by ingredients of green tea (catechins) in the small intestine. We presently investigate the influence of catechins on hepatic uptake transport mediated by OATP1B1 and OATP1B3. Using MDCKII cells stably overexpressing the human renal cation transporters OCT2, MATE1, and MATE2-K, we could clarify the molecular mechanisms underlying the renal secretion of the antiviral drug lamivudine as well as renal drug-drug interactions. In further in vitro investigations as well as in clinical studies in humans, we investigated the impact of the antibiotic trimethoprim on pharmacokinetics and effects of the frequently used oral antidiabetic drug metformin and characterized the endogenous metabolite $N^1$-methylnicotinamide as potential biomarker for renal drug-drug interactions mediated by cation transporters.

### Molecular and clinical characterization of therapeutic targets in the L-arginine-NO-nitrate pathway

Project manager: Prof. Dr. R. Maas

A major focus of the group is the experimental and clinical characterization of new cardiovascular risk factors as potential targets for therapeutic intervention. Presently we study the regulation of the L-arginine-NO-nitrate pathway by endogenously formed compounds, such as the methylarginines ADMA and SDMA and the metabolic fate and transport of these compounds. For in vitro and in vivo investigations, new isotope and mass spectrometry-based methods are developed. In an intramural IZKF-project as well as in cooperation with researchers from the University Hospital in Dresden, the research group investigates alternative pathways for the metabolism of methylarginines. In collaborations with other groups from the Chair of Clinical Pharmacology and Clinical Toxicology, we investigate transporter-mediated translocation of methylarginines. In a DFG-funded collaboration project conducted together with the Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine as well as

the Framingham Heart Study (USA), we could present first data for elevated plasma nitrate as a risk marker for mortality in the general population.



*Characterization of a cell line stably overexpressing human CAT2A (cationic amino acid transporter 2A) using confocal laserscanning microscopy (green: CAT2A, red: nuclei).*
*With kind permission from Springer Science+Business Media: J. Strobel, F. Müller, O. Zolk, B. Endreß, J. König, M.F. Fromm, R. Maas. Amino Acids, Transport of asymmetric dimethylarginine (ADMA) by cationic amino acid transporter 2 (CAT2), organic cation transporter 2 (OCT2) and multidrug and toxin extrusion protein 1 (MATE1), 45, 2013, 989-1002. Middle section of figure 1d.*

### Analysis of drugs and endogenous substances

Project manager: Dr. M. Mieth

The drug analysis unit uses samples from both, cell culture experiments and clinical trials. Analytical methods are developed, optimized, and validated in our laboratory. The spectrum of the analytes ranges from various drugs, such as pravastatin, etoposide, metformin, clopidogrel, trimethoprim and β-lactam antibiotics, to endogenous substances, such as derivatives of arginine, $N^1$-methylnicotinamide and β-aminoiso - butyric acid. Challenges are very low concentrations, small sample volumes, and the determination of an analyte in different matrices (e.g. lysate, plasma, urine).

### Safety in drug therapy

Project managers: Prof. Dr. R. Maas, Prof. Dr. M.F. Fromm

An important research focus is safety in drug therapy. As partners in a project which is part of the "Action Plan for Drug Therapy Safety" (funded by the Federal Ministry of Health, BMG), we implemented and evaluated measures to improve therapeutic safety on an emergency ward. Prerequisite for this was the creation of an infrastructure that permits identification and recording of adverse drug events. This infrastructure is still available and used in new projects. As a partner in the BMBF funded cluster Medical Valley EMN – therapeutic systems project, we currently work on new software and chemoinformatic databases to improve drug safety in psychiatry. As a result of interest to a broader audience, we identified and published critical inconsistencies in officially approved prescribing information. In addition, problems of safety of drug therapy in elderly patients are in the focus of collaborative projects.

## 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 dental medicine, molecular medicine, pharmacy, and Medical Process Management in clinical pharmacology by lectures, seminars, and practical exercises. In a coopertion project with the Technical University of Munich, we developed an online teaching module for drug therapy of common diseases. Students of pharmacy and medicine are welcome to work with us during their final year (clinical rotation).

### Selected Publications


König, J, Müller F, Fromm MF. Transporters and drug-drug interactions: important determinants of drug disposition and effects. Pharmacol Rev 2013, 65(3): 944-66

Zolk O, Schnepf R, Muschler M, Fromm MF, Wendler O, Traxdorf M, Iro H, Zenk J. Transporter gene expression in human head and neck squamous cell carcinoma and associated epigenetic regulatory mechanisms. Am J Pathol 2013, 182: 234-243

Misaka S, Yatabe J, Müller F, Takano K, Kawabe K, Gläser H, Yatabe MS, Onoue S, Werba JP, Watanabe H, Yamada S, Fromm MF, Kimura J. Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. Clin Pharmacol Ther 2014, 95: 432-438

Kittel A, Müller F, König J, Mieth M, Sticht H, Zolk O, Kralj A, Heinrich MR, Fromm MF, Maas R. Alanine-glyoxylate aminotransferase 2 (AGXT2) polymorphisms have considerable impact on methylarginine and -aminoisobutyrate metabolism in healthy volunteers. PLoS ONE 2014, 9: e88544

Schächtele S, Tümena T, Gaßmann K-G, Fromm MF, Maas R. Implementation of warnings from dear doctor letters (Rote-Hand-Briefe): an analysis of medication data from a large cohort of elderly patients. Dtsch Arztebl Int 2014, 111: 255-263

Pfistermeister B, Saß A, Criegee-Rieck M, Bürkle T, Fromm MF, Maas R. Inconsistencies and misleading information in officially approved prescribing information from three major drug markets. Clin Pharmacol Ther 2014, 96: 616-624


### International Cooperations

Prof. J. Backman, Prof. M. Niemi, Department of Clinical Pharmacology, University of Helsinki, Helsinki: Finland

Prof. S. Misaka, Department of Pharmacology, School of Medicine, Fukushima Medical University, Fukushima: Japan

Prof. S.R. Vasan, MD, Boston University School of Medicine, Boston: USA

Prof. C. Zoccali, CNR-IBIM and Nephrology-Transplant Unit, Ospedali Riuniti, Reggio Calabria: Italy

### Research Equipment

Applied Biosystems, API 4000 MS/MS System Package

Zeiss, Konfokales Laserscanning-Mikroskop LSM 5 Pascal

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**Research Focus**
- Molecular mechanisms of cardiac rhythmogenesis and arrhythmia
- HCN channels in the nervous system
- Renal function and sepsis
- Pharmacological imaging and image analysis

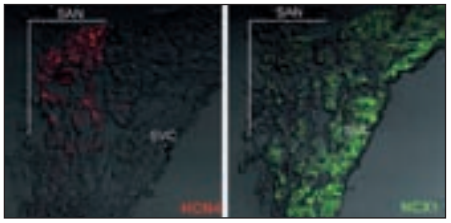
## Structure of the Institute

The Chair of Pharmacology and Toxicology, the Chair of Clinical Pharmacology and Clinical Toxicology, and the Doerenkamp-Chair for Innovations in Animal and Consumer Protection (expired on 30.06.2013) form the Institute of Experimental and Clinical Pharmacology and Toxicology. The position of executive director rotates between the Chair of Pharmacology and Toxicology (Prof. Dr. A. Ludwig) and the Chair of Clinical Pharmacology and Clinical Toxicology (Prof. Dr. M.F. Fromm) on a biennal basis. Research work is carried out by two professors, four Ph.D. graduates, seven postgraduate students, and five research technicians.
Main research areas are the function of various ion channels and exchangers in the heart with a focus on the generation of the cardiac rhythm. In addition, the role of HCN channels in the nervous system is studied. Other research areas are renal function and sepsis and small animal imaging and image analysis.
These areas are explored by combining methods from molecular biology, mouse genetics, whole-animal studies, electrophysiology, and functional MRI. Research is supported by the DFG and BMBF. Together with the Chair of Clinical Pharmacology and Clinical Toxicology, a drug information service is provided for clinicians of the UK Erlangen as well as for physicians in private practices.

## Research

### Molecular mechanisms of cardiac rhythmogenesis and arrhythmia

Project managers: PD Dr. J. Stieber, PD Dr. S. Herrmann, Prof. Dr. A. Ludwig
The mechanisms underlying the generation of the spontaneous cardiac rhythm in the sinoatrial node were studied by using various conditional mouse models. Mice with a selective deletion of the sodium/calcium exchanger NCX1 in the sinoatrial node developed slowing of the heart rate and arrhythmias. Mutant cells displayed irregular spontaneous $Ca^{2+}$ signals with a significantly reduced frequency. These results demonstrate that NCX1 in sinoatrial myocytes is essential for maintaining proper pacemaking. An inducible HCN triple-mutant (HCN1/2/4-KO) was further analyzed at the electrophysiological level by using isolated sinoatrial cells. The results demonstrate that sinoatrial If is generated by the combined activity of three HCN isoforms. We showed earlier that the activity of ventricular HCN channels is increased during cardiac hypertrophy. The potential enhanced arrhythmogenic propensity of isolated ventricular myocytes was analyzed in collaboration with Prof. Dr. F.U. Müller (Westfälische Wilhelms-Universität Münster). A collaboration with Prof. K.R. Chien (Karolinska Institutet, Stockholm) revealed that the cardiac pacemaker channel HCN4 unexpectedly constitutes a selective marker for the first heart field during cardiac development.




*Conditional deletion of the sodium/calcium-exchanger NCX1 in the sinoatrial node. The sinoatrial node (SAN) is marked by staining of HCN4 (red, left). After induction of gene deletion, NCX1 (green, right) is eliminated selectively from the SAN region, but is still present in the superior vena cava (SVC) and other cardiac compartments.*
*(Herrmann S, Lipp P, Wiesen K, Stieber J, Nguyen H, Kaiser E, Ludwig A. The cardiac sodium-calcium exchanger NCX1 is a key player in the initiation and maintenance of a stable heart rhythm. Cardiovasc Res 2013, 99: 780-8. By permission of Oxford University Press).*

### HCN channels in the nervous system

Project managers: PD Dr. S. Herrmann, Prof. Dr. A. Ludwig
We could show that HCN channels are involved in the development of pathological pain including allodynia and hyperalgesia in acute inflammatory conditions. We now studied the role of HCN2 in a model reflecting chronic pain conditions. Our results demonstrate that the absence of HCN2 in primary sensory neurons reduces tactile hypersensitivity in chronic inflammatory conditions, but leaves heat hypersensitivity unaffected. Moreover, we showed that chronic inflammation results in an increased expression of HCN2 and causes sensitization in peripheral and spinal terminals of the pain transduction pathway. In addition, the role of HCN4 in thalamic nuclei was analyzed in collaboration with Prof. Dr. T. Budde (Westfälische Wilhelms-Universität Münster).

### Renal function and sepsis

Project manager: Prof. Dr. K. Höcherl
The pathophysiology of septic acute kidney injury (AKI) is complex. Overall, renal hypoperfusion due to an imbalance between vasoconstriction and vasodilation seems to be a central pathogenetic factor in the development of septic AKI. Thus, the restoration of an adequate renal blood flow should be the primary goal in terms of renal protection in critically ill patients. Hyporeactivity to vasoconstrictors, such as angiotensin II, is commonly observed in patients and animal models of sepsis. The AT1 receptor-associated protein 1 (Arap1) is expressed in vascular smooth muscle cells and increases the surface expression of the AT1-receptor. We hypothesized that dysregulation of Arap1 may contribute to vascular hyporeactivity to angiotensin II during endotoxemia. During endotoxemia, mean arterial blood pressure decreased in Arap1-KO and in wildtype mice, with the time course of sepsis-induced hypotension being markedly accelerated in Arap1-KO as compared to wildtype mice. Following lipopolysaccharide (LPS) injections, Arap1 expression was successively down-regulated in the wildtype mice. The endotoxemia-related decline in Arap1 expression could be recapitulated in cultured mesangial cells by incubation with pro-inflammatory cytokines. Therefore, our data suggest that down-regulation of Arap1 expression during sepsis contributes to the development of hypotension by causing reduced vascular sensitivity to angiotensin II.

### Pharmacological imaging and image analysis

Project manager: PD Dr. A. Hess
Magnetic Resonance Imaging (MRI) plays an ever increasing role in research and clinical practice which is reflected in multiple collaborative research project of our group. In a collaboration with the Department of Medicine 2, we

could demonstrate an increased fat content in the aortic root of ApoE-deficient mice. Together with the Institute of Neuropathology, we could establish a new diagnostic method for hippocampal sclerosis. In addition, we analyzed the invasive growth of a craniopharyngioma. In a collaboration with Prof. Dr. J. Penninger (Institute of Molecular Biotechnology, Vienna), we could demonstrate that CLP1 mutant mice display microcephaly during embryonic development. We observed a markedly reduced cortical thickness in these CLP1 mutants. As part of the Emerging Fields Initiative "Neurotrition" of the FAU, we continued our collaboration with the Institute of Food Chemistry. We could demonstrate that craving for potato chips is not determined by their energy content, but is mainly dependent on an optimal food-to-carbohydrate ratio. In our main research field "pain mechanisms" we performed a translational fMRI study together with Prof. J.S. Mogil (McGill University, Montreal) and Prof. Dr. C. Maihöfner (Klinikum Fürth). By using graph-theoretical methods, we could show for the first time that pain induces a specific interaction pattern between the activated brain structures. In close collaboration with the Department of Medicine 3, the trial PreCePRA was started. This study investigates our hypothesis that fMRI is suitable to predict the effect of TNF-antagonists in the therapy of rheumatoid arthritis. In a collaborative project together with the Department of Medicine 1, we already could demonstrate that fMRI is principally able to predict the effect of an anti-TNF therapy in patients suffering from Crohn`s disease.

*Activity patterns in the rat brain following ingestion of test food with an optimal fat-to-carbohydrate ratio (FCH, left) and potato chips (right) as compared to standard chow (STD). Regions displaying higher activity with the test foods are colored yellow – red; areas showing higher activity with standard chow are green – blue.*

## Teaching

Pharmacology and toxicology is taught to medical students, students of the degree program Molecular Medicine, and pharmacy students. The pharmacology course for medical students consists of lectures and problem-based small group tutorials. Students of the degree program Molecular Medicine are trained by lectures, a seminar focusing on the molecular mechanisms of drug actions, and various laboratory internships. In addition, the Chair of Pharmacology and Toxicology 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.

### Selected Publications


Herrmann S, Lipp P, Wiesen K, Stieber J, Nguyen H, Kaiser E, Ludwig A. The cardiac sodium-calcium exchanger NCX1 is a key player in the initiation and maintenance of a stable heart rhythm. Cardiovasc Res 2013, 99: 780-8

Mederle K, Schweda F, Kattler V, Doblinger E, Miyata K, Höcherl K, Oike Y, Castrop H. The angiotensin II AT1 receptor-associated protein Arap1 is involved in sepsis-induced hypotension. Crit Care 2013, 17: R130

Später D, Abramczuk MK, Buac K, Zangi L, Stachel MW, Clarke J, Sahara M, Ludwig A, Chien KR. A HCN4+ cardiomyogenic progenitor derived from the first heart field and human pluripotent stem cells. Nat Cell Biol 2013, 15: 1098-106

Hoch T, Kreitz S, Gaffling S, Pischetsrieder M, Hess A. Manganese-enhanced magnetic resonance imaging for mapping of whole brain activity patterns associated with the intake of snack food in ad libitum fed rats. PLoS One 2013, 8: e55354

Karaca E et al. Human CLP1 mutations alter tRNA biogenesis, affecting both peripheral and central nervous system function. Cell 2014, 157: 636-50

Schnorr S, Eberhardt M, Kistner K, Rajab H, Käßer J, Hess A, Reeh P, Ludwig A, Herrmann S. HCN2 channels account for mechanical (but not heat) hyperalgesia during long-standing inflammation. Pain 2014, 155: 1079-90


### International Cooperations

Prof. D.M. Chetkovich, Feinberg School of Medicine, Northwestern University, Chicago: USA

Prof. K.R. Chien, Department of Cell and Molecular Biology, Karolinska Institutet: Sweden

Prof. J. Mogil, Department of Psychology, McGill University, Montral: Canada

Prof. J. Penninger, Institute of Molecular Biotechnology, Vienna: Austria

Prof. A. Tinker, William Harvey Heart Centre, Queen Mary University of London, London: USA

Prof. X. Wehrens, Cardiovascular Research Institute, Baylor College of Medicine, Houston: USA

Prof. K.-W. Yau, School of Medicine, Johns Hopkins University: USA

### Research Equipment

Bruker, 4,7 Tesla Kleintier-MRT

Zeiss, Konfokales Laserscanning-Mikroskop LSM 5

# Institute of Experimental and Clinical Pharmacology and Toxicology

## Doerenkamp-Chair for Innovations in Animal and Consumer Protection (until July 2013)

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**Head of Division (until July 2013)**
Prof. Dr. med. Dr. h.c. Kay Brune

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**Research Focus**
- Analgesics (Consumer Protection)
- Non-invasive functional imaging (Animal Protection)

## Structure of the Division

The endowed Doerenkamp-Chair constituted together with the Chair of Clinical Pharmacology and Clinical Toxicology and the Chair of Pharmacology and Toxicology the Institute of Experimental and Clinical Pharmacology and Toxicology. The funding of the Doerenkamp-Chair has ended in 2013.
There was a close collaboration of this Chair with researchers of the other two chairs. The research goals of the endowed Doerenkamp-Chair are pursued in close collaboration with Prof. Dr. B. Hinz (formerly senior scientist at the Institute of Experimental and Clinical Pharmacology and Toxicology, presently chairman of the Department of Toxicology and Pharmacology at the University of Rostock) and PD Dr. A. Hess (member of the Chair of Pharmacology and Toxicology at the Institute of Experimental and Clinical Pharmacology and Toxicology). In collaboration with these senior co-workers, the following results were achieved.

## Research

### Analgesics (Consumer Protection)

Cyclooxygenase (COX) inhibitors (analgesics, anti-rheumatics) are the most widely used drugs. They are effective, but also prone to cause unwanted drug effects. Together with Prof. Dr. B. Hinz, we analyzed PK/PD (pharmacokinetic/pharmacodynamic) of the most common drugs, including acetaminophen, aspirin, diclofenac, etoricoxib, ibuprofen, lumiracoxib, etc., by applying an ex vivo technique in volunteers. We could show that acetaminophen is a selective (preferential) inhibitor of COX-2, associated with unrelated serious hepatotoxicity. The data accrued are presently used as argument to eliminate acetaminophen from the OTC (over-the-counter)-market.
We found that most new and old COX inhibitors are chronically overdosed in most patients. With the aid of our ex vivo PK/PD analyzing concept for tissue, toxicity sparing doses were developed.
The analysis of older drugs, including – aside of acetaminophen – metamizol (dipyrone), showed that dipyrone is overdosed under clinical conditions.
Recently, COX-inhibitors were shown to cause cardiac infarctions and accelerated artherosclerosis in certain patients. Using NT-proBNP, a new biomarker (N-terminal pro-Brain natriuretic peptide), we could show that determining the NT-proBNP level is helpful in singling out patients at risk.
Finally, it is helpful to connect individual data of patients in the clinic of internal medicine with information about the drugs applied in order to detect unwanted drug effects in time.
Searching for undiscovered risks of COX-inhibitors, we observed that amateur and professional athletes abuse these drugs in dangerous proportions. Several publications in German print media led to a first boost of awareness. These investigations will be continued.

### Non-invasive functional imaging (Animal Protection)

One of the central aims of the endowed Doerenkamp-Chair was to establish non-invasive imaging techniques in experimental pain research. This approach turned out to be extremely successful. Together with Prof. Dr. H.U. Zeilhofer (Zurich), we could identify the role of glycinergic receptors in the spinal cord for pain control. Together with Dr. J.M. Penninger (Vienna) and Dr. C.J. Woolf (Boston), we could employ this technology to identify pain controlling genes which had been identified in a drosophila assay system. One gene turned out to be of major importance not only for pain perception, but also for synesthetic experiences encountered by about 4 % of the human population. Moreover, employing genetically modified mice (e.g. overexpressing TNFα), we could show that anti-TNFα-treatment in mice (overexpressing TNFα) and men (rheumatoid arthritis patients) instantaneously relieved pain in experimental animals and men.
The successful implementation of functional MR-imaging has proven to be a successful tool for non-invasive, non-demanding animal experimentation in pain research. The activity of the group will continue under the leadership of Prof. Dr. M. Uder who has taken over the administrational control of the unit devoted to employ imaging techniques in experimental research involving animals. There is hope that this division will continue to flourish.

## Teaching

The engagement of Prof. Dr. Dr. h.c. K. Brune as speaker at international conferences and his membership in several administrative bodies and advisory structures has led to many additional invitations to comment on current problems of drug therapy in man. In addition, Prof. Dr. Dr. h.c. K. Brune is engaged in the production of many national and international guidelines, textbooks, etc. A sample of publications related to these activities can be found on the homepage of the Institute. Prof. Dr. Dr. h.c. K. Brune was a member of the Executive Committee of IUPHAR (International Union of Basic and Clinical Pharmacology) until 2015. Kay Brune has been elected full member of the 'Arzneimittelkommission der deutschen Ärzteschaft' (AkdÄ; Drug Commission of the German Medical Association), 2014-2018.

### Selected Publications

Kuster M, Renner B, Oppel P, Niederweis U, Brune K. Consumption of analgesics before a marathon and the incidence of cardiovascular, gastrointestinal and renal prob - lems: a cohort study. BMJ Open 2013 Apr 19;3(4): pii: e002090

Neubert A, Dormann H, Prokosch HU, Bürkle T, Rascher W, Sojer R, Brune K, Criegee-Rieck M. E-pharmacovigilance: development and implementation of a computable knowledge base to identify adverse drug reactions. British journal of clinical pharmacology 2013, 76: 69-77

Stammschulte T, Brune K, Brack A, Augenstein H, Arends G, Gundert-Remy U. Unexpected hemorrhage complications in association with celecoxib. Spontaneously reported case series after perioperative pain treatment in gynecological operations. Der Anaesthesist 2014, 63: 958-60

Tiegs G, Karimi K, Brune K, Arck P. New problems arising from old drugs: second-generation effects of acetaminophen. Expert review of clinical pharmacology 2014, 7: 655-62

Brune K. Diclofenac: increase of myocardial infarctions at low doses? Pharmacoepidemiology and drug safety 2014, 23: 326-8

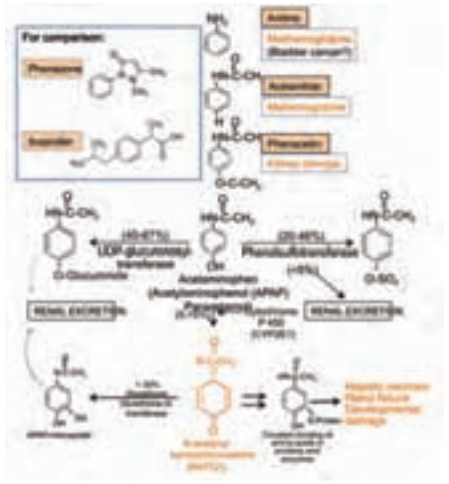
Brune K, Renner B, Tiegs G. Acetaminophen/paracetamol: A history of errors, failures and false decisions. Eur J Pain 2014 Nov 27. doi: 10.1002/ejp.621

### Research Equipment

Bruker, BioSpec 70/30 (Kleintier-MRT 7.0. Tesla)

*Enzymes and metabolic steps that are involved in the chemical conversion of paracetamol within the human body.*
*(Modified and transferred from: 'Pharmacogenomics of acetaminophen in pediatric populations: a moving target', Krasniak et al., Front Genet. 2014; with permission of the publisher. From K. Brune: 'Paracetamol: gefährlicher, als man denkt!': ChiuZ, 2015, in print).*
*Abbreviations:*

| | |
|---|---|
| *SUL* | *Sulfatation* |
| *UG* | *Glucuronidation* |
| *CYP* | *Oxydation* |
| *GS* | *Glutathione S-transferase* |



*From aniline to paracetamol: The complex metabolization and elimination causes many risks.*
*(Modified and transferred from: 'Acetaminophen/paracetamol: A history of errors, failures and false decisions': Eur J Pain, 2014; with permission of the publisher).*

# Institute of Forensic Medicine

## Chair of Forensic Medicine

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**Research Focus**
- Development and validation of PCR-multiplex systems for forensic DNA analysis
- Comparison of laser and mercury-arc lamp for the detection of body fluids on different substrates
- Highly sensitive simultaneous detection of psychoactive drugs and their metabolites using UPLC/MS-MS

## Structure of the Institute

The Institute of Forensic Medicine with its divisions forensic medicine, forensic genetics, and forensic toxicology belongs to the clinical theoretical institutes of the FAU. Beside responsibilities in the field of research and education, official expertises are made for other medical facilities and by order of justice, for prosecution, and police authorities in the North Bavarian region. Moreover – even though less frequently – services are offered to private persons, lawyers, probation officers, and insurance companies. Predominantly, expertises are related to forensic investigations on injury patterns including crime reconstruction in the case of domestic violence, child abuse, and criminal assault. In the case of deceased, the expertises include statements on the cause of death as well as on specific questions (accident? suicide? homicide?). Genetic analyses are carried out for clarification of personal identity, for the individual assignment of biological specimen, and in paternity cases. Toxicological analyses are done to ascertain poisoning and to evaluate personal capacities at a definite time (fitness to drive? criminal responsibility?). The determination of the alcohol concentration is performed in body fluids of dead and living persons. Many findings are used in diagnostic procedures and for the control of therapies applied by different hospitals as well as medical practices.

## Research

### Development and validation of PCR-multiplex systems for forensic DNA analysis

Project manager: PD Dr. T. Lederer

Since the beginning of the development of molecular methods for forensic stain analysis and paternity testing in 1985, in particular the PCR (polymerase chain reaction)-based typing of STR (short tandem repeat)-polymorphisms has been spread around the world. Not only due to a large number of successful investigations which can be put down to the establishment of national and international databases, DNA analysis can be regarded as an indispensable tool in forensic casework analysis. In 1998, the Bundeskriminalamt (BKA) established a central genetic database of offenders and suspects to facilitate comparisons with biological samples of future criminal offenses.

In our recent work, a variety of PCR-multiplex systems was established which allows the simultaneous amplification of up to twelve autosomal STR markers. It could be shown that all multiplexes are robust and reliable typing tools for a diversity of forensic specimen and are well suited in the case of paternity testing.

It has already been mentioned that national and international databases for genetic profiles and a cross-national usage of these data are an important tool of investigations by the police. A European-wide standardization and extension of the respective databases as well as the establishment of new typing systems is in the focus of current discussions and developments. Therefore, within our work, the existing multiplex systems were expanded by five more STR-loci ("European recommended loci"). Furthermore, population data of the new markers have been surveyed.

Beside autosomal polymorphisms, gonosomal localized systems play an upcoming role in the forensic diagnostics. In particular, y-chromosomal DYS-systems have to be mentioned in this context. These systems are well qualified for stain and paternity testing. However, the basis of a further distribution of these systems will be the establishment of worldwide databases containing haplotype frequencies and the development of PCR-multiplex systems. Because of that reason, different analysis-systems for these markers were established.

### Comparison of laser and mercury-arc lamp for the detection of body fluids on different substrates

Project manager: Prof. Dr. S. Seidl

The performance of two detection techniques for body fluids, the Spectra-Physics Reveal portable forensic laser system and the mercury-arc lamp Lumatec Superlite 400, was evaluated with various biological stains on different substrates. Serial dilutions of neat, 1/10, 1/100, and 1/1,000 using fluid semen, saliva, urine, and blood were applied on glazed tiles, glass, PVC, wood, metal, stone, formica, carpet, and cotton. Apart from the fact that blood traces were not detectable with the laser, both light sources showed comparable results regarding their detection capability. Clear advantages of the Lumatec Superlite 400, however, are its lower size, weight, and purchase costs as well as the possibility to operate this light source by battery.

### Highly sensitive simultaneous detection of psychoactive drugs and their metabolites using UPLC/MS-MS

Project manager: Dr. K. Müller

The availability of the coupling of liquid chromatography with mass spectroscopy enables more and more the finding and quantification of uncommon analytes and the parallel detection of a parent compound with phase-I- and phase-II-metabolites. Such results allow increasingly better estimation about acute influence, time, and frequency of consumption and if applicable to individual variants in genetic polymorphisms of the metabolic enzymes.

Especially the analysis of samples of elder people or the suspicion of the administration of a rape drug should lead to the possible detection of a singular exposition. Target compounds are not the classical illicit drugs, but the active agents of pharmaceutical products. Matrix could be especially blood, urine, and hair.

The purchase of an UPLC/MS-MS instrument offers the possibility of an extremely sensitive and specific analysis of a great number of compounds in different biological matrices. Up to now, we established sample preparation procedures and detection routines for 48 psychotropics and their active metabolites (i.e. sedatives, antidepressants, narcotics, antipsychotics). Predominantly these procedures have already passed an external audit. Furthermore, the simultaneous detection of opiates and their glucuronides and the quantification of ethylglucuronide as a specific metabolite of ethanol were validated.

## Teaching

The Institute of Forensic Medicine performs the education given by the Statutes of the Medical Act (ÄAppO) for students residing in the clinical part of the degree program Medicine. This includes lectures, seminars, and specific activities. In addition, courses are held for students of the Faculty of Business, Economy, and Law and the Faculty of Sciences as well as for medical students from the University of Regensburg. Although research units with other facilities of the university do not exist in the classical sense due to the specific character of the subject d"forensic medicine", many smaller cooperations with clinical and theoretical disciplines are maintained. Furthermore students are welcome during the whole year to sit in on autopsies, court trials, and practical courses in the field of forensic analytic.

### Selected Publications

Grobosch T, Schwarze B, Felgenhauer N, Riesselmann B, Roscher S, Binscheck T. Eight cases of fatal and non-fatal poisoning with Taxus baccata. Forensic Sci Int 2013, 227(1-3): 118-26

Topf H-G, Schwarze B, Koehler H, Neubert A, Rascher W. Nasal xylometazoline causes serious side effects. Following administration of a non-medical prescription to an infant. Monatsschrift Kinderheilkunde 2013, 161 (6): 537-541

Buchert R, Tawamie H, Smith C, Uebe S, Innes AM, Al Hallak B, Ekici AB, Sticht H, Schwarze B, Lamont RE, Parboosingh JS, Bernier FP, Abou Jamra R. A peroxisomal disorder of severe intellectual disability, epilepsy, and cataracts due to fatty acyl-CoA reductase 1 deficiency. Am J Hum Genet 2014, 95(5): 602-10

### Research Equipment

Applied Biosystems, DNA-Sequenzierautomat

Waters, UPLC/MS-MS

# Institute of Human Genetics

## Chair of Human Genetics

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**Research Focus**
- Genetic factors of intellectual disability
- Genetics of complex diseases
- Growth retardation
- Developmental genetics

## Structure of the Institute

Members of the Institute of Human Genetics are active in teaching, research, and health care provision. At the end of 2014, a total of 54 persons worked at the Institute of Human Genetics: 20 scientists and physicians, 13 Ph.D.-students, 21 technical and administrative employees, as well as eight graduate students. Twelve colleagues were funded through grants. The Institute of Human Genetics runs a genetic clinic for ambulatory care and genetic counseling of patients as well diagnostic laboratories for highly specialized cytogenetic and molecular genetic investigations. Research activities are organized in research groups. Members of the Institute of Human Genetics participate in various collaborative research groups. The Director, Prof. Dr. A. Reis, is chairman of the Senate (FAU) and of the IZKF (Faculty of Medicine; see own report). The Institute of Human Genetics runs the interfaculty core unit "Ultradeep Sequencing" for massive parallel sequencing.

## Research

### Genetic factors of intellectual disability

Project managers: PD Dr. R.A. Jamra[1], PD Dr. C. Zweier[2], Prof. Dr. A. Reis[3]

The elucidation of the molecular basis of intellectual disability is a major scientific focus at the Institute of Human Genetics. The first working group studies autosomal recessive forms of intellectual disability in families with consanguineous parents using homozygosity mapping and whole exome sequencing. This group discovered several novel genetic defects and pathways affecting this clinically and genetically highly heterogeneous disorder. Among others, they identified mutations in the PGAP2 gene which encodes a GPI-anchor remodeling enzyme, mutations in the mitochondrial gene C12ORF65 in patients with mild intellectual delay, spastic paraplegia, and strabismus and an acyl-CoA reductase deficiency as the basis for a peroxisomal disorder with severe intellectual delay, epilepsy, and cataracts. The second and third working groups focus on the identification of mutations arising de novo as cause for intellectual disability disorders. Loss-of-function mutations in the X-linked gene NAA10 were identified as causing a severe form of non-syndromic developmental delay in boys and girls, as well as mutations in the autosomaly encoded central chromatin organising molecule CTCF. The second working group significantly refined the description of the clinical presentation of Borjeson-Forssman-Lehmann syndrome caused by PFH6 mutations, a paper for which the project manager received the Frank-Majewski Award in 2014. A specialty of this group is the modeling of genetic defects in the fruit fly drosophila melanogaster. It could show that an altered dose of glycoprotein M6A impairs learning in drosophila and that dosage changes of GPM6A influence cholesterol homeostasis, both in drosophila and humans.

### Genetics of complex diseases

Project managers: Prof. Dr. A. Reis, PD Dr. U. Hüffmeier

Complex or multifactorial diseases are caused by a combination of mostly unknown environmental and genetic factors. The groups search for genetic susceptibility factors through association studies with large patient cohorts. The projects were funded by BMBF and DFG, respectively. Variants associated with psoriatic arthritis were identified at the RUNX3-locus, a previously identified susceptibility locus for spondylitis ankylosans und celiac disease. The second working group could show that about 40 % of probands with generalized pustular psoriasis, an extreme form of psoriasis with probably mono- or oligogenic inheritance, carry recessive IL36RN-gene mutations. One of these patients was successfully treated for the first time with Anakinra, a synthetic interleukin-1 receptor antagonist. Furthermore, members of the Institute of Human Genetics cooperated closely with members of the Departments of Obstetrics and Gynecology, Surgery, and Medicine 4 in different projects on the genetics of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, breast- and ovarian cancer, colon cancer, and chronic kidney disease in adulthood, respectively.

### Growth retardation

Project manager: PD Dr. C. Thiel

The velocity of growth as well as growth patterns are fundamentally regulated by genetic factors. The group uses genetic and genomic positional strategies to identify and further characterize the genetic basis of idiopathic short stature and ciliary growth deficits. This work was partially funded by DFG, IZKF, and ELAN-Fond. A large patient cohort was established in collaboration with the Department of Pediatric and Adolescent Medicine (Prof. Dr. H.G. Dörr), and rare copy number variants were identified as a frequent cause of idiopathic short stature in a genomewide approach. Moreover, exome sequencing allowed identifying the microtubule associated protein 4 gene (MAP4) as a novel candidate gene for autosomal recessive idiopathic short stature. Defects of MAP4 disrupts centrosomal, ciliary, and Golgi assembly.

### Developmental genetics

Project manager: Prof. Dr. A. Winterpacht

This group is interested in the molecular basis of developmental processes and their individual variability. This includes epigenetic mechanisms and regulatory networks of organogenesis and cell differentiation as well as the identification of variants in specific components of these processes. The group focused on the gene SPOC1 (PHF13) whose expression is associated with survival time in patients with ovarian cancer. It was able to show that SPOC1 functions as an epigenetic reader and writer of histone modifications which plays a role in mitosis and in the epigenetic regulation of meiosis as well as spermatogonial stem cell maintenance and differentiation.

## Teaching

The Institute of Human Genetics is involved in curricular teaching activities in Medicine and in the B.Sc. and M.Sc. degree programs in Molecular Medicine as well as M.Sc. in cellular and molecular biology, respectively. During the report period, 15 master theses were completed. In addition, doctoral theses in medicine and natural sciences were supervised.

### Selected Publications

Zahnleiter D, Uebe S, Ekici AB, Hoyer J, Wiesener A, Wieczorek D, Kunstmann E, Reis A, Doerr HG, Rauch A,

Thiel CT. Rare copy number variants are a common cause of short stature. PLoS Genet 2013, 9(3): e1003365

Gregor A, Oti M, Kouwenhoven EN, Hoyer J, Sticht H, Ekici AB, Kjaergaard S, Rauch A, Stunnenberg HG, Uebe S, Vasileiou G, Reis A, Zhou H, Zweier C. De novo mutations in the genome organizer CTCF cause intellectual disability. Am J Hum Genet 2013, 93(1): 124-31

Körber A, Mössner R, Renner R, Sticht H, Wilsmann-Theis D, Schulz P, Sticherling M, Traupe H, Hüffmeier U. Mutations in IL36RN in patients with generalized pustular psoriasis. J Invest Dermatol 2013, 133(11): 2634-7

Buchert R, Tawamie H, Smith C, Uebe S, Innes AM, Al Hallak B, Ekici AB, Sticht H, Schwarze B, Lamont RE, Parboosingh JS, Bernier FP, Abou Jamra R. A Peroxisomal Disorder of Severe Intellectual Disability, Epilepsy, and Cataracts Due to Fatty Acyl-CoA Reductase 1 Deficiency. Am J Hum Genet 2014, 95(5): 602-10

Ekici AB et al. Renal fibrosis is the common feature of autosomal dominant tubulointerstitial kidney diseases caused by mutations in mucin 1 or uromodulin. Kidney Int, 2014, 86(3): 589-99

Popp B, Støve S, Endele S, Myklebust LM, Hoyer J, Sticht H, Azzarello-Burri S, Rauch A, Arnesen T, Reis A. De novo missense mutations in the NAA10 gene cause severe non-syndromic developmental delay in males and females. Eur J Hum Genet 2014 doi: 10.1038/ejhg.2014.150

## International Cooperations

Prof. A. Schenck, Donders Centre for Neuroscience, Nijmegen: The Netherlands

Prof. A. Barton, University of Manchester, Manchester: UK

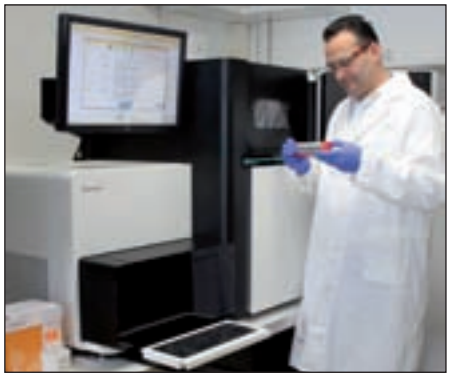
Prof. A. Rauch, University of Zurich, Zurich: Switzerland

Prof. T. Arnesen, University of Bergen, Bergen: Norway

## Research Equipment

Illumina HiSeq 2500 DNA-Sequenzierautomat

Affymetrix, Genomik-Chip-Plattform



*Lab manager of the Core Unit "Ultradeep Sequencing", Dr. A. Ekici, with the DNA sequencer.*

# Institute of Medical Informatics, Biometry, and Epidemiology

## Chair of Medical Biometry and Epidemiology

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**Research Focus**
- Computational Biostatistics
- Dermatoepidemiology
- Cooperative epidemiological and clinical studies

## Structure of the Institute

The Institute of Medical Informatics, Biometry, and Epidemiology comprises the Chair of Medical Informatics (Prof. Dr. H.U. Prokosch) and the Chair of Medical Biometry and Epidemiology. Staff of the Chair of Medical Biometry and Epidemiology includes ten scientists (nine postdocs, one doctoral student) and two further employees. Of all staff positions, six are financed by external funds.
Different working groups address biostatistical methods and epidemiological research. Moreover, the Chair cooperates with various clinical researchers. A computing cluster with 24 nodes is available as infrastructure for computer-intensive biostatistical simulation studies.

## Research

### Computational Biostatistics

Project managers: Dr. W. Adler, Prof. Dr. O. Gefeller, Dr. B. Hofner, Dr. A. Mayr
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, a new boosting algorithm for modeling ordinal outcomes was developed. The suggested algorithm can e.g. be used to predict cancer stages (measured on an ordinal scale), using small sets of marker genes that are automatically selected by the boosting algorithm. 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.

### Dermatoepidemiology

Project managers: Prof. Dr. A. Pfahlberg, Prof. Dr. W. Uter
In clinical contact allergy research, a close cooperation with the German contact dermatitis group (DKG) e.V. and the multi-centric project information network of the 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) and for quality control purposes. Additionally, research projects prompt special analyses, for instance sensitization to common biocides and fragrances. 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.
The epidemiology of malignant melanoma and acquired melanocytic nevi is a further research interest: Acquired melanocytic nevi, surrogate or potential precursor of malignant melanoma, are addressed by the current MONA-study which includes standardized assessment of student cohorts. In 2014, a survey ("Erlking Sun 2014") addressing knowledge on prevention of UV exposure in kindergarden staff, and actual protective measures (shading etc.) in the institutions was conducted with the aim of identifying targets of improvement of primary prevention.

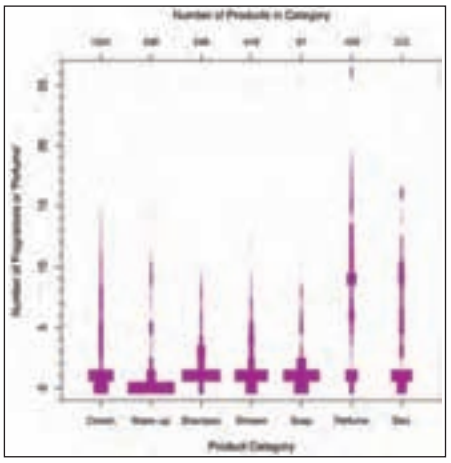
### Cooperative epidemiological and clinical studies

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 our Institute in these cooperative projects. The most important projects in the reporting period include:
- A cross-sectional study in the field of occupational medicine addressing the association between exposure to CS2 in the viscose industry and a number of neurological and cardiovascular endpoints;
- A study coordinated by the Institute of Biomedicine of Aging regarding risk factors of frailty and sarcopenia;
- A multi-centric European studying on "Accelerated Partial Breast Irradiation", a controlled clinical trial on the multimodal therapy of rectal cancer (CAO/ARO/AIO-04), 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 of the UK Erlangen;
- The multi-centric "German Chronic Kidney Disease Study" (GCKD; see own report) funded by the BMBF and the "Kuratorium für Heimdialyse";
- The implementation of the "German Weight Maintenance" registry and biostatistical support of a multi-center study on the therapy of eating disorders (INTERBED), chaired by the Department of Psychiatry and Psychotherapy of the UK Erlangen;
- The multicenter POLYPROBE Study examines the expression of 61 marker genes in patients with carcinoma of the colon, using PCR. The association with UICC stages, survival, and response to (radio-) chemotherapy will be analyzed.

## Teaching

In the context of curricular teaching, the Chair of Medical Biometry and Epidemiology contributes to the "Querschnittsbereich I" (medical informatics, biometry, and epidemiology) for

medical students (lecture and seminars in small groups, one contact hour each). Moreover, this introduction to biometry and epidemiology (lecture and seminars in small groups, one contact hour each) is part of the bachelor phase of the degree program Molecular Medicine together with a seminar on the practice of data analysis (two contact hours) which teaches basic programming knowledge in the statistical program "R". Regarding the M.Sc.-degree program Medical Process Management, the Chair of Medical Biometry and Epidemiology is responsible for a part of module 2.2 "health care management II", namely "public health and evidence-based medicine" (seminar, three contact hours). For students of medicine and dental medicine, a seminar on "design and data analysis in clinical and experimental studies" is being offered. This seminar can be used by the students to discuss any statistical issues they encounter when working at their medical thesis. As compulsory elective seminar in the master part of the degree program Life Science Engineering of the Faculty of Engineering, the Chair of Medical Biometry and Epidemiology offers a module in epidemiology. Moreover, biometry and epidemiology are part of an introductory seminar for students of information science specializing in medical informatics.



*Distribution of the number of fragrances in the categories of cosmetic products as modified "violin plot", accounting for the discrete nature of the count data, corresponding to centered histograms. For instance, the bottom set of rectangles indicates the proportion of products with none of the 26 fragrance substances or "perfume" listed on the product label.*
*(from: Uter W, Yazar K, Kratz EM, Mildau G, Lidén C. Coupled exposure to ingredients of cosmetic products: I. Fragrances. Contact Dermatitis 2013, 69: 335–341. With kind permission of the publisher)*

## Selected Publications


Keller AK, Uter W, Pfahlberg AB, Radespiel-Tröger M, Gefeller O. Seasonality of cutaneous melanoma diagnoses: a comprehensive comparison of results in Bavaria and Northern Ireland. Melanoma Res 2013, 23(4): 321-30

Gefeller O, Li J, Uter W, Pfahlberg AB. The impact of parental knowledge and tanning attitudes on sun protection practice for young children in Germany. Int J Environ Res Public Health 2014, 11(5): 4768-81

Mayr A, Schmid M. Boosting the concordance index for survival data--a unified framework to derive and evaluate biomarker combinations. PLoS ONE 2014, 9(1): e84483

Mayr A, Binder H, Gefeller O, Schmid M. The evolution of boosting algorithms. From machine learning to statistical modelling. Methods Inf Med 2014, 53(6): 419-27

Schwitulla J, Brasch J, Löffler H, Schnuch A, Geier J, Uter W. Skin irritability to sodium lauryl sulfate is associated with increased positive patch test reactions. Br J Dermatol 2014, 171(1): 115-23

Uter W, Schmid M, Schmidt O, Bock C, Wolter J. Cobalt release from earrings and piercing jewellery – analytical results of a German survey. Contact Dermatitis 2014, 70(6): 369-75


## International Cooperations

Prof. J. Duus Johansen, Gentofte Hospital, Copenhagen: Denmark

Prof. G.E. Eide, Haukeland Hospital, Bergen: Norway

Prof. A.-M. Giménez-Arnau, Hospital del Mar, Barcelona: Spain

# Institute of Medical Informatics, Biometry, and Epidemiology

## Chair of Medical Informatics

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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
- Translational cancer research

## Structure of the Division

The endowed Chair of Medical Informatics and the Chair of Medical Biometry and Epidemiology together constitute the Institute of Medical Informatics, Biometry, and Epidemiology within the Faculty of Medicine of the FAU. Furthermore, the Chair of Medical Informatics has a secondary affiliation within the Faculty of Engineering, the research group Medicine.
The Chair of Medical Informatics has 20 staff members, with 15 of them being funded by research grants.
The research projects comprise the design and implementation of electronic medical records, the integration of clinical decision support functions into hospital information systems, the modeling and optimization of clinical workflows, data warehouse and data mining applications, concepts and architectures for intersectoral health networks, the evaluation of electronic information systems, the use of mobile technologies in medicine, and the design of IT-infrastructures for clinical and translational research, especially the reuse of routine data for translational research.
Prof. Dr. H.-U. Prokosch who holds the Chair of Medical Informatics is (as Chief Information Officer of the UK Erlangen) also responsible for the university hospital´s routine operative business and its strategic information processing development.

## Research

### Process support through health information systems

One of the major challenges in the design, establishment, and management of Hospital 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 health information systems. In its final consequence clinical information flow and communication functionalities shall also support the shared decision making paradigm and self-responsible patients.
The challenge of shared decision making processes and digital patient guidance has been especially tackled in the EU-project eHealth Monitor where innovative information and knowledge management technologies synergize to bring the most adequate information to physicians, patients, and their relatives.
In addition to such grant funded projects, the Chair of Medical Informatics also pursues and supports several innovative pilot projects embedded in the SOARIAN® hospital information system environment of UK Erlangen (e.g. a complete clinical cancer documentation embedded in a comprehensive clinical data reuse concept and the introduction of a nursing care information system).

### 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).
In the BMBF project "Personalized Pharmacotherapy in Psychiatry", the chemical structure and physicochemical properties of drug substances are included in the knowledge model. Based on this, a data- and model-driven software prototype for individualized, optimized psychiatric pharmacotherapy is designed, developed, and evaluated.
Within the patient data management system of an ICU, a CDSS (clinical decision support system) has been integrated to monitor dangerously low blood glucose levels with direct feedback as text messages on the DECT telephone for the calculation and trending of scores and for quality assurance measures supporting the DRG-based billing in complex ICU patients.

### 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 questionnaires, observations, thinking aloud, and cognitive walkthrough, to evaluate the acceptance and usability of different kinds of IT artefacts. When introduced early in the design and planning process, major success factors and barriers can be identified and properly dealt with.
Finally, within the project Prospective Health Technology Assessment (ProHTA), part of the cluster of excellence initiative, simulation tools to forecast the potential impact of future technologies and their potential return on invest even before development have been conceptually designed, implemented, and evaluated.

### 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. Further, we start 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 the 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.
Within the project "cloud4health", we have developed a complex architecture with an integrated de-identification workbench for leveraging narrative text findings through cloud-based natural language processing, text mining, and

text annotation mechanisms and thus enriched our research data warehouse with information also drawn from unstructured text documents. In this context, I. Leb received the TELEMED 2013 award for her contribution "Secondary usage of structured and free-text data via cloud architecture conforming to data protection requirements" at the annual German Telemedicine Conference.
In the BMBF-funded IDRT project (Integrated Data Repository Toolkit), a suite of sustainable tools for the optimized extraction and querying of biomedical data was developed.

### IT-infrastructure applications for medical research

Today, medical research is often pursued within networked multi center structures which require efficient and safe IT-infrastructures. The Chair of Medical Informatics has designed and provided such web-based electronic data capture systems for many medical multicenter research projects, such as the Polyprobe Study, the nation-wide registry for chronic kidney diseases (GCKD), and the CONKO-007 study on radiochemotherapy for pancreatic cancer. Current activities further comprise IT infrastructures to support biobanking and single source reuse of patient data for clinical research. The Chair of Medical Informatics is member and active partner in many projects and working groups of the TMF (German technology and methods platform for networked medical research) and leads the GMDS working group "Reusing electronic patient records for clinical research".
The architecture and HIS-integrated modules designed and implemented within the BMBF-funded project "EHR-based patient recruitment for clinical trials" have been applied in several clinical trials of the Faculty of Medicine and have shown to improve patient recruitment processes significantly.
Within the EFPIA-funded Innovative Medicine Initiative, we are partner in the EHR4CR project developing adaptable, reusable, and scalable solutions for reusing data from electronic health record systems for clinical research. The solutions are validated for different scenarios (e.g. patient identification and recruitment, clinical trial execution, adverse event reporting), across different therapeutic areas, and across several European countries.

### Translational cancer research

A special research focus for the reuse of clinical data in research as well as for quality management purposes is the efficient IT support in the context of cancer care and translational cancer research. We have designed and established a comprehensive single source framework of IT components supporting tissue banking, multicenter cancer trials, cancer registration, and routine cancer care documentation.
While interfacing the new cancer registry database of UK Erlangen´s Comprehensive Cancer Center with our EHR system, we designed a reference model for cancer documentation comprising a set of elementary documentation packages, related processes within patient care, quality assurance and research, respective information systems as well as interfaces to be established.

## Teaching

The Chair of Medical Informatics is teaching medical students in the cross-sectional subject medical informatics, biometry, and epidemiology. It further offers medical informatics courses for computer science students of the Faculty of Engineering and has a considerable teaching part in the Master degree program Medical Process Management of the Faculty of Medicine as well as the Bachelor and Master degree program Medical Devices Technology of the Faculty of Engineering.
In this context, the Chair of Medical Informatics has mentored six bachelor theses, eight master and diploma theses as well as four doctoral theses in the years 2013/2014.

### Selected Publications


Zunner C, Bürkle T, Prokosch HU, Ganslandt T. Mapping local laboratory interface terms to LOINC at a German university hospital using RELMA V.5: a semi-automated approach. J Am Med Inform Assoc 2013, 20(2): 293-7

Bürkle T, Müller F, Patapovas A, Sonst A, Pfistermeister B, Plank-Kiegele B, Dormann H, Maas R. A new approach to identify, classify and count drug-related events. Br J Clin Pharmacol 2013, 76 Suppl 1: 56-68

Patapovas A, Dormann H, Sedlmayr B, Kirchner M, Sonst A, Müller F, Pfistermeister B, Plank-Kiegele B, Vogler R, Maas R, Criegee-Rieck M, Prokosch HU, Bürkle T. Medication safety and knowledge-based functions: a stepwise approach against information overload. Br J Clin Pharmacol 2013, 76 Suppl 1: 14-24

Neubert A, Dormann H, Prokosch HU, Bürkle T, Rascher W, Sojer R, Brune K, Criegee-Rieck M. E-pharmacovigilance: development and implementation of a computable knowledge base to identify adverse drug reactions. Br J Clin Pharmacol 2013, 76 Suppl 1: 69-77

Pfistermeister B, Saß A, Criegee-Rieck M, Bürkle T, Fromm MF, Maas R. Inconsistencies and misleading information in officially approved prescribing information from three major drug markets. Clin Pharmacol Ther 2014, 96(5): 616-24

Köpcke F, Prokosch HU: Employing computers for the recruitment into clinical trials: a comprehensive systematic review. J Med Internet Res 2014, 16(7): e161


### International Cooperations

Prof. Dr. K.-P. Adlassnig, Medical University of Vienna, Vienna: Austria

Prof. Dr. E. Ammenwerth, UMIT-University for Health Sciences, Hall: Austria

Prof. Dr. P. Dégoulet, Hôpital Européen George Pompidou, Paris: France

Prof. I. Kohane, MD, Ph.D., i2b2 National Center for Biomedical Computing, Boston: USA

# Institute of Medical Physics

## Chair of Medical Physics

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**Research Focus**
- High-Resolution Computed Tomography of the Breast
- PET/MR Hybrid Imaging
- 3D Imaging and Image Processing for Musculoskeletal Applications

## Structure of the Institute

In addition to the chair and full professorship of Medical Physics, the Institute of Medical Physics (IMP) comprises the professorship of Magnetic Resonance Imaging (held by Prof. Dr. H.H. Quick from 2009 to 2014). IMP employs a total of 55 persons, whereof 38 are financed by third-party funds. The researchers, 21 of them doctoral students, are working on a wide range of topics in the area of medical physics. The projects focus on different issues of the following research areas:
- computed tomography
- dosimetry and radiation protection
- magnetic resonance tomography (MRT)
- medical imaging
- medical image processing
- preclinical imaging
- osteoporosis research.

An important basis for the research at IMP is fundraising: Public grants by the European Union, BMBF, DFG, Bavarian Research Foundation and cooperations with industrial partners reach an amount of about one million Euro per year.
The focus of the 30 ongoing research projects and cooperations is the development and the application of imaging procedures in medical diagnosis and image-guided therapy. Besides the achievements in the field of computed tomography (CT) where IMP has gained a worldwide leading position, the research focuses on magnetic resonance imaging (MRI), PET/MR imaging, and medical imaging processing. Selected research projects are described briefly in the following.

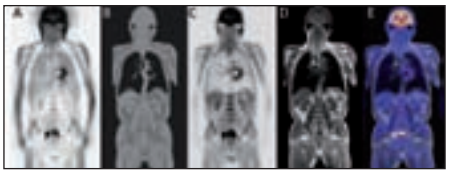
## Research

### High-Resolution Computed Tomography of the Breast

Project manager: Prof. Dr. h.c. W.A. Kalender, Ph.D.
Since 2008, the early detection of breast cancer using CT has been a main topic, based on funding by the European Union (FP 7) and the BMBF. Very good results have been achieved in different respects. Especially the feasibility of the proposed concepts and the target performance parameters were verified.
On the occasion of the worldwide biggest radiology congress (the RSNA 2014 in Canada), the project was presented at the booth of the BMBF "Germany – Land of Ideas" and found great positive feedback. In 2015, clinical testing of two breast-CT demonstrators is planned at the university hospitals in Erlangen and Aachen.

### PET/MR Hybrid Imaging

Project manager: Prof. Dr. H.H. Quick
From April 2010 to September 2014 the world's first installation of a diagnostic system for simultaneous PET/MR whole-body hybrid imaging was available for research at IMP. The hybrid system (Biograph mMR, Siemens AG, Erlangen) consists of a 3.0 Tesla highfield magnetic resonance (MR) system in which a MR compatible positron emission tomography (PET) detector has been fully integrated. This allows for simultaneous acquisition of MR data with excellent soft tissue contrast and high spatial resolution as well as of PET data providing high sensitivity in detecting tumor cells that have been labeled with a specific radiotracer.
This new technology was investigated at IMP in close research collaboration with the industrial partner Siemens AG and with the Department of Nuclear Medicine, the Institute of Radiology, and the Division of Neuroradiology (all UK Erlangen).
The systematic technical testing of the system performed at IMP was followed by first clinical evaluation and validation of 100 oncologic patients. Since July 2011, the hybrid system has been CE certified and has reached medical product status. Currently (03/2015), about 60 of such hybrid systems are installed worldwide. The MR imaging research group at IMP – a team formed of doctoral, diploma, and master students – performed state-of-the-art research to further improve the technology and to assess and to validate further clinical applications of PET/MR hybrid imaging. Also clinical studies were scientifically supported. The spectrum of research projects encompassed development of new methods for MR-based attenuation and motion correction, development and technical integration of PET-transparent radiofrequency coils for integrated PET/MR hybrid imaging, facilitation of the clinical workflow for maximization of diagnostic information while reducing PET/MR data acquisition time, as well as strategies for improving the quantification of PET data, to name just a few. In cooperation with the laboratory for pattern recognition, new methods for MR-based attenuation correction were developed and evaluated.

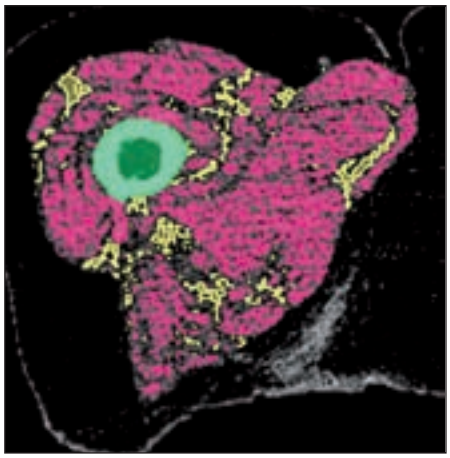


*Whole-body PET/MR images of a patient with metastasis in the pelvis: (A) PET without attenuation correction (AC), (B) MR-based AC, (C) PET after AC, (D) T1-weighted high resolution MRI, and (E) whole-body PET/MR fused from (C) and (D).*

### 3D Imaging and Image Processing for Musculoskeletal Applications

Project manager: Prof. Dr. K. Engelke
The main topics of the medical image processing activities have been musculoskeletal problems in the area of osteoporosis, inflammatory diseases, osteoarthrosis, and sarcopenia.
In the framework of the BMBF funded project 'Biomechanically founded individualized osteoporosis Assessment and treatment' (BioAsset 01EC1005D), a 3D segmentation and analysis module was developed for the complete thoracolumbar spine that includes an analysis of the disk volume and the 3D shape of the vertebrae. The bone mineral density, an important factor to predict the risk of vertebral fractures, can be quantified with high precision. This software is integrated as a module of the 3D segmentation and analysis toolkit MIAF (Medical Image Analysis Framework). Within the project 'A Network on Clinics and Pathophysiology of Osteophytes and Ankylosis' (Ancyloss; see own report), also funded by the BMBF, other modules have been developed, one to measure bone mineral density at the distal forearm and another to determine the volume of bone erosions characterizing rheumatoid arthritis.
Remarkable progress in the quantification of muscle texture has been achieved within the re-

search collaboration 'Research Consortium Muscle Wasting (Sarcopenia) and Osteoporosis – Consequences of impaired tissue regeneration in the elderly (FORMOsA)', funded by the Bavarian Research Foundation. Quite innovative is the approach to use CT as diagnostic procedure instead of MRI even though the soft tissue contrast is considerably higher with MRI. It was shown that parameters describing the muscle structure and the distribution of fat in and around the muscle are more appropriate to predict femoral fracture than muscle volume or cross-sectional area. Industrial partners of IMP within FORMOsA are Miha Body Tech GmbH (Augsburg), Siemens Healthcare (Erlangen), and Physiomed Elektromedizin AG (Schnaittach/ Laipersdorf). Currently, the research within FORMOsA is going to include test persons with sarcopenia.
In 2014, the research group received the award for research groups by the umbrella organization of the German speaking osteological societies.



*CT image showing the distribution of pure muscle (pink) and intermuscular adipose tissue (yellow) within the deep fascia of the thigh.*

## Teaching

IMP participates in the education of medical students in the area of medical imaging by offering lectures and seminars. The course on the basics of medical physics includes practical exercises and gives students studying sciences the opportunity to learn more about this field of physics. Besides these elementary courses, IMP regularly offers lectures and seminars on special subjects of medical physics, medical imaging and medical image processing, and osteoporosis research.
An essential part of the education program at IMP is the supervision of diploma and master theses in different fields and of doctoral studies to graduate as Dr. rer. biol. hum.

### Selected Publications


Engelke K, Libanati C, Fuerst T, Zysset P, Genant HK. Advanced CT based In Vivo Methods for the Assessment of Bone Density, Structure, and Strength. Curr Osteop Rep 2013, 11: 246-255

Quick HH. Integrated PET/MR. J Magn Reson Imaging 2014, 39(2): 243-58

Paulus DH, Thorwath D, Schmidt H, Quick HH. Towards integration of PET/MR hybrid imaging into radiation therapy treatment planning. Med Phys 2014, 41(7): 072505

Oehmigen M, Ziegler S, Jakoby BW, Georgi JC, Paulus DH, Quick HH. Radiotracer Dose Reduction in Integrated PET/MR: Implications from National Electrical Manufacturers Association Phantom Studies. J Nucl Med 2014, 55(8): 1361-1367

Museyko O, Heinemann A, Krause M, Wulff B, Amling M, Püschel K, Glüer CC, Kalender W, Engelke K. A Low Radiation Exposure Protocol for 3D QCT of the Spine. OI 2014, 25: 983-992

Töpfer D, Finzel S, Museyko O, Schett G, Engelke K. Segmentation and quantification of bone erosions in high resolution peripheral quantitative computed tomography images of the metacarpophalangeal joints of patients with rheumatoid arthritis. Rheumatology 2014, 53: 65-71


### International Cooperations

Prof. J.-D. Laredo, Assistance Hôpitaux Publique de Paris, Paris: France

Prof. J.M. Boone, UC Davis Medical Center, Sacramento: USA

Prof. C.A. Mistretta, University of Wisconsin, Madison: USA

### Research Equipment

Siemens, Biograph mMR

CT imaging, Erlangen, In-vivo Micro-CT-Scanner

Siemens, Somatom Dual-Source CT Scanner Flash

# Institute of Neuropathology

## Chair of Neuropathology

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**Research Focus**
- Focal human epilepsies and animal models
- Molecular myopathology
- Neuro-oncology

## Structure of the Institute

Our academic staff and technicians are engaged in studies addressing molecular pathomechanisms of CNS (epilepsy and neuro-oncology) and skeletal muscle disorders. We have established the neuropathological reference center for epilepsy surgery, the European Epilepsy Brain Bank (supported by EU funding) and pathology register for sellar tumors (working group "Hypophyse und Hypophysentumoren" of the German Society for Endocrinology). Five physicians cover all diagnostic issues in surgical neuropathology and neuro-oncology in adults and children. Our laboratories are equipped for histology, cell biology, molecular diagnostics and the Institute of Neuropathology hosts the DFG research unit 1228 addressing pathogenic mechanisms of myofibrillar myopathies (see own report).

## Research

### Focal human epilepsies and animal models

Project manager: Prof. Dr. I. Blümcke

Our working group addresses drug-resistant focal epilepsies in humans to decipher molecular pathomechanisms in brain lesions associated with chronic seizures, e.g. hippocampal sclerosis, glio-neuronal tumors, and focal cortical dysplasias. We perform systematic analysis in surgically resected human brain specimens in correlation to clinical histories and postsurgical follow-up data, and our work contributed in establishing new international standards for clinico-pathological diagnosis of Focal Cortical Dysplasias (ILAE classification 2011) and Hippocampal Sclerosis (ILAE classification 2013). Our group also addresses molecular pathomechanisms of epileptogenesis. We study epigenetic chromatin modifications in human surgical specimens and use an experimental animal model with 24h video-EEG monitoring to quantitatively examine seizure burden in animals. In this model, we also tested new therapeutic approaches modifying DNA methylation by a ketogenic diet regimen. Research of human epilepsies and histopathologically well-characterized surgical specimens obtained from patients with temporal lobe epilepsy opens new avenues to also study higher brain function in humans, as the hippocampus plays a major role in memory formation and recall. In addition, our finding of epilepsy-induced neurogenesis in the human hippocampus offers the possibility to unravel molecular signals for the recruitment, proliferation, and differentiation of adult stem cells in the human brain.

### Molecular myopathology

Project manager: Prof. Dr. R. Schröder

The central research topic of this group is the pathogenesis of myofibrillar myopathies which are morphologically characterized by the pres - ence of pathological protein aggregation in cross-striated muscle cells. These adult onset and often heritable myopathies are clinically characterized by a progressive course leading to severe disability and premature death. To date, no drug treatment is available for these disorders. The main focus of our current research work is the generation and characterization of transgenic mouse models for the IBMPFD disease (Inclusion Body Myopathy associated with Pagets disease of bone and Frontotemporal Dementia), the desmin myopathy and cardiomyopathy, and the filamin C-associated myopathy. The clinical, morphological, biochemical, and molecular analysis of these mouse models shall provide deeper insights into the molecular "sequence" that leads to pathological protein aggregation and progressive muscle damage in these disorders. This work will be the basis for novel targeted treatment strategies. Our research is currently funded by the DFG (research unit FOR 1228, see own report), the Else-Kröner-Fresenius Foundation, the Johannes und Frieda Marohn-Foundation, and the Deutsche Gesellschaft für Muskelkranke.

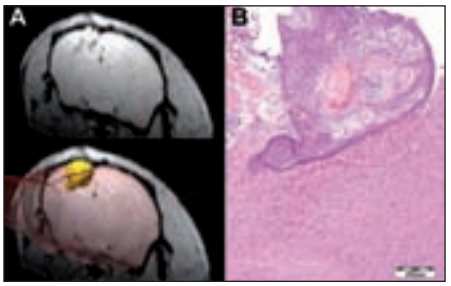
### Neuro-oncology

Project manager: PD Dr. R. Buslei

The field of neurooncology plays an important role within the clinical-neuropathological diagnostics. Due to the longstanding focus of the Department of Neurosurgery in Erlangen on the treatment of tumors of the sellar region (e.g. pituitary adenomas, craniopharyngiomas), a unique collection of surgical tissue samples is available for systematic molecular-neuropathological analyses. Our research comprises three major topics:

(1) Molecular tumorigenesis;
(2) Pathomechanisms of brain invasion;
(3) Molecular prognostic markers and treatment targets.

Concerning craniopharyngiomas, our group identified a potential tumor stem cell population which is held responsible to be the driving force of infiltrating growth of tumor cells into the brain. This specific cell population shows simultaneously a diminished expression of the cell adhesion molecule Claudin-1 and an activation of the EGFR. The latter can be targeted by inhibitors what displays a promising therapeutic approach according to in vitro testing. To clarify the underlying mechanisms in detail, an in vivo model for human craniopharyngioma is of crucial importance. During the last two years our group established a protocol for the generation of an intracranial xenotransplant animal model for human craniopharyngiomas. This model allows not only for the validation of innovative targeted treatment protocols, but also for the refinement of established therapy schedules (e.g. radiotherapy). Moreover, the xenotransplant model enables to further investigate the mechanisms leading to tumor recurrence. Our work is supported by DFG, Dr. Robert-Pfleger-Foundation, Dr. Ernst and Anita Bauer Foundation, and the International Foundation Neurobionik.




*Craniopharyngioma xenotransplantation model*
*Three months after tumor transplantation, 4.7 Tesla magnetic resonance imaging revealed subdural located lesions. T1-weighted sequences enabled 3D-reconstruction of xenotransplants to study the development of finger-shaped tumor protrusions into subjacent brain tissue (A). Hematoxylin and eosin staining of corresponding histologically processed xenotransplant confirms infiltrative growth pattern (B).*
*(From: Stache C et al. Brain Pathool 2015. With kind permission of the publisher Wiley Company.)*

## Teaching

Our Institute is enrolled in pathology training and lectures.

### Selected Publications


Blümcke I et al. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia 2013, 54(7): 1315-29

Kreutzfeldt M, Bergthaler A, Fernandez M, Brück W, Steinbach K, Vorm M, Coras R, Blümcke I, Bonilla WV, Fleige A, Forman R, Müller W, Becher B, Misgeld T, Kerschensteiner M, Pinschewer DD, Merkler D. Neuroprotective intervention by interferon-γ blockade prevents CD8+ T cell-mediated dendrite and synapse loss. J Exp Med 2013, 210(10): 2087-103

Kobow K, Kaspi A, Harikrishnan KN, Kiese K, Ziemann M, Khurana I, Fritzsche I, Hauke J, Hahnen E, Coras R, Mühlebner A, El-Osta A, Blümcke I. Deep sequencing reveals increased DNA methylation in chronic rat epilepsy. Acta Neuropathol 2013, 126(5): 741-56

Coras R, Pauli E, Li J, Schwarz M, Rössler K, Buchfelder M, Hamer H, Stefan H, Blumcke I. Differential influence of hippocampal subfields to memory formation: insights from patients with temporal lobe epilepsy. Brain 2014, 137(7): 1945-57

Stache C, Hölsken A, Fahlbusch R, Flitsch J, Schlaffer SM, Buchfelder M, Buslei R. Tight junction protein claudin-1 is differentially expressed in craniopharyngioma subtypes and indicates invasive tumor growth. Neuro Oncol 2014, 16(2): 256-64

Winter L, Staszewska I, Mihailovska E, Fischer I, Goldmann WH, Schröder R, Wiche G. Chemical chaperone ameliorates pathological protein aggregation in plectin-deficient muscle. J Clin Invest 2014, 124(3): 1144-57


### International Cooperations

Prof. J. Engel Jr., David Geffen School of Medicine at UCLA, Los Angeles: USA

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

Prof. G. Wiche, University of Vienna, Vienna: Austria

Prof. F. Cendes, University of Campinas, Campinas: Brazil

Dr. U. Bartels, Department of Paediatrics, SickKids – Hospital, Toronto: Canada

Dr. J.P. Martinez-Barbera, UCL, London: UK

Prof. A. Pitkänen, University of Eastern Finland, Kupio: Finland

Dr. R. Spreafico, IRCCS Foundation Neurological Institute "Carlo Besta", Milano: Italy

### Meetings and International Training Courses

16. – 20.09.2013: 1st International Summer School for Neuropathology and Epilepsy Surgery (INES 2013), Erlangen

10. – 13.06.2014 Molecular insight into muscle function and protein aggregate myopathies. Special Interest Meeting of the German Society for Cell Biology (DGZ), Potsdam

30.08. – 03.09.2014: 2nd International Summer School for Neuropathology and Epilepsy Surgery (INES 2014), Erlangen

# Institute of Pathology

## Chair of General Pathology and Pathological Anatomy

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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 tumors
- Pathology of immune and inflammatory reactions in carcinogenesis

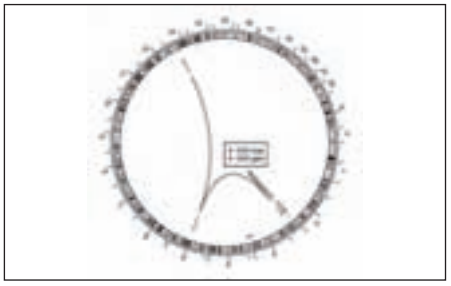
## Structure of the Institute

The Institute of Pathology includes also the Division of Nephropathology. A total of 85 members of staff work at the Institute of Pathology, 30 are medical professionals or scientists.
The Institute of Pathology is responsible for all histopathological diagnostics within the UK Erlangen and for more than 30 external hospitals and physicians. The histopathological diagnoses are carried out using state of the art microscopic, immunohistochemical, and molecular methods. In addition to the histopathological evaluation of approximately 45,000 samples, more than 3,000 molecular pathology investigations are carried out.
The diagnostics specialties of the Institute are urogenital and gynecological pathology as well as breast pathology, diagnosis of soft tissue tumors, and gastrointestinal tumor pathology.

## Research

### Diagnostic molecular pathology

Project managers: Prof. Dr. F. Haller, Dr. E.A. Moskalev
The aim of the group is the development and functional validation of novel molecular markers with diagnostic, prognostic, or predictive impact in solid tumors. Next-generation sequencing is a modern technology that has been successfully established in the group during the last three years and which enabled the identification of novel key molecular events in different rare soft tissue neoplasms. Whole genome sequencing identified oncogenic mutations of the CTNNB1 gene in sinonasal hemangiopericytoma as well as aberrant hypermethylation of the SDHC gene locus in pediatric gastrointestinal stromal tumors as probable tumor-initiating events on a genetic and epigenetic level, respectively. Another focus of the group is the massive parallel sequencing of multi-gene panels in lung cancer and cancer of the urogenital tract, 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 therapeutical options in the future.

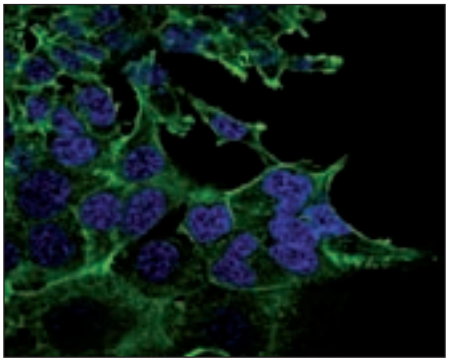


*Circos plot of a gene fusion event and DNA copy number changes in a soft tissue neoplasm detected by whole genome sequencing.*

### Experimental tumor pathology

### - Gastrointestinal tumors

Project managers: Prof. Dr. R. Schneider-Stock, Dr. T. Rau, Dr. K. Erlenbach-Wünsch, 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 tumors and preneoplasias of the gastrointestinal tract. We investigate the molecular regulation of cell death after oxidative, stress-induced DNA-damage in normal and malignant epithelial cells of the gut. We aim at identifying new valid biomarkers for tumor transformation in colorectal carcinogenesis that could be of potential therapeutic interest. This translational approach is reflected in many research projects where we are investigating the significance of epigenetic alterations in inflammation and tumor progression as well as their functional consequences in the intestinal epithelium. Experimental mouse models for studying chronic inflammatory bowel diseases such as ulcerative colitis are established (in close collaboration with the Department of Medicine 1 (Prof. Dr. M. Neurath, Dr. C. Neufert). Since many years we have been studying successfully the anti-cancer effects of plant-derived drugs for colorectal tumor cells.



*Co-immunofluorescence staining of HCT116 colorectal cancer cells for F-actin (phalloidin, green) and DAPI (blue) to show cytoskeletal alterations during migration. Confocal microscopy (x63) by Dr. J. Ivanovska*

### - Breast and gynecological tumors

Project managers: Prof. Dr. A. Hartmann, Prof. Dr. A. Agaimy, Dr. D. Wachter, Dr. J. Strehl, Dr. K. Brunner, R. Erber
This group focuses in cooperation with the Department of Obstetrics and Gynecology (Prof. Dr. M. Beckmann, Prof. Dr. P. Fasching) on the discovery of genetic and epigenetic changes in breast cancer and ovarian carcinomas. The objective of our research is to discover molecular prognostic markers and to identify molecular markers that could be used in the clinical-pathological differential diagnosis and therapeutic stratification of breast and ovarian cancer.

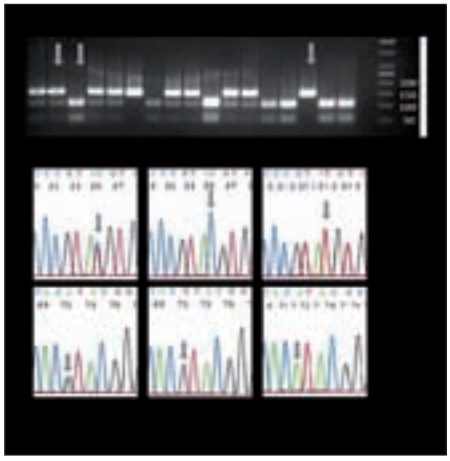
### - Tumors of the head and neck region

Project managers: Prof. Dr. A. Agaimy, Prof. Dr. R. Schneider-Stock, Prof. Dr. A. Hartmann, Dr. D. Wachter, Dr. J. Strehl, Dr. K. Brunner, Prof. Dr. R. Rieker
We investigate the molecular changes in tumors of the head and neck region in cooperation with the Departments of Otorhinolaryngology – Head and Neck Surgery (Prof. Dr. Dr. h.c. H. Iro) and Oral and Cranio-Maxillofacial Surgery (Prof. Dr. Dr. Dr. h.c. F.W. Neukam). This research project has two objectives: One is to compile a molecular-pathological and histopathological classification 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.

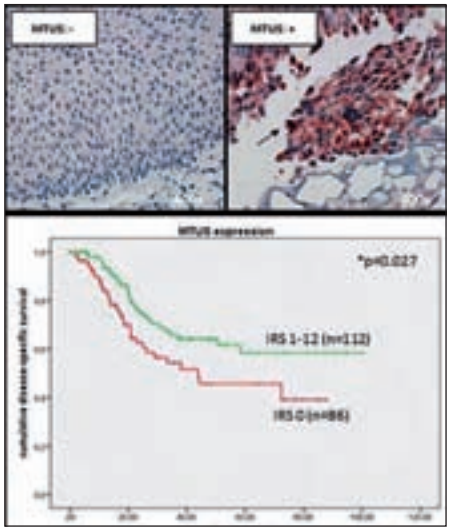
### Clinical and predictive molecular pathology of urogenital carcinomas

Project managers: Prof. Dr. A. Hartmann, PD Dr. R. Stöhr, Dr. C. Stöhr, Dr. J. Giedl, Dr. S. Bertz, Dr. I. Polifka
The research group investigates the basic molecular principles of the development of urothelial carcinoma of the urinary bladder, prostate cancer, and renal cell carcinoma. There is a close co-

operation with the Department of Urology (Prof. Dr. B. Wullich, Prof. Dr. H. Taubert) and also 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.



*a) Genotyping of patients with early-onset bladder cancer for the polymorphism rs3243 using RFLP. Validation of the RFLP results using Sanger sequencing (Rogler et al, Int J Clin Exp Pathol 2013, 6(10): 1984-1998).*




*b) The expression of MTUS1 (microtubule-associated tumor suppressor 1) was identified as a new prognostic marker for bladder cancer. Loss of expression in the tumor was associated with worse outcome in advanced tumors (IRS: immune-reactive score: 0: no expression; 12: strong expression; Rogler et al, BMC Cancer 2014, 14: 214).*

### Pathology of immune and inflammatory reactions in tumor development

Project managers: PD Dr. M. Büttner-Herold, Prof. Dr. A. Hartmann, Dr. C. Geppert

This project examines the interaction between infection and B-cell differentiation in primary and persistent EBV infection and the mechanisms and interactions between the immune system and tumor cells in different tumor types (colorectal cancer, prostate carcinoma, renal cell carcinoma, Hodgkin lymphoma). The objective is the identification of mechanisms through which the tumor cells could escape the immune response of the organism and the characterization of the intratumoral inflammatory cell infiltrate for prognosis and therapy response prediction.

## Teaching

The Institute of Pathology has an essential role in the teaching of students of human, dental, and molecular medicine and in delivering the degree program Medical Process Management. In addition to traditional teaching formats (main lectures, block seminars), the Institute also offers integrated and interdisciplinary courses. In particular, the teaching course in the autopsy ward and the interdisciplinary course "Conference of Clinical Pathology" have to be mentioned. In the degree program Molecular Medicine, we offer teaching courses such as "Basic Principles of Pathology", "Basic Principles of Tumor Biology" (literature seminar), and other subjects of molecular pathology.

### Selected Publications


Chakilam S et al. Death-associated protein kinase cintrols STAT3 activity in intestinal epithelial cells. Am J Pathol 2013, 182(3): 1005-20

Barthelmeß S, Geddert H, Boltze C, Moskalev E, Bieg M, Sirbu H, Brors B, Wiemann S, Hartmann A, Agaimy A, Haller F. Solitary fibrous tumors (SFTs)/haemangiopericytomas (HPCs) with different variants of the NAB2-STAT6 gene fusion are characterized by specific histomorphology and distinct clinicopathological features. Am J Pathol 2014, 184: 1209-18

Agaimy A, Koch M, Lell M, Semrau S, Dudek D, Wachter DL, Knöll A, Iro H, Haller F, Hartmann A. SMARCB1 (INI1)-deficient sinonasal basaloid carcinoma: A novel member of the expanding family of SMARCB1-deficient neoplasms. Am J Surg Pathol 2014, 38(9): 1274-81

Bertz S, Otto W, Denzinger S, Wieland WF, Burger M, Stöhr R, Link S, Hofstädter F, Hartmann A. Combination of CK20 and Ki-67 Immunostaining Analysis Predicts Recurrence, Progression, and Cancer-Specific Survival in pT1 Urothelial Bladder Cancer. Eur Urol 2014, 65(1): 218-26

Tudor CS, Bruns H, Daniel C, Distel LV, Hartmann A, Gerbitz A, Buettner MJ. Macrophages and dendritic cells as actors in the immune reaction of classical Hodgkin lymphoma. PloS One 2014, 9(12): e114345

Geppert CI, Rümmele P, Sarbia M, Langer R, Feith M, Morrison L, Pestova E, Schneider-Stock R, Hartmann A, Rau TT. Multi-colour FISH in oesophageal adenocarcinoma – predictors of prognosis independent of stage and grade. Br J Cancer 2014, 110: 2985-2995


### International Cooperations

Prof. Dr. M. Jasiulionis, University Sao Paulo, Sao Paulo: Brazil

Prof. Dr. S. Jarmalaite, Vilnius University, Vilnius: Lithuania

Prof. Dr. T. Ørntoft, Aarhus University Hospital Skejby, Aarhus: Denmark

Dr. D. Theodorescu, University of Colorado Cancer Center, Denver: USA

Dr. M. Michal, O. Hes, University Plzen: Czech Republic

Dr. P. Real, Dr. N. Malats, CNIO, Madrid: Spain

Prof. Dr. W. EL-Rifai, Vanderbilt University, Memphis: USA

Dr. T. Rau, I. Zlobec, Universität Bern: Schweiz

Prof. Dr. J. Galon, F. Paget, INSERM Paris: France

Dr. E. Zavadova, Institute of Radiation Oncology, Prague: Czech Republic

### Research Equipment

Stratifyer, Automatisiertes DNA-RNA-Isolationsgerät BD Biosciences

Durchflußzytometer, Roche

GS Junior, 454 Sequencing Technology

PALM Laser-Mikrodissektions-Mikroskop, Zeiss

Laser-Mikrodissektions-Mikroskop, Zeiss

Laser Scanning Mikrosko, Decon Science Tec GmbH

Mikroskop Life-cell-Migrationseinheit, Sysmex

Grandmaster, Automatisierte Tissue Microarray-Erstellung, Next-generation Tissue Microarray TMA Grandmaster, 3D-Histech, Sysmex Europe GmbH

Digital Slide Scanner, Panoramic 250 FLASH, 3D-Histech, Sysmex Europe GmbH

# Institute of Pathology

## Division of Nephropathology

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**Research Focus**

- Clinical and experimental nephropathology
- The role of complement activation in the pathogenesis of hypertension and kidney injury due to reduced nephron number
- Cell cycle control in podocytes as a therapeutic target in renal disease
- Pathomechanisms and modulation of impaired angiogenesis and angioadaption in chronic renal failure
- The role of DPP4 in chronic kidney disease and cardiovascular damage
- The role of PAR-2 in hypertensive kidney and heart damage
- Mechanisms of cardiac injury and regeneration
- Role of the receptor GPR126 in heart development
- Cardiac tissue engineering
- Cell cycle control in chronic heart disease
- Terminal differentiation of heart muscle cells

## Structure of the Division

The Division of Nephropathology together with the Chair of General Pathology and Pathological Anatomy constitutes the Institute of Pathology. The Division employs a total of 19 people, five of which are financed by third-party funds. Research is carried out by one postdoc, two Ph.D. students and four technical assistants (TA). Since October 2012, Prof. Dr. F.B. Engel has been holding the new W2-professorship for "Experimental Renal and Cardiovascular Research". He has nine additional employees (seven third-party funded, two Postdocs, three Ph.D. students, one bioengineer, three TA).
The Division of Nephropathology is responsible for the kidney biopsy diagnosis of the UK Erlangen (Department of Medicine 4 and Department of Pediatrics and Adolescent Medicine) and of further 90 external biopsy senders. The kidney biopsy diagnosis is carried out using the latest light-microscopic, immunohistological, electron microscopic, and molecular methods. In this field, there are close links with the corresponding structures of the Institute of Pathology.

## Research

### Clinical and experimental nephropathology

Clinical and experimental cooperations are well established with clinical partners (Departments of Medicine 4 and Pediatrics and Adolescent Medicine) and several 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.

### The role of complement activation in the pathogenesis of hypertension and kidney injury due to reduced nephron number

In cooperation with PD Dr. K. Benz (Department of Pediatrics and Adolescent Medicine), we are especially interested in learning whether a structural malformation of the kidney – using an animal model of low nephron number (GDNF+/– mice) – is pre-conditional for complement activation and pathogenesis of hypertension and kidney diseases.
Funding: Hochdruckliga

### Cell cycle control in podocytes as therapeutic target in kidney diseases

Podocytes are highly specialized glomerular cells which are essential for blood filtration. These cells are terminally differentiated, that means they cannot regenerate or replace damaged podocytes by proliferation. In nearly all kidney diseases a progressive podocyte loss is observed. In addition, injured podocytes re-enter into the cell cycle despite its terminal differentiation, but are unable to divide and die. In this project, we try to inhibit cell cycle progression in podocytes to prevent loss of these cells and progression of kidney disease.
Funding: Emerging Fields Initiative: CYDER

### Pathomechanisms and modulation of impaired angiogenesis and angioadaption in chronic renal failure

This project is performed in collaboration with Prof. Dr. K.F. Hilgers (Department of Medicine 4). Mortality rate is still very high in patients with chronic kidney disease (CKD); it is in fact comparable to that of many cancer patients. Death from cardiac causes is the leading cause of death in these patients. CKD patients show characteristical cardiovascular structural alterations, like left ventricular hypertrophy with reduced myocardial capillary density, increased intercapillary distance, and reduced myocardial ischemia tolerance. Our own data as well as data from the literature indicate that impaired angiogenesis in particular in response to hypertrophy or ischemia plays an important pathophysiological role. Using a well-established animal model of CKD (subtotally nephrectomised rat, SNX), we will investigate mechanisms of CKD-induced impaired angiogenesis.
Funding: IZKF

### The role of DPP4 in chronic kidney disease and cardiovascular damage

In cooperation with Prof. Dr. S. von Hörsten (Division of Experimental Therapeutics), we examine whether the lack or inhibition of dipeptidylpeptidase IV (DPP4) reduces development of CKD and subsequent cardiovascular damage. In a rat model for CKD, we investigate consequences of DPP4 deficiency on disease progression and vascular as well as cardiac damage.
Funding: ELAN-Fond

### The role of PAR-2 in hypertensive kidney and heart damage

Protease activated receptor-2 (PAR-2) is a G-protein coupled receptor that can be activated by numerous serine proteases which were secreted after tissue injury. In this project, we investigate PAR-2 as a potential target for the treatment of inflammatory and fibrotic organ damage. The pathogenetic role of this receptor will be evaluated using PAR-2 deficient and wildtype mice in two different animal models that are suitable to investigate inflammatory as well as pro-fibrotic changes in kidney, heart, and vessels.
Funding: Marohn Foundation

### Mechanism of cardiac injury and regeneration

The problem of cardiomyocyte loss following a heart injury can so far not be corrected by conventional treatment regimen. Zebrafish and newt, however, regenerate many of their organs including heart based on cardiomyocyte proliferation. The working group around Prof. Dr. F.B. Engel tries to identify the mechanisms that regulate cardiomyocyte prolifera-

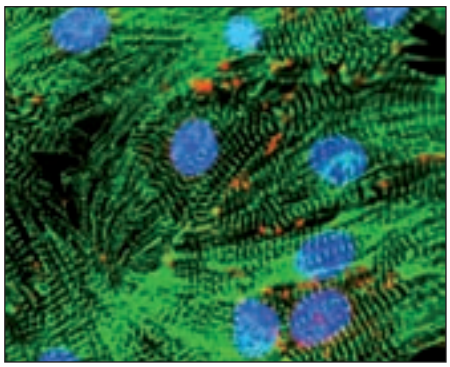
tion during heart development and that allow the zebrafish to regenerate its heart. This knowledge will hopefully result in a therapy for heart failure patients and congenital heart disease.

### Role of the receptor GPR126 in heart development

Having discovered that the adhesion GPCR Gpr126 plays an important role in heart development, it could be shown that Gpr126 is expressed in the endocardium. Adhesion GPCR are characterized by large N-termini and a GPS motif where they are autoproteolytically cleaved into a C-terminal and N-terminal fragment (NTF). Its deletion in mice and zebrafish resulted in markedly reduced cardiac function. Overexpression of various Gpr126 fragments suggested that NTF and CTF have independent functions. These data support a model in which endocardial cells regulate trabeculation of the heart by the binding of NTF-Gpr126 to an unknown receptor on heart muscle cells.
Funding: DFG

### Cardiac tissue engineering

Materials for the generation of artificial heart tissue is tested for tissue replacement therapy. In close collaboration with Prof. Dr. A.R. Boccaccini (Department of Biomaterials, Faculty of Engineering), a novel blend of poly (glycerol sebacate) (PGS) and poly (butylene-co-butylene dilinoleate) (PBS-DLA) was tested. The addition of PBS-DLA to PGS significantly improved the mechanical properties. In addition, the material was characterized by low toxicity and good adhesion properties for heart muscle cells. Thus, it represents a promising biomaterial for cardiac tissue engineering.
Funding: ELAN-Fond



*Analysis of the attachment of heart muscle cells on novel materials for tissue engineering-based therapies.*

### Cell cycle control in chronic heart disease

Chronic heart disease often leads to the re-expression of fetal genes and reactivation of the cell cycle machinery. The Engel group is therefore testing in disease models whether genes that regulate the proliferation of heart muscle cells in embryonic development play a negative role. Pulmonary arterial hypertension (PAH) is a fatal disease; often due to right ventricular heart failure. The Engel group has shown that TWEAK stimulates the proliferation of neonatal heart muscle cells and Fn14, the TWEAK receptor, is highly expressed in PAH. In addition, Fn14 knockout mice exhibited a substantially reduced fibrosis and dysfunction after PAH. Further in vivo and in vitro experiments suggest that Fn14 is an endogenous key regulator of cardiac fibrosis and identify this receptor as a potential new target for therapeutic intervention in heart failure.
Funding: Alexander von Humboldt Foundation

### Terminal differentiation of heart muscle cells

Heart muscle cells of mammals differentiate and become post-mitotic. Therefore, they cannot regenerate their heart by heart muscle cell proliferation as observed in zebrafish. The Engel group has accumulated data for a previously unknown mechanism which could explain the difference in the proliferative properties of mammalian and zebrafish heart muscle cells. In mammals, heart muscle cells lose the integrity of their centrosomes shortly after birth. This loss is coupled with the relocation of various centrosome proteins to the nuclear envelope.
Funding: Emerging Fields Initiative: CYDER

## Teaching

The Division of Nephropathology participates in the teaching curriculum of the Institute of Pathology. In addition, nephropathological conferences with the clinical departments of UK Erlangen and external biopsy senders regularly take place. Furthermore, twice a year a kidney pathology course takes place for both, staff of the UK Erlangen and of external hospitals. Finally, the Division of Nephropathology participates in the teaching curriculum of the Department of Developmental Biology at the Faculty of Science and the training of undergraduate and graduate students in the Department of Biomaterials at the Faculty of Engineering.

### Selected Publications


Novoyatleva T, Schymura Y, Janssen W, Strobl F, Swiercz JM, Patra C, Posern G, Wietelmann A, Zheng TS, Schermuly RT, Engel FB. Deletion of Fn14 receptor protects from right heart fibrosis and dysfunction. Basic Res Cardiol 2013, 108: 325

Goldwich A, Burkard M, Olke M, Daniel C, Amann K, Hugo C, Kurts C, Steinkasserer A, Gessner A. Podocytes are non-hematopoietic professional antigen-presenting cells. Journal of the American Society of Nephrology. JASN 2013, 24: 906-916

Schlote J, Schroder A, Dahlmann A, Karpe B, Cordasic N, Daniel C, Hilgers KF, Titze J, Amann K, Benz K. Cardiovascular and renal effects of high salt diet in GDNF+/- mice with low nephron number. Kidney & blood pressure research 2013, 37: 379-391

Patra C, van Amerongen MJ, Ghosh S, Ricciardi F, Sajjad A, Novoyatleva T, Mogha A, Monk KR, Mühlfeld C, Engel FB. Organ-specific function of adhesion G protein-coupled receptor GPR126 is domain-dependent. Proc Natl Acad Sci U S A 2013, 110: 16898-903

Wang Z, Grigo C, Steinbeck J, von Horsten S, Amann K, Daniel C. Soluble DPP4 originates in part from bone marrow cells and not from the kidney. Peptides 2014, 57: 109-117

Novoyatleva T, Sajjad A, Pogoryelov D, Patra C, Schermuly RT, Enge, FB. FGF1-mediated cardiomyocyte cell cycle reentry depends on the interaction of FGFR-1 and Fn14. FASEB J 2014, 28: 2492-503

# Institute of the History of Medicine and Medical Ethics

## Chair of the History of Medicine

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**Research Focus**

- 200 Years of UK Erlangen, 1815 – 2015
- Galen – Compendium and Catalogue of Galenic Writings
- Receptions of Ancient Psychopathology
- Leprosy and Early Modern Health Policies in Southern German Free Imperial Cities
- Ernst Wilhelm Baader (1892 – 1962), Occupational Medicine and Nazism
- Medical Crime and the Social Practice of Terror – SS-Physicians in Concentration Camps, 1934 – 1945
- NS-"Euthanasia" in Erlangen – "T 4-Aktion" and "B-Kost"
- The German Society for Gynecology under NS
- The Establishment of Medical Applications of X-Ray-Technology: Radiation Poisoning, Radiation Protection, and Radiotherapy in Early 20th Century
- Polish-German Cooperation in the History of Medicine
- History of Hospitals
- Medical History in Objects – Collecting and Displaying Medical Pasts

## Structure of the Institute

The Chair of the History of Medicine and the Professorship for Medical Ethics (see own report) constitute the Institute of the History of Medicine and Medical Ethics. It includes the Forum "Medizin und Menschenrechte" ("Forum on Medicine and Human Rights"), founded in 2006, and the Coordinating Office of the Clinical Ethics Committee. Furthermore, the Institute harbors the Erlangen Medical Collection. In total, the staff of the Institute consists of 18 members, 14 are academic personnel including part-time positions.

## Research

### 200 Years of UK Erlangen, 1815 – 2015

Project managers: Prof. Dr. K.-H. Leven, A. Plöger
Term: 2013 – 2015
Support: UK Erlangen
A historiographical monograph dedicated to the 200 years of its history will be published in autumn 2015 to mark the bicentenary of the UK Erlangen. The book is a chronologic portrayal from its modest beginnings to the modern internationally noted institution, depicting also the UK Erlangen development of branches, important individuals and innovations, and its edificial sprawl. It focuses on the 20th century, including Erlangen medicine during the National Socialism (NS) regime.

### Galen – Compendium and Catalogue of Galenic Writings

Project manager: Prof. Dr. K.-H. Leven
The Greek physician Galenus of Pergamum (129 – approximately 210 AD) figures as the most influential medical author of the Roman imperial period. This research project aims at a comprehensive depiction of Galenism both, in its time of emergence and its impact on medicine in the historical context. Furthermore an annotated catalogue of all remaining Galenic writings is devised (see Meetings).

### Receptions of Ancient Psychopathology

Project manager: Dr. N. Metzger
The look back to ancient medicine and its most illustrious protagonists has been seminal to physicians, their learning and identity for centuries. They have drawn onto ancient texts for orientation, legitimation, and distancing, thus using the ancient for their own purposes. Madness is intertwined like no other medical concept with its cultural background, therefore reception of ancient psychopathology is deeply affected by new medical outlooks, epistemological developments, and cultural surroundings and can be used to line out the changing faces of medicine in history.
This project focuses on reception in Byzantine late antiquity, early modern times, and the 19th century. In all three epochs, fundamental social and epistemological changes left their mark on how physicians read their ancient counterparts. Case studies include the medical encyclopedia of Paulos Nikaios (approximately 7th/9th AD), the early modern receptions of ancient illnesses contributed by physicians to the contemporaneous witchcraft debate (lycanthropy, incubus), and trauma concepts in Byzantine late antiquity and 19th century medicine.

### Leprosy and Early Modern Health Policies in Southern German Free Imperial Cities

Project managers: PD Dr. F. Dross, Dr. A. Kinzelbach
Extensive research has been done on medieval leprosaria; nevertheless, their contextualization with (municipal) health care especially in the 16th century is still deficient. Therefore, this project aims at shedding light on the very beginnings of health care policies in early modern urban communities.

### Ernst Wilhelm Baader (1892 – 1962), Occupational Medicine and Nazism

Project managers: Prof. Dr. K.-H. Leven, P. Rauh
Term: 2011 – 2013
Support: Stifterverband für die Deutsche Wissenschaft and Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin e.V. (DGAUM)
This project evaluated the contribution of E.W. Baader, one of the dominating figures in the field during the times of Weimar Republic, NS, and early Federal Republic of Germany, in relation to its respective cultural and ideological background. The concluding volume was published in May 2013.

### Medical Crime and the Social Practice of Terror – SS-Physicians in Concentration Camps, 1934 – 1945

Project managers: Prof. Dr. K.-H. Leven, P. Rauh
Support: Johannes und Frieda Marohn-Stiftung, DFG-project 2013 – 2016
This project surveys the biographical development of "Schutzstaffel" (SS)-physicians active in German concentration camps (KZ) between 1934 and 1945, focusing on their group-specific characteristics. Consisting of two parts, the study aims at outlining socialization, mentality, and actions, including their role in KZ on the one hand and their subsequent careers in both German states after 1945 on the other hand. In this second part of the project, this well-defined group is employed to methodically analyze – for the first time – how both German states dealt with these people and their criminal past.

### NS-"Euthanasia" in Erlangen – "T 4-Aktion" and "B-Kost"

Project managers: Prof. Dr. K.-H. Leven, Dr. S. Ude-Koeller
Support: Forschungsstiftung Medizin at the UK Erlangen (2014), Staedtler-Stiftung
The so-called "T 4-Aktion" (forced euthanasia) and systematic starvation to death were implemented in Erlangen Heil- und Pflegeanstalt dur-

ing the NZ regime. This interdisciplinary project examines these killings of patients from multiple perspectives, both within its clinical context and the town of Erlangen. Until now unstudied source material will provide the basis for reconstructing both, the (criminal) acts of individuals or institutions and the life stories of their victims.

### The German Society for Gynecology under NS

Project managers: PD Dr. F. Dross, PD Dr. W. Frobenius, Dr. U. Thoms (since 2014)
Under NS, the German Society for Gynecology acted as an agent between the official NS race and health policies, the involved government authorities and party institutions, and their physician members. The society adapted to the changed powers and policies early on. Their presidents functioned as communicational links between government and their members, not only in implementing policies, but in lobbying gynecological interests. Significant sources are the large society conferences in 1933, 1935, 1937, and 1947, and their two publication organs, the Archiv für Gynäkologie and the Zentralblatt für Gynäkologie.

### The Establishment of Medical Applications of X-Ray-Technology: Radiation Poisoning, Radiation Protection, and Radiotherapy in Early 20th Century

Project manager: PD Dr. F. Dross
The curator of the Medical Collection Erlangen was member of the advisory board for the establishment of the Siemens MedMuseum (opened in 2014) at the Siemens Med Archiv (director: D.M. Vittinghoff) and curated the part on radiation protection and radiotherapy.

### Polish-German Cooperation in the History of Medicine

Project manager: PD Dr. F. Dross
Since 2005 the project manager has been board member of the German-Polish Association for the History of Medicine. Main activities are biennial joint conferences and the publication of the conference proceedings.

### History of Hospitals

Project manager: PD Dr. Fritz Dross
The history of hospitals can be addressed as the history of the distribution of medical care via large institutions. They serve as an essential frame - work for modern medicine – the endpoint of a long and intricate development since medieval times. In January 2014, the project manager was elected president of the German Society for the History of Hospitals.

### Medical History in Objects – Collecting and Displaying Medical Pasts

Project manager: PD Dr. Fritz Dross
Support: Universitätsbund Erlangen-Nürnberg
In 2000, the Medical Collection Erlangen was constituted to preserve instruments and devices no longer needed in clinical practice, medical research, and education. Aim is to make this important source for medical historiography accessible to the public.

## Teaching

Medical Terminology (1st term students in Medicine/Dentistry); Querschnittsbereich Q 2 "History, Theory, and Ethics of Medicine" (7th term Medicine) and "History of Science and Ethics" (degree program Molecular Medicine), Querschnittsbereich Q 7 "Medicine and Aging". Medical Terminology introduces students to the specific technical language employed in anatomy and clinical medicine. At the same time it aims at placing medicine in its social and historical context.
History, Theory, and Ethics of Medicine includes lectures dedicated to the basic principles of the medical humanities while the specific skills are imparted in seminars. Teaching methods include text interpretation, discussion of case histories, role play, multimedia presentations, and excursions.
Elective seminars offer further insight into historical and ethical subjects to students with special interest in the medical humanities (elective), such as "Death and Dying in Cultural Perspective" (in collaboration with the Chair of Anatomy I), furthermore "Introduction to methods and objectives of medical historiography". Seminars on selected topics close to current research interests are offered each term, in certain cases in conjunction with the Master Program "Mittelalter- und Renaissance-Studien" and/or colleagues in the Faculty of Humanities, Social Sciences, and Theology. The lecture series "Über den Tellerrand" caters current research topics to a wider audience. Invited external medical historians give insight into their work in the monthly "Medizinhistorische Vortragsreihe".

### Selected Publications


Metzger N. Battling Demons with Medical Authority. Werewolves, physicians and rationalization. In: History of Psychiatry 24 (2013): 341–355

Rauh P, Leven KH. Ernst Wilhelm Baader (1892-1962) und die Arbeitsmedizin im Nationalsozialismus. (= Medizingeschichte im Kontext, Bd. 18). Frankfurt/M., Berlin, Bern: Peter Lang, 2013

Dross F. Hospital / Krankenhaus. In: Europäische Geschichte Online (EGO), hg. vom Leibniz-Institut für Europäische Geschichte (IEG), Mainz 2014-03-20

Metzger N. Railway Spine, Shell Shock and Psychological Trauma. The limits of retrospective diagnosis. In: Trauma and Traumatization in Individual and Collective Dimensions. Insights from Biblical Studies and Beyond, ed. by E.-M. Becker, J. Dochhorn, E. Holt, Göttingen: Vandenhoeck & Ruprecht, 2014: 43–61

Prüll L, Rauh P (Hg). Krieg und medikale Kultur. Patientenschicksale und ärztliches Handeln in der Zeit der Weltkriege 1914-1945, Göttingen: Wallstein 2014

Ude-Koeller S. "ein bißchen verkrüppelt, aber doch der Alte geblieben." Kriegsinvalide im Ersten Weltkrieg. In: Zeitschrift für medizinische Ethik 60 (2014): 259-269


### Meetings and International Training Courses

19. – 22. 09.2013: German – Polish bilateral conference, topic: Medicine and Language – the Language of Medicine

3. – 4.10.2013: Training course of the German Professional Society of Medical Historians, topic: Medicine in Antiquity

17. – 19.10.2013: International symposium, topic: Galen of Pergamon. Medicine and Philosophy in Roman Imperial Times, Erlangen

10. – 12.10.2014: 50 Years of the German Society for the History of Hospitals Münster

# Institute of the History of Medicine and Medical Ethics

## Professorship for Medical Ethics

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**Research Focus**
- Clinical Ethics and Ethics Consultation
- Medicine and Human Rights
- Human Rights in Healthcare (EFI Project)
- Global Health Ethics and Philosophy of Medicine

## Structure of the Department

The Professorship for Medical Ethics together with the Chair of the History of Medicine constitutes the Institute of the History of Medicine and Medical Ethics. It includes the Forum Medicine and Human Rights ("Forum Medizin und Menschenrechte"), founded in 2006, and the Coordinating Office of the Clinical Ethics Committee. Furthermore, the Institute harbors the Erlangen Medical Collection. In total, 18 employees work at the Institute, of which 16 are academic personnel with ten in part-time positions. Chair and Professorship cooperate in joint research projects on history and contemporary history of medical ethics (e.g. medicine in NS-Germany, history of the Faculty of Medicine Erlangen, medical ethics in Germany after 1945). Ten academic book series are being edited at the Professorship for Medical Ethics and 20 doctoral theses are being supervised.
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 deal with 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, euthanasia, terminal care). 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 field "Medicine and Human Rights" deals with several aspects of the relationships between human rights, medicine, and the biological sciences ("dual obligations" of physicians, health care for migrants and "Sans Papiers", female genital mutilation, torture and medicine etc.). This topic is unique at a Faculty of Medicine in Germany. It is grounded institutionally in the "Forum Medicine and Human Rights".
The field "Global Health Ethics and Philosophy of Medicine" covers theoretical questions concerning the concept "disease" and medical ethical issues with respect to the increase of the life span and the enhancement of cognitive and emotional capacities.

## Research

### Clinical Ethics and Ethics Consultation

Project managers: Prof. Dr. A. Frewer, PD Dr. L. Bergemann, Dr. D. Dörr, L. Fröhlich-Güzelsoy, Dr. K. Krása, Dr. Dr. D. Preuß, A. Koberg
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".
A further field of research 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.

### Medicine and Human Rights

Project managers: Prof. Dr. A. Frewer, H. Furtmayr, M. Mylius, Dr. S. Kolb, Dr. J. Graf, Dr. K. Krása, W. Bornschlegl
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 investigated 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 "prophylaxis" 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 is being organized and the academic book series "Medicine and Human Rights" is being edited.

### Human Rights in Healthcare (EFI Project)

Project managers: Prof. Dr. A. Frewer (in cooperation with Prof. Dr. H. Bielefeldt, UN Special Rapporteur), Dr. M. Schmidhuber, F. Scheller
The Emerging Fields 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 such 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 project 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

Project managers: Prof. Dr. A. Frewer, Dr. A. Reis, Dr. M. Schmidhuber, Dr. S.L. Sorgner
This 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, an academic book series is being edited: "Ars moriendi nova".

## Teaching

The Institute of the History of Medicine and Medical Ethics is responsible for teaching the following courses according to medical curriculum: Medical Terminology (1st term students in Medicine/Dentistry); Querschnittsbereich (cross-sectional area) Q 2 "History, Theory, and Ethics of Medicine" (7th term Medicine) and "History of Science and Ethics" (degree program in Molecular Medicine). Furthermore, it contributes to cross-sectional area Q 7 "Medicine and Aging" in the section concerned with old age in past and present.

Medical Terminology introduces students to the specific technical language employed in anatomy and clinical medicine; this includes basic understanding of Latin grammar and vocabulary necessary for anatomical terms, furthermore Greek for clinical usage. At the same time it aims at placing medicine in its social and historical context.

History, Theory, and Ethics of Medicine includes lectures dedicated to the basic principles of the medical humanities while the specific skills are imparted in seminars. In these seminars, small groups of students are made familiar with current questions, methods, and approaches in the field. They aim at sharpening the student's eye for social, ethical, and institutional problems. Teaching methods include text interpretation, discussion of case histories, role play, multimedia presentations, and excursions.

In addition, courses in ethics and interpersonal skills are procured as part of the "Introduction to Clinical Medicine". Courses range from "Skills in Ethical Communication" over "Breaking Bad News" and "Speaking about Death and Dying", "Intercultural Communication" to "Medical Acting on Borders", some of those featuring simulated patients to practice difficult communicative situations.

In cooperation with the Faculty of Humanities, Social Sciences, and Theology, courses on medical ethics and bioethics are being offered. Furthermore, a lecture course on "Medicine, Ethics, and Human Rights" and an interdisciplinary series of presentations on questions concerning the history and ethics of medicine entitled "Jenseits des Tellerrands" ("Beyond one's own Nose") are being offered.

### Selected Publications


Frewer A, Schmidt K, Bergemann L. (Hrsg.) Fehler und Ethik in der Medizin. Neue Wege für Patientenrechte. JEK 2013, 6. Würzburg

Frewer A, Bruns F. (Hrsg.) Klinische Ethik. Konzepte und Fallstudien. 2013 Freiburg

Emrich IA, Fröhlich-Güzelsoy L, Bruns F, Friedrich B, Frewer A. Clinical Ethics and Patient Advocacy. The Power of Communication in Health Care. HEC Forum 2014, 26(2): 111-24

Frewer A, Reis A, Bergemann L. (Hrsg.) Gute oder vergütete Behandlung? Ethische Fragen der Gesundheitsökonomie. JEK 2014, 7. Würzburg

Frewer A, Schmidt U. (Hrsg.) Forschung als Herausforderung für Ethik und Menschenrechte. Jahrbuch Medizin-Ethik 27, 2014, Köln

Erices R, Frewer A, Gumz A. Testing Ground GDR: Western Pharmaceutical Firms conducting Clinical Trials Behind the Iron Curtain. J Med Ethics 2014 Oct 23. pii: medethics-2013-101925


### International Cooperations

Dr. A. Reis, World Health Organization, Geneva: Switzerland

Prof. U. Schmidt, Ph.D., Rutherford College, University of Kent, Canterbury: UK

### Meetings and International Training Courses

29.05.2013: Workshop of the Clinical Ethics Committee and the Professorship for Ethics in Medicine: "Warte-'Listen'. Gerechtigkeit und Ethik in der Medizin", Erlangen

12. – 13.09.2013: International Brocher Conference "Research within Bounds" (Geneva). Professorship for Medical Ethics in Cooperation with University of Kent (GB) and University of Neuchâtel (SUI), Geneva

02.11.2013: 12. "Ethiktag" of the Clinical Ethics Committee and the Professorship for Ethics in Medicine: "Good or reimbursed treatment?" – "Gute oder vergütete Behandlung?", Erlangen

26.04.2014: Kick-Off Workshop of the EFI-Project "Human Rights in Healthcare", Nürnberg

21.05.2014: Workshop of the Clinical Ethics Committee and the Professorship for Ethics in Medicine in Cooperation with SAKI/BMBF/EFI: "Der überwachte Patient", Erlangen

18.10.2014: 13. "Ethiktag" of the Clinical Ethics Committee and the Professorship for Ethics in Medicine: "Dementia and Ethics in Medicine", Erlangen

21. – 22.11.2014: Conference of the EFI Research Group "Human Rights in Healthcare": Autonomie und Menschenrechte am Lebensende, Erlangen


# Nikolaus-Fiebiger-Center of Molecular Medicine

## Chair of Experimental Medicine I (Molecular Pathogenesis Research)

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**Research Focus**
- Cellular Plasticity: a driving force for cancer progression and other disease processes
- The role of fibulin-4 in the mechanostability of the musculoskeletal connective tissue
- Molecular mechanisms of endochondral ossification and skeletal development

## Structure of the Institute

The Chair of Experimental Medicine I is located at the NFZ and is, together with the Chair of Experimental Medicine II, responsible for the organization and administration of the Center. In 2013 – 2014, about seven scientists and technical staff were involved in research and teaching at the Chair of Experimental Medicine I, three of them supported by grants. Prof. Dr. D.N. Müller held the Chair from April 2011 until October 2012. Prof. Dr. J. Behrens acted as temporary chairman after Prof. Dr. D.N. Müller left until April 2014. Since May 2014, Prof. Dr. T. Brabletz has been holding the Chair of Experimental Medicine I. Until the end of 2014, there was an increase in staff members with the result that eight persons are presently working in Prof. Dr. T. Brabletz' group. In addition, Prof. Dr. K. von der Mark (retired) continued to lead a research group financed by grants and participated in teaching molecular medicine. In a translational approach, the Brabletz lab focuses on cancer research with the aim to develop new diagnostic and prognostic tools as well as novel therapeutic strategies.

## Research

### Cellular Plasticity: a driving force for cancer progression and other disease processes

Project managers: Dr. M. Stemmler, Dr. S. Brabletz, Prof. Dr. T. Brabletz

It became evident that cancer cells are highly adaptive to the demanding environmental conditions – a property which can be summarized as aberrant cellular plasticity. In addition to accumulation of genetic alterations, aberrant cellular plasticity is now considered as a major driving force for cancer progression towards a therapy resistant, metastatic disease, as well as for the pathogenesis of other diseases. Our group has discovered one underlying molecular mechanism controlling cellular plasticity: A phenotypic switch between a stemness/EMT state and a differentiated state which is exerted by a double-negative feedback loop between the EMT-activator ZEB1 and the miR-200 family of microRNAS, the so-called ZEB1/miR-200 feedback loop. Future work will address the role of cellular plasticity in cancer and other diseases and explore it as a target of therapeutic intervention. We will:
- investigate the role of the ZEB1/miR-200 feedback loop in cancer initiation and metastasis;
- investigate the microenvironment as a modulator of cellular plasticity in cancer;
- identify novel mechanisms underlying cellular plasticity;
- explore the translational and clinical relevance by developing novel treatment strategies;
- investigate the role of cellular plasticity in other disease processes, such as organ fibrosis, kidney diseases, inflammation.

To address our research questions, we use molecular, epigenetic, and genetic in vitro approaches, cell, and animal models (e.g. mouse tumor models and conditional knockout and transgenic models of plasticity-related genes), as well as human tumor material and patients' data.

### The role of fibulin-4 in the mechanostability of the musculoskeletal connective tissue

Project managers: Dr. T. Sasaki, Prof. Dr. K. von der Mark

Fibulin-4 is a 50 kDa extracellular matrix protein which is essential – together with elastin and fibrillin – for assembly and function of elastic fibers of the cardiovascular, musculoskeletal, and lung elastic tissues. Patients with a recessive missense mutation in fibulin-4 display not only defects in elastogenesis resulting in cutis laxa and aneurisms, but also in multiple bone fractures at birth; two patients showed arachnodactyly. Fibulin-4 deficiency in mice is perinatally lethal due to cardiovascular and lung abnormalities and leads to joint contractures during fetal development. The goal of this DFG-funded project was to clarify the role of fibulin-4 in connective tissue development and homeostasis. The skeletal phenotype of fibulin-4 deficient mouse embryos was analyzed using morphological, immunohistochemical, and in situ hybridization techniques. Surprisingly, in fibulin4 deficient mice the size of collagen fibrils and collagen crosslinking was affected, explaining the joint contracture on fibulin-4 null mice. In order to clarify the genotype-phenotype relation of fibulin-4 mutations, several mutagenized recombinant proteins with clinically relevant fibulin-4 mutations were prepared. Most mutations, in particular those affecting calcium binding sites, affected secretion, matrix assembly and enhanced resistance against proteinases, resulting in fibulin deficiency. Furthermore, multiple interactions with collagens, fibrillin and elastin, as well as with lysyloxidases and LTBP were impaired, explaining the defect in collagen crosslinks in fibulin4 null mice. Molecular dynamic simulations were performed which provided new insight into the structure of the fibulin molecule and the conformational instability of mutations affecting the calcium binding site.
The proposed studies will provide novel insights into the role of fibulin-4 in the assembly and stability of elastic fibers as well as in the development and homeostasis of cardiovascular tissue.

### Molecular mechanisms of endochondral ossification and skeletal development

Project manager: Prof. Dr. K. von der Mark

During development of the vertebral skeleton, chondrocytes shape the cartilage models of the subsequent bony elements of the extremities, ribs and the spine. Chondrocytes grow and differentiate rapidly and are replaced by bone cells in a complex process called "endochondral ossification". For reproducible skeletal growth, a precise spatially and temporally coordinated control of endochondral ossification is an absolute requirement. Similar processes also occur during fracture callus healing and development of osteophytes in osteoarthritic joints. Therefore, elucidation of factors and mechanisms involved in endochondral ossification is essential not only for our understanding of the regulation of normal skeletal growth and skeletal dysplasias, but also for the development of new tools in the diagnosis and therapy of joint degeneration, fracture healing, and cartilage and bone repair. The analysis of these factors by means of molecular biological techniques, cell and organ culture systems, and transgenic mouse models is currently the major focus of a DFG-funded research project.

The development of a collagen10-specific targeting vector for recombination into BAC (bacterial artificial chromosomes) allowed the specific overexpression or deletion of genes in hypertrophic chondrocytes. Mating BACCol10-Cre deleter mice to conditional β-catenin knockout mice (Prof. Dr. R. Kemler, Max-Planck-Institute Freiburg) resulted in transgenic mice lacking trabecular bone in the subchondral zone of the diaphysis. This deficiency was due to enhanced RANKL activity stimulating osteoclast differentiation in β-catenin deficient chondrocytes.

An unexpected finding resulting from genetic lineage tracing studies with BACCol10;Cre induced YFP-reporter gene expression in transgenic mice provided new insight into the mechanism of cartilage – bone conversion in endochondral ossification. According to general understanding, the chondrocyte lineage terminates with the elimination of late hypertrophic cells by apoptosis in the growth plate. In our cell tracking studies, however, we demonstrated that hypertrophic chondrocytes can survive beyond "terminal" differentiation and give rise to a progeny of osteoblasts participating in endochondral bone formation. In searching for transitory cells between hypertrophic chondrocytes and trabecular osteoblasts, we identified by confocal microscopy a novel, small reporter gene positive cell type with mitotic activity in the lower hypertrophic zone at the chondro-osseous junction. We propose that these cells mark the initiation point of a second pathway giving rise to endochondral osteoblasts, alternatively to perichondrium derived osteoprogenitor cells. These findings add to current concepts of chondrocyte-osteocyte lineages and give new insight into the complex cartilage-bone transition process in the growth plate.

## 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. Special lectures, including tumor biology and oncology, molecular mechanism of cell differentiation, and development, cell-cell and cell-extracellular matrix interactions, are given.

### Selected Publications


Brabletz T, Lyden D, Steeg PS, Werb Z. Roadblocks to translational challenges on metastasis. Nat Med 2013, 19: 1104-9

Siebzehnrübl F, Silver DJ, Tugertimur B, Deleyrolle LP, Siebzehnrübl D, Sarkisian MR, Devers KG, Yachnis AT, Kupper MD, Neal D, Nabilsi NH, Kladde MP, Suslov O, Brabletz, S, Brabletz T Reynolds BA, Steindler DA. The ZEB1 pathway links glioblastoma initiation, invasion and chemoresistance. EMBO Mol Med 2013, 5: 1196-212

Vannier C, Mock C, Brabletz T, Driever W. ZEB1 regulates E-Cadherin and Epcam expression to control cell behavior in early zebrafish development. J Biol Chem 2013, 288: 18643-59

Golovchenko S, Hattori T, Hartmann C, Gebhardt M, Gebhard S, Hess A, Pausch F, Schlund B, von der Mark K. Deletion of beta catenin in hypertrophic growth plate chondrocytes impairs trabecular bone formation. Bone 2013, 55(1): 102-12

Puisieux A, Brabletz T, Caramel J. Oncogenic roles of EMT-inducing transcription factors. Nat Cell Biol 2014, 16: 488-94

Zhou X, von der Mark K, Henry S, Norton W, Adams H, de Crombrugghe B. Chondrocytes transdifferentiate into osteoblasts in endochondral bone during development, postnatal growth and fracture healing in mice. PLoS Genet 2014, 10(12): e1004820


### International Cooperations

Prof. Dr. G. Goodall, University of Adelaide: Australia

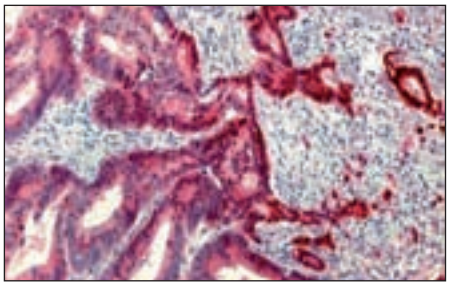
Prof. Dr. R. Fodde, Erasmus University, Rotterdam: The Netherlands

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

Prof. Dr. C. Hartmann, Institute of Molecular Pathology, IMP, Vienna: Austria

Prof. T. Hattori, Graduate School of Dentistry and Medicine, Okayama University, Okayama: Japan

Prof. B. de Crombrugghe, MD, Anderson Cancer Center, Texas University, Houston: USA



*Plasticity of tumor cells in colon cancer.*

# 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 conductin as a negative Wnt regulator
- Tumor suppressor APC
- Functional genomics of renal cell carcinoma

## Structure of the Institute

The Chair of Experimental Medicine II (Molecular Oncology) is situated at the NFZ and exclusively devoted to basic medical research. Staff members include post-docs, Ph.D. students, technical staff (all with a background in cellular and molecular biology), and secretarial assistance. Our main goal is to investigate the molecular mechanisms of tumor development and progression by cell and molecular biological methods to find new ways for diagnosis, prognosis, and therapy.

## Research

### Molecular oncology of Wnt signaling

The Wnt signaling pathway regulates various processes during embryonic development and can lead to cancer. Wnts 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 which consists of the scaffold component 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 conductin or mutations 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. During the report period, we have further characterized the Amer proteins which are APC binding partners identified by our group and act as regulators of Wnt signaling and the cytoskeleton. We also found that the capacity of conductin/Axin2 as negative feedback factor in Wnt signaling is based on its insensitivity to upstream signaling. We have further explored the structure-function relationship of the tumor suppressor APC in Wnt signaling.

### Amer proteins

Project manager: Dr. K. Brauburger

APC membrane recruitment (Amer) family proteins, Amer1and Amer2, are binding partners of the APC tumor suppressor protein and act as negative regulators in the Wnt signaling cascade. So far, nothing has been known about the third member of the family, Amer3. We found that Amer3 binds to the armadillo repeat domain of APC, similarly to Amer1 and Amer2. Amer3 also binds to the Wnt pathway regulator conductin/axin2. Furthermore, we identified Amer1 as binding partner of Amer3. Whereas Amer1 and Amer2 are linked to the plasma membrane by an N-terminal membrane localization domain, Amer3 lacks this domain. Amer3 localizes to the cytoplasm and nucleus of epithelial cells, and this is dependent on specific nuclear import and export sequences. Functionally, exogenous Amer3 enhances the expression of a β-catenin/T-cell factor-dependent reporter gene. Knockdown of endogenous Amer3 reduces Wnt target gene expression in colorectal cancer cells. Thus, Amer3 acts as an activator of Wnt signaling, in contrast to Amer1 and Amer2 which are inhibitors, suggesting a non-redundant role of Amer proteins in the regulation of this pathway. Our data, together with those of previous studies, provide a comprehensive picture of similarities and differences within the Amer protein family.

### Role of conductin as a negative feedback regulator of Wnt signaling

Project managers: Dr. M. Hadjihannas, 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. We found that axin and conductin differ in their functional interaction with the upstream Wnt pathway component Dvl. Conductin shows reduced binding to Dvl2 as compared to axin, and degradation of β-catenin by conductin is only poorly blocked by Dvl2. We propose that insensitivity to Dvl is an important feature of the role of conductin as a negative feedback regulator of Wnt signaling.

### Tumor suppressor APC

Project manager: Dr. J. Schneikert

Truncating mutations affect the APC gene in most cases of colon cancer, resulting in the stabilization of β-catenin and uncontrolled cell proliferation. We found that colon cancer cell lines express also the paralog APC-like (APCL or APC2). RNA interference revealed that APCL controls the level and/or the activity of β-catenin, but it is less efficient and binds less well to β-catenin than APC, thereby providing one explanation as to why the gene is not mutated in colon cancer. APCL down-regulates the β-catenin level despite the lack of the 15R region known to be important in APC. Using RNA interference and domain swapping experiments, we showed that APCL uses the 15R of truncated APC to target β-catenin for degradation, in a process likely involving heterodimerization of the two partners.

### Functional genomics of renal cell carcinoma

Project managers: Dr. I. Wacker, Dr. M. Sachs

Activin B belongs to the TGFβ family of growth factors and is upregulated in clear cell renal cell carcinoma cells by hypoxia inducible factors. Expression of Activin B is required for tumor growth in vivo and tumor cell invasion in vitro. We found that activation of RhoA signaling counteracts Activin B mediated disassembly of actin stress fibers, mesenchymal cell morphology and invasiveness, whereas inhibition of RhoA rescues these effects in Activin B knockdown cells. Conversely, Activin B inhibits RhoA signaling suggesting that there is an antagonistic connection between both pathways. In addition we found that Rac1 plays an opposite role to RhoA, i.e. activation of Rac1 initiates loss of actin stress fibers, promotes a mesenchymal cell morphology, and induces invasion in Activin B knockdown cells, whereas inhibition of Rac1 abolishes these Activin B effects. Collectively, our data provide evidence that reduction of RhoA signaling by Activin B together with persistent Rac1 activity is a prerequisite for inducing

an invasive phenotype in clear cell renal cell carcinoma.

## Teaching

Training in cell biology for students of the degree program Molecular Medicine in cooperation with the Chair of Experimental Medicine I and the Division of Experimental Surgery.

### Selected Publications


Schneikert J, Vijaya Chandra SH, Ruppert JG, Ray S, Wenzel EM, Behrens J. Functional comparison of human adenomatous polyposis coli (APC) and APC-like in targeting catenin for degradation. PloS one 2013, 8: e68072

Brauburger K, Akyildiz S, Ruppert JG, Graeb M, Bernkopf DB, Hadjihannas MV, Behrens J. Adenomatous polyposis coli (APC) membrane recruitment 3, a member of the APC membrane recruitment family of APC-binding proteins, is a positive regulator of Wnt-catenin signaling. The FEBS journal 2014, 281: 787-801

Knaup KX, Monti J, Hackenbeck T, Jobst-Schwan T, Klanke B, Schietke RE, Wacker I, Behrens J, Amann K, Eckardt KU, Warnecke C, Wiesener MS. Hypoxia regulates the sperm associated antigen 4 (SPAG4) via HIF, which is expressed in renal clear cell carcinoma and promotes migration and invasion in vitro. Mol Carcinog 2014, 53: 970-978

Kriz V, Pospichalova V, Masek J, Kilander MB, Slavik J, Tanneberger K, Schulte G, Machala M, Kozubik A, Behrens J, Bryja V. -arrestin promotes Wnt-induced low density lipoprotein receptor-related protein 6 (Lrp6) phosphorylation via increased membrane recruitment of Amer1 protein. J Biol Chem 2014, 289: 1128-1141

Schneikert J, Ruppert JG, Behrens J, Wenzel EM. Different Roles for the axin interactions with the SAMP versus the second twenty amino acid repeat of adenomatous polyposis coli. PloS one 2014, 9: e94413

Wacker I, Behrens J. Activin B antagonizes RhoA signaling to stimulate mesenchymal morphology and invasiveness of clear cell renal cell carcinomas. PloS one 2014, 9: e111276


### International Cooperations

Dr. V. Bryja, University of Brno, Brno: Czech Republic

Dr. E. Wenzel, The Norwegian Radium Hospital, Oslo: Norway

### Research Equipment

Dako Cytomation, MoFlo – cell sorter Applied Biosystems

# Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

## Chair of Orthopedics and Orthopedic Surgery

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**Research Focus**
- Radiostereometric analysis (RSA) for quality control in total hip and knee arthroplasty
- Neuromuscular disorders
- Computer assisted surgery of the hip joint
- Computertomography-assisted periprosthetic osteodensitometry after total hip arthroplasty (THA)

## Structure of the Department

Five medical doctors work in the Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH. The research is accomplished by two postdoctorate medical doctors, 50 graduate students, and two study nurses.

In the endoprosthesis working group, apart from the standardized clinical and radiological long-term investigations for quality control after navigated and non-navigated total hip and knee surgery, periprosthetic bone density measurements are accomplished by means of computer tomography (CT)-assisted osteodensitometrie and radiostereometric analysis (RSA) for the evaluation of the migration pattern of the prostheses. The influence of navigation, the prosthesis design, and the prosthesis coating on the longevity of the implant is investigated by these procedures.

The research group for neuromuscular disorders is engaged in the study and evaluation of conservative and operative treatment in children and adult patients with neuromuscular disorders (anterior horn cell diseases, spinal muscular atrophies, post polio syndrome, muscular dystrophies).

The common aim of research in care for patients with cerebral palsy is the evaluation of results of botulinum toxin therapy and the optimization of orthopedic treatment strategies to improve the quality of life of these patients.

The clinical focuses of our Department are:
- Total hip-, knee-, and shoulderarthroplasty,
- spine surgery,
- pediatric orthopedics,
- foot surgery,
- tumorsurgery,
- arthroscopic operations.

## Research

### Radiostereometric analysis (RSA) for quality control in total hip and knee arthroplasty

Project managers: Prof. Dr. R. Forst, Dr. S. Sesselmann

Recent studies lead to the conclusion that a measurement of migration within the first two years forms a basis for predicting the long-term outcome of hip and knee arthroplasty components when considered separately. The quality control is achieved with thorough documentation and precise analysis of fixation.

Measurements on conventional radiographs can have an accuracy of 1 – 5mm and 1° – 6° depending on the technique employed, the anatomic region investigated, and the number of examiners. RSA has proven to be an accurate and safe method to objectify skeletal kinematics. RSA is based on radiographic examinations of calibration cages and object markers implanted in the skeleton. Accurate measurement of radiographs and computer-assisted calculation can provide a three-dimensional motion analysis. RSA can be performed with an accuracy of 10 – 250 μm and 0.03° – 0.6°. Altogether, 200 patients have been supervised with RSA after total hip replacement in Erlangen since 1998. The following examinations are carried out with these clients in different studies:

Measuring of
- migration of polyethylene cups after bone grafting and reinforcement of acetabular ring with hook for severe acetabular dysplasia,
- initial stability of acetabular components with alumina and polyethylene liner in a comparison essay,
- migration of cemented femoral components into dependence of various cementing techniques in a comparison essay,
- migration of uncemented femoral components after early load transfer.

Worldwide unique knee endoprostheses completely made of ceramics are being analyzed in experimental RSA studies. These RSA studies are the first ones analyzing metal-free implants. Another novelty is the assessment of the femoral component of an artificial knee and RSA analyses using the lateral projection of the knee.

### Neuromuscular disorders

Project managers: 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, 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 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 of the FAU, 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 are examined.

### Computer assisted surgery of the hip joint

Project managers: Prof. Dr. R. Forst, PD Dr. L. Müller

The aim of this study is to develop a navigation system for total hip arthroplasty and to use it for the surgery process as well as to test the accuracy of the system with integrated modules. The system works with three-dimensional CT-data. The data received are used for the virtual positioning of the implant preoperatively. Intraoperatively, the navigation system compares the virtual data with the surgical view to achieve an exact position of the implant. The preoperative CT is then compared with a new postoperative CT to evaluate the accuracy of the implantation. Postoperatively, osteointegration of the implant

is analyzed using CT-osteodensitometry. Thus for all steps (planning, surgery, and evaluation) of computer assisted surgery, highly precise measurements are conducted which allow an exact comparison of the received data. 50 patients will be analyzed.

### Computertomography-assisted periprosthetic osteodensitometry after total hip arthroplasty (THA)

Project managers: Prof. Dr. R. Forst, PD Dr. L. Müller

The reaction of the bone which occurs after THA is important for the stability of the implant and thus the long term prognosis. This study was designed to analyze the changes of femoral and periacetabular bone after THA, introducing a novel method of CT-assisted bone density measurement in vivo. A special software tool is used (CAPPA postOP, CAS Innovations AG Erlangen) which allows for a separate view of femoral and acetabular bone. CT-investigations are performed ten days, one, three, five, and ten years post-operatively. Cortical and cancellous bone density as well as bone area and bone-implant contact are measured. Bone density measurements are undertaken in respect to fixation methods (cemented/uncemented), coating (e.g. hydroxyapatite), and design (collum femoris preserving/standard).

## Teaching

Beside the traditional teaching forms (main lecture and practical courses), hospitations and fellowships can be undertaken anytime.

### Selected Publications


Schilling L, Forst R, Forst J, Fujak A. Orthopaedic Disorders in Myotonic Dystrophy Type 1: descriptive clinical study of 21 patients. BMC Musculoskelet Disord 2013, 14: 338

Fujak A, Raab W, Schuh A, Richter S, Forst R, Forst J. Natural course of scoliosis in proximal spinal muscular atrophy type II and IIIa: descriptive clinical study with retrospective data collection of 126 patients. BMC Musculoskelet Disord 2013, 14: 283

Wierer T, Forst R, Mueller LA, Sesselmann S. Radiostereometric migration analysis of the Lubinus SP II hip stem: 59 hips followed for 2 years. Biomed Tech (Berl) 2013, 58(4): 333-41

Sumer J, Schmidt D, Ritt P, Lell M, Forst R, Kuwert T, Richter R. SPECT/CT in patients with lower back pain after lumbar fusion surgery. Nucl Med Commun 2013, 34(10): 964-70

Haaker G, Forst J, Forst R, Fujak A. Orthopedic management of patients with Pompe disease: a retrospective case series of 8 patients. ScientificWorldJournal 2014, 2014: 963861

Mauerer A, Lange B, Welsch GH, Heidenau F, Adler W, Forst R, Richter RH. Release of Cu2+ from a copper-filled TiO2 coating in a rabbit model for total knee arthroplasty. J Mater Sci Mater Med 2014, 25(3): 813-21


### International Cooperations

Institute Duchenne de Boulogne, Poitiers: France

RSAcore, Department of Orthopaedics, LUMC, Leiden: The Netherlands

# Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

## Division of Orthopedic Rheumatology

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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

The Division of Orthopedic Rheumatology is an independent institution of the FAU which is associated with the Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH. Clinical activities focus on the treatment of patients with degenerative and inflammatory joint diseases. The Head of the Division is also speaker of the Erlangen Arthritis Center which is an interdisciplinary association of physicians treating these patients.
Clinical research activities concentrate on the evaluation of surgical treatments. Of interest are preventive procedures, like synovectomies. Comparing joint replacements in patients with degenerative and inflammatory joint diseases will help to identify different preoperative findings, different intraoperative challenges as well as long term patients´ satisfaction. Another focus of basic research are the mechanisms of induction and progression of osteoarthritis.

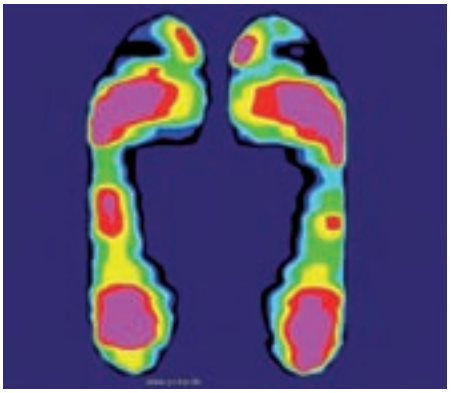
## Research

### Arthroscopic synovectomy

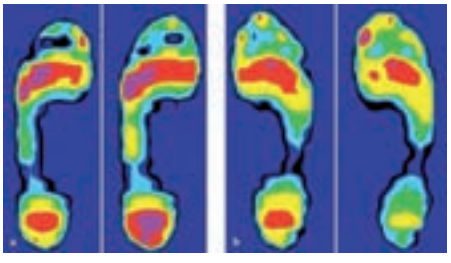
Project managers: Prof. Dr. H.-D. Carl, Prof. Dr. B. Swoboda
Clinical studies investigated the effect of arthroscopic synovectomies in patients with rheumatoid arthritis. Arthroscopic synovectomies of the knee joint were combined with a radiosynoviorthesis. The long-term effect of this procedure was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

### Dynamic pedobarography

Project managers: Prof. Dr. H.-D. Carl, Dr. T. Hotfiel
Dynamic pedobarography has been established as a tool to assess plantar foot loading. This method was applied for the following projects:
- Implementation of a neutral shoe for a standardized comparison of sensor loaded insoles and a platform;
- Compliance of total hip and total knee arthroplasty patients to limited weight bearing;
- Assessment of foot loadings in male adult and adolescent soccer players;
- Evaluation of orthotic devices intended to relief foot loadings.



*The figure illustrates the mean peak pressure values (kPa) of an elite male soccer player and demonstrates asymmetric midfoot load as a possible risk factor for metatarsal stress fractures.*



*Increase of plantar pressure in case of knee joint restriction of the contralateral leg with 45° extension lag (right side) in comparison to free range of motion (left side).*

### 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. First and foremost, the long-term treatment results are observed in these different patient groups. The main focus of this work is knee replacement.

### Mechanisms of chondrocyte differentiation and endochondral ossification

Project manager: PD Dr. K. Gelse
The identification of the mechanisms of chondrocyte differentiation and endochondral ossification is one central issue to establish novel strategies for cartilage repair and osteoarthritis. Comparative whole-genome gene expression analyses between transient osteophytic cartilage and permanent articular cartilage identified pigment epithelium-derived factor (PEDF) as one of the most differentially expressed genes between these two cartilage tissues. PEDF is particularly expressed in terminally differentiated chondrocytes within the growth plate, osteophytes and repair cartilage. In chondrocytes, PEDF stimulates the expression of cartilage-degrading enzymes (in particular MMP13) and also induced apoptosis by Fas ligand (FasL). These mechanisms indicate that PEDF is importantly involved in the process of endochondral ossification. Therefore, PEDF could represent an interesting therapeutic tool to promote ossification and bone healing, whereas the inhibition of the PEDF-pathway may stabilize in a favorable manner the chondrocyte phenotype in cartilage repair tissue.

## Teaching

Staff of the Division of Orthopedic Rheumatology is active in the curriculum for general orthopedics. Specialized lectures are offered on problems of arthritis surgery and the basics of osteoarthritis induction and progression.
Students are welcome to visit us when treating ambulant patients or in the operation room when doing surgery on rheumatoid patients.

### Selected Publications

Klinger P, Beyer C, Ekici A, Carl H.D., Schett G, Swoboda B, Hennig F, Gelse K. The transient chondrocyte phenotype in human osteophytic cartilage: A Role of Pigment Epithelium-Derived Factor? Cartilage 2013, 4: 249-255

Kluger AK, Carl HD, Jendrissek A, Swoboda B, Hotfiel T. Introduction of a neutral shoe to assess reference values for dynamic pedobarography. Biomed Tech (Berl) 2014, 59(3): 213-7

Hahn T, Carl HD, Jendrissek A, Brem M, Swoboda B, Rummel P, Pauser J. Assessment of plantar pressure in hindfoot relief shoes of different designs. J Am Podiatr Med Assoc 2014, 104(1): 19-23

Carl HD, Pauser J, Swoboda B, Jendrissek A, Brem M. Soccer boots elevate plantar pressures in elite male soccer professionals. Clin J Sport Med 2014, 24(1): 58-61

Reiss L, Stolle J, Carl HD, Swoboda B. [Recovery of knee function after total knee arthroplasty: different outcomes in patients with osteoarthritis and rheumatoid arthritis]. Z Rheumatol 2014, 73(6): 559-64

## International Cooperations

Prof. Dr. T. Kirsch, Ph.D., Musculoskeletal Research Center NYU Hospital for Joint Diseases, New York City: USA

## Meetings and International Training Courses

22.06.2013: "Aktuelles aus internistischer und orthopädischer Rheumatologie", Waldkrankenhaus St. Marien, Erlangen

19.07.2014: "Aktuelles aus internistischer und orthopädischer Rheumatologie", Waldkrankenhaus St. Marien, Erlangen

# Institute for Biomedicine of Aging

## Chair of Internal Medicine (Geriatrics)

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**Research Focus**
- Clinical nutrition in the elderly
- Impact of long term high fat diets on the development of sarcopenia
- Sarcopenia
- Mobility in the elderly

## Structure of the Institute

The Institute for Biomedicine of Aging (IBA) is part of the Chair of Internal Medicine – Geriatrics at the FAU under the direction of Prof. Dr. C.C. Sieber. Further professors at IBA are Prof. Dr. D. Volkert (Theo and Friedl Schöller Foundation Professorship for Clinical Nutrition in the Elderly) and Prof. Dr. C. Bollheimer. Since April 2013 there has been a cooperation between the FAU and the Department of General Internal Medicine and Geriatrics, St. John of God Hospital, Regensburg, Germany (where Prof. Dr. C.C. Sieber is Director and Prof. Dr. C. Bollheimer assistant Director of the Department). Research is clinically-epidemiologically and experimentally oriented and focused on the areas nutrition and metabolism in the elderly, age-related decline of muscle mass and function (sarcopenia), and mobility and frailty. Clinical nutrition research is performed by Prof. Dr. D. Volkert, PD Dr. E. Freiberger is responsible for the area of mobility and frailty. Experimental research is led by Prof. Dr. C. Bollheimer, Dr. R. Kob, and Dr. B. Fischer with a translational approach. The IBA is part of the Interdisciplinary Center of Aging Research (ICA; see own report) of the FAU.

## Research

### Clinical nutrition in the elderly

Project manager: Prof. Dr. D. Volkert

In the field of clinical nutrition, a major focus of research is the investigation of the relationship between nutrition and physical functionality, performance and frailty in the elderly in various health and life situations. During the reporting period projects were performed on nutrition in dementia in the home environment, the nutritional situation of elderly patients with hip fracture and its influence on the post-operative period and the link between obesity and functionality. Thereby a close relationship between malnutrition on the one hand and functionality, respectively frailty, on the other hand could be demonstrated. However, obesity was surprisingly not associated with poorer functional status, neither in independent living seniors nor in seniors in need of care, which needs further investigation.

In addition to these research projects a working group of the German Society for Nutritional Medicine (DGEM) led by Prof. Dr. D. Volkert consolidated existing guidelines of the German and European Societies for Nutritional Medicine (DGEM, ESPEN – European Society for Clinical Nutrition and Metabolism) on enteral and parenteral nutrition in geriatrics, followed by an update and expansion in accordance with the generally accepted guidelines of the Association of the Scientific Medical Societies (AWMF) and the Agency for Quality in Medicine (ÄZQ) as S3 guidelines. The new guidelines "Clinical nutrition in geriatrics" include 60 evidence-based recommendations to prevent the development of malnutrition, respectively to treat malnutrition. The current guidelines include for the first time structural and organizational requirements for professional geriatric nutritional care. An international working group of ESPEN is presently developing specific guidelines for clinical nutrition in dementia, based on these guidelines.

### Impact of long-term high fat diets on the development of sarcopenia

Project managers: Prof. Dr. C. Bollheimer, Dr. R. Kob, Dr. B. Fischer

Sarcopenia denotes the exceeding decline of muscle mass, strength, and performance during aging. Obesity and high amounts of dietary fat have been supposed to be major risk factors for genesis and progression of this syndrome. Therefore, we developed the animal model of the aging rat which chronically receives a high fat diet to study the molecular mechanisms of sarcopenic obesity. Employing magnetic resonance imaging techniques, we monitored the morphology of the muscle and the whole body fat distribution during the aging process. With the help of gas chromatography mass spectrometry, the fatty acid profiles in blood, muscle, heart, and liver of the rats were analyzed to search for new metabolic biomarkers of diet induced sarcopenia. Thus, we gained insight into the storage and metabolism of the different fatty acid species in these organ systems. Additionally the muscles of the animals were characterized histologically, biochemically, and molecular biologically. Based on these findings a new animal study has been conducted which is focused on the earlier phases of adulthood. Additionally, in this study, muscle power and performance are monitored during whole lifetime. This project is part of the Bavarian research association "Sarcopenia and Osteoporosis – consequences of reduced regeneration at old age" (FORMOsA). With the help of third-party funding, the necessary equipment to establish a cell culture unit (incubator, sterile bench) in our Institute has been acquired. Furthermore, new laboratories on the former AEG area in Nuremberg have been made available to the IBA which are co-financed by the St. John of God Hospital in Regensburg.

### Mobility and frailty

Project manager: PD Dr. E. Freiberger

Specific promotion of physical activity can significantly improve the performance and social participation in life and improve the maintenance of independence. Targets of corresponding intervention vary from physical to psychical level to the point of social level. Over and above the intervention framework, introduction and binding to physical and sports activities play a central role. Movement-related interventions in the elderly lead to positive effects on physical function parameters such as strength and balance and reduce the risk of falls (PreFall ID – Gait prevention in Persons with Intellectual Disability). The specific target groups are particularly vulnerable and new methods of intervention are required (FORMOsA). Even people with intellectual disabilities are faced with the aging process with corresponding challenges. In this field basic scientific knowledge is still missing (PreFall ID). In addition to the individual, the organizational and political level plays a central role in promoting physical activity for older people. The aim is to improve the internal capacity (e. g. personal development, objective target and resource allocation) as well as the organizational and cross-sectoral networking of organizations in the fields of exercise, health, and social issues, in order to develop and optimize exercise programs for older people (EUNAAPA – European Network for Action on Ageing and Physical Activity). In particular, the

binding of physical activity to maintain the independence of the elderly is of high importance. A reduction of sedentary activity reduces the risk of mortality (DEDIPAC – Determinants of Diet and Physical Activity Choice, SPRINTT – Sarcopenia and Physical Frailty in Older People: Multicomponent Treatment Strategies). The field of function of the IBA is actively involved nationally and internationally at many levels in promotion of physical activities and maintenance of function/independence in the elderly.

### Neurodegenerative aspects of sarcopenia

Project manager: Dr. M. Drey

The Institute for Biomedicine of Aging was involved in an international, multicentric randomized controlled trial for sarcopenia, sponsored by Danone Research. The data of the study on the influence of nutritional supplements on physical performance and muscle mass was analyzed and is currently under review.

In an EU-Cooperation Project FP7 (support code: 01QE1107B) the hypothesis was tested whether the loss of motoneurons causes sarcopenia. For this purpose an electrophysiological technique (Motor unit number index – MUNIX) was used. It could be shown that a low number of motoneurons is associated with sarcopenia. Furthermore, the concentration of C-terminal-Agrin Fragment (CAF) was measured to investigate the relationship to the degeneration of the neuromuscular junction as a cause of muscle loss. Here we found that the specificity of the current CAF-ELISA is insufficient and has to be developed further. The correlation of CAF and creatinine seems to qualify CAF as a marker for kidney function.

## 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 subject "Clinical Nutrition" focuses on nutritional issues of hospital patients.

### Selected Publications


Bollwein J, Diekmann R, Kaiser M, Bauer JM, Uter W, Sieber CC, Volkert D. Dietary quality is related to frailty in community dwelling older adults. J Gerontol Ser A Biol Sci Med Sci 2013, 68: 483-489

Buettner R, Ascher M, Gäbele E, Hellerbrand C, Kob R, Bertsch T, Bollheimer LC. Olive oil attenuates the cholesterol-induced development of nonalcoholic steatohepatitis despite increased insulin resistance in a rodent model. Horm Metab Res 2013, 45: 795-801

Freiberger E, Blank WA, Salb J, Geilhof B, Hentschke Ch, Landendoerfer P, Halle M, Siegrist M. Effects of a multimodal intervention on fall risk in the general practitioner setting: a cluster randomized controlled trial. Clin Interv Aging 2013, 8: 1079-1088

Volkert D, Bauer J, Frühwald T, Gehrke I, Lechleitner M, Lenzen-Großimlinghaus R, Wirth R, Sieber C. Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin (DGEM) in Zusammenarbeit mit der GESKES, der AKE und der DGG: Klinische Ernährung in der Geriatrie. Teil des laufenden S3-Leitlinienprojektes Klinische Ernährung. Aktuel Ernahrungsmed 2013, 38: e1-e48

Fellner C, Schick F, Kob R, Hechtl C, Vorbuchner M, Büttner R, Hamer OW,Sieber CC, Stroszczynski C, Bollheimer LC. Diet-induced and age-related changes in the quadriceps muscle: MRI and MRS in a rat model of sarcopenia. Gerontology 2014, 60: 530-538

Rapp K, Freiberger E, Todd C, Klenk J, Becker C, Denkinger M, Scheidt-Nave C, Fuchs J. Fall incidence in Germany: results of two population-based studies, and comparison of retrospective and prospective falls data collection methods. BMC Geriatr 2014, 14: 105-112


### International Cooperations

European Academy for Medicine of Ageing (EAMA), Gent: Belgium

EUNAAPA (European Network for Action on Aging and Physical Activity)

# Department of Anesthesiology

## Chair of Anesthesiology

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**Research Focus**
- Clinical and experimental pharmacology of anesthesia
- Research projects furthering the curriculum and the medical education
- Medical technology of diagnostic and therapeutic procedures
- Experimental pain research: Pathomechanisms of cold hyperalgesia and cold allodynia
- Clinical pain research in perioperative and palliative pain

## Structure of the Department

The Department of Anesthesiology maintains 50 anesthesia units, 37 of which are run continuously, to provide anesthesia service to 15 surgical departments or independent divisions and several diagnostic and interventional departments of the UK Erlangen. The Department of Anesthesiology also includes an outpatient's anesthesia division with a unit for cardio-pulmonary function diagnostics and a pain clinic. The Department of Anesthesiology is responsible for the management of two interdisciplinary surgical intensive care units with 36 beds and, together with the Department of Neurology, holds the Center for Interdisciplinary Pain Therapy, including four beds for stationary pain therapy. Additionally, the Department of Anesthesiology is responsible for the management of the ambulance service for the city of Erlangen, the county of Erlangen-Höchstadt, and the Herzogenaurach location. The Department also engages in the field of air rescue with the air ambulance of the region (Christopher 27) as well as ambulance aircrafts for repatriation of patients.
The Chair of Anesthesiology (Prof. Dr. Dr. h.c. J. Schüttler) as well as the professorship for Experimental Anesthesiology (Prof. Dr. Dr. H. Schwilden) and the Heisenberg professorship for Experimental Pain Research (Prof. Dr. K. Zimmermann) are located at the Department of Anesthesiology. An autonomous unit with the professorship for Molecular Pneumology (Prof. Dr. S. Finotto) is affiliated to the Chair of Anesthesiology. An endowed Chair for Palliative Medicine (Prof. Dr. C. Ostgathe) was established in 2010. The Department of Anesthesiology employs 115 medical doctors and nine scientific members with responsibilities in research and teaching.

## Research

### Clinical and experimental pharmacology of anesthesia

This research is focused on the quantitative mathematical modeling of the pharmacokinetics and pharmacodynamics of anesthetic drugs with the following aims: model identification, computer simulation of the dynamics in time of anesthetic interventions to improve scientific study design and for educational purposes, and model based dosing strategies for therapeutic optimization.
Pharmacokinetic and pharmacodynamic modeling was performed for hydromorphone and sufentanil with a special focus on protein binding during intensive care therapy in cardiac surgery patients. In cooperation with the Department of Anesthesiology, Wenzhou Medical University, China, the pharmacokinetics of the $\alpha$2-agonist dexmedetomidine were investigated in pediatric Chinese patients with a special focus on interindividual variability and the influence of covariates.

### Research projects furthering the curriculum and the medical education

The Department of Anesthesiology implemented several educational projects in order to gain further scientific insight as well as to improve the quality of the curriculum, medical education, and training.
The Department of Anesthesiology significantly supported the compilation of the new sample-curriculum for the specialization in anesthesiology on behalf of the German Medical Association. The Department of Anesthesiology gave further important impetus for the additional trainings in intensive care, emergency, and pain medicine, particularly by developing a new curriculum for a simulation based training in emergency medicine (concept "NASIM25").
In cooperation with the company Dräger and by using new methods for online visualization of pharmacokinetics and pharmacodynamics, the Department of Anesthesiology initiated a project featuring the learning process of anesthetic drug dosing, thus bridging the gap between research in clinical pharmacology of anesthesia and research in education.
In the field of continuing medical education, a simulation based interprofessional and interdisciplinary one-day-course on crisis management for all staff of the Department of Anesthesiology was carried out over several weeks. Lately, this course was performed with great success in cooperation with the Department of Pediatric and Adolescent Medicine, with a special scientific focus on "safety culture" within a clinical department.
In cooperation with the Department of Oral and Cranio-Maxillofacial Surgery and financially supported by ELAN, we successfully realized a research project to improve the emergency competencies of dentists. Following a multiperspective needs analysis, we developed a three-days-course using an e-learning platform, thus closing a gap in the curriculum of dentistry.

### Medical technology of diagnostic and therapeutic procedures

Within the scope of the National Leading Edge Cluster Medical Valley EMN, our research is focused on the development of new technologies for continuous and variable application of fluid drugs through miniaturized infusion pumps for a personalized, patient-individual, and effect-controlled drug treatment. New methods for a more precise measurement of opioid concentration in blood plasma have been developed, and the accuracy of existent dosing algorithms has been investigated. On the basis of the gathered experiences, the next step will be the implementation of new dosing strategies including the patient response to the target effect and the monitoring of analgesic adverse effects by respiratory and cardio-vascular parameters.
In the Medical Technology Test and Application Center (METEAN; see own report), we investigated new methods for continuous and non-invasive acquisition of biosignals of the respiratory and cardiovascular system for therapy-relevant parameters for hemodynamic monitoring in cooperation with the Fraunhofer Institute for Integrated Circuits and the Max-Schaldach Chair for Medical Technology. An important goal of this research concentrated on the development of techniques for continuous, non-invasive, long-term acquisition of the central arterial blood pressure under daily standard conditions. A further research goal con-

centrated on the mathematical modeling of the arterial pulse wave.

### Experimental pain research: Pathomechanisms of cold hyperalgesia and cold allodynia

In the field of experimental pain research, a Heisenberg Professorship has been funded by the DFG since May 2014. Major topic of this program is unveiling molecular pathomechanisms of cold hyperalgesia and cold allodynia in the somatic and trigeminal system. Two preclinical projects are concerned with the role of specific sodium channel subtypes in the development of cold allodynia caused by consumption of certain fish poisons (ciguatoxins) and the role of the TRPC5 receptor channel in dentin hypersensitivity and pulpitis. Another translational project examines genetic factors which predispose individuals to develop or protect individuals from developing painful cold hyperalgesia following antineoplastic therapy with platinum derivatives or consumption of fish contaminated with ciguatoxins (ciguatera disease).

### Clinical pain research in perioperative and palliative pain

Pain research in palliative medicine focuses on the improvement of pain therapy of in- and outpatients with cancer.

Further research in perioperative medicine investigates post-operative pain in patients with Crohn's disease, including genetic methods.

## Teaching

The Department of Anesthesiology organizes the three cross-sectional areas Q8, Q12, and Q14. Professional lecturers and instructors of the Department of Anesthesiology organize the cross-sectional area Q8 "Emergency Medicine" and are firmly committed to apply new concepts of teaching, such as the use of simulators installed in the simulation and training center of the Department of Anesthesiology. The cross-sectional area Q8 was completely revised, creating a longitudinal structure of the clinical section in order to achieve a high competence of the students in emergency medicine already at the start of the practical year. The cross-sectional area Q12 "Rehabilitation" is organized as an interdisciplinary lecture series in the first lecture week of each term. The area Q14 "Pain Medicine" was first introduced in 2012 and includes contributions not only from anesthesiology, but also from neurology and psychiatry. The curricular class "Clinical Anesthesiology" teaches the scientific foundation of anesthesia. Additionally, the Department of Anesthesiology offers eight electives and some non-curricular classes in the fields of anesthesiology, intensive care medicine, emergency medicine, pain therapy, and palliative medicine as lectures, internships, seminars, and exercises.

The Department of Anesthesiology hosts the oral examination for the European Diploma in Anesthesiology and Intensive Care (EDA).

### Selected Publications


Heinrich S, Birkholz T, Irouschek A, Ackermann A, Schmidt J. Incidences and predictors of difficult laryngoscopy in adult patients undergoing general anesthesia : a single-center analysis of 102,305 cases. J Anesth 2013, 27: 815-21

Breuer G, Schweizer K, Schüttler J, Weiß M, Vladut A. "Jump in at the deep end": simulator-based learning in acute care. Anaesthesist 2014, 63: 16-22

Jeleazcov C, Saari TI, Ihmsen H, Mell J, Fröhlich K, Krajinovic L, Fechner J, Schüttler J. Population pharmacokinetic modeling of hydromorphone in cardiac surgery patients during postoperative pain therapy. Anesthesiology 2014, 120: 378-91

Mattei C, Vetter I, Eisenblätter A, Krock B, Ebbecke M, Desel H, Zimmermann K. Ciguatera fish poisoning: A first epidemic in Germany highlights an increasing risk for European countries. Toxicon 2014, 91: 76-83

Saari TI, Ihmsen H, Mell J, Fröhlich K, Fechner J, Schüttler J. Jeleazcov C. Influence of intensive care treatment on the protein binding of sufentanil and hydromorphone during pain therapy in postoperative cardiac surgery patients. Br J Anaesth 2014, 113: 677-87

Schaffer T, Hensel B, Weigand C, Schüttler J, Jeleazcov C. Evaluation of techniques for estimating the power spectral density of RR-intervals under paced respiration conditions. J Clin Monit Comput, 2014, 28: 481-6


### International Cooperations

Prof. S. Brauchi, University Austral de Chile, Valdivia: Chile

Prof. R. Lewis, Dr. I. Vetter, University of Queensland, Brisbane: Australia

Prof. Q. Lian, Medical University, Wenzhou: China

Prof. S. Rees, Aalborg University, Aalborg: Denmark

Prof. T. Saari, University of Turku, Turku: Finland

Prof. S. Shafer, Stanford University Medical School, San Francisco: USA

Prof. Y. Tian, Huazong University for Science and Technology, Wuhan: China

Prof. B. Yu, Shanghai Jiao Tong University, Shanghai: China

# Department of Anesthesiology

## Division of Molecular Pneumology

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**Research Focus**

- Immunopathogenesis of lung tumor and allergic asthma

## Structure of the Division

The Division of Molecular Pneumology consists of twelve employees, currently supported by the Department of Anesthesiology as well as by grants from the DFG (SFB 643: Role of NFAT family members in allergic asthma and lung tumor – see own report; and GK: Role of BATF in allergic asthma), an European grant (Post-infectious reprogramming and its association with persistence and chronicity of respiratory allergic diseases, PreDicta), the Comprehensive Cancer Center within the Department of Obstetrics and Gynecology, and an IZKF-project (Role of Interleukin 10 in lung cancer). Research is conducted by twelve scientists (besides Head of the Division one postdoctoral fellow, five Ph.D. students, and five technicians). The team investigates the immunological responses present in experimental lung tumor and allergic asthma. This comprises analysis of the lung tumor infiltrating lymphocytes and lung lymphocytes present in allergic asthma. In collaboration with the Division of Thoracic Surgery (directed by Prof. Dr. H. Sirbu), the Institute of Pathology (Prof. Dr. A. Hartmann and Prof. Dr. R. Rieker), and Prof. Dr. L. Bräuer/Dr. M. Schicht of the Chair of Anatomy II at the FAU, our Division analyzes changes in immunological parameters at the protein and mRNA level in tissue after lung resection, obtained from patients with lung tumor. The aim of this study is to identify important genes involved in the pathogenesis of lung cancer to set up new experimental, molecular, therapeutical strategies to cure lung cancer. In addition, in 2010 we received support from a European grant, investigating the immunological response in asthmatic and non-asthmatic children after rhinovirus infection (PreDicta). For this study, we collaborate with several European working groups and the Department of Pediatrics and Adolescent Medicine (Prof. Dr. Dr. h.c. W. Rascher, Dr. T. Zimmermann, Dr. W. Melichar). A variety of molecular and cellular methods is applied for the investigation of isolated and purified lung immunocompetent cells. We are indebted to the numerous collaborations with different scientific departments worldwide which are providing us with updated material to advance our understanding and improvement of the therapy against these two lung diseases spread all over the world.

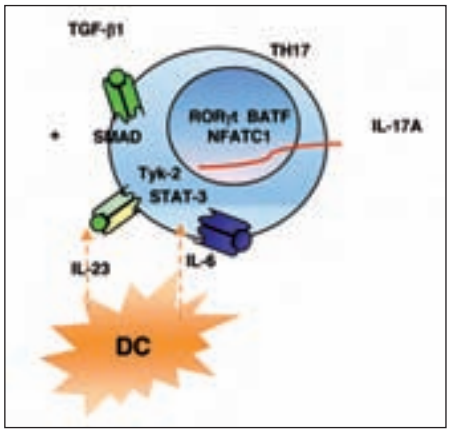
## Research

### Immunopathogenesis of lung tumor and allergic asthma

During the last five years our laboratory identified a number of genes which play a protective or pathogenetic role in the immuno-regulation of lung cancer development. Some examples for those genes are described below:

- EBV-induced gene 3 (EBI-3) encodes for a soluble type I receptor homologous to the p40 subunit of IL-12 that is expressed by APCs following activation. In a study we demonstrated that targeting EBI-3 leads to a T-bet-mediated CD8+ anti-tumor T cell response in a murine model of lung melanoma. T-bet (T-box-expressed in T cells) is a transcription factor expressed by T cells which controls Interferon γ (IFN-γ) production. T regulatory cells are also known as T suppressor cells because they inhibit the immuno-response and as such are increased in tumor. It is therefore the aim of our research to set up therapeutical tools to inhibit the T regulatory cells which are present in the lung bearing tumor. It has been recognized that the most important transcription factor of the T regulatory cells is forkhead box P 3 (FoxP-3).
- We also described reduction of nuclear factor of activated T cells-2 (NFATc2) mRNA expression in the lungs of patients with bronchial adenocarcinoma. Engagement of GITR with an agonistic antibody, known to suppress T regulatory cells and expand effector T cells, in NFATc2 (-/-) mice induced IFN-γ in the airways which reversed the suppression by T(reg) cells and co-stimulated effector and memory T cells, resulting in abrogation of carcinoma progression delineating new possible strategies to turn on an immunoresponses in lung cancer.
- We recently described that targeted deletion of T-bet (T-box expressed in T cells), the main transcription factor inducing IFN-γ, resulting in enhanced lung tumor load and metastasis far beyond that seen in the wild type littermates in the same model. We are thus currently investigating disregulation of anti-tumor immune response present in T-bet deficient mice to better understand this disease.
- Moreover, we recently found increased IL-17A in the absence of T-bet and are investigating the role of IL-17A in lung adenocarcinoma both, in experimental setting as well as in translational studies in humans.
- Along with IL-17A, we are investigating the role of IL-6 and TGF-β, two Th17 inducing cytokines in lung adenocarcinoma.

Allergic asthma is a disease characterized by imbalance of the CD4+ T helper cell subsets Th2/Th1 cytokines and transcription factors with a pathological expansion of the Th2 cells associated with a defect in T regulatory cells. We first identified GATA-3 as the main transcription factor of Th2 cells involved in the pathogenesis of allergic asthma and blocked it locally by intranasal delivery of an antisense molecule achieving inhibition of inflammation, airway hyperresponsiveness in treated mice comparable to steroid treatment. We then discovered that targeted deletion of T-bet in experimental asthma resulted in an asthmatic phenotype. Local blockade of IL-13 in T-bet deficient mice resulted in amelioration of the asthmatic phenotype in the absence of T-bet. Moreover, blockade of the α chain of the IL-6R resulted in local expansion of positive CD4+CD25+FoxP3+ tregs with increased immunosuppressive functions. Thus, we found that local inhibition of IL-6 signaling emerges as a novel molecular approach for the treatment of allergic asthma. We are currently investigating the role of IL-6 in T-bet deficiency induced asthma. In addition, tyrosine kinase 2 (Tyk2) is an ubiquitously expressed member of the mammalian janus kinase (JAK) family of non-receptor protein tyrosine kinases which consists of three additional kinases (JAK1-3). We recently discovered that Tyk-2 signaling is involved in IL-9 and IL-17A production and are analyzing the molecular mechanism involved in this disregulation. Finally, we reported that targeting NFATc1 in T lymphocytes ameliorated the allergic trait seen in asthma and targeted deletion of BATF ubiquitously ameliorated experimental allergic asthma. NFATc1 and BATF thus emerge as a novel target for anti-allergy intervention.




*Signaling pathways and key transcription factors that regulate Th17 differentiation in the lung.*

## Teaching

The Division of Molecular Pneumology is teaching basic immunology at the Division of Molecular Immunology, the Department of Medicine 3, and at the Institute of Clinical Microbiology, Immunology, and Hygiene. Seminars using electronic media are given on a weekly basis to train new students in the Division of Molecular Pneumology.

### Selected Publications

Koch S, Mousset S, Graser A, Reppert S, Übel C, Reinhardt C, Zimmermann T, Rieker R, Lehr HA, Finotto S. IL-6 activated integrated BATF/IRF4 functions in lymphocytes are T-bet-independent and reversed by subcutaneous immunotherapy. Sci Rep 2013, 3: 1754

Ubel C, Mousset S, Trufa D, Sirbu H, Finotto S. Establishing the role of tyrosine kinase 2 in cancer. Oncoimmunology. 2013, 2(1): e22840

Balabko L, Andreev K, Burmann N, Schubert M, Mathews M, Trufa DI, Reppert S, Rau T, Schicht M, Sirbu H, Hartmann A, Finotto S. Increased expression of the Th17-IL-6R/pSTAT3/BATF/Rorγ T-axis in the tumoural region of adenocarcinoma as compared to squamous cell carcinoma of the lung. Sci Rep 2014, 4: 7396

Übel C, Graser A, Koch S, Rieker RJ, Lehr HA, Müller M, Finotto S. Role of Tyk-2 in Th9 and Th17 cells in allergic asthma. Sci Rep 2014, 4: 5865

Schicht M, Rausch F, Finotto S, Mathews M, Mattil A, Schubert M, Koch B, Traxdorf M, Bohr C, Worlitzsch D, Brandt W, Garreis F, Sel S, Paulsen F, Bräuer L. SFTA3, a novel protein of the lung: three-dimensional structure, characterisation and immune activation. Eur Respir J 2014, 44(2): 447-56

Übel C, Sopel N, Graser A, Hildner K, Reinhardt C, Zimmermann T, Rieker RJ, Maier A, Neurath MF, Murphy KM, Finotto S. The activating protein 1 transcription factor basic leucine zipper transcription factor, ATF-like (BATF), regulates lymphocyte- and mast cell-driven immune responses in the setting of allergic asthma. J Allergy Clin Immunol 2014, 133(1): 198-206

### International Cooperations

Prof. S.T. Weiss, Channing Division of Network Medicine, Boston: USA

Prof. N.G. Papadopoulos, National and Kapodistrian University of Athens (NKUA), Athenus: Greece

Dr. T. Vuorinen, MD, University of Turku, Turku: Finland

Dr. T. Jartti, MD, Hospital District of Southwest Finland, Turku: Finland

Prof. M.L. Kowalski, Medical University of Lodz, Lodz: Poland

Dr. C. Bachert, University of Ghent, Ghent: Belgium

Prof. S. Johnston, Imperial Healthcare NHS Trust, London: United Kingdom

Prof. Dr. C. I. Ho, MD, Brigham and Women's Hospital, Boston: USA

Prof. Dr. L.H. Glimcher, MD, Weill Cornell Medical College, New York: USA

# Department of Anesthesiology

## Division of Palliative Medicine

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**Research Focus**
- Ethical aspects in palliative care
- Informal caregiver research
- Health care research
- Need for palliative care in patients suffering from heart, lung, and neurological diseases

## Structure of the Division

The Division of Palliative Medicine consists of a multi-professional team of physicians, nurses, psychologists, a spiritual carer, a physiotherapist, social worker as well as music- and arts-therapists. They provide care to patients suffering from advanced or terminal disease and aim at improving quality of life for patients and their relatives. The holistic view of care requires flexible and individual concepts of different professionals.
Advice can be given for palliation of symptoms, palliative care, psychosocial support, counseling in modification of therapy objective, medical information, and clarification of further patient care for all patients of the UK Erlangen either at the palliative care unit, by the palliative care consultation team, or in the division's policlinic.

## Research

### Ethical aspects in palliative care

Project manager: 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. In 2009, the European Association for Palliative Care (EAPC) published a framework for the use of PS in palliative care which is so far the most comprehensive recommendation for clinical practice of PS. Nevertheless, it remains unclear to what extent the clinical practice in Germany matches the EAPC recommendations. Therefore, the work group developed a questionnaire alongside the EAPC framework and sent it out to German palliative care units, hospices, and outpatient palliative care teams to evaluate the accordance. In summary, many differences exist in frequency and clinical handling of PS in Germany. The implementation of international and national recommendations into clinical practice remains inconsistent. This project was funded by ELAN for one year.

### Informal caregiver research

Project managers: Prof. Dr. C. Ostgathe, PD Dr. S. Stiel
"Quality of Dying and Death"
The Quality of Dying and Death questionnaire (QoDD) which includes items on physical, nursing, psychological, and social aspects of quality of dying and death is one of the first international instruments considering the multidimensional approach of palliative care. In cooperation with the University Hospital Mainz, two versions – for informal caregivers as well as health care professionals – were translated into German and validated at two palliative care units. The aim of the study is to provide validated German versions with good psychometric properties for standard implementation in German hospice and palliative care institutions to meas - ure quality of dying and death. The study is funded by the German Cancer Aid (Deutsche Krebshilfe e.V.).
"Experiences of family caregivers of deceased tumor patients – an analysis of physical and psychological symptoms as well as their burdens and needs"
Family caregivers are under severe strain. This often affects their physical and psychological wellbeing in a negative way. The project "Experiences of family caregivers of deceased tumor patients – an analysis of physical and psychological symptoms as well as their burdens and needs" of the research group evaluates and compares experiences of family caregivers of A) patients with a brain tumor and B) patients with non-brain tumors by using quantitative questionnaires and qualitative interviews with the caregivers. The results shall help to develop tailored support programs for family caregivers. The project which was completed in the report period was funded by the Johannes und Frieda Marohn-Stiftung.

### Health care research

Project managers: Prof. Dr. C. Ostgathe, PD Dr. S. Stiel
"MRSA in end of life care"
Little is known about the effects that MRSA colonization and/or infection and the respective isolation measures have on end-of-life patients' quality of life and the health-related outcomes for the family members as well as on job satisfaction and work load of staff. The interdisciplinary multi-center study "MRSA in end-of-life-care" (project partners: Institute for Biomedicine of Aging, Prof. Dr. C. Sieber; Institute of Psychogerontology, Prof Dr. F. Lang; Chair for Health Management, Prof. Dr. O. Schöffski; Institute of Clinical Microbiology, Immunology, and Hygiene, Prof. Dr. C. Bogdan) uses a mixed methods approach. The aim of the study is to develop a patient-, family-, and team-centered approach to deal with MRSA-positive hospitalized patients during their last phase of life. The study is funded by the BMBF.
"Coordination Office Palliative Care in the network of German Comprehensive Cancer Centers"
The extent of integration of palliative care in German Comprehensive Cancer Centers (CCC) in Germany is unknown. Therefore, this scientific project aims at developing a "best practice strategy" for a systematic integration of palliative care in clinical care, education, and research. In a first project phase between May and August 2014, structured quantitative and qualitative interviews were performed with the heads of all palliative care institutions and additional external persons to investigate the current situation and structures of palliative care within these CCC. Upcoming projects parts will further investigate standards, quality indicators, and educational concepts and raise new research projects. The project is funded by the German Cancer Aid (Deutsche Krebshilfe e.V.).
"Care trajectories and survival after discharge from specialized inpatient palliative care"
Due to the multitude of structures and processes and the wide range of available generalist and specialist palliative and hospice care, little is known about the patients' individual care trajectories after discharge or transfer from inpatient palliative care units (PCU) to other care settings. Therefore, this study surveyed the further care trajectory, indications for changes in care settings, symptom burden, general condition, overall survival and place of death of 245 patients after discharge. Insights into these trajectories will help to detect gaps in discharge planning and to choose an adequate network of care providers in the future.

### Need for palliative care in patients suffering from heart, lung, and neurological diseases

Project managers: PD Dr. S. Stiel, Prof. Dr. C. Ostgathe
Up to date, patients suffering from non-cancer diseases are the minority in palliative care. Due

to demographic changes, patients with chronical illnesses such as cardiac insufficiency, chronic obstructive pulmonary disease (COPD), or neurological diseases will become more important in palliative care. Increasing percentages of non-cancer patients are expected in the future. To better prepare and define trends and changes in patient characteristics over the time, the work group analyzed and compared core data set from the German Hospice and Palliative Care Evaluation (HOPE), a national, long-term quality assurance project, from 2002 - 2005 versus 2007 - 2011. Additionally, a cluster analysis of cancer versus non-cancer patients' symptoms and problems contributed to the knowledge about palliative care needs for this specific patient group.

## Teaching

Our goal in teaching palliative care is to relate medical knowledge in specific aspects of palliative medicine (symptom control, communication skills, weighing possible therapeutic goals and treatment regimens in advanced disease, ethical decisions). We also try to support our students to reflect their perceptions and values related to advanced diseases, dying, and death. Almost exclusively, we teach small groups of students and our tutors come from all sections of the multidisciplinary team.

Our teaching scope encompasses:

– Mandatory classes in palliative care;
– Elective course (symptom control, measures in dying patients, hospice work in Germany, ethical questions, nursing in palliative care, psychology in palliative care);
– Elective course (treatment of two virtual patients in a setting of case-based learning);
– Elective participation in rounds and team meetings;
– Talks on contemporary aspects of palliative care medicine (students, health professionals, and open to the public);
– Colloquium on scientific approaches in medicine.

Mandatory and elective teaching by the Division of Palliative Medicine is continually evaluated.

In addition to classes held exclusively by our Division, we take part in classes held by other disciplines of the Faculty of Medicine (e.g. Anesthesiology, Anatomy, Medical Process Management, Medical Psychology, Medical Sociology, Physiotherapy, Psychogerontology, Logopedics).

### Selected Publications

Bükki J, Klein J, But L, Montag T, Wenchel HM, Voltz R, Ostgathe C. Methicillin-resistant Staphylococcus aureus (MRSA) management in palliative care units and hospices in Germany: a nationwide survey on patient isolation policies and quality of life. Palliat Med 2013, 27(1): 84-90

Klosa P, Klein C, Heckel M, Bronnhuber AC, Ostgathe C, Stiel S. The EAPC Framework on Palliative Sedation and Clinical Practice – A Questionnaire based Survey in Germany. Support Care Cancer 2014, 22(10): 2621-28

Stiel S, Matthies DMK, Seuß D, Walsh D, Lindena G, Ostgathe C. Symptoms & problem clusters in cancer and non-cancer patients in specialised palliative care – Is there a difference? J Pain Symptom Manage 2014, 28(1): 26-35

Hess S, Stiel S, Hofmann S, Klein C, Lindena G, Ostgathe C. Trends in Specialized Palliative Care for Non-Cancer Patients in Germany – Data from the National Hospice and Palliative Care Evaluation (HOPE). Eur J Intern Med 2014, 25: 187-92

Bartz L, Klein C, Seifert A, Herget I, Ostgathe C, Stiel S. Subcutaneous administration of drugs in palliative care – Results of a systematic observational study. J Pain Symptom Manage 2014, 48(4): 540-47

### Meetings and International Training Courses

08. – 09.02.2013: Schmerz- und Palliativmedizin – Update 2013, 13. Erlanger Schmerz- und Palliativtage, 4. Erlanger Schmerztage für Pflegekräfte, Erlangen

12. – 13.04.2013: 1. Wissenschaftliche Arbeitstage der Deutschen Gesellschaft für Palliativmedizin (DGP), Erlangen

21. – 22.03.2014: 2. Wissenschaftliche Arbeitstage der Deutschen Gesellschaft für Palliativmedizin (DGP), Erlangen

# Department of Cardiac Surgery

## 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
- Neuropeptide release of the heart
- Hospital-economics and management
- The arterialization of cardiac veins as an alternative myocardial revascularization strategy in an experimental long term model in pigs
- Tissue engineering of cardiovascular implants
- Development of a non-blood contacting heart actor
- High speed camera investigations on heart valves in a pulse duplicator

## Structure of the Department

20 medical doctors work at the Department of Cardiac Surgery. The research is accomplished by all medical doctors, seven graduate students, and two technical assistants.

## Research

### Chronic rejection of allografts

Project manager: Dr. C. Heim

Transplant arteriosclerosis is the main reason for late graft failure 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 arteriosclerosis is essential. We have recently established and characterized the abdominal aortic allograft model as a suitable tool to study the development of transplant arteriosclerosis. Ongoing projects involve the role and importance of chemokines and chemokine-receptors, in particular CCR7 and CXCR5, in the development of transplant arteriosclerosis. CCR7, the major homing receptor for trafficking of T and B cells, plays a crucial role in leukocyte homing. Experiments using CCR7-/- mice as recipients of aortic allografts showed increased amounts of transplant arteriosclerosis during the absence of this receptor and suggest an interesting role of this receptor in this disease. Recent findings implicate an important role of human cytomegalovirus infection (HCMV) for the development of inflammatory-proliferative vascular lesions in transplanted vascularized allografts. Therefore, the major aim of this project is to develop a human peripheral blood lymphocyte (hu-PBL)/severe combined immunodeficiency (SCID) mouse xenograft-model to investigate the immunological and pathological mechanisms of HCMV in the modulation and progression of transplant arteriosclerosis.

### Therapy of end-stage heart failure: Heart transplantation or support with a left or right ventricular assist device

Project manager: 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.

### Neuropeptide release of the heart

Project manager: PD Dr. T. Strecker

Calcitonin-Gene Related Peptide (CGRP) is a neuropeptide consisting of 37 amino acids and its biological action results in a strong vasodilatation. CGRP is mainly produced by the sensoric A-δ- and C-fibres. Recent data suggests that it may play an important role in myocardial ischemia. Neural fibres with a high CGRP content are found in both atria, the pericardium and within the adventitia of coronary arteries. Changes in CGRP production correlate with increased activity within cardiac afferent fibres. It was shown in vitro that elevated CGRP concentrations were able to increase the coronary blood flow and reduce the coronary resistance and the mean arterial blood pressure. Furthermore, CGRP was demonstrated to be cardio-protective and reduce the infarct size of myocardial infraction.
The aim of our project (cooperation with Prof. Dr. K. Messlinger, Institute of Physiology and Pathophysiology) is to develop an experimental mouse model in order to investigate the effects and kinetics of CGRP production in greater detail. In addition, analyses of human CGRP production are planned by using tissue from the right ventricle or ascending aortic tissue.

### Hospital-economics and management

Project managers: Prof. Dr. R. Feyrer

One of the main tasks of this group has been to face the changes in hospital reimbursement from retrospective payment to a prospective flat rate payment. Other current projects involve the development of the so called 'clinical pathways' in order to improve cost unit calculations and enable us to create computer-simulated scenarios of complex problems of hospital cost management. In cooperation with the Department of Anesthesiology, we perform a study analyzing the costs involving intensive care patients, and together with the German Heart Center in Berlin, we are trying to set up a database regarding long-term costs of patients on cardiac assist devices.

### The arterialization of cardiac veins as an alternative myocardial revascularization strategy in an experimental long term model in pigs

Project manager: PD Dr. F. Harig

In ischemic hearts, venous retroperfusion is a potential myocardial revascularization strategy. The goal underlying retrograde coronary sinus (CS) perfusion is perfusion of the ischemic myocardium proximal to the occlusion or stenosis. The lack of suitable target vessels remains a challenge for aortocoronary bypass grafting in end stage coronary heart disease. This study aimed at investigating the arterialization of cardiac veins as an alternative myocardial revascularization strategy in an experimental long term model in pigs.
In a pig model of myocardial ischemia, selective retrograde perfusion of a coronary vein was performed. A ligation of the ramus interventricularis paraconalis (equivalent to the left anterior descending artery (LAD) in humans) was performed in 20 German landrace pigs (Sus scrofa domestica). Retroperfusion (RP) of the concomitant vein of the LAD was performed in four pigs (RP+), but not in the other four (RP-), and the vena cordis magna (VCM) was ligated (L+) in four pigs in each of these groups, but left open (L-) in the remaining animals.
Hemodynamic performance (e.g. cardiac output) was significantly better in RP+L+ pigs that underwent selective retroperfusion with proximal ligation of vena cordis magna as compared to all other animals. Long term survival was significantly better in RP+L+ pigs than in all other

groups. Histological follow-up studies showed significantly smaller area of necrosis in all animals of the RB+L+ group.
Consequently, venous retroperfusion is an effective technique to achieve long term survival after acute LAD occlusion in a pig model. The clinical application is still pending.

### Tissue engineering of cardiovascular implants

Project manager: Dr. C Heim
The background for these studies is the development of an ingrowth matrix within the tissue engineering of cardiovascular grafts. The purpose of these investigations is to show whether it is possible to influence the mobility of endothelial cells, smooth muscle cells, and fibroblasts within a fully synthetic matrix by incorporating bioactive peptides. The purpose is to define a matrix which provides optimal mobility for those cells needed for a functional cardiovascular implant. Such a matrix could be integrated into a cardiovascular prosthesis in order to facilitate and direct the ingrowth of the patient's own tissue. A single cell migration model was used to compare the influence of different cell interactive peptides on the mobility of vascular cell lines as microvascular endothelial cells (MVEC) and aortic vascular smooth muscle cells (SMC). In previous studies it could already be shown that selectively MVEC, but not SMC accelerate on a PEG matrix covered with RGD (fibronectin) and YIGSR (laminin) in comparison to a matrix covered only with RGD. These experiments were extended to the peptide sequences SIKVAV, RYVVLPR (both laminin), and DGEA (collagen) also known from the literature as being vascular cell interactive. For sufficient cellular adhesion, RGD was added to the matrix again. At an average migration speed, both cell lines showed a reduced cell speed on RGD plus RYVVLPR and RGD plus DGEA. For the combination of SIKVAV and RGD, only MVEC showed a small, but not significant increase in mobility whereas SMC did not show any difference.

### Development of a non-blood contacting heart actor

Project manager: 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 heart-circulatory system. Within a clinical-medical setting, the investigation of a new research project which will be submitted in 2015 with the DFG 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 di- or piezoelectric based actor material patterns.

### High speed camera investigations on heart valves in a pulse duplicator

Project manager: 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

Beside the traditional teaching forms (main lecture and practical courses), observerships and clinical rotations can be undertaken anytime.

### Selected Publications

Pizon M, Friedel N, Pizon M, Freundt M, Weyand M, Feyrer R. Impact of epicardial ablation of concomitant atrial fibrillation on atrial natriuretic peptide levels and atrial function in 6 months follow-up: does preoperative ANP level predict outcome of ablation? J Cardiothorac Surg 2013, 8: 218

Heim C, Nooh E, Kondruweit M, Weyand M, Tandler R. Single centre experience with prolonged waiting time on transplant list with "high-urgency" status. Thorac Cardiovasc Surg 2013, 61(3): 251-4

Strecker T, Rösch J, Weyand M, Agaimy A. Frequency and spectrum of metachronous malignancies in heart transplant recipients: a 11-year-experience at a German heart center. Int J Clin Exp Pathol 2013, 6(3): 411-20

Kondruweit M, Friedl S, Heim C, Wittenberg T, Weyand M, Harig F. A new ex vivo beating heart model to investigate the application of heart valve performance tools with a high-speed camera. ASAIO J 2014, 60(1): 38-43

Feyrer R, Ballazhi F, Seitz T, Weyand M, Harig F. Impact of medical treatment on long-term results after surgical ablation of atrial fibrillation in cardiac surgical patients. Ann Thorac Cardiovasc Surg 2014, 20(3): 207-12

# Department of Cardiac Surgery

## Division of Pediatric Cardiac Surgery

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**Research Focus**
- Aortic arch surgery
- Biomaterial bank for congenital heart diseases
- Development of new surgical procedures and treatment strategies for the univentricular heart
- Myocardial protection – comparative study of various cardioplegic solutions
- Reconstruction of the right ventricular outflow tract
- Role of thymic tissue in immune cell differentiation
- Migration of DEHP (Di-ethyl-hexylphthalate) plasticizers into patient's blood

## Structure of the Division

Four surgeons cover the medical service in the Division of Pediatric Cardiac Surgery. Patient care is provided in close cooperation with the Division of Pediatric Cardiology (Department of Pediatric and Adolescent Medicine). In May 2009, the " Competence Network for Patients with Congenital Heart Disease in Northern Bavaria" was founded. The use of telemedicine platforms enables optimal patient care after surgical or interventional procedures. Currently, 17 Ph.D. students are involved in scientific projects.

## Research

### Aortic arch surgery

For years, surgical repair of congenital aortic arch lesions has been a research focus of the Division of Pediatric Cardiac Surgery. We successfully introduced various cutting-edge organ protective perfusion methods into clinical practice. Based on our own research results, pediatric aortic arch surgery is currently performed in hypothermic low-flow perfusion, avoiding the use of deep hypothermic circulatory arrest. Our research in this topic was awarded with the highest scientific award of the German Society for Thoracic and Cardiovascular Surgery in 2008. Previous parts of the research project received the "Congenital Heart Surgery Award" from the EACTS (European Association for Cardio-Thoracic Surgery). Animal experiments to validate the practicability of hypothermic low-flow perfusion in combination with a beating-heart technique have been successfully completed. The experimental setup was funded by the ELAN-Fond of the Faculty of Medicine. Scientific articles related to this topic are currently under review.

### Biomaterial bank for congenital heart diseases

In cooperation with the Division of Pediatric Cardiology (Dr. O. Toka, Department of Pediatric and Adolescent Medicine), a database and storage option for tissue samples was established in September 2008. Tissue samples which are routinely removed during surgery are systematically collected for examination. These samples are then preserved and collected in close collaboration with the Institute of Pathology for later investigations. In cooperation with German Competence Network for Congenital Heart Defects (Berlin, supported by BMBF), the largest database of tissue sample for children with congenital heart disease was established in Erlangen. Dr. O. Toka (Department of Pediatric and Adolescent Medicine) received a grant for this project by the "German Foundation for Cardiac Research".

### Development of new surgical procedures and treatment of strategies for the univentricular heart

One of the most hazardous lesions in congenital heart disease is the hypoplastic left heart syndrome. Staged treatment requires three operations; each of them carries a substantial risk to the mortality. Thus, reduction of surgical risk to the level of standard neonatal surgery has been and continues to be the key purpose of our Division. Currently, the first surgical step (Norwood I) carries a 30 % mortality risk in Europe. Together with the Division of Pediatric Cardiology, we have established management strategies to lower the mortality risk significantly (<15 %) in these complex cases.

### Myocardial protection – comparative study of variant cardioplegic solutions

Another project investigates myocardial protection during routine surgery. Various cardioplegic solutions are being investigated in relation to their cardioprotective properties. The use of cold crystalloid cardioplegic solutions represents a standard method in pediatric cardiac surgery, both in newborns and in infants. In adult cardiac surgery however, blood cardioplegia has been established, especially in critically ill patients. Our study group aims at optimizing myocardial protection in children with congenital heart disease through the use of a modified blood cardioplegia. Therefore, extensive blood and hemodynamic analyses are being completed and results are collected in a detailed patient register.

### Reconstruction of the right ventricular outflow tract

A large number of patients with congenital heart defects require surgical reconstruction of the right ventricular outflow tract which can be achieved with or without surgical placement of a pulmonary valve. Patients are generally well managed by the implantation of biological valves. However, limitations related to their durability remain, necessitating further valve replacement over time. Major issues are the lack of growth and valvar degeneration. Implantation of decellularized valves is widely propagated as being the ultimate solution to this dilemma. In collaboration with the Department of Medicine 2 – Cardiology and Angiology (Prof. Dr. C. Garlichs, PD Dr. Y. Cicha), explanted decellurized tissue valves were systematically examined. It could be shown that pathological mechanisms responsible for degeneration of decellularized valves are similar to those of other valved conduits (xenografts, homografts). Nevertheless, tissue-engineered biologic implants with a non-antigenic surface may one day possess growing potential. Thus, further research in tissue engineering should be encouraged.

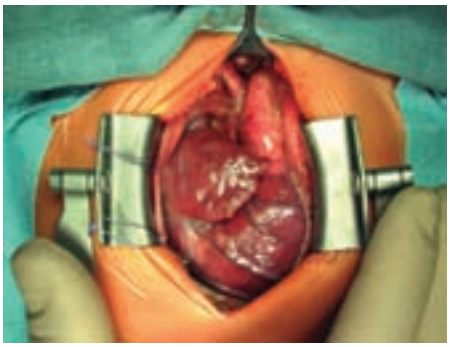
### Role of thymic tissue in immune cell differentiation

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 periph - eral blood of patients. Research is focused on thymus subpopulations in order to gain information related to the natural maturation of the immune system.

### Migration of plasticizers into patient's blood

Current studies focus on migration of phthalate plasticizers (DEHP) from the cardiopulmonary bypass circuit into the patients blood. These plasticizers are toxic, especially in children. In cooperation with the Institute and Outpatient

Clinic of Occupational, Social, and Environmental Medicine (Prof. Dr. T. Göen), the Division of Pediatric Cardiac Surgery investigates plasticizers in respect of their migration, as well as alternative materials which do not contain plasticizers. The topic is of paramount importance. In the past years, phthalate contaminants were repeatedly found in plastic toys, baby bottles, and soothers. However, it has been proven that phthalate plasticizers are endocrinal disruptors and provoke disruptive changes in the development of reproductive organs and fertility.



Heart with hypoplastic left heart syndrome in comparison to the surgeon's hand

## 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 theater.

View in the operating theater

### Selected Publications


Sandrio S, Purbojo A, Arndt F, Toka O, Glöckler M, Dittrich S, Cesnjevar R, Rüffer A. Feasibility and related outcome of intraluminal pulmonary artery banding. Eur J Cardiothorac Surg 2014 Dec 16. pii: ezu464

Münch F, Purbojo A, Kellermann S, Janssen C, Cesnjevar RA, Rüffer A. Improved contractility with tepid modified full blood cardioplegia compared with cold crystalloid cardioplegia in a piglet model. Eur J Cardiothorac Surg 2014 Nov 20. pii: ezu440

Cosgun KN, Rahmig S, Mende N, Reinke S, Hauber I, Schäfer C, Petzold A, Weisbach H, Heidkamp G, Purbojo A, Cesnjevar R, Platz A, Bornhäuser M, Schmitz M, Dudziak D, Hauber J, Kirberg J, Waskow C. Kit regulates HSC engraftment across the human-mouse species barrier. Cell Stem Cell 2014, 15(2): 227-38

Eissing N, Heger L, Baranska A, Cesnjevar R, Büttner-Herold M, Söder S, Hartmann A, Heidkamp GF, Dudziak D. Easy performance of 6-color confocal immunofluorescence with 4-laser line microscopes. Immunol Lett 2014, 161(1): 1-5

Rüffer A, Münch F, Potapov S, Purbojo A, Toka O, Dodge-Khatami A, Dittrich S, Cesnjevar RA. Troponin I levels in extracorporeal membrane oxygenation following congenital heart surgery. World J Pediatr Congenit Heart Surg 2014, 5(2): 229-35

Ihlenburg S, Rompel O, Rueffer A, Purbojo A, Cesnjevar R, Dittrich S, Gloeckler M. Dual source computed tomography in patients with congenital heart disease. Thorac Cardiovasc Surg 2014, 62(3): 203-10


### International Cooperations

Prof. Dr. M.R. de Leval, Great Ormond Street Hospital, London: UK

Prof. Dr. A. Philips, Cedars-Sinai Mediacl Center, Los Angeles: USA

Prof. Dr. M. Rodefeld, Indiana University, Indianapolis: USA

# Department of Dermatology

## Chair of Skin and Venereal Diseases

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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
- The role of miRNAs 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
- Identification and modulation of allergenic structures

## Structure of the Department

More than 182 people are employed at the Chair of Skin and Venereal Diseases, among them 39 medical doctors and 23 scientists. In the different working groups, clinically-relevant questions are addressed in the areas of dendritic cell (DC) biology, DC-based vaccine development, oncology with a focus on malignant mel - anoma, and allergy. The Department of Dermatology focuses on the development and clinical validation of innovative cellular therapies with an emphasis on ex-vivo generated DC-based vaccines. For this, a modern GMP-laboratory (good manufacturing practice) is available. The projects at the Department of Dermatology are all third-party funded, e.g. by the SFB 643 "Strategies of cellular immune intervention" (see own report).

## Research

### Cellular immune intervention

Project manager: PD Dr. B. Schuler-Thurner
The production and clinical testing of innovative cellular therapies is the task of this working group which consists of the GMP laboratory and a clinical trial unit. After seven successfully performed phase I and II trials, in July 2014 we started a unique phase III trial in cooperation with nine German university hospitals employing DC transfected with autologous tumor mRNA. The goal of this adjuvant trial is the prevention of metastases in patients with high risk uveal melanoma by induction of tumor-specific T cells (200 patients planned).The production of the PCR-amplified tumor mRNA as well as the generation of the DC vaccine is performed by the GMP laboratory of the experimental immunotherapy unit. Currently we are exploring new analytical methods, such as next generation Exon and RNA sequencing in conjunction with HLA-epitope prediction algorithms to vaccinate against mutated tumor antigens. We are also cooperating with Milteny Biotec GmbH to adapt their Prodigy™ cell processing unit for the simple and cost-effective production of such highly individualized RNA-transfected DC vaccines.
Based on respective preclinical work (see below), the adoptive transfer of T cells reprogrammed by RNA transfection as well as the transfer of regulatory T cells is planned. The GMP-quality team is crucial for implementation of all these novel cellular therapies. The essential immunomonitoring is performed by the Core Unit FACS and Immunomonitoring.

### RNA electroporation to improve DC vaccines and to generate antigen-specific T cells

Project managers: PD Dr. N. Schaft, Dr. J. Dörrie
We showed that – next to the maturation by cytokines – DC need an activation signal (like T cell help) to efficiently induce memory-like cytotoxic T cells. By RNA-transfection, we were able to render DC independent from exogenous activation for the use in therapeutic cancer vaccination.
By TCR transfection, we generated human adenovirus-specific γ/δ and CD8+ T cells for treating life-threatening adenovirus infection (collaboration with Children's Cancer Research Institute, Vienna). Furthermore, we established the transfection of patient-derived T cells with MCSP-specific CARs for treatment of malignant melanoma.

### Functional role of DC subpopulations and antigen presentation

Project manager: Prof. Dr. D. Dudziak
This research group focuses on the characterization of murine and human primary DC subsets. Recently, the group could show that antigen targeting induces protective immune responses in a murine mouse melanoma model which were independent from the targeted DC subpopulation. Besides, in close collaboration with various clinical institutions (Erlangen, Bamberg), DC subpopulations and other antigen presenting cells from human tissues are characterized by multicolor confocal immunofluorescence analysis and 17-color flow cytometry and human antigen targeting antibodies are generated.

### The role of miRNAs in cancer and immune-related diseases

Project manager: Prof. Dr. J. Vera-González
MicroRNAs are non-coding RNAs involved in complex regulatory biochemical networks. Our aim is to combine patient data, quantitative experimental data, computational biology tools, and mathematical modeling to elucidate the role played by miRNAs in cancer and other immune-related diseases. In collaboration with Dr. A. Baur, we are working on a systems-biology-oriented diagnostic tool for assessing the probability of tumor relapse in melanoma based on miRNA profiling of plasma-derived extracellular vesicles. In association with Prof. Dr. B. Schmeck (University Hospital Giessen and Marburg), we are working on the reconstruction of miRNA networks involved in lung infection and inflammation.

### Composition, function, and clinical relevance of plasma extracellular vesicles (pEV)

Project manager: Dr. A. Baur
The research group investigates the molecular mechanisms leading to the generation of extracellular vesicles (EV) and analyzes their content and function. The group focuses on the assessment of factors and biomarkers contained in plasma EV (pEV) and their prognostic value with respect to the development of disease. An important discovery was made when circulating pEV were measured in the periphery and found to be significantly elevated in tumor patients and in individuals with chronic infections and neurodegenerative diseases. 'The pEV biomarker profile seems particularly distinct and therefore promising in operated tumor patients (melanoma) with a different risk for relapse.

### Characterization of the toponome of tissue and cells by multi-epitope-ligand cartography (MELC)

Project manager: Dr. A. Baur

This research team aims at correctly rising human tissue and cells, using the innovative multi-epitope ligand cartography (MELC)-technology which allows the staining of up to 100 antigens on one tissue section or slide. In the last year, the technology has been used very successfully in several projects, analyzing human tissue and PBMC (peripheral blood mononuclear cells). For example, the early development of cutaneous melanoma was analyzed thoroughly and new factors were identified that lead to early tumor formation.

### Pathomechanisms of chronic inflammatory skin diseases

Project manager: 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.

### Identification of biomarkers in malignant melanoma

Project manager: Prof. Dr. L. Heinzerling

This research group focuses on predictive and therapeutic biomarkers in melanoma to optimize selection of therapeutic options. With a semi-automated mRNA extraction from formalin fixed paraffin-embedded (FFPE) sections of primary melanomas and melanoma metastases, a set of 20 indicator genes, previously identified by array analyses, was evaluated. The comparison of responders and non-responders for different immunotherapy options (DC-vaccination, anti-CTLA-4 antibody ipilimumab) resulted in differential gene expression signatures. Furthermore, a large biobank of melanoma patients (including tumor mutations) is established (in collaboration with the Institute of Pathology).

### Regulatory T cells for cell-based therapy in inflammatory bowel disease

Project managers: Dr. C. Bosch-Voskens, Prof. Dr. G. Schuler

The focus of this project funded by KFO 257 (see own report) is on regulatory T cells (Treg). In inflammatory bowel disease, it is postulated that insufficient numbers of Treg cells expand to attenuate local proliferation of effector T cells in the gut. A protocol has been established for the optimized in vitro expansion of Treg cells of colitis ulcerosa patients. Such cells will be intravenously administered in an upcoming clinical trial to mitigate disease activity (collaboration with Prof. Dr. M.F. Neurath, Department of Medicine 1).

### Identification and modulation of allergenic structures

Project manager: Prof. Dr. V. Mahler

This group focuses on the elucidation of relevant allergenic structures in plants and plant-derived food and their modification with the aim to obtain hypoallergenic crops as proof of principle. After the identification of allergic target-structures and the use of RNAi-constructs, relevant allergens could be silenced in planta, resulting in reduced allergen content in tomato fruits and carrot roots.

## Teaching

The Chair of Dermatological and Venereal Diseases teaches students of Medicine, Dentistry, Molecular Medicine, and Biology in molecular and cellular immunology in combination with translational applications (GMP-laboratory). The educational program is organized in seminars, practical training courses in the clinic and the laboratories, lectures as well as bachelor, master, and medical theses. The Department of Dermatology is responsible for the organization of dermatological advanced training courses for physicians.

### Selected Publications


Pfeiffer IA, Hoyer S, Gerer KF, Voll RE, Knippertz I, Gückel E, Schuler G, Schaft N, Dörrie J. Triggering of NF-κB in cytokine-matured human DCs generates superior DCs for T-cell priming in cancer immunotherapy. Eur J Immunol 2014, 44(11): 3413-28

Dörrie J, Krug C, Hofmann C, Müller I, Wellner V, Knippertz I, Schierer S, Thomas S, Zipperer E, Printz D, Fritsch G, Schuler G, Schaft N, Geyeregger R. Human Adenovirus-Specific γ/δ and CD8+ T Cells Generated by T-Cell Receptor Transfection to Treat Adenovirus Infection after Allogeneic Stem Cell Transplantation. PLoS One 2014, 9(10): e109944

Hoyer S, Prommersberger S, Pfeiffer IA, Schuler-Thurner B, Schuler G, Dörrie J, Schaft N. Concurrent interaction of DCs with CD4+ and CD8+ T cells improves secondary CTL expansion: It takes three to tango. Eur J Immunol 2014, 44(12): 3543-59

Neubert K, Lehmann CH, Heger L, Baranska A, Staedtler AM, Buchholz VR, Yamazaki S, Heidkamp GF, Eissing N, Zebroski H, Nussenzweig MC, Nimmerjahn F, Dudziak D. Antigen delivery to CD11c+CD8- dendritic cells induces protective immune responses against experimental melanoma in mice in vivo. J Immunol 2014, 192(12): 5830-8

Khan FM, Schmitz U, Nikolov S, Engelmann D, Pützer BM, Wolkenhauer O, Vera J. Hybrid modeling of the crosstalk between signaling and transcriptional networks using ordinary differential equations and multi-valued logic. Biochim Biophys Acta 2014, 1844(1 Pt B): 289-98

Nikolov S, Wolkenhauer O, Vera J. Tumors as chaotic attractors. Molecular Biosystems 2014, 10(2): 172–179

# Department of Dermatology

## Division of Immune Modulation

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**Research Focus**
- Immune-modulation in autoimmunity and transplantation by soluble CD83
- Transcriptional in vivo targeting of dendritic cells (DC) using the human CD83 promoter
- Intracellular signal transduction of CD83 in DC
- Immune-modulation by TSLP and CD83
- Interaction DC cells und viruses

## Structure of the Division

More than 20 researchers are working In the Division of Immune Modulation, headed by Prof. Dr. A. Steinkasserer. Five research groups concentrate on basic immunological questions, whereby the translation of basic results into clinically applicable therapeutic strategies is a major goal. Especially autoimmune disorders and the transplantation studies are in the focus of our research activities. The interaction between viruses and dendritic cells (DC) represents the second major research area of the Division. The identification and characterization of specific viral immune escape strategies will be exploited to develop new antiviral strategies. This research work is mainly supported by research grants funded by the DFG, SFB, GK, and scientific foundations.

## Research

### Immune-modulation in autoimmunity and transplantation by soluble CD83

Project manager: Dr. E. Zinser

The project group focuses on the immuno-suppressive properties of soluble CD83 (sCD83). Using a recombinantly expressed sCD83 molecule, it was possible to inhibit the paralyses associated with EAE, an animal model for the early, inflammatory phase of Multiple Sclerosis in a prophylactic as well as in a therapeutic setting. Furthermore, the rejection of heart-, skin-, and cornea-transplants could be prevented by the use of sCD83. Regarding the mode of action of sCD83, we could show that it induces regulatory T cell (Tregs) and that indoleamine 2,3-dioxygenase (IDO) plays a major role. Interestingly, a naturally occurring sCD83 molecule has been identified in the serum of tumor patients. High concentrations of sCD83 correlated with a reduced treatment free survival in CLL (chronic lymphocytic leukemia) patients, indicating its relevance in tumor patients. In the long run, sCD83 will be developed as a new therapeutic option for humans.

### Transcriptional in vivo targeting of dendritic cells (DC) using the human CD83 promoter

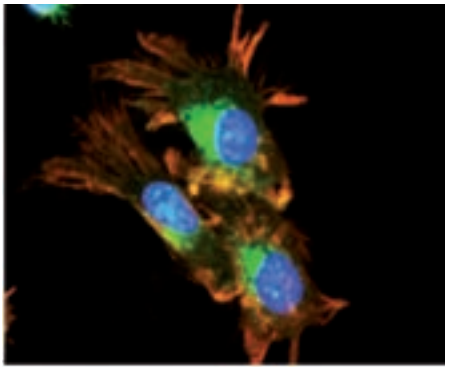
Project manager: Dr. I. Knippertz

The major aim of the research group is the functional characterization of the human DC-specific CD83 promoter. The membrane-bound CD83 molecule is a 45 kDa glycoprotein expressed on the surface of mature DC and is to date one of the best known markers for human mature DC. Since CD83 is not expressed on immature DCs, its regulatory DNA region, the CD83 promoter, is of high interest in the context of a DC-mediated vaccination strategy for the modulation of mature DC by the targeted in vivo gene expression of different therapeutic transgenes. For this purpose, different immune-modulatory and therapeutic transgenes will be expressed in vivo (directly in patients) under the control of the cell type- and stadium specific CD83 promoter. Initially, the characterization of the human CD83 promoter was accomplished by a ChIP-chipTM Microarray analysis by which, in addition to the minimal promoter, a short enhancer sequence was identified. Further bioinformatical analysis identified an additional promoter region which was shown to build a ternary promoter-complex together with the minimal promoter and the enhancer. Moreover, we have demonstrated that this ternary promoter-complex is not only highly inducible, but it is also cell type- and maturation specific. Finally, we have identified the transcription factors involved in this process.

### Intracellular signal transduction of CD83 in DC

Project manager: Prof. Dr. A. Steinkasserer

The main research focus of the project concentrates on structural- and signal transduction pathway analyses of the membrane bound CD83 molecule. Specific binding domains/-partners have been identified using a yeast two hybrid screen. Site directed mutagenesis-, transfection-, immune-precipitation-, and co-immunofluorescence-studies have been used to further characterize the protein-protein interaction, the N-linked glycosylation, and the activation of mCD83 on a molecular level. To identify possible binding motifs in silico, a bioinformatic modeling study has been performed. The elucidation of the mCD83 signaling pathway in mature human DC will open new and specific therapeutic targets.



*Immune-fluorescence staining of mature dendritic cells.*

### Immune-modulation by TSLP und CD83

Project manager: Dr. M. Lechmann

This research group is interested in the regulatory mechanisms balancing TH1/TH17-TH2 immune responses on the one hand and in the development and activation of regulatory T cells in vivo on the other hand. It is focusing on two modulators of the immune system, namely the thymic stromal lymphopoietin (TSLP) and CD83. TSLP is thought to be the “missing link” between DC activation and allergic responses. To further analyze the role of TSLP in vivo, a TSLP KO-mouse was generated. Using this KO-mouse the function of TSLP will be addressed in different inflammatory and infectious diseases models as well as in models for autoimmunity. In the second project the CD83-specific reporter mouse was generated which now allows us to carry out in vivo monitoring of CD83 expressing cells. In this project, the expression and function of CD83 in T cell subpopulations is of particular interest. With regard to the therapeutic application of sCD83, a pilot study in an animal model of inflammatory bowel disease, i.e. the DNBS-induced colitis, has been performed. Interestingly sCD83 treatment ameliorated DNBS-induced colitis, whereby these animals showed less severe progress of disease and significant faster recovery.

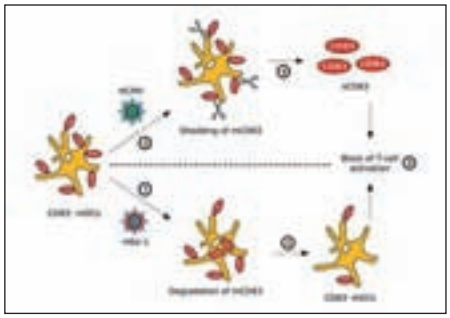
In addition, a rapid and highly specific aptamer-based screening technology for the detection of

biomarkers on living cells has been established. One aim using this technique is to isolate specific aptamers for T cell epitopes of known tumor antigens. Furthermore, new tumor targets will be identified to improve tumor-specific DC-vaccination strategies.

### Interaction of DC und viruses

Project manager: Dr. C. Heilingloh

This project group analyzes the interaction between DC and viruses. Particular attention has been given to HSV-1 and HCMV infections. In this respect, the group was able to identify several new immune-escape mechanisms. For instance, the infection of DC with HSV-1 leads to a complete degradation of CD83 which correlates with a reduced immuno-stimulatory capacity of these infected DC. This degradation is mediated by the viral immediate early protein ICP0 and the cellular proteasome. The exact mechanism of this degradation is subject of current research. Interestingly, infection of mature DC with HCMV induced the shedding of a soluble CD83 molecule from the cell surface which has immune-suppressive activities. Moreover, it could be shown that the infection of mature DC with HSV-1 leads to an inhibition of STAT1 signaling, presumably via loss of the IFNγ-receptor 1. Furthermore, the group is also interested in the replication of HSV-1 in mature DC. In contrast to earlier publications, the replication of HSV-1 in mature DC could be reported recently. Although this replication is very inefficient, it could very well be of biological importance in vivo, since progeny virus could be passed on to primary keratinocytes. During this cell-to-cell mediated infection, the viral glycoprotein gE plays a major role. An additional project deals with the HSV-1 mediated modulation of DC migration. It could be shown that HSV-1 interferes with the chemokine mediated DC-migration which is an absolutely essential step in order to induce potent antiviral immune responses.



*HSV-1 and HCMV specifically target CD83 to evade immune responses.*

## Teaching

The Division of Immune Modulation teaches students of molecular medicine and biology in the field of molecular and cellular immunology. The training takes place in form of lectures, seminars, practical courses as well as bachelor, master, and Ph.D. theses. In addition, the SFB 643 (strategies of cellular immune intervention; see own report) is coordinated together with the Department of Dermatology.

### Selected Publications


Baur AS et al. Denileukin diftitox (ONTAK) induces a tolerogenic phenotype in dendritic cells and stimulates survival of resting Treg. Blood 2013, 122(13): 2185-94

Bock F, Rössner S, Onderka J, Lechmann M, Pallotta MT, Fallarino F, Boon L, Nicolette C, DeBenedette MA, Tcherepanova IY, Grohmann U, Steinkasserer A, Cursiefen C, Zinser E. Topical application of soluble CD83 induces IDO-mediated immune modulation, increases Foxp3+ T cells, and prolongs allogeneic corneal graft survival. J Immunol 2013, 191(4): 1965-75

Goldwich A, Burkard M, Olke M, Daniel C, Amann K, Hugo C, Kurts C, Steinkasserer A, Gessner A. Podocytes are nonhematopoietic professional antigen-presenting cells. J Am Soc Nephrol 2013, 24(6): 906-16

Stein MF, Lang S, Winkler TH, Deinzer A, Erber S, Nettelbeck DM, Naschberger E, Jochmann R, Stürzl M, Slany RK, Werner T, Steinkasserer A, Knippertz I. Multiple interferon regulatory factor and NF-κB sites cooperate in mediating cell-type- and maturation-specific activation of the human CD83 promoter in dendritic cells. Mol Cell Biol 2013, 33(7): 1331-44

Heilingloh CS, Mühl-Zürbes P, Steinkasserer A, Kummer M. Herpes simplex virus type 1 ICP0 induces CD83 degradation in mature dendritic cells independent of its E3 ubiquitin ligase function. J Gen Virol 2014, 95(Pt 6): 1366-75

Eckhardt J, Kreiser S, Döbbeler M, Nicolette C, DeBenedette MA, Tcherepanova IY, Ostalecki C, Pommer AJ, Becker C, Günther C, Zinser E, Mak TW, Steinkasserer A, Lechmann M. Soluble CD83 ameliorates experimental colitis in mice. Mucosal Immunol 2014, 7(4): 1006-18


### International Cooperations

Prof. Dr. H. Wang, University of Western Ontario, London: Canada

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

Prof. Dr. R.D. Everett, University of Glasgow, Glasgow: UK

Prof. Dr. N. Romani, Medical University Innsbruck, Innsbruck: Austria

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

# Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology

## Chair of Internal Medicine I

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**Research Focus**
- Intestinal diseases
- Endocrinology
- Experimental hepatology
- Immunomodulatory strategies for the treatment of chronic inflammatory diseases
- Division of clinical and experimental pulmonology
- Molecular endoscopy
- Molecular gastroenterology
- Patient-oriented research in IBD
- Ultrasound
- Cytokines and transcription factors in IBD

## Structure of the Department

The Department of Medicine 1 covers research in the fields of gastroenterology, hepatology, endocrinology, pneumology, intensive care medicine, infectious diseases as well as endoscopy and ultrasound. Several research groups cover these fields in clinical and basic research. In the past two years, the research division of the Department of Medicine 1 has continuously expanded. This has become possible due to the very successful raising of financial means from public bodies, including the DFG (18 projects) and the EU (two projects). A special highlight is the leadership of a DFG-funded Clinical Research Unit on the topic of inflammatory bowel disease (KFO 257 CEDER; see own report).
The laboratories of the Department of Medicine 1 are located at the Kussmaul campus for Medical Research. In these laboratories, twelve research groups with overall 80 staff members investigate the cause of different diseases and develop new therapeutical strategies.

## Research

### Intestinal diseases
Project managers: Dr. C. Neufert, Prof. Dr. M. Waldner
Our research focus is on intestinal inflammation and colon cancer. Herein, we address molecular mechanisms associated with the pathogenesis of these frequent diseases. Current studies investigate the role of intestinal immune cells and their communication with other gut cell populations. Our studies could help to pave the way for the development of better therapeutic options for people suffering from intestinal inflammation or colon cancer.

### Endocrinology
Project manager: Prof. Dr. C. Schöfl
The Calcium-Sensing-Receptor (CaSR) is pivotal for calcium homeostasis. Mutations of the CaSR cause hyper- and hypocalcemic disorders. Our group characterizes inactivating and activating CaSR mutations and tests how the detrimental effects of these mutations can be corrected pharmacologically.
Treatment of patients suffering from hypocalcemia due to activating CaSR mutations is unsatisfactory and often has side effects. Recently published results from our group indicate that novel calcilytics currently in clinical testing may offer a superior treatment option for patients suffering from Autosomal Dominant Hypocalcemia and Bartter-Syndrome type V.

### Experimental hepatology
Project manager: PD Dr. S. Wirtz
In this research area, we work on clinically relevant questions in the field of acute and chronic liver diseases. We are particularly interested in novel signal pathways that drive massive hepatocyte cell death in the context of acute inflammation and toxic insults. Moreover, we analyze the role of the novel pro- and anti-inflammatory cytokines, such as IL-28, IL-33, and IL-27, in the context of acute and chronic liver diseases. Thereby, we have observed that the expression of these factors is upregulated early during hepatocellular stress and inflammatory liver diseases. Preclinical studies showed that they significantly contribute to gradual accumulation of extracellular matrix components and hepatic tissue remodeling. In the long run, we want to identify new molecular mechanisms of liver pathophys - iology and potential prognostic markers or therapeutic targets in liver disease in these translational research projects.

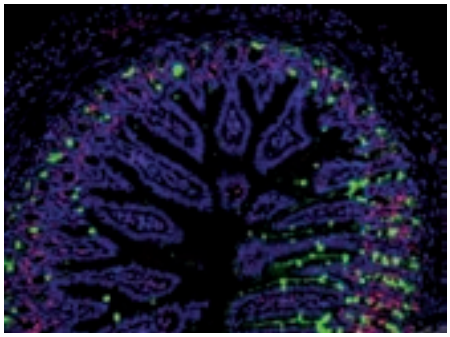
### Therapeutic targets for treatment of inflammatory bowel diseases
Project manager: Dr. I. Atreya
We are interested in those signalling pathways in the gut which are centrally involved in the pathogenesis of inflammatory bowel diseases (IBD) and thereby represent potential targets for innovative therapeutic strategies. In particular, we focus on the process of post-translational prenylation and the activation of Rho proteins in intestinal epithelial cells and lamina propria immune cells. Experimental blockade of these intracellular processes enables us to define the resulting impact on pro-inflammatory immune cell function and on epithelial barrier integrity. Our investigations intend to identify new therapeutic target structures for an improved treatment of inflammatory gut pathology.

### Division of clinical and experimental pulmonology
Project managers: PD Dr. F. Fuchs, Prof. Dr. K. Hildner
Our clinical research attempts to evaluate new imaging methods during bronchoscopy. Our data highlight in vivo confocal laser-endomicroscopy as a real time and safe method to visualize malignant lesions. Furthermore, we perform feasibility and surplus studies of chromobronchoscopy in vivo.
Our preclinical studies try to shed light on the immunopathogenesis of lung cancer both, in murine model systems and patients. We are establishing clinically relevant mouse tumor models and started to bank human lung tissue for further molecular analysis.

### Molecular endoscopy
Project manager: Prof. Dr. H. Neumann
Molecular endoscopy enables highly specific diagnosis of disease specific targets during ongoing endoscopy. Based on molecular features this new imaging modality allows adjustment of therapeutic regimens and a personalized and optimized care of each individual patient. Main objective of our working group is to evaluate molecular endoscopy in the setting of IBD, Barrett's esophagus, and in colorectal polyps.

### Molecular gastroenterology
Project manager: Prof. Dr. C. Becker
The research group focuses on the immunological and molecular mechanisms that lead to the development of infection, chronic inflammation, and cancer within the gut. In the past two years, this group has developed a new concept for the pathogenesis of chronic IBD. The researchers could show that the regulation of the molecule caspase-8 in the intestinal epithelium by cFLIP has a crucial role for the health and function of the gut. To maintain the intestinal barrier, cell death signaling in the epi-

thelium must be strictly controlled. The research group was able to show that the molecule cFLIP plays an extremely important role in keeping epithelial cells alive. cFLIP blocks caspase-8 activity and prevents that cell death mediators in the intestine induce an activation of the cellular suicide program. If cFLIP is lacking in the intestinal epithelium, an excessive number of epithelial cells die, making the body a vulnerable target for invading bacteria. The results show the importance of a strict regulation of cell death in epithelial cells of the intestine for the whole body and indicate the great importance of these cells as guardians of the organism.



*Double staining of proliferating cells and secretory cells in the small intestine.*

### Patient-oriented research and innovative therapeutic strategies in IBD

Project manager: Prof. Dr. R. Atreya

Aim of our research group is the identification of biomarkers for the prediction of therapeutic response to immunosuppressive therapies in IBD. In a translational approach, we aim at characterizing the molecular mechanism of action of immunosuppressive therapies and presentation of molecular targets for a successful therapeutic approach. The use of endoscopic molecular imaging for the individual prediction of therapeutic response in IBD represents another field of our research group. Furthermore molecular imaging is used for the identification and characterization of mucosal lesions in vivo due to their molecular composition rather than their morphological structure alone.

### Ultrasound

Project manager: Prof. Dr. D. Strobel

Research includes contrast enhanced ultrasound (CEUS), elastography, acoustic radiation force imaging (ARFI), and interventional ultrasound.

- CEUS for the detection of liver metastasis in colorectal cancer (multicenter trial German Society for Ultrasound in Medicine)
- CEUS for the characterization of hepatic tumors and monitoring of antiangiogenetic therapy
- CEUS in IBD
- CEUS quantification
- ARFI of chronic hepatic diseases and tumors
- ARFI of extrahepatic disorders (pancreas, gastrointestinal tract)
- Sonographically guided abdominal interventions (multicenter trial German Society for Ultrasound in Medicine).

### Cytokines and transcription factors in IBD and carcinoma

Project manager: PD Dr. B. Weigmann

Crohn's disease and ulcerative colitis are distinct disease entities of IBD which are characterized by a characteristic mediator profile. Patients with Crohn's disease and ulcerative colitis have increased levels of Th1 cytokines and Th2 cytokines, respectively. The research focus of the working group are special proteins called transcription factors and cytokines. A special role is played by the transcription factor NFATc2: It is important for the activation of T cells and has been brought in connection with ulcerative colitis earlier. NFATc2 controls the development of pro-inflammatory interleukin-6 messenger that plays an important role in carcinoma induction. Another focus is interleukin-9 which was identified in connection with IBD and which is expressed from a specific T-cell population, Th9 cells. A regulation of IL-9 by the use of specific antibodies could be found as a basis for a new effective therapeutic approach.

## Teaching

The Department of Medicine 1 contributes to curricular teaching for medical students from second to final year. The necessary skills are taught in practical courses (introduction to clinical medicine, physical examination course, internal medicine) and with models and simulators. Several lectures deal with general internal medicine and the different foci of the Department of Medicine 1.

### Selected Publications


Wittkopf N, Günther C, Martini E, He G, Amann K, He YW, Schuchmann M, Neurath MF, Becker C. Cellular FLICE-like inhibitory protein secures intestinal epithelial cell survival and immune homeostasis by regulating caspase-8.Gastroenterology 2013, 145(6): 1369-79

Mchedlidze T, Waldner M, Zopf S, Walker J, Rankin AL, Schuchmann M, Voehringer D, McKenzie AN, Neurath MF, Pflanz S, Wirtz S. Interleukin-33-dependent innate lymphoid cells mediate hepatic fibrosis. Immunity 2013, 39(2): 357-71

Neufert C, Becker C, Türeci Ö, Waldner MJ, Backert I, Floh K, Atreya I, Leppkes M, Jefremow A, Vieth M, Schneider-Stock R, Klinger P, Greten FR, Threadgill DW, Sahin U, Neurath MF. Tumor fibroblast-derived epiregulin promotes growth of colitis-associated neoplasms through ERK. J Clin Invest 2013, 123(4): 1428-43

Neumann H, Vieth M, Dallemagne B, Marescaux J, Inoue H, Perretta S Confocal laser endomicroscopy guided endoscopic myotomy. Gastroenterology 2014, 147(1): 31-2

Gerlach K, Hwang Y, Nikolaev A, Atreya R, Dornhoff H, Steiner S, Lehr HA, Wirtz S, Vieth M, Waisman A, Rosenbauer F, McKenzie AN, Weigmann B, Neurath MF. TH9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells. Nat Immunol 2014, 15(7): 676-86

Atreya R et al. In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease. Nat Med 2014, 20(3): 313-8


*In 2010 the Department of Medicine 1 moved into the new research building in the Hartmannstraße.*

# Department of Medicine 2 – Cardiology and Angiology

## Chair of Internal Medicine II

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**Research Focus**
- Electrophysiology
- Interventional cardiology
- Interventional valve therapy
- Sports cardiology
- Echocardiography
- Cardiac magnetic resonance tomography
- Cardiac computed tomography
- Molecular and experimental cardiology

## Structure of the Department

The Department of Medicine 2 focuses on cardiology and angiology. Together with the Department of Cardiac Surgery and the Divisions of Pediatric Cardiology of Pediatric Cardiac Surgery, the Department of Medicine 2 forms the University Heart Center of Erlangen. It is a tertiary referral center offering the full array of in- and outpatient diagnostic and therapeutic options for cardiovascular diseases. The Department of Medicine 2 employs 43 physicians, three of them with permanent teaching positions at the Faculty of Medicine ("Habilitation"), three biologists, and 166 non-physician nursing or supporting staff. It harbors two wards, a coronary care unit, two catheterization labs, one hybrid-lab, and an outpatient clinic with several specialized clinics for heart failure, congenital heart disease in adults, arrhythmias, and pacemakers/defibrillators. Furthermore, the Department of Medicine 2 disposes of a large basic-science laboratory.

## Research

### Electrophysiology

Project manager: Dr. M. Arnold

The research group is part of the Leading Edge Cluster "Medical Valley". The project IS 08b is funded by the BMBF. It aims at developing an algorithm which predicts the worsening of the clinical condition of heart failure patients. Implantable cardioverter defibrillators with new developed sensors and a home monitoring platform are applied for this study. In the iChart-study, confounding factors that influence the measurement of the intrathoracic impedance were identified. The measurement of the intracardiac impedance is the main focus of the iGraph-study. Acute hemodynamic changes in patients are correlated to measurements of the intracardiac impedance. In an accompanying registry, again potentially confounding factors for the intracardiac impedance are documented.

### Interventional cardiology

Project managers: Dr. C. Schlundt, PD Dr. H. Rittger, Prof. Dr. J. Ludwig

The working group is involved in the interventional therapy of coronary artery and structural heart disease. One focus is the systematic evaluation of coronary pressure wire measurements. In a randomized trial, the group could show that intracoronary administration of adenosine is not inferior to the intravenous administration, but is more convenient for the patient. Furthermore a model was developed to generate FFR (fractional flow reserve) measurements from anatomic angiographic data sets based on fluid dynamic modeling. Another focus is the evaluation of fully bioresorbable vascular stents (scaffolds).

In the treatment of chronic total occlusions (CTO), first recanalizations were successfully carried out using also a fusion imaging with cardiac computed tomography.

The group collaborates nationally and internationally to develop artificial prostheses for interventional aortic valve replacement, investigates new methods for the treatment of mitral regurgitation and device implantation for left ventricular partitioning in terminal heart failure.

### Interventional valve therapy

Project manager: Dr. M. Arnold

The Department of Medicine 2 performs transcatheter valve implantations in close collaboration with the Department of Cardiac Surgery. The Department participates in several international registries for the evaluation of different transcatheter valve types (PREVAIL, SOURCE XT, SOURCE 3) and in a project which investigates the performance of the transcatheter prosthesis in pure aortic insufficiency (Jupiter Study). Together with the Department of Cardiac Surgery, a modified surgical access for transfemoral transcatheter valve implantation was developed and is currently under evaluation.

### Sports cardiology

Project manager: PD Dr. C. Stumpf

This working group is concerned with the effects of physical activity on the cardiovascular system in the different age groups and areas. Major focus is the evaluation of exercise therapy in patients with chronic heart failure and to what extent the remodeling as well as inflammatory mechanisms may be affected (EndoHEART). Another focus of the working group is cardiovascular prevention, in particular pathophysiological mechanisms of endothelial dysfunction and their suggestibility by exercise training. The group cooperates with the working group molecular and experimental cardiology.

### Echocardiography

Project manager: Dr. M. Schmid

This research group focuses on tissue Doppler and deformation ("strain") imaging, especially in the field of ischemia detection, the identification of heart failure patients who benefit from cardiac resynchronization therapy, and myocardial deformation characteristics in patients with aortic valve disease before and after valve replacement.

### Cardiac magnetic resonance tomography (MRT)

Project manager: Dr. M. Schmid

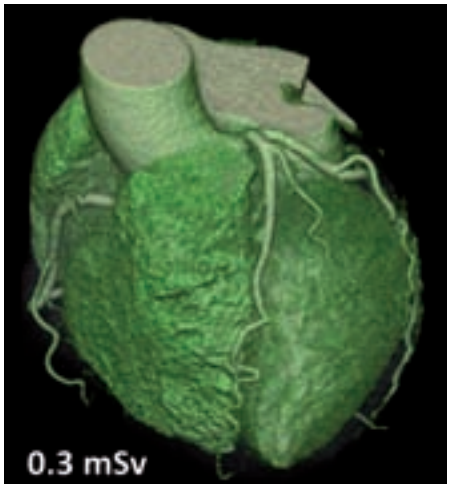
In collaboration with the Institute of Radiology, the research group focuses on the development and validation of new cardiac MRT techniques. One field is the prognostic importance of T2 weighted and contrast-enhanced imaging after myocardial infarction and the determination of infarct size as a surrogate endpoint. Studies of myocardial perfusion with adenosine stress using new high-resolution sequences are another focus of interest. Furthermore, in suspected perimyocarditis, so-called edema-sequences are evaluated to detect the acute inflammatory process and the extent of myocardial involvement. Additional research topics are the non-invasive quantitation of valvular heart disease as compared to established standards, morphologic and functional MRI imaging in stress cardiomyopathy, and characterization and localization of myocardial fibrosis in dilated cardiomyopathy.

### Cardiac computed tomography

Project manager: Dr. M. Marwan

The working group is involved with various aspects of CT imaging of the heart and especially the coronary arteries. The main focus of the working group is the characterization of coronary atherosclerosis. Funding is provided –

among others – by the BMBF. In addition to assessing the diagnostic accuracy and clinical value of coronary CT angiography, the group cooperates with the Institute of Radiology and several international partners in the development and validation of methods for radiation dose reduction. Novel post processing techniques as "iterative reconstruction" play a special role in this field. Moreover, clinical integration of cardiac CT in the sense of "therapeutic imaging" is of particular interest. A detailed and comprehensive evaluation of the use of CT for planning coronary interventions (especially in chronic total occlusions) and in non-coronary cardiac interventions (transcatheter aortic valve replacement, left atrial appendage closure and other interventions for structural heart disease) is performed. The group collaborates nationally and internationally with large registries and participates as a Core-Lab in international multicenter studies. Furthermore, the working group is very active in the field of education and training and runs courses on various topics of cardiac CT with national as well as international attendance.




*CT 3-dimensional reconstruction of the heart showing the three coronary arteries. Effective radiation dose 0.3 mSv.*

### Molecular and Experimental Cardiology

Project managers: Dr. B. Dietel, Dr. D. Raaz-Schrauder, PD Dr. C. Stumpf

The research projects of the group concentrate on

a) Pathomechanisms of atherosclerosis,

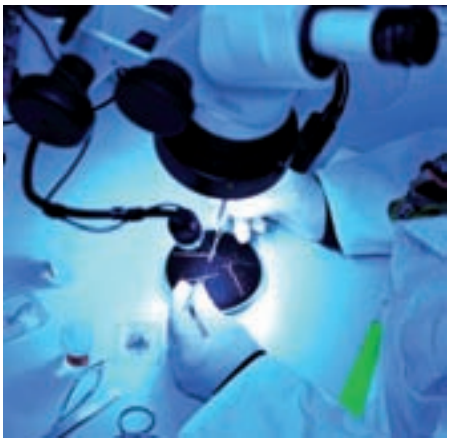
b) Biomarkers in cardiovascular diseases, and

c) The construction of new vessels.

Furthermore, the working group examines the effects of chinese herbal medicine on endothelial function in vitro and in vivo. For these studies the group cooperates with the Nanjing University of traditional Chinese medicine.

Additional projects envision the creation of biological, artificial vessels. As part of the 'Emerging Field Initiative' at the FAU, we currently establish cell lineages as well as culture techniques allowing the construction of three-layered, biological active vessels.

With our projects and biobanks, we participate in national and international projects (e.g. national projection about gen-polymorphisms in coronary artery disease).



*En-face preparation of the murine aortic arch and thoracoabdominal aorta for the quantification of the plaque size.*

## Teaching

The Department of Medicine 2 provides 35 teaching activities (from lecture to practical exercise) per term. Members of the Department repeatedly won the first prize for good teaching of the Faculty of Medicine.

### Selected publications

Hadamitzky M et al. Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry). J Am Coll Cardiol 2013, 62(5): 468-76

Stumpf C, Fan Q, Hintermann C, Raaz D, Kurfürst I, Losert S, Pflederer W, Achenbach S, Daniel WG, Garlichs CD. Anti-inflammatory effects of danshen on human vascular endothelial cells in culture. Am J Chin Med 2013, 41: 1065-77

Dietel B, Cicha I, Voskens CJ, Verhoeven E, Achenbach S, Garlichs CD. Decreased numbers of regulatory t cells are associated with human atherosclerotic lesion vulnerability and inversely correlate with infiltrated mature dendritic cells. Atherosclerosis 2013, 230: 92-9

Klinghammer L, Urschel K, Cicha I, Lewczuk P, Raaz-Schrauder D, Achenbach S, Garlichs CD. Impact of telmisartan on the inflammatory state in patients with coronary atherosclerosis-influence on IP-10, TNF-α and MCP-1. Cytokine 2013, 62: 290-6

Dietel B, Muench R, Kuehn C, Kerek F, Steinkasserer A, Achenbach S, Garlichs CD, Zinser E. Mcs-18, a natural product isolated from helleborus purpurascens, inhibits maturation of dendritic cells in apoe-deficient mice and prevents early atherosclerosis progression. Atherosclerosis 2014, 235: 263-72

Schuhbaeck A, Achenbach S, Pflederer T, Marwan M, Schmid J, Nef H, Rixe J, Hecker F, Schneider C, Lell M, Uder M, Arnold M. Reproducibility of aortic annulus measurements by computed tomography. Eur Radiol 2014, 24: 1878-88

### International Cooperations

U. Hoffmann, MD, MPH, Massachusetts General Hospital, Boston: USA

D.S. Berman, MD, Cedars Sinai Medical Center, Los Angeles: USA

K. Yao, MD, Nanjing University, Nanjing: China

### Research Equipment

Siemens Healthcare, Herzkatheter-Angiographieanlage (drei Labore)

Siemens Force Dual Source CT

St. Jude Medical, OCT-System

Biosense Webster (Johnson & Johnson), Carto 3 Biosense Webster, Electroanatomical Mapping System

# Department of Medicine 3 – Rheumatology and Immunology

## Chair of Internal Medicine III

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**Research Focus**
- Activation of neutrophile granulocytes
- Activation of synovial fibroblasts by microparticles in rheumatoid arthritis (RA)
- Adipose derived stromal cells for osteoarthritis
- Analysis of inflammatory mechanisms in adult onset Still's disease
- Analysis of risk factors and long-term outcome in patients with systemic lupus erythematosus (SLE)
- Apoptosis, necrosis, and NETosis as immune modulators
- Immunodeficiencies and infectious diseases
- Immunogenetics and transplantimmunology
- Mechanisms for the activation of fibroblasts in systemic sclerosis (SSc)
- Molecular signaling pathways in RA
- National and international clinical trials
- Pathomechanisms of bone destruction in RA
- The role of 12/15-lipoxygenase (12/15-LO) in the regulation of innate and adaptive immunity

## Structure of the Department

The Department of Medicine 3 covers the fields of rheumatology, immunology, and allergology. It involves the diagnosis and therapy of rheumatologic and immunologic diseases. For the treatment of patients, the Department of Medicine 3 is supplied with inpatient and outpatient wards where patients are cared for.
Our physicians are specialized in recognizing and treating these hard to diagnose diseases. The Department of Medicine 3 is among the few European "Centers of Excellence" according to the guidelines of the European League Against Rheumatism (EULAR) which mirrors its expertise on these fields.

## Research

### Activation of neutrophile granulocytes
Project manager: Dr. M. Hoffmann
Neutrophil granulocytes can either fuel or downregulate inflammation. We investigate the influence of neutrophils on inflammatory diseases and bone metabolism (gout, RA, or SLE). We focus on the formation of neutrophil extracellular traps (NET) and on chemical redox reactions. Finally we are going to translate data from animal models and in vitro-findings to humans and develop new treatment strategies.

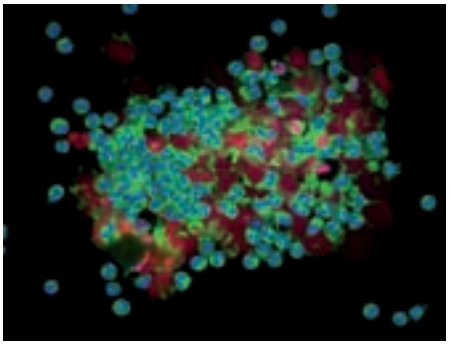
### Activation of synovial fibroblasts by microparticles in rheumatoid arthritis (RA)
Project manager: Prof. Dr. J. Distler
Microparticles are realised by activated and apoptotic leukocytes- and accumulate in the involved joints in patients with RA. We demonstrated that microparticles represent a novel mechanism for inter-cellular communication and that they play a role in the pathogenesis of RA by triggering a vicious circle of inflammation and bone-erosion. The mechanisms by which microparticles activate synovial fibroblasts are currently in focus.

### Adipose derived stromal cells for osteoarthritis
Project managers: Prof. Dr. G. Schett, Prof. Dr. A. Bozek
The FP7-EU-funded ADIPOA develops mesenchymal stem cell based therapy for the treatment of osteoarthritis. We test the improvement of the treatment efficacy by genetically modifying adipose-derived mesenchymal stem cells in mice.

### Analysis of inflammatory mechanisms in adult onset Still's disease
Project managers: Dr. J. Rech, Prof. Dr. B. Manger
Inflammatory mechanisms and cytokine profiles in patients with adult onset Still's disease are analyzed with respect to clinical presentation and outcome to identify therapeutic strategies for this rare disease.

### Analysis of risk factors and long-term outcome in patients with systemic lupus erythematosus (SLE)
Project manager: Prof. Dr. B. Manger
In a cohort of 410 SLE patients, genetic, serological, and clinical predictors for long-term outcome are analyzed in retrospective and prospective studies. One focus is on the investigation of premature atherosclerosis and ovarian failure in SLE.

### Apoptosis, necrosis, and NETosis as immune modulators
Project manager: Prof. Dr. Dr. M. Herrmann
We use controlled suicide systems to analyze generation and role of ROS (reactive oxygen species) and their intracellular accumulation. We employ the MSU (monosodium urate)-driven inflammation to analyze recruitment of granulocytes to sites of inflammation, NET formation, and aggregation.



*Nanodiamods induce NETosis*

### Immunodeficiencies and infectious diseases
Project manager: Prof. Dr. T. Harrer
The major interest of research of the group are aspects of HIV-infection, such as immunology, drug resistance, and research on new therapeutic and diagnostic procedures, like T cell receptor transfer and immunomonitoring using mRNA electroporation. We are developing immunotherapies, like vaccines and immunomodulators and participate in clinical studies on therapeutics for HIV-infection. Other projects focus on further infectious and immunologic diseases and chronic fatigue syndrome.

### Immunogenetics and transplant-immunology
Project manager: PD Dr. B. Spriewald
One research area is the induction of transplantation tolerance and modulation of transplant arteriosclerosis through the application of donor alloantigen and co-stimulation blockade. An important contribution to clinical research is the detection and differentiation of anti-HLA alloantibodies.

### Mechanisms for the activation of fibroblasts in systemic sclerosis (SSc)
Project manager: Prof. Dr. J. Distler
SSc is characterized by organ fibrosis, mediated by an uncontrolled production of ECM by fibro-

blasts. However, therapies to inhibit selectively the overproduction of ECM are lacking. We investigate novel signaling cascades that activate fibroblasts and study therapeutic approaches to inhibit the overproduction of ECM by SSc fibroblasts.

### Molecular signaling pathways in RA

Project managers: Prof. Dr. G. Schett, Dr. M. Stock

RA is characterized by perpetuating synovial inflammation and progressive joint destruction based on cartilage damage and bone erosion as a result of an imbalance of formation and resorption of cartilage and bone. Wnt signals link inflammation to this structural damage in arthritis and may play a major role in the pathogenesis of RA. We focus on regulation of the Wnt signaling network in rheumatic diseases and evaluate the potentials to interfere with cartilage damage caused by dysregulated Wnt signaling.

### National and international clinical trials

Project managers: Dr. J. Rech, Dr. A. Kleyer, Dr. A. Hueber, Dr. S. Bayat

Various national and international phase Ib-IV studies are conducted to investigate new treatment approaches in rheumatic diseases. The major focus are on treatments with "biologicals and small molecules", e.g. blockade of the proinflammatory cytokine TNFa, IL-6, IL-17, IL-12/23, JAK3-kinase.

We initiated and conducted a multicenter phase II trial in patients with erosive finger osteoarthritis.

### Pathomechanisms of bone destruction in RA

Project manager: Prof. Dr. G. Schett

RA is one of the most common inflammatory rheumatic joint diseases with an estimated prevalence of 1 %. Chronic arthritis, if poorly controlled, typically provokes extensive joint damage with the emergence of bone destruction associated with significantly decreased functional capacities. Hence, the project group focuses on the pathophysiology of bone destruction by the use of experimental arthritis models. They investigate the mechanisms leading to increased synovial activation of osteoclasts and decreased ability to repair bone destruction with the help of osteoblasts.

### The role of 12/15-lipoxygenase (12/15-LO) in the regulation of innate and adaptive immunity

Project manager: Dr. G. Krönke

12/15-LO is a central arachidonic acid-metabolizing enzyme. We elucidate the molecular role of 12/15-LO and its metabolites in macrophages and DC (dentritic cells) and a potential involvement of 12/15-LO in the phagocytosis of apoptotic cells, during the interaction between DC and T-lymphocytes and during chronic inflammatory diseases. We employ 12/15-LO deficient mice and various disease models (TNF-transgenic mice, CIA).

## Teaching

The education offered by the Department of Medicine 3 is embedded into the master plan of teaching in the internal medicine with lectures, courses, and internships. The GRK within SFB 643 is engaged with strategies of cellular immune intervention (compare own report).

### Selected Publications


Scholtysek C, Katzenbeisser J, Fu H, Uderhardt S, Ipseiz N, Stoll C, Zaiss MM, Stock M, Donhauser L, Böhm C, Kleyer A, Hess A, Engelke K, David JP, Djouad F, Tuckermann JP, Desvergne B, Schett G, Krönke G. PPARβ/δ governs Wnt signaling and bone turnover. Nat Med 2013, 19(5): 608-13

Harre U, Schett G. Bone research in 2012: the ups and downs of bone in health and rheumatic disease. Nat Rev Rheumatol 2013, 9(2): 67-8

Schett G, Bozec A. Removing the bone brake. Cell Metab 2014, 20(3): 394-5

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Dees C, Schlottmann I, Funke R, Distler A, Palumbo-Zerr K, Zerr P, Lin NY, Beyer C, Distler O, Schett G, Distler JH. The Wnt antagonists DKK1 and SFRP1 are downregulated by promoter hypermethylation in systemic sclerosis. Ann Rheum Dis 2014, 73(6):1232-9


### International Cooperations

Prof. Dr. J. Penninger, Prof. Dr. K. Redlich, Prof. Dr. J. Smolen, Institut of Molecular Biotechnology, Vienna: Austria

Prof. Dr. S. Kiechl, Prof. Dr. L. Wildt, Innsbruck Medical University: Austria

Dr. D. McIlroy, Université de Nantes: France

Prof. Dr. C. Jorgensen, CHU Montpellier: France

Prof. Dr. S. Muller, Institut de Biologie Moléculaire et Cellulaire du CNRS, Strasbourg: France

Prof. Dr. B. Autran, Hôpital Pitié-Salpêtrière, Paris: France

Prof. Dr. D. Isenberg, Center for Rheumatology Research, London: UK

Prof. Dr. J. Savill, Prof. Dr. I. Dransfield, The University of Edinburgh: UK

Prof. Dr. A. Manfredi, Immunologia Clinica, Milano: Italy

Prof. Dr. A. Tincani, Hospital and University of Brescia: Italy

Prof. Dr. O.-P. Rekvig, University of Tromso: Norway

Prof. Dr. I. Mcinnes, University of Glasgow: Scotland

Prof. Dr. L. Klareskog, Karloniska Institutet, Stockholm: Sweden

Prof. Dr. P.-P. Tak, University of Amsterdam: The Netherlands

Prof. Dr. J. van de Winkel, University Medical Center Utrecht: The Netherlands

Prof. Dr. A. Vandamme, Prof. Dr. R. Lories, Katholieke Universiteit Leuven: The Netherlands

Prof. Dr. T. Huizinga, University Medical Center, Leiden: The Netherlands

Prof. Dr. L. Joosten, Radboud University, Nijmegen: The Netherlands

Prof. Dr. T. Swaak, Erasmus Universiteit Rotterdam: The Netherlands

Prof. Dr. D.S. Pisetzky, Durham University: UK

Prof. Dr. B. Walker, Boston Medical Center: USA

Prof. Dr. G. Firestein, University of California, San Diego: USA

### Meetings and International Training Courses

27. - 28.06.2014: Crystal clear workshop, Erlangen

### Research Equipment

Beckman Coulter GmbH, Durchflußzytometer Gallios 3L/10C

Scanco Medical AG, XtremeCT in vivo MicroCT Scanner

Scanco MEDICAL samples 1ccm-20ccm, Micro-CT 40

# Department of Medicine 3 – Rheumatology and Immunology

## Division of Molecular Immunology

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**Research Focus**

- The role of miRNA in B cell maturation and pathogenesis of multiple myeloma
- Nonsense-codon mediated decay of non-functional mRNA
- Molecular control of early B cell differentiation
- Molecular control of peripheral B cell and plasma cell differentiation
- Selection of B cells

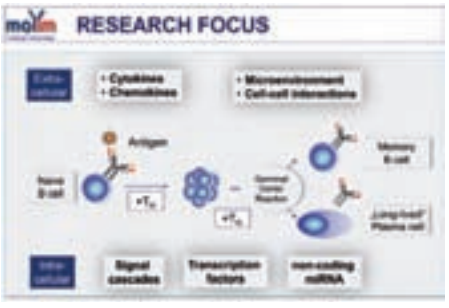
## Structure of the Division

The Division of Molecular Immunology was founded as an independent section within the Department of Medicine 3 in 1997 and resides in the NFZ. Besides the Head of the Division, a Professor emeritus (Prof. Dr. Dr. h.c. J.R. Kalden), seven senior postdoctoral scientists who supervise currently six Ph.D. students, two technicians, and various rotation students work at the Division. The main scientific focus concentrates on the humoral immune response with a special emphasis on B cell biology. In addition, members of the Division participate in teaching at undergraduate, graduate, and doctoral levels which is reflected by a broad offer of lectures, seminars, and lab courses.

Several research groups examine molecular mechanisms of development, activation, and differentiation of B cells in cell culture systems and transgenic mouse lines. Methods include state of the art molecular biology, cultivation of primary B cells, flow cytometry with cell sorting, and mouse immunology. Cell culture systems are used to identify new regulatory factors, e.g. miRNA, adaptor proteins, and transcription factors. Subsequently, new mouse models are established by homologous recombination in ES cells and blastocysts as well as by pronucleus injections. The Division of Molecular Immunology is well integrated into the Erlangen research environment through its central location in the NFZ and through its leading role in research groups and GK (e.g. FOR 832, GK 1660; see own reports). Nationally, the Division of Molecular Immunology is an important part of the research study group Biology of B lymphocytes within the DGfI (German Society for Immunology).

The overall research activities focus on molecular aspects of maturation and activation of antibody-producing B cells as well as the pathogenesis of B cell leukemia and autoimmune diseases. B-Lymphocytes express immunoglobulin (Ig) receptors on their surface which allow to recognize foreign antigens and pathogens. Ig receptors consist of two covalently associated identical immunoglobulin heavy (IgH) and two identical immunoglobulin light (IgL) chains which differ from cell to cell in their variable regions. When B cells are activated by contact to pathogen, they develop into either memory B cells or so-called plasma cells, the latter of which then produce huge amounts of soluble antibody molecules. These antibodies then bind to the pathogen, leading to its elimination and/or destruction.

B cells emerge from hematopoietic stem cells in the bone marrow. During their maturation process, B cells pass different developmental stages characterized by the rearrangement of Ig gene segments which starts at the IgH locus and later at the IgL locus. Each of these processes needs to be carefully and tightly controlled to avoid the generation of self-reactive or leukemic B cells. One part of the first critical checkpoint in early B cell development is the expression of the pre-B cell receptor (pre-BCR) in early progenitor B cells. Only cells that express a functional IgH chain can assemble a pre-BCR and subsequently receive signals for survival, proliferation, and differentiation. During the next developmental stage, rearrangement takes place at the IgL locus, leading to the synthesis of an IgL chain that is then assembled with the IgH chain to form the B cell receptor (BCR). The BCR is then controlled for binding to self-structures in the bone marrow environment. B cells with a non-self BCR leave the bone marrow and differentiate via transitional stages into mature antigen-responsive B cells.




## Research

### The role of miRNA in B cell maturation and pathogenesis of multiple myeloma

Project managers: Prof. Dr. H.-M. Jäck, Dr. J. Wittmann

One research focus is on the role of microRNA 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 (messanger RNA) which results either in a block of translation or an acceleration of the degradation of the target mRNA. MiRNA play a central 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-codon mediated decay of non-functional mRNA

Project managers: Prof. Dr. H.-M. Jäck, Dr. J. Wittmann

Another research focus is the molecular control of recognition and decay of non-functional Ig-mRNA, a pathway that is termed nonsense-codon mediated decay (NMD) of non-functional mRNA (mRNA surveillance). Nonsense Ig mRNA is encoded from non-productively rearranged Ig genes during B cell development as a consequence 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 particular 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 lab can be conditionally deleted in developing B cell progenitors. In parallel, immunprecipitation 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 early B cell differentiation

Project managers: Prof. Dr. H.-M. Jäck, Dr. W. Schuh

One major focus is the analysis of mechanisms that control early B cell development and signaling of the pre-B cell receptor. For example, the interaction of the pre-BCR with structures and ligands in the bone marrow microenvironment and its impact on survival and proliferation of progenitor B cells is studied using different mouse models. Using transcriptome- and proteome analyses, we identified various cellular components of the pre-BCR signaling cascade, for example the transcription factor Krüppel-like factor 2 (KLF2) and a number of small non-coding microRNA. However, investigations of the function of KLF2 in B cell maturation and activation showed that KLF2 cannot be solely responsible for termination of pre-BCR induced proliferation. In future studies, we will analyze further potential target genes of pre-BCR signaling and their role in pre-B cell differentiation. A novel candidate gene for termination of pre-B cell expansion is KLF4, a transcription factor closely related to KLF2. Using a KLF2/KLF4-double deficient mouse model, we are currently analyzing the function of KLF4 in early B cell development.

### Molecular control of peripheral B cell and plasma cell differentiation

Project managers: Prof. Dr. H.-M. Jäck, Dr. W. Schuh

Immune responses are strictly dependent on proper positioning of effector cells in the body. KLF2, a target gene of the pre-BCR, plays a crucial role in differentiation, activation, and proper positioning of B cells in peripheral compartments. Furthermore, analyses of a B cell-specific KLF2 deletion showed that KLF2 is essential for the migration of plasma cells to their survival niches in the bone marrow. In future studies, we will dissect the underlying mechanisms by identifying new target genes of KLF2 using comparative transcriptome analyses of normal plasma cells and KLF2-deficient plasma cells.

### Selection of B cells

Project manager: PD Dr. D. Mielenz

The unique passport of each single B cell is BCR. The BCR allows a specific antigen to select its cognate B cells via binding to the BCR from a pool of billions of B cells. On one hand, this permits an effective and specific immune response; on the other hand, it prevents the activation of potentially dangerous B cells with self-antigens. The specificity of a BCR may furthermore decide which anatomic niche will be populated by a given B cell. Since expression of the BCR per se controls B cell survival, newly formed B cells are positively selected for proper surface expression of the BCR and negatively for self-reactivity. The selected B cell pool, however, should recognize any kind of antigen presented in the blood or on antigen-presenting cell. The diverse requirements that are imposed upon the BCR require thus a fine-tuned intracellular signal transduction machinery whose elements are not fully characterized yet and that are also employed by other receptors on B cells, such as CD40 or toll-like receptors. Therefore, the main goal of this project is to identify new signal elements in B cells. So far, three new adaptor proteins have been identified. The function of these proteins in the proximal and distal signaling pathways of the BCR and CD40 is currently being investigated in cell culture systems and transgenic as well as knock-out mouse lines.

## Teaching

The Division of Molecular Immunology participates in undergraduate and graduate education within the bachelor and master programs in biology, life science engineering, and molecular medicine. Students have the opportunity to work on their bachelor and master theses embedded in the research focus of the Division. Furthermore, the Division engages in educating and training doctoral students from GK 1660 and the research group FOR 832 by offering numerous workshops and seminars.

### Selected Publications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Gabler J, Wittmann J, Porstner M, Renz H, Jäck HM, Abram M, Zemlin M. Contribution of microRNA 24-3p and Erk1/2 to interleukin-6-mediated plasma cell survival. Eur J Immunol 2013, 43(11): 3028-37

Brachs S, Turqueti-Neves A, Stein M, Reimer D, Brachvogel B, Bösl M, Winkler T, Voehringer D, Jäck HM, Mielenz D. Swiprosin-1/EFhd2 limits germinal center responses and humoral type 2 immunity. Eur J Immunol 2014, 44(11): 3206-19

Freitag J, Heink S, Roth E, Wittmann J, Jäck HM, Kamradt T. Towards the generation of B-cell receptor retrogenic mice. PLoS ONE 2014, 9(10): e109199

Winkelmann R, Sandrock L, Kirberg J, Jäck HM, Schuh W. KLF2-a negative regulator of pre-B cell clonal expansion and B cell activation. PLoS ONE 2014, 9(5): e97953


### International Cooperations

Prof. Dr. K. Knight, Loyola University of Chicago, Chicago: USA

Prof. Dr. M. Wabl, University of California, San Francisco: USA

### Meetings and International Training Courses

27. – 29.09.2013: 4th International GK Symposium "Regulators of Adaptive Immunity"

### Research Equipment

Hochgeschwindigkeits-Zellsorter mit 5 Lasern

Beckman Coulter Flow analyzer

# Department of Medicine 4 – Nephrology and Hypertension

## Chair of Internal Medicine IV

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**Research Focus**
- Development and progression of chronic kidney disease
- Pathophysiologic relevance of hypoxia-inducible gene expression
- Pathogenesis of arterial hypertension and hypertensive endorgan damage
- Acute and chronic renal allograft failure
- Systemic consequences of kidney disease and renal replacement therapy

## Structure of the Department

The Department of Medicine 4 comprises the Department of Medicine 4 – Nephrology and Hypertension at the UK Erlangen and the Nuremberg Hospital. Together they represent the largest research and treatment center for kidney disease and hypertension in Germany.
More than 90 physicians and basic scientists work in the Department of Medicine 4.
Patient-related and experimental research aims at better understanding the pathogenesis of kidney disease and hypertension and their progression and adverse consequences, at identifying novel therapeutic strategies, and at evaluating therapeutic options. Research projects at this Department have played a major role in research networks, such as the Clinical Research Group 106 (Endorgan Damage in Arterial Hypertension), the SFB 423 (Kidney Injury: Pathogenesis and Regenerative Mechanisms) and the German Chronic Kidney Disease (GCKD) study (see own report), and contribute significantly to the research focus "Kidney and Circulation Research" of the Faculty of Medicine.
The main clinical areas comprise diagnosis and therapy of kidney diseases, primary and secondary hypertension, renal transplantation, sepsis, and multiorgan failure.

## Research

### Development and progression of chronic kidney disease

In order to better understand the course of chronic kidney disease and to identify novel risk factors and molecular markers, a national prospective cohort study, the GCKD study (see own report), has been initiated. Nine regional centers and several institutes at other universities collaborate with the coordinating center in Erlangen to study 5,000 patients with chronic kidney disease and to follow them for up to ten years. This large consortium is funded by the BMBF and the Foundation for Preventive Medicine of the Kuratorium für Heimdialyse. Studies of the genetic causes of kidney disease play an important role within this consortium.
Besides the observational studies, interventional clinical trials are performed in patients with kidney disease of different etiologies, in particular with certain forms of glomerulonephritis and polycystic kidney disease.
Experimental projects in this research area aim at determining processes that lead to the initiation of kidney injury and at identifying the mechanisms which result in regeneration or progressive loss of function. To this end, analyses are being performed in isolated cells, human kidney tissue, and animals. Another focus comprises studies determining the influence of renal autonomous innervation on inflammatory processes in the kidney.

### Pathophysiologic relevance of hypoxia-inducible gene expression

One pathomechanism which is intensively investigated concerns hypoxia and its relevance for kidney disease. 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 modulation of the HIF system. It could be shown that inhibitors of HIF degradation result in a marked nephroprotection. This approach is potentially transferable into the clinic in order to prevent acute kidney injury and reduce ischemia reperfusion injury in the context of kidney transplantation. In parallel, the potential long term consequences of hypoxia on renal structure are being analyzed, in particular fibrogenesis, epithelial mesenchymal transition, and the growth of renal cysts.

### Pathogenesis of arterial hypertension and hypertensive endorgan damage

A further important research area relates to studies of arterial hypertension. A specific focus in this area lies on target organ damage induced by hypertension in kidneys, heart, eye, and vasculature. In addition, the etiology and pathogenesis of arterial hypertension are being investigated.
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. Mechanisms in the skin where alterations in sodium content influence lymph-angiogenesis appear to be of particular relevance in this context. Sodium balance studies during the Mars mission project (MARS 500) and innovative imaging techniques (sodium-MRI) were used that allowed to analyze in sodium homeostasis and tissue sodium content in humans.
Additional experimental projects deal with the role of the renin-angiotensin system and the sympathetic nervous system for the pathogenesis of hypertension and kidney injury. These studies include electrophysiological investigations of ganglion cells, measurements of tissue hormones, and studies in transgenic mice as well as tissue analyses. Electrophysiological measurements of sympathetic nerve activity are not only being conducted in animal models, but – using microneurography – in humans, too. In addition, symphathetic outflow to the kidney and endothelial function of renal vessels are indirectly measured through determination of renal perfusion and sodium excretion. Additional studies in patients are dealing with the regulation of endothelial function and in particular the influence of lipids and hormones. A special focus in recent years have been studies on the efficacy and value of renal denervation in the treatment of hypertension.

### Acute and chronic renal allograft failure

In cooperation with the Departments of Urology and Surgery, up to 100 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 with particular emphasis on grafts from marginal donors. Several multicenter trials are being conducted to evaluate novel immunosuppressive drugs or their combination.

In parallel to the clinical trials, experimental studies are performed in a rat transplant model in order to identify novel strategies for the improvement of organ function.

### Systemic consequences of kidney disease and renal replacement therapy

More than 10 % of the population suffer from chronic kidney disease, as defined by reduced kidney function and/or increased urinary protein excretion. Kidney disease is associated with the risk of progressive loss of renal function as well as a marked increase in cardiovascular risk. Research projects at the Department of Medicine 4 in this context deal with epidemiological questions, aspects of public health care, the causes of an increased cardiovascular risk, and the optimization of renal replacement therapy. Partly in collaboration with the Department of Medicine 2, mechanisms of atherosclerosis are being investigated as well as the specific consequences of impaired renal function on vascular pathology. This includes e.g. experimental studies of the role of asymmetric dimethylarginin (ADMA) and of impaired angiogenesis in kidney disease.

The characteristic systemic consequences of chronic kidney disease include also anemia and disturbances in bone and mineral metabolism which have both been identified as cardiovascular risk factors. The Department of Medicine 4 participates in several multicenter trials aiming at optimizing management of these complications. A rare complication of treatment with recombinant human Erythropoietin (EPO) is the development of neutralizing antibodies leading to pure red cell aplasia. The Department is leading an international therapeutic trial in such patients with a novel EPO-mimetic that does not cross-react with the antibodies.

Additional clinical research deals with acute kidney injury, in particular in the context of sepsis and multiorgan failure. The North Bavarian SepNet Regional Center, located at the Departments of Medicine 4 in Erlangen and Nürnberg, participates in several observational and treatment trials.

## Teaching

The Department of Medicine 4 with its clinical units in Erlangen and Nürnberg contributes to the entire spectrum of curricular teaching in internal medicine, including main lectures, different courses, and training of final year medical students. In addition, several specialized seminars are being offered as well as optional courses in intensive care medicine, transplantation, kidney and vascular system.

There is also the opportunity for clinical electives and observerships.

### Selected Publications


Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Kottgen, Levey AS, Levin A. Evolving Importance of Kidney Disease: From Subspecialty to Global Health Burden. Lancet 2013, 382: 158-69

Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, Muller DN, Hafler DA. Sodium Chloride Drives Autoimmune Disease by the Induction of Pathogenic Th17 Cells. Nature 2013, 496: 518-22

Ott C, Mahfoud F, Schmid A, Ditting T, Sobotka PA, Veelken R, Spies A, Ukena C, Laufs U, Uder M, Böhm M, Schmieder RE. Renal Denervation in Moderate Treatment-Resistant Hypertension. J Am Coll Cardiol 2013, 6: 1880-6

Buchholz B, Schley G, Faria D, Kroening S, Willam C, Schreiber R, Klanke B, Burzlaff N, Jantsch J, Kunzelmann K, Eckardt KU. Hypoxia-Inducible Factor-1 $\alpha$ Causes Renal Cyst Expansion through Calcium-Activated Chloride Secretion. J Am Soc Nephrol 2014, 25: 465-74

Ekici AB et al. Renal Fibrosis Is the Common Feature of Autosomal Dominant Tubulointerstitial Kidney Diseases Caused by Mutations in Mucin 1 or Uromodulin. Kidney Int 2014, 86: 589-99

Jacobi J, Rebhan D, Heller K, Velden J, Hilgers KF, Wullich B, Eckardt KU, Amann KU. Donor Acute Kidney Injury (AKI) and Short-Term Graft Outcome in Renal Transplantation. Clin Transplant 2014, 28: 1131-41


### International Cooperations

For further information, please visit our homepage: www.medizin4.uk-erlangen.de.

### Meetings and International Training Courses

02.03.2013: Intensivsymposium, Klinikum Nürnberg Süd

30.11.2013: Post ASN Fortbildung, Nürnberg

15.02.2014: Intensivsymposium, Klinikum Nürnberg Süd

29.11.2014: Post ASN Fortbildung, München

# Department of Medicine 5 – Hematology and Oncology

## Chair of Hematology and Oncology

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**Research Focus**
- T cell based immunotherapy
- Adoptive cell therapy with memory B-lymphocytes for patients after stem cell transplantation (alloSCT)
- $CD4^+$ T cell based immunotherapy
- Immunoregulation of alloSCT
- Immunregulation in cancer biology and SCT
- Immunotherapy and magnetic flowcytometry with $CD4^+$ T cells
- Tumor immune escape
- Cellular immunotherapy
- HLA-laboratory

## Structure of the Department

The Department of Medicine 5 is the clinic of Hematology and Oncology. As a hospital providing maximum care, it offers the complete range of diagnostic and therapeutic options for malignancies of the blood, lymphnodes, and solid tumors for both, ambulatory and stationary patients. The Department focuses on the transplantation of allogeneic and autologous bone marrow stem cells in adults.
It has a total of 81 employees (24 on extra-departmental funding). The scientific section counts nine post-doctoral fellows, eleven graduate students, and twelve technicians.

## Research

### T cell based immunotherapy

Project managers: Prof. Dr. A. Mackensen, Dr. M. Aigner, Dr. S. Völkl
The group develops new approaches to generate and improve adoptive T cell therapy against malignant diseases. Main focus of this project is to establish a protocol for the expansion and differentiation of highly functional tumor-specific T cells. The population of human $TCR\alpha/\beta^+$ $CD4^-$ $CD8^-$ 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.
Funded by DFG and IZKF

### Adoptive cell therapy with memory B-lymphocytes for patients after allogeneic stem cell transplantation (alloSCT)

Project managers: 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, five patients received the B cell product and no severe adverse events were observed.
Funded by SFB 643 "Strategies of Cellular Immune Intervention" (see own report)

### $CD4^+$ T cell based immunotherapy

Project manager: PD Dr. A.N. Kremer
In HLA-matched stem cell transplantation, the beneficial graft versus leukemia (GvL) effect is mediated by donor-derived T-lymphocytes which recognize patient-derived polymorphic peptides. These so-called minor histocompatibility antigens (MiHA) also play an important role in the induction of detrimental GvHD. By characterization of the intracellular processing pathways of HLA class II restricted MiHA, we could identify a group of antigens whose pres - entation is dependent on expression of the non-classical HLA molecule HLA-DO. Based on the selective expression profile of HLA-DO, these results could open the possibility to separate GvL effect and GvHD.
In an additional project, we analyze the $CD4^+$ T cell mediated eradication of HLA class II negative tumors via indirect antigen presentation in mice and involved intracellular mechanisms.
Funded by ELAN, IZKF, and Jung-Foundation

### Immune metabolism in cancer biology and SCT

Project manager: PD Dr. D. Mougiakakos
Our research group is mainly interested in studying the alterations of the metabolism and the immune system due to cancer and after stem cell transplantation. A better understanding regarding the tumor-associated (metabolic) strategies contributing to an immunosuppression will support the development of novel therapeutic strategies. Furthermore, we aim at "learning" from tumors how they specifically weaken immune responses in order to translate these findings into potential experimental approaches for the treatment of rejection reactions (GvHD) following SCT. Our main research interests include studies regarding
- Metabolism-associated immunosuppression in leukemia,
- Myeloid derived suppressor cells in various tumor entities and following stem cell transplantation, and
- The suppressive effects exerted by human mesenchymal stem cells.

Funded by ELAN, IZKF, German Cancer Aid, European Hematology Association, German José Carreras Leukaemia-Foundation, Elite Network of Bavaria

### Immunotherapy and magnetic flowcytometry with $CD4^+$ T cells

Project manager: Dr. J. Bosch
The main focus of our research group is to develop immunotherapy with $CD4^+$ T cells for treatment of ocular melanoma and to develop a novel magnetic flowcytometry technique. Current research aims at determining which immune cells infiltrate the primary tumor in the immune-privileged eye and if uveal melanoma vaccines activate different subpopulations of $CD4^+$ T cells. The studies on magnetic flowcytometry focus on a novel technique which applies magnetophoresis to perform cell enrichment, focusing, and background elimination in a single step. Time-of-flight measurements are performed with integrated magnetic sensors to detect specifically cancer cells and cell diameters in whole blood.
Funded by DFG and WING-program of the BMBF.

### Tumor immune escape

Project managers: Prof. Dr. A. Mackensen, Dr. M. Aigner
In the last years, the study of tumor metabolites and their effects on the adaptive immune system moved into the center of interest of tumor

immunology. 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 malignacies. The influence of MTA produced by tumors on the activation, proliferation, and various effector functions of cytotoxic $CD8^+$ and $CD4^+$ T cells is studied by the research unit in cooperation with the University Hospital Regensburg and funded by the DFG.

### Cellular immunotherapy

Project managers: Prof. Dr. A. Gerbitz, Dr. M. Aigner, Dr. H. Bruns, Dr. R. Gary

The "Cellular Immunotherapy" group works on the development of T cell therapies directed against B-cell specific self-antigens, such as CD19. The main goal is the development of lymphoma specific T cell therapies in murine models and the development of HLA A201 restricted CD19 specific TCR. In addition, the group focuses on the development of CMV/EBV specific T cells for adoptive transfer in patients after allogeneic stem cell transplantation. A multicenter clinical phase I study was initiated in 2014. Parallel to the development of a GMP grade T cell product, the group established a broad immunomonitoring platform for patients. Within the 643, the immunomonitoring was extended in collaboration with the Institute of Pathology (Charité Berlin) by single cell TCR analysis using Next Generation Sequencing.

Funded by DFG, German Cancer Aid, and Bay-ImmuNet

### HLA-laboratory

Project manager: 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

A traditional teaching program (lectures, seminars, practica) covering all subjects in the field of hematology and oncology is being offered by qualified staff in an integrated and interdisciplinary fashion. A new internal medicine program in hematology and oncology was introduced. In this comprehensive program, small groups of medical students learn the basics of hematology and oncology in a patient-oriented setting.

### Selected Publications


Helou M, Reisbeck M, Tedde SF, Richter L, Bär L, Bosch JJ, Stauber RH, Quandt E, Hayden O. Time-of-flight magnetic flow cytometry in whole blood with integrated sample preparation. Lab Chip 2013, 13(6): 1035-8

Aigner M, Feulner J, Schaffer S, Kischel R, Kufer P, Schneider K, Henn A, Rattel B, Friedrich M, Baeuerle PA, Mackensen A, Krause SW. T lymphocytes can be effectively recruited for ex vivo and in vivo lysis of AML blasts by a novel CD33/CD3-bispecific BiTE antibody construct. Leukemia 2013, 27(5): 1107-15

Kremer AN, van der Meijden ED, Honders MW, Pont MJ, Goeman JJ, Falkenburg JH, Griffioen M. Human leukocyte antigen-DO regulates surface presentation of human leukocyte antigen class II-restricted antigens on B cell malignancies. Biol Blood Marrow Transplant 2014, 20(5): 742-7

Tudor CS, Bruns H, Daniel C, Distel LV, Hartmann A, Gerbitz A, Buettner MJ. Macrophages and dendritic cells as actors in the immune reaction of classical Hodgkin lymphoma. PLoS One 2014, 9(12): e114345

Rensing-Ehl A et al. Abnormally differentiated $CD4^+$ or $CD8^+$ T cells with phenotypic and genetic features of double negative T cells in human Fas deficiency. Blood 2014, 124(6): 851-60

Jitschin R, Braun M, Büttner M, Dettmer-Wilde K, Bricks J, Berger J, Eckart MJ, Krause SW, Oefner PJ, Le Blanc K, Mackensen A, Mougiakakos D. CLL-cells induce IDOhi $CD14^+$HLA-DRlo myeloid-derived suppressor cells that inhibit T-cell responses and promote TRegs. Blood 2014, 124(5): 750-60


### International Cooperations

Prof. R. Kiessling, Karolinska Institutet, Stockholm: Sweden

Prof. Dr. J.H.F. Falkenburg, Leiden University, Leiden: The Netherlands

B.R. Ksander, Ph.D., Harvard Medical School, Boston: USA

### Research Equipment

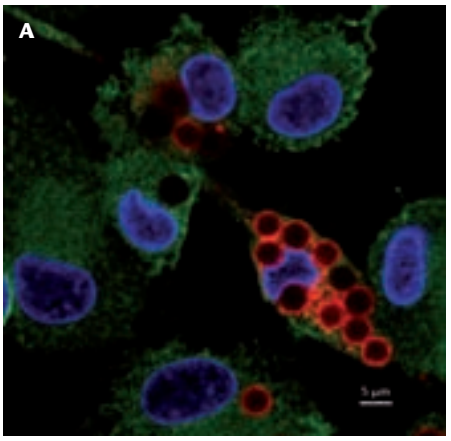
Applied Biosystems, Sequencer AB Genetic Analyser 3130

Becton Dickinson, FACS Canto II

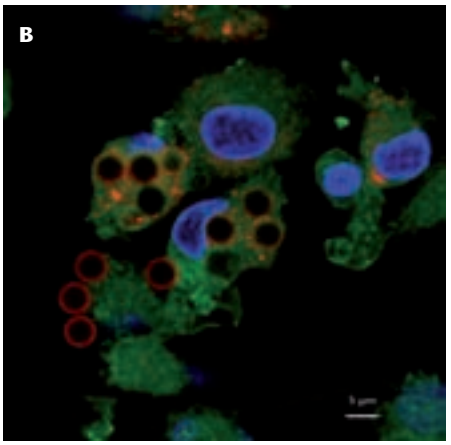
Seahorse Bioscience, XFe96 Analyzer

### Meetings and International Training Courses

14. – 15.03.2013 Cellular Therapy – 7th International Symposium on the Clinical Use of Cellular Products, Erlangen




*aAPCCD47$^+$ are protected from phagocytosis of human macrophages.*




Confocal image of (A) aAPC or (B) aAPCCD47$^+$ after co-culture (2 h) with human macrophages. aAPC/aAPCCD47$^+$ were stained with a succinimidylester-Alexa647 prior to co-culture and macrophages were visualized by DAPI (blue) and anti-CD11b (green) staining. CD47on artificial antigen presenting cells (aAPC) inhibits phagocytosis by macrophages. (Photos: Dr. H. Bruns)

# Department of Neurology

## Chair of Neurology

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**Research Focus**
- Intensive care, stroke, emergency care
- Telemedicine and health services
- Epilepsy
- Neuroimmunology
- Pain and functional imaging
- Autonomic nervous system
- Neuromuscular diseases
- Dystonia and botulinum toxin therapy
- Cognitive neurology

## Structure of the Department

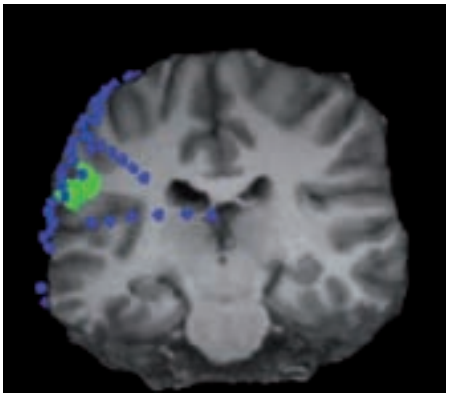
The Department of Neurology is one of the largest neurological centers in Germany treating 4,500 inpatients and more than 17,000 outpatients each year. It maintains close collaborations with the Division of Molecular Neurology, the Departments of Neurosurgery, and the Division of Neuroradiology.
Particularly the emergency unit of the "Kopfklinik", coordinated by our Department, guarantees immediate and best medical treatment and is directly linked to the Department of Neuroradiology. For treatment of inpatients, the Department of Neurology provides 78 beds altogether. 14 beds are located at one of the largest stroke units in Germany and twelve on the intensive care unit which has been completely remodeled in 2012. The Epilepsy Center (EZE) represents another outstanding facility including a monitoring unit and an interdisciplinary team for surgery in epilepsy. Last but not least, a telemedical network for stroke care and a number of specialized outpatient services provide neurological treatment beyond the borders of our region. On the basis of this specialized know-how, the Department of Neurology is able to provide up-to-date and competent diagnosis and treatment as well as scientific work within all areas of modern clinical neuroscience.

## Research

**Intensive care, stroke, emergency care**
Project managers: PD Dr. M. Köhrmann (stroke unit), PD Dr. H. Huttner (neurocritical care unit), PD Dr. D. Staykov (emergency room)
Neurointensive care: Clinical and translational research are major columns of neurointensive care research in Erlangen. Examples include brain edema treatment after intracerebral hemorrhage (ICH), temperature management in subarachnoid hemorrhage cerebral ischemia (including management of the Europe-wide EuroHYP-1 study), intraventricular fibrinolysis and lumbar drainage after intraventricular hemorrhage as well as multimodal monitoring for patients with intracranial pressure.
Emergency room: Each year the initial assessment of about 6,000 patients takes place in the emergency room. After an immediate clinical examination, adequate diagnostic procedures and prompt specific emergency treatment are initiated, if necessary. For a multitude of clinical studies, especially vascular ones, screening and inclusion is managed directly in the emergency room.
Stroke-unit: We treat more than 1,000 inpatients on our 14-bed stroke unit. An extremely high level of medical care (iv-thrombolysis rate > 25 %) is combined with state-of-the-art research, including e.g. MRI-based interventions, ECG-monitoring, and new oral anticoagulants.

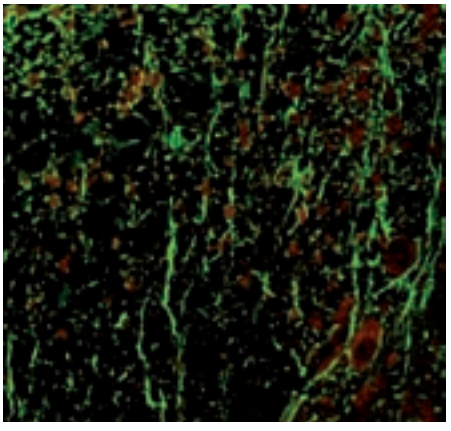
**Telemedicine**
Project manager: Dr. D. Stark
Since 2007, the Department of Neurology has been coordinating the Stroke Network using Telemedicine in Northern Bavaria (STENO) which comprises three stroke centers and 18 regional hospitals and has been certified in 2011 as the only network of its kind to DIN ISO for its quality management system. STENO ensures the treatment of stroke patients in North Bavaria and southern Thuringia at the highest level of comprehensive stroke care and has become part of the medical standard care. The impact and effects of STENO are investigated in scientific studies. In the coming years, other telemedicine projects are to be established regionally and internationally.

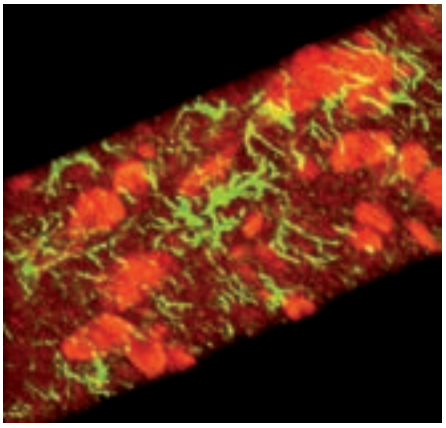
**Epilepsy**
Project manager: Prof. Dr. H.M. Hamer
The Erlangen Epilepsy Center ranks among the top five university epilepsy centers in Germany. Scientific hot spots in 2013/2014 included:
1) Changes of the innate immune-system in epilepsy; 2) Epilepsy in CNS-malformations; 3) Studies correlating clinical parameters, e.g. neuropsychology, with hippocampal pathology; 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. Funding sources are DFG and the Bavarian State Ministry of Health and Care.



*Invasive EEG recording*

**Neuroimmunology**
Project manager: Prof. Dr. R. Linker
One of the main aims in neuroimmunological research is the rapid transfer of new experimental insights from bench to bedside and vice versa. Besides participation in several multicenter trials on new multiple sclerosis (MS) therapies, three research groups successfully focus on 1) immunregulation and biomarkers in experimental research, 2) neuroprotection and neurodegeneration in experimental models, and 3) the influence of environmental factors on the pathogenesis of MS. In a more patient centered approach, studies focus on new imaging modalities including magnetic resonance imaging and optic coherence tomography. The group is supported by the Else-Kröner-Fresenius-Foundation and several industry-funded research projects.



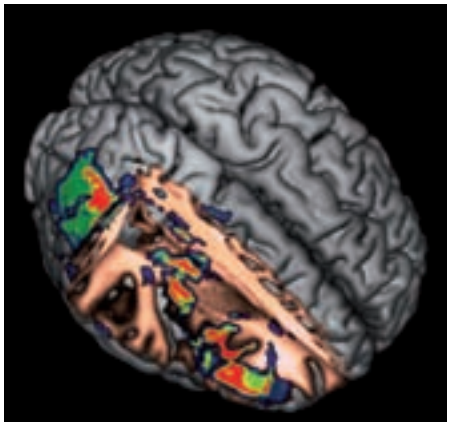


*Neuroprotective effects of glia cells in MS lesions*

### Pain and functional imaging

Project manager: PD Dr. F. Seifert

This group investigates neural mechanisms of sensory, autonomic and cognitive processing in pain diseases (neuropathic pain, headache disorders) and stroke. 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).



*Voxel-based lesion-symptom mapping (VLSM)*

### Autonomic nervous system

Project manager: Prof. Dr. M. J. Hilz

The autonomic research laboratory evaluates cardiovascular autonomic function in patients with central and peripheral autonomic network disorders. Additional quantitative sensory testing of thermal and vibratory perception refines the evaluation of small fiber neuropathies. In patients with lysosomal orphan diseases (M. Fabry, M. Pompe), we evaluate the effects of enzyme replacement therapy. We study the clinical organization of the central autonomic network by assessing cardiovascular autonomic function in patients with central nervous system lesions such as stroke, multiple sclerosis, traumatic brain injury, and in athletes who are exposed to repetitive mild head and brain injuries.

### Neuromuscular diseases

Project managers: Prof. Dr. R. Linker (speaker), Prof. Dr. R. Schröder

The Neuromuscular Disease Center is an interdisciplinary center providing a specialized outpatient clinic and a neuropathological laboratory for diagnostic biopsies and for the investigation of neuromuscular diseases. The neuromuscular research is composed of three task forces with the following key aspects: 1) immunopathogenesis of autoimmune myositis and myasthenia gravis, 2) studies on the pathogenesis of myofibrilar myopathy, 3) work related to genetic and pathogenesis of hereditary as well as inflammatory neuropathies.

### Dystonia and botulinum toxin therapy

Project manager: Dr. A. Schramm

The focus of our clinical research interest especially lies in improving diagnosis and botulinum toxin therapy in patients with cervical dystonia, writer's cramp and spasticity. The innovative approaches involve particularly the use of high-resolution ultrasound or sonography-guided electromyography to identify involved muscles, 3D video analysis of movement patterns, and ultrasound-guided injections of smaller and less accessible muscles.

### Cognitive neurology

Project manager: Prof. Dr. T. Schenk

We are interested in visual and movement disorders occurring after selective damage to the brain. We use 3D movement recordings and psychophysicial experiments to gain a better understanding of how the brain uses sensory information to guide our movements. These techniques are also used to develop new treatment approaches for patients with hemi-blindness and hemispatial neglect. In cooperation with the neuroimmunological group, we examine the cognitive consequences of neuroimmunological disorders. In cooperation with the Institute of Psychiatry, London, we examine the role of the post-traumatic stress disorder in patients' ability to recover after a neurological disease.

## Teaching

Between everyday clinical practice and the teaching segments of the Department of Neurology, the block training gained widespread recognition by the students. Also the clinical course "Einführung in die klinische Medizin" (EKM), giving a short introduction in the everyday clinical practice, as well as the main lecture are appreciated by many students. Due to increased demand, we were not always able to integrate all candidates for the final year. A detailed evaluation on scientific basis of teaching activities demonstrated positive results.

### Selected publications


Breuer L, Ringwald J, Schwab S, Köhrmann M. Ischemic stroke in an obese patient receiving dabigatran. N Engl J Med 2013, 368: 2440-2

Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, Muller DN, Hafler DA. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature 2013, 496: 518-22

Huttner HB et al. The age and genomic integrity of neurons after cortical stroke in humans. Nat Neurosci 2014, 17: 801-3

Winder K, Seifert F, Ohnemus T, Sauer EM, Kloska S, Dörfler A, Hilz MJ, Schwab S, Köhrmann M. Neuroanatomic correlates of poststroke hyperglycemia. Ann Neurol 2014, Dec 2. doi: 10.1002/ana.24322

Hopfengärtner R, Kasper BS, Graf W, Gollwitzer S, Kreiselmeyer G, Stefan H, Hamer H. Automatic seizure detection in long-term scalp EEG using an adaptive thresholding technique: A validation study for clinical routine. Clin Neurophysiol 2014, 125: 1346-1352

Kiphuth IC, Utz KS, Noble AJ, Köhrmann M, Schenk T. Increased Prevalence of Posttraumatic Stress Disorder in Patients After Transient Ischemic Attack. Stroke 2014, 45: 3360-3366


### International Cooperations

Department of cell and molecular biology, Karolinska Institute, Stockholm: Sweden

Zhengzhou University und Huazhong University of Science and Technology: China

Europäische Kooperation Thrombolyse: multizentrisch, europaweit

FP7-EU-Projekte "EpimiRNA" und "DESIRE": multizentrisch, europaweit

Europäisches Forschungsnetzwerk zur Hypothermie bei Schlaganfall "EuroHYP": multizentrisch, europaweit

D. Hafler, Yale University, New Haven: USA

A. Noble, University of Liverpool: UK

### Meetings and International Training Courses

08.02.2013: Conference on Pain and Palliative Medicine, Erlangen

26. – 28.06.2013: Stroke Summer School, German Stroke Society (DSG), Erlangen

22.07.2013: EEG-workshop, Erlangen

11. – 12.07.2014: EEG-workshop, Erlangen

29.11.2014: Annual Conference of Neuromuscular Centers in Bavaria, Erlangen

17. – 18.12.2014: MEG-symposium, Erlangen

# Department of Neurology

## Division of Molecular Neurology

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**Research Focus**
- Neurodegenerative diseases
- Translational neuroscience
- Sensor-based Gait-analysis

## Structure of the Division

The Division of Molecular Neurology aims at establishing a link between daily patient care and the development of novel diagnostic tools and therapies in the field of neurodegenerative diseases. The main focus of the Division is on neurodegenerative diseases, such as Parkinson's disease, multiple systems atrophy, Huntington's disease, and hereditary spastic paraplegia. In addition, the Division aims at integrating the ongoing clinical work up and projects with the neighboring departments. A large outpatient clinic for movement disorders offers the entire spectrum of clinical, electrophysiological, imaging, and diagnostics for patients affected with these diseases. During the last two years, based on a close collaboration with the stereotactic surgery the Department of Neurosurgery, the complex operation procedures for deep brain stimulation were established for Parkinson's disease, essential tremor, and dystonia. A major focus of the movement disorder outpatient clinic is to assess and measure movements using embedded sensor systems. This project is jointly developed with the pattern recognition laboratory and a local industry partner.

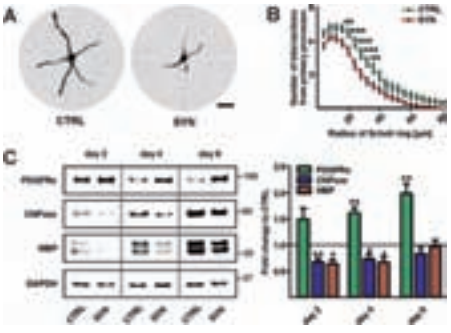
## Research

### Neurodegenerative diseases

The neuroscientific focus of the Division emphasizes on stem cell biology and neurogenerative mechanisms in Parkinson's disease, multiple systems atrophy, Huntington's disease, and hereditary spastic paraplegia. Neuroregenerative processes with particular emphasis on adult neuro- and gliogenesis and the generation of new neurons and glial cells in the adult brain are analyzed by using cell culture approaches, such as induced pluripotent stem cells and transgenic models of Parkinson's disease, multiple system atrophy, and Huntington's disease. In a complementary approach, neurodegenerative mechanisms underlying the interplay of intracellular and extracellular α-synuclein in synucleinopathies are analyzed in detail in order to better understand the molecular mechanisms underlying the pathogenesis of Parkinson's disease and Lewy-Body-Dementia. The interaction between neurodegenerative processes and inflammatory pathomechanisms within the CNS has become an additional main focus within the Division.

### Translational neuroscience

The Division is interested in the molecular and cellular biology of adult neural stem- and progenitor cells in two regions of the adult brain, the subventricular zone and the hippocampus, where new neurons are generated throughout the entire life span. Adult neurogenesis is severely altered in the context of numerous neurodegenerative diseases. Several findings indicate that impaired adult neurogenesis may be one of the underlying cell biological events in developing non-motor symptoms like depression, cognitive impairment, and olfactory dysfunction in Parkinson's disease. These symptoms are likely to reflect the compromised ability of the brain to generate new neurons in both neurogenic regions. Furthermore, we initiated a program to characterize myelin producing oligodendrocytes, particular affected in atypical Parkinson syndromes, such as multiple systems atrophy. Moreover, cell and molecular techniques have been established to delineate and modify pathological mechanisms associated with protein aggregation of α-synuclein in the respective disorders, focusing recently on mechanisms of α-synuclein propagation in typical and atypical Parkinson's disease. Finally, during the last two years we successfully established a biobank for patient specific stem cells, so called induced pluripotent stem cells, originally generated from skin fibroblasts of affected patients. The patient-derived neurons may provide for the first time an important tool to study disease processes and define novel interventions.



*α-synuclein expressing oligodendrozytes show shorter processes (A, B) and delayed maturation (C, D).*
*From: Ettle B et al. Intracellular alpha-synuclein affects early maturation of primary oligodendrocyte progenitor cells. Mol Cell Neurosci 2014, 62: 68-78. With kind permission of the publisher.*

### Clinical research and development

The outpatient clinic for movement disorders (in particular Parkinson's disease, Huntington's disease, and hereditary spastic paraplegia) is offering state-of-the-art diagnostic procedures and long-term care for patients and their caregivers. In particular, the scientific focus targets disease modifying strategies. In close collaboration with the Departments of Neurology and Neurosurgery, a deep brain stimulation program for movement disorders has been established. In this regard, all invasive therapies thus far approved for these diseases are available now. Automated motion and gait analysis systems for stationary and mobile diagnostics have been developed in close collaboration with the Faculty of Engineering (pattern recognition lab) and a local industry partner (ASTRUM IT GmbH). This joint effort was awarded the Erlanger Prize for Medicine, Technology, and Health in 2014 and is a registered trademark (eGait®-embedded Gait Analysis using Intelligent Technology).
Moreover, participation in multicenter studies is offered to all patients of the movement disorder outpatient clinic.

*A sensor-based gait analysis uses sensors attached to a shoe whereby sensor raw data are transferred wireless to a tablet PC that performs the gait analysis based on pattern recognition algorithms.*

## Teaching

The Division of Molecular Neurology is involved in the curricular teaching of Medicine (Department of Neurology) and Molecular Medicine. In addition, internships, bachelor, and master theses as well as medical and scientific doctoral theses are supervised.

## Selected Publications


Klucken J, Barth J, Kugler P, Schlachetzki J, Henze T, Marxreiter F, Kohl Z, Steidl R, Hornegger J, Eskofier B, Winkler J. Unbiased and Mobile Gait Analysis Detects Motor Impairment in Parkinson's Disease. PlosOne 2013, 8(2): e56956

Poehler AM, Xiang W, Spitzer P, May VEL, Meixner H, Rockenstein E, Chutna O, Fleming Outeiro T, Winkler J, Masliah E, Klucken J. Autophagy modulates SNCA/ -synuclein release, thereby generating a hostile microenvironment. Autophagy 2014, 10(12): 2171-2192

Pérez-Branguli F, Mishra HK, Prots I, Havlicek S, Kohl Z, Saul D, Rummel C, Dorca-Arevalo J, Regensburger M, Graef D, Sock E, Blasi J, Groemer TW, Schlötzer-Schrehardt U, Winkler J, Winner B. Dysfunction of spatacsin leads to axonal pathology in SPG11-linked hereditary spastic paraplegia. Hum Mol Genet 2014, 23(18): 4859-4874

Schlachetzki JCM, Marxreiter F, Regensburger M, Kulinich A, Winner B, Winkler J. Increased tyrosine hydroxylase expression accompanied by glial changes within the non-lesioned hemisphere in the 6-hydroxydopamine model of Parkinson's disease. Restorative Neurology and Neuroscience 2014, 32: 447-462

May EM, Ettle B, Pöhler AM, Nuber S, Ubhi K, Rockenstein E, Winner B, Wegner M, Masliah E, Winkler J. alpha-Synuclein impairs oligodendrocyte progenitor maturation in multiple system atrophy. Neurobiol of Aging 2014, 35: 2357-2368

Ettle B, Reichprich S, Deusser J, Schlachtzki JC, Xiang W Prots I, Masliah E, Winner B, Wegner M, Winkler J. Intracellular alpha-synuclein affects early maturation of primary oligodendrocyte progenitor cells. Mol Cell Neurosci 2014, 62: 68-78


## International Cooperations

Prof. Dr. L. Aigner, Paracelsus Medical University, Salzburg: Austria

Prof. Dr. F.H. Gage, Salk Institute for Biological Studies, San Diego: USA

Prof. Dr. C. Glass, University of California San Diego, San Diego: USA

Prof. Dr. B.T. Hyman, Massachusetts General Hospital – MIND, Boston: USA

Prof. Dr. E. Masliah, University of California San Diego, San Diego: USA

Prof. Dr. T.F. Outeiro, University of Lisbon, Lisbon: Portugal

Prof. Dr. G. Wenning, Neurologische Universitätsklinik, Innsbruck: Austria

Prof. Dr. T. Wyss-Coray, Stanford School of Medicine, Stanford: USA

## Meetings and International Training Courses

10.07.2013: Fortbildungsveranstaltung der Neurologie, Erlangen

06.05.2013: 1st International Symposium on Automated Sensor Based Mobility Analysis for Disease Prevention and Treatment, Boston

27.11.2013: 4th Automated Mobility Analysis Symposium Erlangen (AMASE), Erlangen

22.01.2014: Fortbildungsveranstaltung der Neurologie, Erlangen

17.06.2014: 2nd International Symposium on Automated Sensor Based Mobility Analysis for Disease Prevention and Treatment, Zürich

28.11.2014: 5th Automated Mobility Analysis Symposium Erlangen (AMASE), Erlangen

# Department of Neurosurgery

## Chair of Neurosurgery

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**Research Focus**
- Functional neuronavigation and intraoperative imaging
- Neuroendocrinology
- Neurooncology

## Structure of the Department

The Department of Neurosurgery is one of the largest departments of neurosurgery in Germany. There is a total of 78 beds for inpatients, including beds on the intensive care unit. The number of outpatients is 4,000 per year. Up to 2,600 patients get inpatient treatment. Caseloads include approximately 2,200 major neurosurgical procedures per year. The range of operations covers the whole spectrum of neurosurgery with a focus in the microsurgical treatment of processes of the skull base, particularly in the sellar region, in eloquent brain areas (e.g. central region, brain stem), the vascular neurosurgery, spine surgery, pediatric neurosurgery, and epilepsy surgery. Modern microsurgical techniques, endoscopic procedure, intraoperative electrophysiological monitoring, neuronavigation, and intraoperative MRI with the novel DiVA (Dual Intraoperative Visualisation Approach) protocol are used. A molecular biological laboratory with an integrated cell culture and a wide range of cellular and molecular biological methods is available for basic scientific issues.

## Research

### Functional neuronavigation and intraoperative imaging

The research group "functional neuronavigation and intraoperative imaging" is divided in three subgroups that work in part independently, but use the intraoperative 1.5 T MRI-scanner as a common interface.

Subgroup I (intraoperative imaging):
A major effort of this group is the acquisition of all parameters that are connected to intraoperative imaging of pituitary and suprasellar tumors, intra- and extraaxial brain tumors, and epilepsy-associated procedures. The analysis of these data is currently in progress. In addition, the group worked on the visualization of important eloquent brain areas with the implementation of diffusion-tensor-imaging, functional MRI and magnetoencephalography. Moreover, studies of implementation of tractography data in the surgical treatment of brain stem lesions were completed. Two important studies analyzed the connectivity of eloquent brain areas with different DTI algorithms using probabilistic fiber tracking and investigated the amount of susceptibility artifacts in linear registration of fiber tracts. We further established the novel DiVA-Protocol which combines the fluorescence-guided resection with intraoperative MRI resulting in an increased glioblastoma patient survival.
Subgroup II (functional imaging):
This group focused on correlative studies for cortical plasticity after resection of gliomas. Also the connectivity of receptive and expressive language areas was investigated with fMRI and DTI following reports of other groups with electrical stimulation.
Subgroup III (metabolic imaging):
Major focus of this group was on studies of metabolic imaging for the characterization of the infiltration of gliomas with proton MR spectroscopy and FET-PET. Furthermore, studies of the tumor invasion into fiber tracts and its influence on their reconstruction and neurologic symptoms and studies of metabolic changes in temporal lobe lesions with 1H MR spectroscopy were investigated. Furthermore, we investigate the cortical plasticity after gliome resection adjacent to eloquent brain areas and intraoperative MR spectroscopy in gliomas.

### Neuroendocrinology

The Department of Neurosurgery represents a nationally and internationally specialized center for the whole spectrum of sellar pathologies. Clinically we investigate the influence of interventional/operative, radiotherapeutic, and pharmacological approaches on normal and hypersecretory pituitary gland function in the course of the "Acrostudy" (treatment and MRI follow-up of the medicinal therapy with Somavert®). Also, investigations on somatostatin analoga and their clinical relevance in the treatment of growth hormone secreting pituitary adenoma represent a central part. Our clinical and laboratory chemical analyses and screening studies are supported by the companies Pfizer and Novartis. The efficacy of novel intra-operative technologies in pituitary adenoma surgery and craniopharyngiomas is evaluated. Novel procedures include endoscopic surgery, such as endoscopic assisted microsurgery and intraoperative MRI. These techniques allow controlling resections in cases of intrasellar and suprasellar tumors. Goal of these clinical long-term studies is to define the relapse frequencies of sellar tumors, including different prognostic factors.
The field of neuroendocrinology within the Department of Neurosurgery was established in 2007 in the framework of an endowed professorship for clinical and experimental neuroendocrinology (Prof. Dr. C. Schöfl, now Department of Medicine 1). In cooperation with the Institute of Radiology, body composition, liver and muscle fat content are determined by MRI in patients with various hypothalamic-pituitary diseases (e.g. pituitary deficiency, acromegaly, and M. Cushing). The results are correlated with various metabolic characteristics and with novel parameters involved in the metabolic control. The aims of these studies are to obtain novel insights in the neuroendocrine control of metabolic and energetic processes. Another translational scientific project involves the functional characterization of mutations of the metabotropic calcium-sensing receptor (CaSR) that occur in patients with specific disorders of calcium homeostasis. The CaSR is also expressed in pituitary cells and in hypothalamic nuclei involved in the control of endocrine systems. In this project, the patients are screened for clinical evidence of neuroendocrine dysfunction, and clinical and in-vitro data are correlated to define a potential genotype-phenotype relation. Furthermore, agonists and antagonists of the CaSR are tested in vitro whether they can rescue the molecular defect of the mutated CaSR. This potentially offers a therapeutic approach specifically tailored to patients' molecular CaSR defect (individualized medicine). Further projects investigate various aspects of growth-hormone secreting human adenoma cells in vitro, like the expression of certain membrane receptors (e.g. somatostatin receptors) and the characteristics of signaling cascades (cAMP- and Ca2+-PI-signaling pathway). The in vitro data are related to various clinical data in order to extract potential prognostic factors concerning therapeutic outcome and to define potential new therapeutic targets.

### Neurooncology

Gliomas are the most common primary tumors of the brain, and about 70 % of these tumors are malignant gliomas. Currently, there is no promising therapy for the treatment of malignant tumors which targets the high proliferation and diffuse brain invasion. Therefore, investigation and characterization of the molecular mechanisms of glioma growth and invasion are essential steps in developing novel therapeutic strategies. The neurooncology research group deals with the biology and therapy of brain tumors and could demonstrate that malignant gliomas secrete high amounts of the neurotransmitter glutamate which results in neuronal cell death in the peritumoral brain parenchyma and induces perifocal edema. These data correlate with a reduced quality of life of patients suffering from malignant gliomas. Another focus of the group is to decipher the interaction of different brain cells and glioma proliferation. One candidate molecule for tumor-associated cell interaction is the protein MIF (macrophage migration inhibitory factor). This cytokine is secreted by glioma cells and interacts with the adjacent parenchyma. The aim of this project is the analysis of MIF effects on immune competent cells in the brain, such as microglial cells, and its role in glioma proliferation and invasion. Moreover, the preliminary data indicate that microglial cells participate at edema formation surrounding malignant gliomas. The presented studies are funded by a grant from the DFG.

## Teaching

Aside of the neurosurgical main lecture with case demonstrations and live broadcasts from the operating theater, neurosurgical diseases are also discussed in smaller groups. As part of the practical course, students learn how to examine neurosurgical patients. Moreover, they have the possibility to participate in clinical routines, such as examination of outpatients, inpatients, and visit the operating theater.

### Selected Publications


Eyüpoglu IY, Buchfelder M, Savaskan NE. Surgical resection of malignant gliomas-role in optimizing patient outcome. Nat Rev Neurol 2013, 9(3): 141-51

Wolf IM, Fan Z, Rauh M, Seufert S, Hore N, Buchfelder M, Savaskan NE, Eyüpoglu IY. Histone deacetylases inhibition by SAHA/Vorinostat normalizes the glioma microenvironment via xCT equilibration. Sci Rep 2014, 4: 6226

Berkmann S, Schlaffer S, Nimsky C, Fahlbusch R, Buchfelder M. Intraoperative high-field MRI for transsphenoidal reoperations of nonfunctioning pituitary adenoma. J Neurosurg 2014, 121(5): 1166-75

Fan Z, Sehm T, Rauh M, Buchfelder M, Eyupoglu IY, Savaskan NE. Dexamethasone alleviates tumor-associated brain damage and angiogenesis. PLoS One 2014, 9(4): e93264

Roessler K, Sommer B, Grummich P, Coras R, Kasper BS, Hamer HM, Blumcke I, Stefan H, Buchfelder M. Improved resection in lesional temporal lobe epilepsy surgery using neuronavigation and intraoperative MR imaging: favourable long term surgical and seizure outcome in 88 consecutive cases. Seizure 2014, 23(3): 201-7

Sehm T, Fan Z, Weiss R, Schwarz M, Engelhorn T, Hore N, Doerfler A, Buchfelder M, Eyüpoglu IY, Savaskan NE. The impact of dietary isoflavonoids on malignant brain tumors. Cancer Med 2014, 3(4): 865-77


### International Cooperations

Prof. Dr. T. Lei, Huazhong University of Science and Technology, Wuhan: China

Prof. Dr. A. Devin, Université Bordeaux, Bordeaux: France

Prof. Dr. I. Shachar, Weizmann Institute of Science, Rehovot: Israel

Prof. Dr. R. Bucala, Yale University School of Medicine, New Haven: USA

Prof. Dr. D.L. Kleinberg, New York University Langone Medical Center, New York: USA

# Department of Nuclear Medicine

## Chair of Clinical Nuclear Medicine

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**Research Focus**
- Correlative Imaging
- Molecular Imaging and Radiochemistry

## Structure of the Department

At the Department of Nuclear Medicine, the Chair of Clinical Nuclear Medicine (Prof. Dr. T. Kuwert, Director) and the Professorship of Radiochemistry and Molecular Imaging (Prof. Dr. O. Prante), founded in 2010, are established. For patient-oriented clinical research, the hybrid cameras SPECT/spiral-CT and PET/CT are being used in an interdisciplinary setting. Since October 2010, owing to a research cooperation with Siemens Healthcare, the Department of Nuclear Medicine has been having access to a simultaneous whole-body MR/PET hybrid system that is being operated together with the Institutes of Radiology and Medical Physics. The radiochemical laboratory of the Department of Nuclear Medicine is equipped with synthesis modules for synthesizing radiotherapeutics. In addition, a laboratory for producing tracers under good-manufacturing-practice (GMP) conditions is being built. In the laboratory of molecular imaging of the Department, new radiopharmaceuticals are being developed and evaluated. The methodology implemented for this purpose includes chemical, radiochemical, and cell biological facilities. In addition, the laboratory operates a highly resolving autoradiographic detector system and a micro-PET.

## Research

### Correlative Imaging

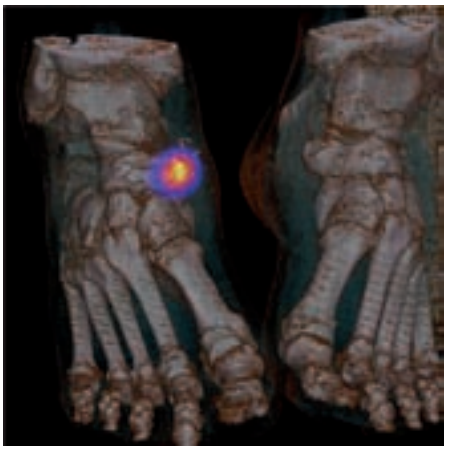
The tremendous progress in technology has created a wide array of new ways to image the human body and considerably improved already existing methodology. However, the complexity of the diagnostic process has increased correspondingly. Therefore, the integration of information from different imaging modalities has become an important issue. Ideally, image datasets from two different modalities are registered to one common coordinate system to allow for true correlative imaging. The manufacturers of medical imaging devices have developed two different solutions to this problem: On the one hand, devices have been designed that unify two cameras of different modalities, the so-called hybrid systems. In particular, hybrid systems combining emission tomographic cameras with X-ray computerized tomographs (CTs) are currently commercially available. On the other hand, user platforms and data structures have been homogenized so that the exchange of image data between different modalities and also the registration of independently acquired images have been facilitated a lot. In cooperation with the Chair of Pattern Recognition (Faculty of Engineering) and Siemens Healthcare, the Department of Nuclear Medicine develops a new methodology of correlative imaging and investigates its clinical value. Currently investigated combinations of modalities are SPECT/CT, PET/CT, and MR/PET.

### Molecular Imaging and Radiochemistry

Diagnostic nuclear medicine images the distribution of radioactively labeled substances within the body of patients. This distribution is a consequence of the interaction of the radiopharmaceuticals with functionally relevant proteins. By visualizing this interaction and thus expressing and activating the proteins, nuclear medicine can bridge the gap between molecular biology and clinical imaging and can correlate imaging results to the specific reason of disease or metabolic disorder. Following this idea and the use of molecular tracers in functional imaging, the term molecular imaging has recently been implemented in this field of research.

The main research area of the Professorship of Molecular Imaging and Radiochemistry (Prof. Dr. O. Prante) is the development of new radiochemical labeling methods for the production of radiopharmaceuticals, the preclinical evaluation of novel radiotracers in vitro and in vivo, and the translation of the research results into the clinic. Recent examples for these studies are the development of F-18-labeled glycoconjugates for imaging ETA receptor expression and for the neurotensin receptor, and glycopeptide tracers for in vivo imaging of angiogenesis. These projects were supported by the DFG.

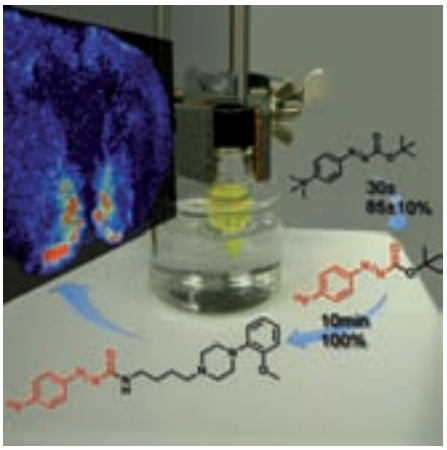
In cooperation with the Chair of Pharmaceutical Chemistry (Prof. Dr. P. Gmeiner, Faculty of Sciences), this methodology has supported and accelerated the development of tracers for various molecular targets suitable for PET imaging studies. Moreover, radioligands for the D3 and D4 subtype of the dopamine receptor have been evaluated. As yet, radiopharmaceuticals suited to study the receptor subtypes supposedly to be implicated in the pathogenesis of several neuropsychiatric disorders are lacking so that this project may be considered to be truly innovative. In 2011 and 2012, this project was supported by the DFG. Further radiopharmaceutical chemistry projects include the development of radiopeptides addressing the neuropeptide-Y receptor and neurotensin receptor that are studied as targets for imaging of mamma and prostate carcinoma in the preclinical setup by small-animal PET. In 2013 and 2014, this research was supported by the DFG within the GK 1910. In the project "Neurotrition" (EFI project of the FAU), an emerging research field that studies the interactions between neurofunction and nutrition, studies on the tracer development for D3 radioligands, dopamine transporter ligands, and a PET ligands for MAO-A for preclinical studies were performed. The project has been successfully continued and party finished. Moreover, some radiopharmaceuticals, for example targeted against prostate cancer, were translated into the clinic. These tracers will be available for clinical use under GMP conditions in the new clean room labs within the Department of Nuclear Medicine at the beginning of 2015 when the GMP laboratory of the clinic is starting to operate.



*55-year-old patient four months after bullet injury. Focal area with increased uptake indicating an inflammatory lesion (Osteomyelitis) in the Os naviculare.*

## Teaching

The Director of the Department of Nuclear Medicine teaches nuclear medicine to students of medicine. Furthermore, the Head of the Department organizes the course on radiation safety for students of molecular medicine. He also participates in teaching physiology, pharmacology, and computer sciences. In a broad fashion, the Head of the Department performs postgraduate teaching for physicians in Middle and Upper Franconia. The Professor for Molecular Imaging and Radiochemistry offers practical trainings for students of Molecular Medicine and provides lectures for students of molecular sciences in the Faculty of Sciences.




Development of radiochemical labeling methods for PET chemistry
(from: Fehler SK, Maschauer S, Höfling SB, Bartuschat AL, Tschammer N, Hübner H, Gmeiner P, Prante O, Heinrich MR. Fast and efficient $^{18}$F-labeling by [$^{18}$F]fluorophenylazocarboxylic esters. Chemistry 2014, 20: 370-375. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

### Selected Publications

Ziegler S, Braun H, Ritt P, Hocke C, Kuwert T, Quick HH. Systematic evaluation of phantom fluids for simultaneous PET/MR hybrid imaging. J Nucl Med 2013, 54(8): 1464-71

Cachovan M, Vija AH, Hornegger J, Kuwert T. Quantification of $^{99m}$Tc-DPD concentration in the lumbar spine with SPECT/CT. EJNMMI Res 2013, 3(1): 45

Wiesmüller M, Quick HH, Navalpakkam B, Lell MM, Uder M, Ritt P, Schmidt D, Beck M, Kuwert T, von Gall CC. Comparison of lesion detection and quantitation of tracer uptake between PET from a simultaneously acquiring whole-body PET/MR hybrid scanner and PET from PET/CT. Eur J Nucl Med Mol Imagin 2013, 40(1): 12-21

Lang C, Maschauer S, Hübner H, Gmeiner P, Prante O. Synthesis and evaluation of a $^{18}$F-labeled diarylpyrazole glycoconjugate for the imaging of NTS1-positive tumors. J Med Chem 2013, 56(22): 9361-5

Cumming P, Maschauer S, Riss PJ, Tschammer N, Fehler SK, Heinrich MR, Kuwert T, Prante O. Radiosynthesis and validation of $^{18}$F-FP-CMT, a phenyltropane with superior properties for imaging the dopamine transporter in living brain. J Cereb Blood Flow Metab 2014, 34(7): 1148-56

Maschauer S, Haubner R, Kuwert T, Prante O. $^{18}$F-glyco-RGD peptides for PET imaging of integrin expression: efficient radiosynthesis by click chemistry and modulation of biodistribution by glycosylation. Mol Pharm 2014, 11(2): 505-15

### International Cooperations

Dr. A.H. Vija, Siemens Medical Solutions, Hoffman Estates, Chicago: USA

Dr. R. Haubner, Innsbruck Medical University, Innsbruck: Austria

### Research Equipment

Siemens, mCT (PET/CT)

Siemens, SPECT/CT Symbia T6

Siemens, SPECT/CT Symbia T2

Siemens, mMR (PET/MR)

Siemens, Tier PET Inveon

# Department of Obstetrics and Gynecology

## Chair of Obstetrics and Gynecology

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**Research Focus**
- Gynecological oncology (Laboratory for Molecular Medicine)
- Clinical trials (Clinical Trial Center, CTC; Institute for Women's Health, IFG®)
- Specialized obstetrics and perinatal medicine
- Gynecological endocrinology and reproductive medicine (Laboratory for Reproductive Biology)

**Structure of the Department**
The versatile field of obstetrics and gynecology with its subspecialties and focus areas is represented clinically, scientifically, and educationally in the following organizational units in the Department of Obstetrics and Gynecology:
- University Breast Center Franconia (UBF),
- Gynecological University Cancer Center Franconia (GKF),
- University Perinatal Center Franconia (UPF),
- University Center for Reproductive Medicine Franconia (UFF),
- University Endometriosis Center Franconia (UEF).

These centers are monitored for its professional competence and certified by the appropriate national and international professional societies and by quality management and have been recertified repeatedly. The Department of Obstetrics and Gynecology obtained an approval of the European Board and College of Obstetrics and Gynecology (EBCOG) as a training clinic for the training of physicians.
Interfaces of the scientific work are provided by the Laboratory for Molecular Medicine, Laboratory for Reproductive Biology, and the associated Clinical Trial Center (Institute for Women's Health, IFG®). In total, more than 50 physicians work in the Department of Obstetrics and Gynecology. They are supported by two mathematicians, three scientists, two medical records technicians, and seven study nurses.

The development of research strategies and supervision of the scientific projects is performed by the two established W2 professorships for Translational Gynecology and Obstetrics (Prof. Dr. P. A. Fasching) and Experimental Reproductive Medicine (Prof. Dr. R. Dittrich).

## Research

**Gynecological Oncology (Laboratory for Molecular Medicine)**
Project managers: PD Dr. R. Strick, Prof. Dr. P.A. Fasching, Prof. Dr. M.P. Lux, Dr. M. Rübner, Dr. A. Hein, Dr. C. Rauh, PD Dr. C.R. Löhberg, PD Dr. M.G. Schrauder, Prof. Dr. S.P. Renner
The Laboratory for Molecular Medicine is pursuing various research approaches in gynecology and obstetrics with the focus on gynecological oncology including breast cancer. The core of the research is the bank for biomaterials. It comprises more than 81,000 blood and DNA samples from patients and – in cooperation with the Institute of Pathology – more than 11,500 tissue samples of benign and malignant tumors. In breast cancer research, we examined 660,000 genetic variants (OncoChip, blood samples) of 4,200 breast cancer patients in cooperation with the BCAC (Breast Cancer Association Consortium). This presents the worldwide largest number of patients genotyped within a randomized, multicenter trial. Furthermore 500 gene expression profiles of the tumors have been prepared allowing association studies of germline and somatic mutations.
Additionally, more than 3,500 out of 10,000 tumor samples of five cooperating, nationwide breast cancer trials (SUCCESS-A, -B, -C, PREFACE, ADEBAR) have been submitted to our biomaterial bank for further mutation and gene expression analysis in cooperation with the Institute of Pathology.
In cooperation with the OCAC (Ovarian Cancer Association Consortium) and the ECAC (Endometrial Cancer Association Consortium), the research on ovarian and endometrial cancer targets the identification of cancer-associated gene variants. For both malignancies disease specific loci could be identified with studies involving more than 10,000 or 6,600 patients, respectively.
The formerly reported research in regulatory microRNA (miRNA, miR) in breast cancer, in a cell invasion model with primary endometriosis cells (cooperation with the Center for Medical Physics and Technology, Faculty of Sciences), and in genes of endogenous retroviruses (ERV) in ovarian carcinoma cells by inducing genomic demethylation have been continued and published.

**Clinical Trials (Clinical Trial Center, CTC; Institute for Women's Health, IFG®)**
Project managers: Prof. Dr. P.A. Fasching, PD Dr. C.R. Löhberg, Dr. L. Häberle, PD Dr. F. Thiel, Prof. Dr. M.P. Lux, Dr. A. Hein, Dr. C.M. Bayer, Dr. F. Heindl
Until 2014, over 177 research projects have been carried out in the IFG®. This includes clinical phase I - IV trials with the focus on gynecological oncology including breast cancer. In addition to genetic testing and innovative chemotherapy protocols, current "target therapies", like PI3K- and CDK4/6-Inhibitors, are examined in various trials.
Noteworthy for breast cancer research is the PPREFACE trial within the Evaluate-study program (Evaluation of Predictive Factors Regarding the Effectivity of Aromatase Inhibitor Therapy) which was carried out throughout Germany under the guidance of Erlangen. A total of 3,500 patients were included from more than 220 study centers. The Phase-IV study examines pharmacogenetic markers which should predict treatment effects and side effects of aromatase inhibitors. Initial analyses of side effects have been presented at scientific meetings.
In 2014, the nationwide PRAEGNANT study network (Prospective Academic Translational Research Network for the Optimization of Oncological Health Care Quality in the Advanced Therapeutic Setting) for metastasized breast cancer patients was co-initiated by our Department. 108 patients could be enrolled in this multicentric, prospective and translational research project. Among other questions the study examines new biomarkers for the survival of patients with metastasized breast cancer. The central biobanking for the study is managed by the Laboratory for Molecular Medicine.

**Specialized Obstetrics and Perinatal Medicine**
Project managers: Prof. Dr. P.A. Fasching, PD Dr. F. Faschingbauer, PD Dr. S. Kehl, PD Dr. R. Strick, Dr. M. Rübner
This research group was awarded two ELAN- and one Doktor Robert Pfleger grants in 2014 to investigate the specific expression of human and murine MART (Mammalian Retrotransposon-derived Transcripts) as well as the tumor-suppressor gene RARRES1 in the placenta. MART genes showed a cell type specific expression in placental tissue. RARRES1 expression was limited to trophoblastic cells and was probably

epigenetically regulated during pregnancy.
The pilot phase of the Clinical Gravidity Association Trials and Evaluation Program (CGATE-study) has been completed. A total of 681 patients could be recruited. Of these patients, both, clinical data and several bio-materials (maternal, paternal, and fetal blood samples, placental tissue), have been collected. Analysis of the collected data resulted in the first publication regarding maternal breast changes during pregnancy. Several other projects are in preparation: for example, sonographic texture analysis of the placenta are currently performed and correlated to the duration of the pregnancy.

### Gynecological Endocrinology and Reproductive Medicine

Project manager: Prof. Dr. R. Dittrich, Dr. T. Hildebrandt, PD Dr. K. Heusinger, Prof. Dr. S. Cupisti, Dr. L. Lotz, PD Dr. P.G. Oppelt
The research in UFF and the Laboratory for Reproductive Biology concentrates on the cryopreservation of germ cells, the physiology of the non-pregnant uterus, and the pathology of genital malformations.
The efforts to restore fertility in young cancer patients after chemo- or radiotherapy have resulted in further success: Until now five children were born after transplantation of ovarian tissue to their mothers. By means of xenotransplantation models where human ovarian tissue of children was transplanted into immunodeficient mice, it could be demonstrated that mature human oocytes developed in the mice even without further hormonal stimulation. This data also shows that pre-pubertal tissue is able to produce mature oocytes when being transplanted.

## Teaching

Since the end of 2010, the specific functional area for undergraduate and graduate teaching has been acquiring a quality management system especially for medical education (DIN EN ISO 9001:2008) among the first university clinical institutions in Germany. Re-certification was performed in May 2014.
On the basis of the certification process, further improvement in the structure of the practical clinical courses (Blockpraktika) for the students of the 8$^{th}$ to the 10$^{th}$ terms were performed.
Additionally, we could demonstrate the positive effect of continuous examination (CME-questions) in the gynecological main-lecture on the final examination results of medical students.

### Selected Publications


Dittrich R, Lotz L, Mueller A, Hoffmann I, Wachter DL, Amann KU, Beckmann MW, Hildebrandt T. Oncofertility: combination of ovarian stimulation with subsequent ovar - ian tissue extraction on the day of oocyte retrieval. Reprod Biol Endocrinol 2013, 11: 19

Ruebner M, Strissel PL, Ekici AB, Stiegler E, Dammer U, Goecke TW, Faschingbauer F, Fahlbusch FB, Beckmann MW, Strick R. Reduced Syncytin-1 Expression Levels in Placental Syndromes Correlates with Epigenetic Hypermethylation of the ERVW-1 Promoter Region. PLoS ONE 2013, 8(2): e56145

Cortazar P et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014, 384(9938): 164-72

Khan S t al. MicroRNA related polymorphisms and breast cancer risk. PLoS One 2014, 9(11): e109973

Perry JR et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. Nature 2014, 514(7520): 92-7

Lotz L, Liebenthron J, Nichols-Burns SM, Montag M, Hoffmann I, Beckmann MW, van der Ven H, Töpfer D, Dittrich R. Spontaneous antral follicle formation and metaphase II oocyte from a non-stimulated prepubertal ovarian tissue xenotransplant. Reprod Biol Endocrinol 2014, 12: 41


### International Cooperations

Prof. Dr. P. Cortazar, US Food and Drug Administration, Silver Spring: USA

Prof. Dr. D. Easton, Breast Cancer Consortium, Cambridge: UK

Prof. Dr. D. Lambrechts, Katholische Universität, Leuven: Belgium

Prof. Dr. M. Press, University of Southern California, Los Angeles: USA

Prof. Dr. D. Slamon, MD, Ph.D., UCLA, Los Angeles: USA

Prof. Dr. V. Velculescu, Johns Hopkins Medical Center, Baltimore: USA

Prof. Dr. R. Weinshilboum, MD, L. Wang, MD, J. Ingle, MD, Mayo Clinic, Rochester: USA

### Meetings and International Training Courses

16. – 17.03.2013 XIV. Erlanger Kolposkopie Workshop, Erlangen

20.03.2013 Mammakarzinom 2013 – Individualisierte Diagnostik & Therapie, Erlangen

13.05. – 12.08.2013 Modularer GCP-Kurs für Prüfer Klinische Prüfungen nach AMG, Erlangen

09.11.2013 Pränataldiagnostik von Kopf bis Fuß, Erlangen

02.04.2014 10 Jahre UBF Mammakarzinom 2014, Erlangen

07.04.14 – 21.07.2014 Modularer GCP-Kurs für Prüfer Klinische Prüfungen nach AMG, Erlangen

11. – 12.04.2014 Geburtshilfe Basiskurs, Nürnberg

09. – 11.05.2014 XV. Erlanger Kolposkopie-Tage mit Fortgeschrittenen-Kurs der AG CPC, Erlangen

14.05.2014 Erlanger Symposium des UFF

17. – 19.10.2014 Psychosomatische Grundversorgung, Erlangen

08.11.2014 Das kleine Kind – Prä- und perinatales Management Grundlagen und Expertenwissen, Erlangen

03.12.2014 1. Adventstreffen GKF und UBF – Aktuelles zum Genital- und Mammakarzinom, Erlangen

# Department of Ophthalmology

## Chair of Ophthalmology

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**Research Focus**
- Biomorphometry of the optic nerve
- Functional aspects of retinal neurodegeneration
- Retinal physiology
- Clinico-pathological concepts in diagnosis and management of ocular diseases
- Corneal stem cells
- Pseudoexfoliation syndrome/glaucoma
- Improvements in corneal transplantation
- Circulation of the eye and the visual pathway, computer-aided-diagnosis & virtual education

## Structure of the Department

In total 169 persons are employed at the Department of Ophthalmology. Of these, 43 are physicians and ten scientific staff members. Nine of these are employed as professors. In addition, 78 persons are employed for nursing service and 38 as non-scientific staff (technicians etc.).
The clinical expertise of the Department of Ophthalmology includes the complete spectrum of surgical and conservative ophthalmology.
In the surgical ophthalmology, a diverse spectrum of operations is performed, including surgery of the frontal eye, cornea surgery, reconstructive surgery of the frontal eye, glaucoma surgery, oculoplastic, orbita, tumor, tear gland, and vitreo-retinal surgery.
In the surgical area, innovative surgical procedures are developed and evaluated. These developments include 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, and intraocular injections of compounds to treat age related macular degeneration (AMD).
In the field of the conservative medicine, special consultation areas are established. Special divisions (optometry, fluorescence angiography and laser, outpatients department, and the cornea bank) are in place. In addition, there is support from different laboratories.

## Research

### Biomorphometry of the optic nerve

Project managers: Prof. Dr. C. Mardin, PD Dr. R. Lämmer, Dr.-Ing. R. Tornow
Main focus of the research is the development and application of imaging methods for early detection of glaucoma and to quantify progression. Especially the possibilities of the spectral domain OCT (optical coherence tomography) to measure retinal layers will be optimized. The developed imaging methods are complemented by functional tests. The findings are also applied to other diseases, like diabetic retinopathy and age related macular degeneration.

### Functional aspects of retinal neurodegeneration

Project managers: Prof. Dr. J. Kremers, Dr.-Ing. F. Horn, 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. 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

Project manager: 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.

### Clinico-pathological concepts in diagnosis and management of ocular diseases

Project managers: Prof. Dr. L. Holbach, Prof. Dr. F.E. Kruse, Prof. Dr. G. Gusek-Schneider, Prof. Dr. A. Bergua
1. Diagnosis and management of orbital diseases – a multidisciplinary approach.
2. Surgical management of periocular malignant tumors using frozen section control and plastic reconstruction – indications, methods, and results.
The aim of this study is the long-term evaluation of surgical results following intraoperative frozen section control and immediate plastic repair regarding recurrence rates and adequacy of reconstructive techniques.
3. Diagnosis and surgical management of 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.

### Corneal stem cells

Project managers: 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.

### Pseudoexfoliation syndrome/ glaucoma

Project manager: Prof. Dr. U. Schlötzer-Schrehardt
Pseudoexfoliation (PEX) syndrome is worldwide 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 the PEX-associated coding and non-coding risk variants in the LOXL1 (lysyl oxidase-like 1) gene as well as the interaction of LOXL1 with profibrotic mediators such as TGF-ß1, oxidative stress, and mechanical stress.

### Development of new methods for lamellar corneal transplantation

Project managers: Prof. Dr. F.E. Kruse, Prof. Dr. T. Fuchsluger, Dr. T. Tourtas, Dr. J. Menzel-Severing
The Department of Ophthalmology has an internationally leading position in the performance and advancement of new minimally in-

vasive 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.

### Circulation of the eye and the visual pathway, computer-aided diagnosis & virtual education

Project manager: Prof. Dr. G. Michelson

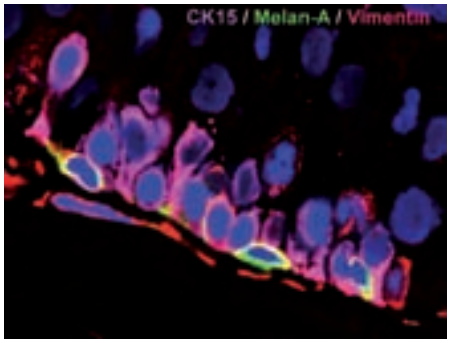
1. Ocular circulation of the eye and the visual pathway

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.

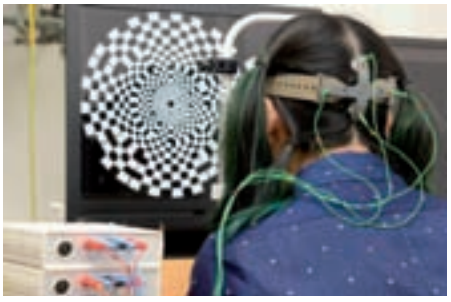
2. Computer-aided-diagnosis & virtual education

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.

3. 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.




*Confocal microscopy of the human corneal stem cell niche. Fluorescence markers highlight epithelial progenitor cells (purple), associated melanocytes (green), and mesenchymal niche cells (red).*



*Experimental set up for measurements of multifocal visual evoked potentials in human observers.*

## Teaching

Results of research are directly implemented in medical student and postgraduate teaching. In the course of the standard curriculum, project leader and research fellows are involved in the regular student education and practical courses. Moreover, they are involved in the education and training activities for doctoral students.

As a result of 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

Menzel-Severing J, Kruse FE, Schlötzer-Schrehardt U. Stem cell-based therapy for corneal epithelial reconstruction: present and future. Can J Ophthalmol 2013, 48(1): 13-21

Berta AI, Naumann-Bartsch N, Agaimy A, Metzler M, Kruse FE, Holbach L. Einseitige Tränendrüsenschwellung bei 15-jähriger Patientin (myeloisches Sarkom). Ophthalmologe 2013, 110: 876-8

Atorf J, Scholz M, Garreis F, Lehmann J, Bräuer L, Kremers J. Functional Protective Effects of Long-Term Memantine Treatment in the DBA/2J Mouse. Doc Ophthalmol 2013, 126: 221-232

Schoemann J, Engelhorn T, Waerntges S, Doerfler A, El-Rafei A, Michelson G. Cerebral microinfarcts in primary open-angle glaucoma correlated with DTI-derived integrity of optic radiation. Invest Ophthalmol Vis Sci 2014, 55(11): 7241-7

Kruse FE, Schlötzer-Schrehardt U, Tourtas T. Optimizing outcomes with Descemet's membrane endothelial keratoplasty. Curr Opin Ophthalmol 2014, 25(4): 325-34

Huchzermeyer C, Schlomberg J, Welge-Lüssen U, Berendschot TTJM, Pokorny J, Kremers J. Macular pigment optical density measured by heterochromatic modulation photometry. PLoS One 2014, 9(10): e110521

### International Cooperations

Prof. D.S. Fix Ventura, University of Sao Paulo, Sao Paulo: Brazil

Dr. N. Parry, University of Manchester, Manchester: UK

Prof. A. Zele, Prof. B. Feigl, Queensland University of Technology, Brisbane: Australia

Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto: Japan

Department of Ophthalmology, University of Cincinnati, Cincinnati: USA

# Department of Otorhinolaryngology – Head and Neck Surgery

## Chair of Otorhinolaryngology

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**Research Focus**
- Ultrasound, endoscopy, and salivary glands
- Computer assisted surgery/robotics
- Cochlear implant outcome in the elderly
- Neurootology/vestibular laboratory
- Neurophysiology
- Allergology/clinical immunology and rhinology
- Experimental otorhinolaryngology
- Nanomedicine
- Laboratory for sleep disorders/somnology (SEON)

## Structure of the Department

In the Department of Otorhinolaryngology, altogether an average of 339 people are employed in part- and full-time. Out of this staff, 43 people are engaged as physicians, 25 in the scientific-medical-technical, 76 in the medical-technical area, 24 in the administration, 157 in the nursing, and 14 in house staff.

## Research

### Ultrasound, endoscopy, and salivary glands

In modern ultrasound systems and endoscopy units, studies about sonographic imaging of head and neck malignancies and salivary gland tumors remain an important role of scientific efforts. Identification and classification of tissues using tissue harmonic imaging and compound imaging were evaluated in the neck area. The gland preserving surgery for benign salivary gland tumors is the main focus. The main topics are currently the long-term outcomes after limited, extracapsular resection in particular of pleomorphic adenoma and zystadenolymphoma of the parotid gland.
Results of treatment of ranula during the last ten years have been published and showed that gland preserving procedure was possible in nearly 90% of the cases. Combined endoscopic and open surgical procedures offer a new option for the treatment of obstructive, but also of further salivary gland diseases, such as traumatic duct injuries. The long-term results and subjective patient outcome of such a treatment were evaluated and published. In vitro experiments on the effectiveness of a new device for endoscopically controlled, pneumatic, intracorporeal lithotripsy in salivary stones were performed in 2014. The device that is already in use for the therapy of kidney stones will now be first tested and also used for the treatment of salivary stones.
Results on the short-, medium-, as well as long-term outcomes after treatment of stenosis of the parotid gland and submandibular gland were published which showed that a gland removal after treatment of duct stenosis with endoscopically-dominated process no longer seems necessary in almost all cases.

### Computer assisted surgery/robotics

In this research sector, studies to assess the accuracy of intraoperative electromagnetic (EM) navigation are performed. Therefore, we compared three different EM navigation systems with the established optoelectric system. On the basis of the EM technique, it was possible to test potential applications and apply them successfully to the patient. One main focus was the navigation controlled balloon sinuplasty of the frontal sinus. Possibilities, but also limits of the entire technique could be explored. In the research area "Robotics", laboratory trials for the development of an automated endoscope holder for the skull base have been performed.

### Cochlear implant outcome in the elderly

Today cochlear implants (CI) provide an efficient treatment of profound hearing loss and inner ear deafness. Due to the ageing of people in developed countries, more and more seniors are to be implanted. The aim of this project was to investigate speech perception and electrophysiology of elderly CI listeners. Founding was provided by industry and the Johannes-and-Frieda-Marohn-Foundation.

### Neurootology/vestibular laboratory

The emphasis of the neurotology/vestibular laboratory was in particular on the pre- and postoperative diagnostics concerning cochlear implants and octavusneurinomas.

### Neurophysiology

The neurophysiology and electromyography (EMG) laboratory focuses on diagnosis and therapy of cranial nerves involved in ear, nose, and throat procedures.
In paresis or during accordant operations, the function of the facial nerve or the inferior laryngeal nerve is controlled.

### Allergology/clinical immunology and rhinology

Endonasal endoscopic sinus surgery and ASS desensitization come into question as a treatment for ASS-intolerant patients. A functional blood test to determine Eicosanoid-imbalance (FET-AIT®) is under investigation. There is an evaluation regarding the success of aspirin desensitization in patients with recurrent polyposis and aspirin intolerance. The efficiency of oral corticosteroids as a postoperative treatment for chronic rhinosinusitis is investigated in a multicenter, double-blind, placebo controlled trial.

### Experimental otorhinolaryngology

Damage to the auditory system, e.g. due to noise trauma, do not only lead to hearing impairments, but may also cause subjective tinnitus. We could demonstrate in our (gap-noise) animal model that prophylactic as well as therapeutic treatment with EGb 761®, a Ginkgo extract, counteract both, noise induced hearing loss (NIHL) and behavioral signs of tinnitus. Furthermore, we compare maladaptive neuroplastic processes that underlie the development of tinnitus with those of neuropathic pain. In addition to the electrophysiological characterization and modelling of this neuroplasticity, we investigate possible effects of NIHL on the cortical perineuronal net and characterize trauma induced subcellular changes within the cochlea.

### Nanomedicine

Project manager: Prof. Dr. C. Alexiou
Main focus of the Section of Experimental Oncology and Nanomedicine (SEON) is targeted local cancer therapy by using magnetic nanoparticles as drug carriers (Magnetic Drug Targeting; MDT). This interdisciplinary research project was funded amongst others by the Else Kröner-Fresenius-Stiftung and the BMBF Excellence Cluster "Medical Engineering". In the frame of this work, the largest preclinical animal study for local cancer therapy with magnetic nanoparticles was published by SEON in 2013. Furthermore the broadening of the research fields was continued and a project funded by the Bavarian State Ministry of the Environment and Consumer Pprotection that investigates the toxicity of nanoparticles dedicated to medical use was started. In cooperation with the Institute and Outpatient Clinic of Occupational, Social,

and Environmental Medicine and within the DFG Excellence-Cluster "Engineering of Advanced Materials" (EAM), SEON has taken over the task of toxicological testing of new synthesized – mostly technical – nanoparticles in 2013. In the same year, the subgroup "Cardiovascular Nanomedicine" was launched. This group is funded by the FP7-EU-Project "Nanoathero". Here, a consortium of 16 research laboratories and companies from ten European countries is aiming at improving the diagnosis and therapy of cardiovascular diseases. In the field of regenerative nanomedicine, the intramural funding by the Emerging Field Initiative project "TopBiomat" was complemented in 2013 by a funding of the DFG. In this priority program (SPP1681), the focus of SEON lies on investigating the interactions of magnetic nanoparticles and biological matrices. In a collaboration project with the Division of Phoniatics and Pediatric Audiology, it is the aim to develop an implant for reconstructing the vocal fold, especially after tumor resections. This project has been funded by the German Cancer Aid since 2014.

*Zeiss Life Cell Imaging System Axio Observer. Z1 with incubation unit for the morphologic and toxicologic observation and quantification of eukaryotic cells.*

### Laboratory for sleep disorders/ somnology (SEON)

Our sleep laboratory focuses on individual evaluation, management, and long-term care of sleep-related breathing disorders, like obstructive sleep apnea (OSA) and sleep-related hypoventilation. We offer a wide range of therapy options, including CPAP (continous positive airway pressure) titration and surgical modification of the upper airway for OSA and primary snoring.

In a prospective study, we analyze the significance of drug-induced sleep endoscopy (DISE) concerning diagnostic and surgical treatment factors of OSA. In collaboration with the Department of Anesthesiology, we investigate the neurocognitive outcome after surgical and non-surgical treatment in OSA patients, and in cooperation with the Institute of Anatomy II, we analyze the pathogenetic role of salivary mucins in patients with OSA.

## Teaching

Traditional instruction forms (main lecture with case-demonstration and live transmission of operations, block practical courses) are supplemented by interdisciplinary meetings. Furthermore the possibility for hospitation in the outpatient clinic and operating theater exists all through the year.

### Selected Publications


Koch M, Iro H, Zenk J. Combined endoscopic-transcutaneous surgery in parotid gland sialolithiasis and other ductal diseases: reporting medium- to long-term objective and patients' subjective outcomes. European Archives of Oto-Rhino-Laryngology 2013, 270: 1933-1940

Cicha I, Garlichs CD, Alexiou C. Cardiovascular therapy through nanotechnology – how far are we still from bedside? European J Nanomedicine 2013, 6: 63–87

Tietze R, Lyer S, Dürr S, Struffert T, Engelhorn T, Schwarz M, Eckert E, Göen T, Vasylyev S, Peukert W, Wiekhorst F, Trahms L, Dörfler A, Alexiou C. Efficient drug-delivery using magnetic nanoparticles – biodistribution and therapeutic effects in tumour bearing rabbits. Nanomedicine 2013, 9: 961-71

Tziridis K, Korn S, Ahlf S, Schulze H. Protective effects of Ginkgo biloba extract EGb 761® against noise trauma-induced hearing loss and tinnitus development. Neural Plast 2014, 2014: 427298

Hoppe U, Hast A, Hocke T. [Speech perception with hearing aids in comparison to pure-tone hearing loss]. HNO 2014, 62: 443-8

Zaloga J, Janko C, Nowak J, Matuszak J, Knaup S, Eberbeck D, Tietze R, Unterweger H, Friedrich R, Dürr S, Heimke-Brinck R, Baum E, Cicha I, Dörje F, Odenbach S, Lyer S, Lee G, Alexiou C. Development of a lauric acid/albumin hybrid iron oxide nanoparticle system with improved biocompatibility. Int J Nanomed 2014, 9: 4847-4866


### International Cooperations

Prof. C. Bachert, Ghent University, Ghent: Belgium

Prof. M. Mc Gurk, Guy's, King's and St. Thomas' Dental Institute: UK

Prof. D. A. Sherris, University of Buffalo, Buffalo: USA

Dr. L. Vekas, Center for Fundamental and Advanced Technical Research, Timisoara: Romania

Prof. Dr. E. Tombácz, University of Szeged: Hungary

Prof. Dr. H. Mangge, Medizinische Universität Graz: Austria

### Meetings and International Training Courses

16. – 19.04.2013: International Course In Facial Plastic Surgery

19. – 21.06.2013: International Course on Diagnostics and Surgery of Salivary Gland Diseases in Consideration of New Minimal Invasive Techniques

31.01.2014 Nano World Cancer Day 2014

22. – 24.10.2014: International Course on Diagnostics and Surgery of Salivary Gland Diseases in Consideration of Minimal Invasive Techniques

14.05./16.07./17.09./12.11./10.12.2014: Expertenforum HNO

# Department of Otorhinolaryngology – Head and Neck Surgery

## Division of Phoniatrics and Pediatric Audiology

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(until 30 September 2014)

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**Research Focus**
- Kinesthetic and auditory feedback during phonation and articulation
- Modeling of tracheoesophageal voice
- Development of vocal fold transplants
- Phonovibrography – objective analysis of vocal fold vibrations
- Differentiated objective analysis of the speech quality of chronically hoarse patients to enhance evidence-based diagnostics
- Fluid mechanical basis of the human voice

## Structure of the Division

Phoniatrics and pediatric audiology is a medical field which addresses diseases and disorders of voice, speech, language, hearing, and swallowing. Research deals basically with communication disorders on the perception (hearing research) and production side (speech and voice research). The principle contents of the research projects within the Division of Phoniatrics and Pediatric Audiology connect the medical field with applied natural sciences and technology. 21 employees in all work at the Division of Phoniatrics and Pediatric Audiology, four of them are financed via third-party funds.

## Research

### Kinesthetic and auditory feedback during phonation and articulation

The precision of the human speech signal is controlled by parallel working feedback processes while speaking. The feedback mechanisms are developed during language acquisition and can be divided into kinesthetic and auditory control. The feedback mechanisms can be affected by voice and speech disorders in different ways.
This project investigates the feedback mechanisms of phonation and articulation of healthy test persons and compares their performance with patients suffering from voice (hyper-, hypotension dysphonia; MTD) and speech disorders (Apraxia of Speech; AOS). The synchronous data acquisition (visual, acoustical, and EEG) enables for the first time the analysis of the connection between kinesthetic and auditory feedback processes. Current methods of electrophysiology and quantitative endoscopy are used simultaneously. The goal of the study is a first understanding of the cooperating auditory and kinesthetic feedback control.

### Modeling of tracheoesophageal voice

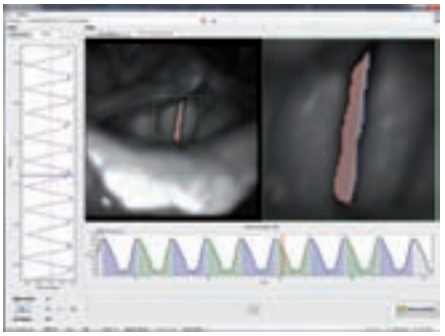
After laryngectomy, the loss of natural voice is the most prominent functional defect. It can be rehabilitated best by means of shunt valves. So far, there is no consensus on how to evaluate tracheoesophageal voice.
In a study funded by the German Cancer Aid, we objectively analyze the dynamics and the resulting acoustical signal of the remaining pharyngoesophageal segment after total laryngectomy. The goal is to find correlations between dynamics as well as tissue structures and the quality of the resulting acoustic signal. High-speed recordings in combination with a newly developed laser grid projection system are applied. This combination allows a quantitative registration of occurring dynamics. The dynamics are adopted by numerical biomechanical models. The resulting parameters, like damping and swinging masses, are further analyzed and interpreted.

### Development of vocal fold transplants

Partly or full excision of the larynx results in the loss of voice production. Additionally to the cancer, the patients then have to deal with a very reduced ability to communicate. The goal of this project, funded by the German Cancer Aid, is to reconstruct new vocal fold tissue by means of nano-technologic approaches which can be implanted after surgery. This project is jointly executed with Prof. Dr. C. Alexiou (professorship for Nanomedicine, Department of Otorhinolaryngology).

### Phonovibrography – objective analysis of vocal fold vibrations

The causes of hoarseness are not yet completely understood. The presumed irregularities of vocal fold oscillation cannot be proven with the conventional investigation instrument (stroboscopy) as this is only designed for periodic events. Thanks to funding of the DFG, a novel approach of phonovibrography could be developed which enables a visualization and analysis of vocal fold dynamics. In this approach, digital high-speed recordings of vocal fold vibrations, captured at a frame rate of 4000 Hz, are analyzed. For an objective analysis, a specialized image segmentation algorithm was developed which extracts the vibrating vocal fold edges from the high-speed recordings. The results of the procedure were extensively evaluated in a clinical trial. To visualize the relevant vibration information within a single image, the so-called phonovibrogram (PVG) was developed. A PVG image contains the entire vocal fold oscillation pattern and enables a novel classification of vocal fold vibrations. First studies show the robustness as well as the reliability of this new approach. For further quantification, a laser-grid projection device was developed which enables a three-dimensional quantification of the image data in the future. Thus, absolute measures of vocal fold elongation and velocities can be performed.
Within this project, we further developed an application software (Glottis Analysis Tools, GAT). The software is thought to be applicable in the clinical environment and routine in the future. In this research area, we closely collaborate with respected international colleagues who already apply and also review the software regarding the clinical benefit and applicability.



*Screenshot of the developed software. The vocal folds (middle) to be segmented and a close-up of this picture (right) is given. On the left, the corresponding acoustical signal, on the bottom, the segmented glottal area is given.*

### Differentiated objective analysis of the speech quality of chronically hoarse patients to enhance evidence-based diagnostics

For differentiated diagnostics of functioning and evaluation of distorted voice and speech production, there are currently no validated objective approaches. Voice and speech disorders are usually assessed by perceptive evaluations with only restricted reliability for clinical or scientific use.

Perceptual evaluations are very time consuming and of limited suitability in clinical routine. For a differentiated, objective analysis, automatic methods are developed which take this into account. Subjective clinical evaluation criteria are described by objectively computed parameters. The involved patient groups include patients with voice disorders, e.g. chronic hoarseness, partial and total laryngectomy, and patients with articulation disorders, e.g. children with cleft lip and palate and patients with oral squamous cell carcinoma.

The automatic methods analyzed voice parameters as well as speech aspects with a strong focus on a detailed (phoneme) analysis. Thus, the communication problem is not described as one single unit, but phoneme classes have been identified which are specifically affected by the distortion.

Systems for a detailed phoneme analysis in children with cleft lip and palate and patients with oral squamous cell carcinoma were also established. These systems are based on automatic speech processing techniques, prosodic analysis, phonemic and phonological features. Additionally, the current topic is the quantification of hoarseness which will also include speech-related parameters for the first time. The objective measurement of nasality without complex and expensive equipment is also part of the research project. In this way, an objective clinical evaluation is created.

The automatic analysis is the basis for future telemedical applications for the control of the progress of voice and speech therapy. Furthermore, this analysis will serve as objective addition to the established subjective voice and speech evaluation in clinical practice. The approach is another important step towards evidence-based diagnostics in phoniatrics.

This project is jointly executed with the Pattern Recognition Lab (Prof. Dr. E. Nöth, Faculty of Engineering). The project is supported by the Else Kröner-Fresenius Stiftung.

### Fluid mechanical basis of the human voice

More detailed information is given in the separate report of FOR 894, supported by DFG.

## Teaching

The Division of Phoniatrics and Pediatric Audiology is dedicated to a first-class academic teaching which is of the same value as patient care and scientific research. The offer of lectures follows the clinical focus of the area. Phoniatrics and pediatric audiology are taught during both, the pre-clinical and clinical phase. Complementarily, practical trainings on voice, swallowing, speech, and hearing impairments are given.

The training of speech therapists takes place at the Institute of Speech Therapy (B.Sc. Logopedics) within the Faculty of Medicine.

We also give lectures for the degree program "Medical Engineering" where we teach the students how to transfer engineering knowledge towards clinical questions (Computational Medicine I).

### Selected Publications


Bartke B, Haderlein T, Döllinger M, Nöth E, Graf S, Eysholdt U, Ziethe A. Perzeptive und maschinelle Stimm- und Sprechanalyse bei chronischer Laryngitis und T1-Stimmlippenkarzinom. HNO 2013, 61(8): 672-7

Echternach M, Döllinger M, Sundberg J, Traser L, Richter B. Vocal fold vibration at high soprano fundamental frequencies. J Acoust Soc Am 2013, 133(2): EL82-EL87

Unger J, Meyer T, Herbst CT, Fitch WTS, Döllinger M, Lohscheller J. Phonovibrographic wavegrams: Visualizing vocal fold kinematics. J Acoust Soc Am 2013, 133(2): 1055-64

Patel R, Dubrovskiy D, Döllinger M. Characterizing vibratory kinematics in children and adults with high-speed digital imaging. J Speech Lang Hear R 2014, 57(2): 674-86

Schulz A, Bocklet T, Eysholdt U, Bohr C, Döllinger M, Ziethe A. Validierung einer automatischen Analyse der Sprechproben von Kindern mit isolierter Gaumenspalte. HNO 2014, 62(7): 525-9

Bohr C, Kräck A, Dubrovskiy D, Eysholdt U, Svec JG, Psychogios G, Ziethe A, Döllinger M. Spatiotemporal Analysis of High-Speed Videolaryngoscopic Imaging of Organic Pathologies in Males. J Speech Lang Hear R 2014, 57(4): 1148-61


### International Cooperations

Prof. J.G. Švec, Ph.D., C. Herbst, Ph.D., Palacký University, Olomouc: Czech Republic

Prof. Y.J. Moon, Ph.D., Korea University, Seoul: South Korea

Prof. R.E. Hillman, Ph.D., MD, D. Mehta, Ph.D., Massachusetts General Hospital, Boston: USA

Prof. D.A. Berry, Ph.D., University of California, Los Angeles: USA

Prof. S.L. Thomson, Ph.D., Brigham Young University, Idaho: USA

Prof. M. Kunduk, Ph.D., Louisiana State University, Baton Rouge: USA

Prof. R. Patel, Ph.D., Indiana University, Bloomington: USA

# Department of Pediatrics and Adolescent Medicine

## Chair of Pediatrics

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**Research Focus**
- Medication safety
- Perinatal programming and early determination of renal and cardiovascular disorders
- Genetic skin diseases of the neonate
- Genomic aberrations in childhood malignancies
- Differentiation pathways during skeletal development
- Perinatal hypoxic brain injury and neuroprotection

## Structure of the Department

The Department of Pediatrics and Adolescent Medicine comprises five specialized divisions (Neonatology, Neuropediatrics and Social Pediatrics, Pediatric Oncology/Cell Therapy, Nephrology, and Molecular Pediatrics), an endowed professorship for Pediatric Endocrinology and Diabetology, and a number of specialized outpatient clinics. Academic staff of the Department of Pediatrics and Adolescent Medicine includes 102 physicians and scientists. Of these, 20 positions are financed by external funds.

Research is focused on the field of perinatal medicine with particular emphasis on molecular and developmental biology. Project coordination and scientific guidance are provided by a professorship for Experimental Perinatal Medicine. Other main research activities are related to pediatric oncology, neuropediatrics, and nephrology. In addition, clinical trials are conducted by all five divisions of the Department of Pediatrics and Adolescent Medicine and by the section of endocrinology/diabetology (e.g. interventional trials, studies on genetic conditions, infection epidemiology or medication safety, studies investigating long-term effects of surgical interventions, anti-cancer therapy or growth hormone application during childhood). The clinical studies are supported by the Department's site management organization. Many medical experts work together to bring novel research to the bedside. Patient care is based on close collaboration with the Divisions of Pediatric Cardiology, Pediatric Surgery, and Cardiac Surgery as well as with various subspecialties, often planned and carried out by interdisciplinary teams (Center for Perinatal Medicine, Center for Epilepsy, Heart Center, Cleft Lip and Palate Center, Transplantation Center).

## Research

### Medication safety

Project managers: PD Dr. A. Neubert, Prof. Dr. W. Rascher

Newborns and infants are particularly at risk for adverse drug reactions and medication errors due to common off-label use and lack of age-appropriate formulations. We have been working for many years on methods to improve medication safety. Data on adverse drug reactions (ADR) have been collected systematically; high-risk medications were detected and particularly vulnerable groups of patients were identified. We are currently investigating the impact of electronic prescription on medication safety, aiming at developing evidence-based, structured dosing information to be integrated into the prescribing system (AVOID). Moreover, the Department of Pediatrics and Adolescent Medicine is leading the organization of the "AMTS-Aktionsplan 2013 - 2015" (item 16: Development of recommendations for the use of drugs in children particularly in the inpatient care). We actively participate in several EU-funded multicenter pharmacovigilance studies (e. g. long-term safety of the iron-chelating agent deferiprone and long-term safety of methylphenidate in children with ADHD). Furthermore, an EU-funded multicenter phase III study – coordinated by our Department – is being conducted to investigate the use of clonidine as sedative agent in pediatric intensive care units (CloSed). In addition, we are also engaged in the EU-funded project "GAPP" which explores the efficacy and safety of gabapentin in neuropathic pain. The aim of both projects is a pediatric-use marketing authorization of the studied drugs.

### Perinatal programming and early determination of renal and cardiovascular disorders

Project managers: Prof. Dr. A. Hartner, PD Dr. K. Benz

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 pathogenic 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 Franconia.

### Genetic skin diseases of the neonate

Project manager: Prof. Dr. H. Schneider

Our primary research goal is to identify pathogenetic mechanisms underlying genodermatoses (hereditary disorders of the skin and its appendages) at a molecular level and to develop appropriate therapeutic approaches. These diseases are rare, but 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 studies of patients of different age groups allowed the characterization of genotype-phenotype relationships as a prerequisite for specific therapeutic attempts. In mouse models of epidermolysis bullosa, lamellar ichthyosis, and hypohidrotic ectodermal dysplasia, we have been investigating the feasibility of gene therapy in utero or perinatal protein replacement therapy. In September 2013 we started the first clinical trial in neonates with hypohidrotic ectodermal dysplasia, a multicenter interventional study based on the promising preclinical data collected over the last years.

### Genomic aberrations in childhood malignancies

Project managers: Prof. Dr. M. Metzler, Prof. Dr. T. Langer (until 06/2013)

Modern molecular biology has advanced understanding of the impact of both, heritable and acquired genetic alterations on the development and progression of pediatric tumors. We have been trying to exploit such new information for diagnostic purposes and novel therapeutic approaches, placing emphasis on acute and chronic childhood leukemia, non-Hodgkin lymphoma, Ewing's sarcoma, and other frequent pediatric malignancies. In addition to acquired mutations in the tumor genome, the impact of hereditary single nucleotide polymor-

phisms on the development of late adverse effects of current cancer therapy, such as hearing loss or cardiomyopathy, is being investigated. Rare tumor entities have been recorded in the German Pediatric Rare Tumor Registry (STEP) which is located in our Department and have been further characterized in scientific projects.

### Differentiation pathways during skeletal development

Project managers: Prof. Dr. M. Rauh, Prof. Dr. H. Schneider

To clarify the origin of osteoprogenitor cells and the role of certain signaling molecules during skeletal development, we have been using a broad spectrum of methods including immunohistochemical approaches, gene expression assays, special cell culture systems, 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 common congenital malformation), to reduce the number of surgical interventions required.

### Perinatal hypoxic brain injury and neuroprotection

Project manager: Prof. Dr. R. Trollmann

Aiming at an early detection and prevention of perinatal brain injury caused by acute or chronic hypoxia, we have been analyzing the regulation and function of hypoxia-inducible transcription factors (HIF) in the immature brain. HIF-regulated factors with strong impact on the adaptation to hypoxic conditions have been characterized as placental indicators of severe hypoxic-ischemic CNS injury in term neonates. In a mouse model of perinatal brain hypoxia, gestational age-dependent and cell-specific molecular effects of hypoxia on endogenous neuroprotective mechanisms have been demonstrated. Furthermore, the impact of perinatal hypoxia on early neuronal migration, astrocytic, and blood-brain barrier function has been investigated – as well as experimental approaches to stabilize HIF by pharmacological means.

## Teaching

Besides traditional forms of teaching (compulsory lecture series with case presentations, revision course, and hands-on training in pediatrics), special lectures, research seminars, and interdisciplinary courses are offered to medical students. Members of the research staff give lectures and practical courses for students enrolled in the degree programs Molecular Medicine and Medical Process Management. 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 the Department of Pediatrics and Adolescent Medicine.

### Selected Publications


Krieg P, Rosenberger S, de Juanes S, Latzko S, Hou J, Dick A, Kloz U, van der Hoeven F, Hausser I, Esposito I, Rauh M, Schneider H. Aloxe3 knockout mice reveal a function of epidermal lipoxygenase-3 as hepoxilin synthase and its pivotal role in barrier formation. J Invest Dermatol 2013, 133: 172-80

Berger M, Dirksen U, Braeuninger A, Koehler G, Juergens H, Krumbholz M, Metzler M. Genomic EWS-FLI1 fusion sequences in Ewing sarcoma resemble breakpoint characteristics of immature lymphoid malignancies. PLoS One 2013, 8: e56408

Radtke S, Zolk O, Renner B, Paulides M, Zimmermann M, Möricke A, Stanulla M, Schrappe M, Langer T. Germline genetic variations in methotrexate candidate genes are associated with pharmacokinetics, toxicity, and outcome in childhood acute lymphoblastic leukemia. Blood 2013, 121: 5145-53

Marek I, Volkert G, Hilgers KF, Bieritz B, Rascher W, Reinhardt DP, Hartner A. Fibrillin-1 and alpha8 integrin are co-expressed in the glomerulus and interact to convey adhesion of mesangial cells. Cell Adh Migr 2014, 8: 389-95

Hermes K, Schneider P, Krieg P, Dang A, Huttner K, Schneider H. Prenatal therapy in developmental disorders: drug targeting via intra-amniotic injection to treat X-linked hypohidrotic ectodermal dysplasia. J Invest Dermatol 2014, 134: 2985-7

Trollmann R, Richter M, Jung S, Walkinshaw G, Brackmann F. Pharmacologic stabilization of hypoxia-inducible transcription factors protects developing mouse brain from hypoxia-induced apoptotic cell death. Neuroscience 2014, 278: 327-42


### International Collaborations

Prof. Dr. D. Tibboel, Erasmus MC-Sophia Children's Hospital, Rotterdam: The Netherlands

Dr. J. Standing, Dr. C. Tuleu, University College London School of Pharmacy, London: UK

Prof. Dr. P.A. Lönnqvist, Karolinska Institutet, Stockholm: Sweden

Prof. Dr. M. Gassmann, University of Zurich, Zurich: Switzerland

Prof. Dr. I. Wong, University of Hongkong, Hongkong: China

Prof. Dr. A. Shlien, Hospital for Sick Children, Toronto: Canada

Dr. G. Te Kronnie, University of Padua, Padua: Italy

Prof. Dr. A. Clarke, Cardiff University School of Medicine, Cardiff: UK

Dr. P. Schneider, University of Lausanne, Epalinges: Switzerland

Prof. Dr. M. Gibson, University of Pittsburgh, Pittsburgh: USA

Dr. K. Huttner, Edimer Pharmaceuticals Inc., Cambridge: USA

### Meetings and International Training Courses

11. – 12.04.2013: Annual meeting of the European Pediatric Rare Tumor Group, Erlangen

### Research Equipment

Beckman Coulter, DNA-Sequenzierautomat

Becton Dickinson, FACS Calibur

AB Sciex, 2 Tandem-Massenspektrometer Tecan, Analyseplattform EVO 150

Carl Zeiss, Inverses Mikroskop Axio Observer (live cell imaging)

# Department of Pediatrics and Adolescent Medicine

## Division of Pediatric Cardiology

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**Research Focus**
- Integrated multimodality imaging in pediatric cardiology
- Establishment of a Fontan-rat mode
- Genetic factors of congenital heart disease
- Pathophysiology of the Failing-Fontan circulation
- Duchenne muscular dystrophy

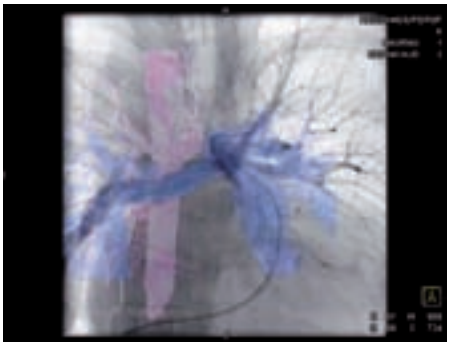
## Structure of the Division

The independent Division of Pediatric Cardiology was established in 2007. Clinical work and research activities are performed in close cooperation with the Department of Pediatrics and Adolescent Medicine and the Division of Pediatric Cardiac Surgery. A total of 19 medical doctors are involved in clinical work, teaching, and research. In the Division of Pediatric Cardiology, two "Habilitationen" (postdoctoral qualification showing ability to lecture and do research at professorial level) and two doctorates have been completed. Currently, we are supervising eleven Ph.D. students. Several projects were established to study the genetic mechanisms responsible for congenital heart disease. There is a collaboration with the Competence Network Congenital Heart Defects in multicenter clinical trials. Additionally, we prepare an own multicenter study to evaluate the efficiency of drug treatment for cardiac failure in patients with Duchenne muscular dystrophy. The clinical focus is on interventional therapy of congenital heart defects in the catheter laboratory, on surgical therapy of congenital heart defects in close cooperation with the Division of Pediatric Cardiac Surgery, and on intensive care after cardiac surgery.

## Research

### Integrated multimodality imaging in pediatric cardiology

Optimized application of different imaging modalities (Rotational angiography, Dual-Source Computed Tomography, and 3D Imaging) in the structured clinical pathway of our patients of all ages with congenital heart disease.
With modern flat detector CT technology, a sectional imaging technique is on hand for the first time that is generated directly by the angiography system. Despite the relatively unfavorable temporal resolution, high quality 3D-datasets are produced. These datasets are perfectly usable for diagnostics as well as for 3D-guidance during catheter based interventions, also by integration of previously received MRI- or CT-datasets. Corresponding application protocols for the visualization of different heart defects have been developed and successfully applied. The outlook shows the extended application of various tracking systems and also imaging fusion with 4D modalities like ultrasound.
In association with the Institute of Radiology, we developed the optimal application of the ultra-rapid dual source computed tomography in pediatric cardiology. Due to the extremely fast image acquisition, this technique is particularly suitable for critically ill children with complex cardiac defects. Special application protocols could reduce the effective dose constantly below 0.4 mSv.
Three-dimensional models of the heart and vessels acquired by above-mentioned techniques as well as by classical CT or MRI are produced with different techniques. Accordingly, the often complex anatomy is quickly to understand, largely independent from the skilled imagination of the single investigator. Therefore an optimized planning for surgery or interventions is feasible on a high level. Additionally, 3D models can effectively be used for teaching and training.



*3-D road mapping: integrative imaging with CT- and rotational angiography – dataset, overlaid on fluoroscopy-image*

### Establishment of a Fontan-rat model

Children with complex congenital heart diseases often display severe structural dysfunctions in one of both ventricles resulting effectively in the loss of function of one heart chamber. A consequence is the permanent mixture of blood with high oxygen content deriving from the pulmonary circulation and oxygen-deficient blood from the systemic circulation in the heart of those children, leading to an insufficient supply of all organs.
Without any therapy, children display remarkable developmental delays and show a limited overall survival. The strategy pursued for the last 30 years was a surgical adjustment leading blood from the large blood vessels directly from the systemic circulation to the pulmonary artery under complete circumvention of the right atrium. Consequently solely pulmonary blood with high oxygen content is led to the heart chamber and can be pumped properly in the whole body. This method initially described by Dr. F.M. Fontan (1971) is called Fontan-procedure.
Children undergoing this procedure often display characteristic secondary diseases in the course of the following years, known as Failing-Fontan. However, the pathogenesis is not yet understood, but is of life limiting influence. A successful transfer of a Fontan-model in small animals has not yet been possible. Research approaches have so far been performed on healthy large animals.
Our research group is working on a standardized procedure to implement a Fontan circulation in rats to investigate long-term consequences. A better understanding of Failing-Fontan will allow to develop targeted therapeutic strategies for the patients.

### Genetic factors of congenital heart disease

Project managers: Dr. O. Toka, Dr. J. Moosmann
The investigations of our molecular cardiology team focuses on the evaluation of genetic factors and subcellular mechanisms responsible for congenital heart malformation. In 2008, we could establish a biomaterial bank for individuals with congenital heart defects which currently counts about 2,000 DNA samples and about 1,800 cardiac tissue samples of all four chambers of the heart. Since 2009, a close cooperation and funding through the Competence Network Congenital Heart Defects has been existing. The research projects include mutation and expression analysis in familial and sporadic cases of congenital heart disease which are realized by national and international cooperations.
Our collaborators are the Institute of Human Genetics (FAU), the Department of Cardiovascular Genetics (Harvard University, Boston, USA), the Experimental and Clinical Research

Center (Charité and MDC Berlin), and the Department for Medical Genetic and Human Genetic (Charité Berlin).
Current projects:
1. Expression analyses of vasoactive signaling cascades in human aortic tissue of patients with congenital coarctation of the aorta
2. Exome sequencing in mendalian traits of complex cardiac malformations.

### Pathophysiology of the Failing-Fontan circulation

Another scientific focus of our group is to evaluate pathophysiological and immunological alteration in Failing-Fontan patients. Fontan patients are children, adolescents, and young adults who were born with only one functional ventricle (single ventricle malformation) and were palliated by the Fontan procedure. 3 - 15% of those patients develop a protein loosing enteropathy which leads to a so called failing of the Fontan circulation. Our investigations are currently funded by the Gerd-Killian Award of the German Heart Foundation.
Our collaborators are the Institute of Human Genetics, the Department of Medicine 1, and the Department of Medicine 5.
Current projects:
1. Near-infrared spectroscopy for peripheral muscle oxygenation of Fontan and Failing-Fontan patients during ergometric exercise
2. Micro-RNA analysis for identifying inflammatory pathways in Failing-Fontan patients
3. Identification of immunologic alterations of lymphocytes in Failing-Fontan patients.

### Duchenne muscular dystrophy

In our study "Effect and safety of preventive treatment with ACE inhibitors and beta blockers on the onset of left ventricular dysfunction in Duchenne muscular dystrophy", we are investigating the start of cardiomyopathy and the changes in quality of life in patients with confirmed diagnosis of Duchenne muscular dystrophy. These patients aged 10 to 14 are without any signs of impaired left ventricular function. The study is sponsored by the BMBF and was initiated in March 2010. The drugs Enalapril and Metoprolol are used in a randomized double-blinded study design and tested against placebo. In current clinical practice, only patients with already impaired ventricular function are treated with anticongestive therapy. The objective of the study is to examine if the time of onset of cardiomyopathy can be postponed by a preventive treatment with ACE inhibitors and beta blockers. Possibly, quality of life for these patients would improve and perhaps even a prolonged life expectancy may result. This is a nationwide multi-center study with the involvement of the Competence Network Congenital Heart Defects. In the meantime, patient enrollment has been completed. The last patient visit will be at the end of 2015, so first study results will be presented in 2016.

## Teaching

The Division of Pediatric Cardiology takes part in the general teaching program of the Department of Pediatrics and Adolescent Medicine (traditional main lecture, compulsory lecture series with case presentations, seminars, hands-on training in pediatrics, practical training courses). 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.

### Selected Publications


Moesler J, Dittrich S, Rompel O, Glöckler M. Flat Detector Computed Tomography in Diagnostic and Interventional Pediatric Cardiology. Rofo 2013, 185(5): 446-453

Seitz S, Rauh M, Glöckler M, Cesnjevar R, Dittrich S, Koch AM. Cystatin C and neutrophil gelatinase-associated lipocalin: biomarkers for acute kidney injury after congenital heart surgery. Swiss Med Wkly 2013, 143: w13744

Glöckler M, Koch A, Halbfaß J, Greim V, Rüffer A, Cesnjevar R, Achenbach S, Dittrich S. Assessment of cavopulmonary connections by advanced imaging: value of flat-detector computed tomography. Cardiol Young 2013, 23(1): 18-26

Al Turki S et al. Rare variants in NR2F2 cause congenital heart defects in humans. Am J Hum Genet 2014, 94(4): 574-585

van den Boogaard M et al. A common genetic variant withinSCN10A modulates cardiac SCN5A expression. J Clin Invest 2014, 124(4): 1844-1852

Glöckler M, Halbfaß J, Koch A, Dittrich S, Achenbach S, Rüffer A, Ihlenburg S, Cesnjevar R, May M, Uder M, Rompel O. Preoperative assessment of the aortic arch in children younger than 1 year with congenital heart disease: utility of low-dose high-pitch dual-source computed tomography. A single-centre, retrospective analysis of 62 cases. Eur J Cardiothorac Surg 2014, 45(6): 1060-1065


### Meetings and International Training Courses

In October 2013, Prof. Dr. S. Dittrich and Prof. Dr. R. Cesnjevar (Division of Pediatric Cardiac Surgery) were joint event organizers and Co-Presidents of the 45th Annual Meeting of the German Society of Pediatric Cardiology in Weimar.

# Department of Plastic and Hand Surgery

## Chair of Plastic and Hand Surgery

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**Research Focus**
- Tissue engineering
- Tumor biology
- Clinical experimental research
- Clinical retrospective studies

## Structure of the Department

Under the auspices of the Director of the Department of Plastic and Hand Surgery, Prof. Dr. Dr. h.c. R.E. Horch, six attending plastic surgeons, nine physicians-in-training, four lab technicians, two veterinarians, one biologist, and 28 medical students are working in different groups on various projects including basic science and clinical research.

## Research

### Tissue engineering

Project managers: PD Dr. J. Beier[1,3], PD Dr. A. Arkudas[2,4], Dr. A.M. Boos[3], Dr. A. Weigand[3], Dr. D. Steiner[2,4], G. Bührer[2,4], Prof. Dr. Dr. h.c. R.E. Horch

1) Tissue engineering of skeletal muscle

In collaboration with the Institutes of Polymer Materials and Biomaterials (Faculty of Engineering) electrospun nanofibers are developed for skeletal muscle generation. In the rat AV-loop model, axial vascularization of such nanoscaffolds and growth of cultivated muscle tissue will be evaluated. A newly developed animal mode including motor nerve branches will be used for inducing muscle differentiation in vivo. The final aim of this DFG-funded 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 tissue-engineered bone in the irradiated femur defect model of the rat using mesenchymal stem cells (MSC) and the growth factor BMP2 in cooperation with the Chair for Material Science and Metal Technology, Biomaterials as well as Glass and Ceramics (Faculty of Engineering). In the course of the Emerging Fields Initiative (EFI) TOPbiomat, new scaffolds, provided by the Chair for Biomaterials, have been investigated in vitro and in vivo.

3) Generation of axially vascularized tissue in the large animal

Ongoing studies are evaluating a load-stable nanocrystalline bone substitute material in combination with angiogenic and osteogenic cells and growth factors. Subsequently the transplantation of the bone substitute will be evaluated in clinically relevant dimension in the sheep tibia defect model in order to offer this new therapeutic method in human medicine in the near future.

4) Tissue engineering of small diameter vascular grafts

The aim of this study is to generate nanofiber-based small diameter vascular grafts in cooperation with the Institute for Biomaterials and the Institute of Polymer Materials (Faculty of Engineering) using electrospinning methods and to evaluate graft patency and vascularization potential in the rat. Furthermore, the effect of EPC (endothelial progenitor cells) on the endothelialization of the vascular grafts is investigated.

### Tumor biology

Project managers: Dr. A.M. Boos, Dr. A. Weigand, Prof. Dr. Dr. h.c. R.E. Horch

1) Effects of tumors on a developing blood vessel network

A tumor can influence and use either the existing blood vessel cells or networks or develop its own blood vessel network from mutated or reprogrammed tumor or tumor stem cells. 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 EPC in tumor associated angiogenesis. Different in vitro angiogenesis assays as well as the AV-loop rat model will be used as toolbox.

2) Therapeutic approaches on the lymphatic vessel system in the context of regenerative medicine and tumor progression

A better understanding of the mechanism of lymphangiogenesis could help to get deeper insights in the growth of lymphatic vessels in pathological situations as well as in lymphatic metastasis to develop effective pro- and anti-lymphangiogenic therapies in the future. The goal of the project – besides the characterization of the interaction of lymphatic endothelial cells and MSC – is the establishment of an autonomous lymphatic vessel network in the rat AV-loop-model that can be subsequently used for lymphangiogenesis assays.

3) Tumor angiogenesis and vasculogenesis in breast cancer

The tumor vascularization as the critical step for local tumor progression and metastasis represents an attractive target for cancer therapeutics. The effect of breast cancer cells on angiogenic properties of EPC will be evaluated in angiogenesis assays in vitro as well as in vivo in the rat AV-loop-model. The identification of the role of EPC in neovascularization could be the first step for the development of a new specific therapy for breast cancer patients.

4) Paracrine and cell-cell interaction of adipose derived stem cells and mammary epithelial cells in the focus of development of breast cancer

Currently, the tumorigenicity and angiogenic properties of lipoaspirates that are transplanted in residual breast tissue are not exactly identified. In this study, the influence of adipose derived MSC and fat cells on the behavior of cells in the breast and breast cancer tissue will be evaluated. The risk of enhancing the recurrence rate and the safety of lipotransfer for the reconstruction of breast tissue after tumor excision will be assessed. Understanding the interaction between these cell types could be decisive for developing new breast cancer therapies.

### Clinical experimental research

Project managers: PD Dr. J. Beier[1-3], PD Dr. A. Arkudas[4,5,7], Dr. M. Schmitz[8], Dr. C.D. Taeger[1,6,7], Dr. I. Ludolph[2,8], Dr. V. Haug[3], G. Bührer[5], Prof. Dr. Dr. h.c. R.E. Horch

1) Perfusion studies using laser Doppler spectrophotometry to investigate the impact of harvesting the mammaria interna artery on sternal perfusion patterns

This prospective study with cardiac surgical patients was set up to validate the hypothesis that using the internal mammary artery for coronary artery bypass leads to malperfusion of the sternum. This is done using laser Doppler spectrophotometry pre- and postoperatively at the sternum of cardiac surgical patients.

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, we perform intraoperative fluorescence imaging of tissue perfusion using indocyanin-green and a laser camera. Based on these observations, a further increase of free tissue transplantation survival and a decrease of flap complications could be achieved.

3) Analysis of grip force in common hand conditions using the Manugraphy System®

Hand conditions (such as Carpal Tunnel Syndrome or CRPS) may be accompanied by a loss of hand function or grip force. This study evaluates load distribution patterns and skin perfusion changes (using the o2c-device) in the above mentioned hand conditions.
4) Evaluation of carpal instability regarding Scapholunate ligament injuries
The aim of this study is to evaluate wrist mobility between carpal bones using µCT analysis in cooperation with the Institute for Anatomy and the Department of Otorhinolaryngology (SEON) in order to invent new strategies to treat scapholunate ligament injuries.
5) Cellu-Tome: Evaluation of epidermal grafts in a standardized wound model
The goal of this study is the evaluation of Cellu-Tome-generated epidermal grafts after transplantation in split skin donor sites. Evaluation is performed by clinical assessment and various measurements.
6) Optimization of extracorporeal tissue conserving protocols by continuous tissue perfusion in plastic-reconstructive surgery
This project deals with continuous extracorporeal perfusion of transplants. The question is whether this treatment is superior to classical cold storage of transplants regarding ischemia-related cell damage. For this study, skeletal muscle from pigs is used.
7) Analysis of pressure gradients and perfusion patterns using negative pressure wound therapy
This prospective study was planned to investigate physical pressures beneath the dressings using vacuum assisted wound therapy (npwt). Furthermore, perfusion patterns of the skin beneath npwt are planned to be investigated. The findings should help to learn more about the underlying mechanisms of action of npwt.
8) Biomaterials for coverage of silicone implants to prevent capsular fibrosis
Capsular fibrosis represents a significant complication following implantation of silicone breast implants, requiring further surgical intervention. Numerous studies investigating methods to prevent capsular fibrosis have been carried out so far, but without success. Experimental animal studies will be conducted to investigate if diverse biomaterials (e.g. xenogenic acellular dermis) can be used as an envelope for submuscular silicone implants to reduce foreign body reaction.

### Clinical retrospective studies

Project managers: Prof. Dr. Dr. h.c. R.E. Horch[1], PD Dr. J.P. Beier[2,3], Dr. M. Schmitz[4], Dr. C.D. Taeger[1,4], Dr. R. Brodbeck[2], Dr. D. Steiner[3]

1) Retrospective analysis of patients treated for carpal tunnel syndrome in the years 2010 and 2011 in the Department of Plastic and Hand Surgery
To learn more about carpal tunnel syndrome, health records of patients who underwent carpal tunnel release between 2010 and 2011 are analyzed.
2) The role of plastic reconstructive surgery in multidisciplinary surgical treatment of sarcomas – a retrospective study 2004 – 2014
In this study, a comprehensive picture of interdisciplinary sarcoma treatment is obtained through an analysis of medical records and a questionnaire-based survey.
3) Scalp reconstruction: a retrospective analysis of the years 2004 – 2014
In this study operative means and outcomes for reconstruction of scalp defects over a ten-year period are analyzed in order to develop optimal surgical strategies to reconstruct these complex defects.
4) Retrospective ten year analysis of postbariatric surgery for body contouring after massive weight loss
Postbariatric surgery as the last step for the patient's reintegration in society after massive weight loss gains more and more attention. In the framework of a retrospective ten year study, we analyze main factors such as the postoperative course, possible complications, long term results, and the individual surgical plan to optimize future therapy.

## Teaching

According to the German medical licensure act (ÄAppO), a lecture series is held as part of the general surgery lecture series. It covers general principles of plastic and hand surgery. Additionally, the following teaching courses are conducted regularly by the Department of Plastic and Hand Surgery:
- Lecture series on "Specific issues in plastic and hand surgery"
- Tutorial "Tissue engineering"
- Clinical ward round of the Department of Plastic and Hand Surgery
- Surgical anatomy of the hand and techniques of hand examination
- Interdisciplinary consultation hour in "Breast Reconstruction"
- Teaching ward round and advanced course in plastic surgery
- Microsurgical suture techniques
- Teaching ward round and advanced course in reconstructive microsurgery

### Selected Publications


Horch RE, Beier JP, Kneser U, Arkudas A. Successful human long-term application of in situ bone tissue engineering. J Cell Mol Med 2014, 18(7):1478-85

Taeger CD, Müller-Seubert W, Horch RE, Präbst K, Münch F, Geppert CI, Birkholz T, Dragu A. Ischaemia-related cell damage in extracorporeal preserved tissue – new findings with a novel perfusion model. J Cell Mol Med 2014, 18(5):885-94

Horch RE, Hohenberger W, Eweida A, Kneser U, Weber K, Arkudas A, Merkel S, Göhl J, Beier JP. A hundred patients with vertical rectus abdominis myocutaneous (VRAM) flap for pelvic reconstruction after total pelvic exenteration. Int J Colorectal Dis 2014, 29(7): 813-23

Strobel LA, Rath SN, Maier AK, Beier JP, Arkudas A, Greil P, Horch RE, Kneser U. Induction of bone formation in biphasic calcium phosphate scaffolds by bone morphogenetic protein-2 and primary osteoblasts. J Tissue Eng Regen Med 2014, 8(3): 176-185

Zhong A, Wang G, Yang J, Xu Q, Yuan Q, Yang Y, Xia Y, Guo K, Horch RE, Sun J. Induction of bone formation in biphasic calcium phosphate scaffolds by bone morphogenetic protein-2 and primary osteoblasts J Cell Mol Med 2014, 18(7): 1257-66

Brandl A, Yuan Q, Boos AM, Beier JP, Arkudas A, Kneser U, Horch RE, Bleiziffer O. A novel early precursor cell population from rat bone marrow promotes angiogenesis in vitro. BMC Cell Biol 2014, 15(1): 12

# Department of Psychiatry and Psychotherapy

## Chair of Psychiatry and Psychotherapy

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**Research Focus**
- Depression
- Dementias
- Schizophrenia
- Addictive behavior
- Clinical neurochemistry and neurochemical dementia diagnosis
- Neurophotonics
- Medical care research

## Structure of the Department

The Department of Psychiatry and Psychotherapy combines all psychosocial specialties under one roof regarding organization and location. The Department encompasses the independent Divisions of Psychosomatics and Psychotherapy and of Child and Adolescent Mental Health as well as the specialties Medical Psychology and the Medical Sociology. Content-related networking is supported by the DIN EN ISO 9001:2008 certified quality management system. The Department of Psychiatry and Psychotherapy incorporates the Laboratory for Clinical Neurochemistry and Neurochemical Dementia Diagnostics, the National Reference Center for Neurochemical Dementia Diagnostics within the Kompetenznetz Demenzen (KND). In addition, the Laboratories for Molecular Neurobiology, the Neurophotonics Laboratory, and a Sensor Laboratory are part of the Department of Psychiatry and Psychotherapy.

## Research

### Depression

The Boulder-therapeutic group intervention was investigated for the first time in a pilot study on people with depression. The extent to which the parenting style experienced in childhood exerts a protective or risk factor for later suicidal behavior was examined in a representative sample of more than 40,000 adolescents. It was found that adolescents who had experienced a rejecting-neglecting parental mode in childhood had a markedly higher risk of serious suicide attempts. By contrast, an experienced authoritative mode of parenting was a protective factor for later suicidal behavior. In FRAMES (Franconian Maternal Health Evaluation Study), socioeconomic status was investigated as a predictor for depressive symptoms during and after pregnancy as well as single nucleotide polymorphisms in genes of the stress-hormone pathway and alcohol-associated markers in the meconium of the neonate. In stimulation procedures, the effect of the stimulation parameter on depressive symptoms in vagus-nerve stimulation, the effect of transcutaneous vagus-nerve stimulation, and biochemical effects of transcranial magnetic stimulation were investigated.
In preclinical studies, we were able to demonstrate an important role of the lipid ceramide in the emergence of depressions. Elevated hippocampal ceramide concentration leads to depression-like behavior in mice and to a reduced rate of newly-formed nerve cells; opposite effects are found with reduced hippocampal ceramide concentration. Antidepressives inhibit an important ceramide-forming enzyme, the acid sphingomyelinase. The effects of the antidepressive on behavior and neurogenesis cannot be detected in mice with a genetic deficiency of this enzyme. Ceramide is thus a not-yet recognized depression-inducing molecule and a new target for the development of future antidepressives. These studies are supported by the DFG, the Research Foundation of Medicine, and the Annika Liese Prize 2014. Studies of the acid sphingomyelinase also addressed its genetic regulation and changes in serum and liquor.

### Dementias

In psychometry, a test sponsored by the DFG was developed to record everyday practical competence in people with mild dementia or mild cognitive impairment (Erlangen Test for Activities of Daily Living in Mild Dementia and Mild Cognitive Impairment – ETAM). Starting from the randomized controlled study MAKS aktiv in which a multimodal non-drug therapy for nursing home residents with dementia was evaluated, another controlled randomized study was started in the area of medical psychology. In this study, the effect of MAKS therapy on day-care patients with mild dementia is to be examined, combined with an intervention for reducing the burden on care-giving family members (Project DeTaMAKS). DeTaMAKS is being financed by the National Association of Statutory Health Insurance Funds (GKV) as a model project. Moreover, a registry of people in whom dementia is diagnosed for the first time (Erlanger Dementia Registry EDR) was created at the UK Erlangen in an interdisciplinary project. For this, patients with dementia and their family members were studied in their own care environments in order to obtain insight into requirements and needs.
The role of memory-modulating peptide receptors for the diagnostics and treatment of Alzheimer's dementia was investigated within the KND. The neurokinin3 receptor could be identified both, as predictor and as a pharmacological target to improve memory performance in the elderly organism.
Comparative studies of neurons and glia cells showed that modified Aβ-peptides, such as are deposited in Alzheimer plaques, have a cell-type-specific pattern and are formed via different enzymatic pathways. This potentially provides new pharmacological approaches to reducing the β-amyloid burden in the brain. Modified Aβ-peptides are also excreted by activated macrophages, but at the same time are effective in a soluble form and as opsonin in promoting phagocytosis. Thus, they may have a physiological function in inherited immunodefense. At the methodical level, a new computer-based procedure was developed which considerably facilitates the automated analysis of Aβ-peptides in two-dimensional gel-electrophoresis.

### Schizophrenia

A major step forward in dissecting the underlying genetic architecture for schizophrenia has been achieved with the publication of the largest genome wide association study completed in schizophrenia so far. This effort included the collaboration of researchers around the globe, including our own group. Based on almost 37,000 patients and about 113,000 controls, it was possible to identify 108 gene loci, providing robust biological pathways, opening new corridors for the development of innovative treatments for schizophrenia. Included in the long list of genetic loci are well known genes, such as the dopamine D2 receptor and genes involved in glutamatergic neurotransmission, but also a number of loci with genes which play important roles in immunity.

### Addictive behavior

In cooperation with the Criminological Research Institute of Lower Saxony and the Hannover Medical School, an investigation was performed

to what extent victimization experiences in adolescents are related to binge drinking. Significant and especially marked correlations were found among girls who experienced sexual abuse and among boys who experienced physical violence. Factors which reduced the risk of binge drinking were relocation, associated with the loss of friends, and the experience of bullying by peers.

The focus of addiction research was developed to a translational approach with which important knowledge gained in basic animal experiments on the pathogenesis of addiction could be applied to humans. The role of memory processes in the development of drug addiction was one special focus. We were able to demonstrate how molecular mechanisms which are normally responsible for the development of normal memory content contribute to the development of alcohol and cocaine consumption behavior. Genetic mutations in the genes involved alter the probability of addiction development. In research into the biomarkers of alcohol and cannabis addiction, difference in DNA methylization and repetitive polymorphisms could be identified as clinically-relevant markers. Research in the area of nicotine addiction showed that cigarette smoking exerts direct influence on the control of glutamatergic activity in the brain which returns to normal in withdrawal. In studies of new drugs, the focus was on the phytodrug kratom and its main active ingredient mitragynine.

### Clinical neurochemistry and neurochemical dementia diagnosis

The ISO 9001:2008-certified and ISO 15189-accredited laboratory is an internationally recognized Center for Neurochemical Dementia Diagnostics (NDD). The analysis of Liquor cerebrospinalis offers outstanding diagnostic possibilities in numerous neurological and psychiatric disorders, such as neurodegenerative diseases, stroke, Multiple Sclerosis and other neuroinflammatory diseases.

### Neurophotonics

In 2013, Dr. O. Welzel and PD Dr. T.W. Groemer were awarded a prize by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie for proof of the effect of fluoxetin on marked synaptic activity. A project supported by the DFG is running to investigate the effect of psychopharmaceuticals on synapses. With a grant from the Else-Kröner-Fresenius-Foundation, a new method for optical measurement of connective strengths in nerve-cell networks could be established. Many basic questions can be investigated with this method in the coming years.

### Medical Care Research

Colleagues at the Center for Medical Care Research developed and published a theoretical model for evidence-based care research. This is intended to establish a gold standard on which to measure the topic selection and quality of future care research studies. Moreover, work is being performed to address PRO (Patient Reported Outcomes), a topic which is under considerable discussion in care research. A cooperation project with the Interdisciplinary Pain Center at the UK Erlangen could be established to enable using routine care data with respect to PRO.

## Teaching

The Department of Psychiatry and Psychotherapy offers a wide spectrum of courses for students of Medicine as well as for the students of the degree programs Molecular Medicine and Medical Process Management. Evaluation of training regularly places psychiatry among the best clinical subjects. Planning and evaluation of the exams is carried out in accordance with scientific principles. Particular attention is focused on training of communication skills in the doctor/patient interaction. The performance record of this training is assessed by a competence-oriented test. The portfolio to be written for it can be prepared by the students in a flexible time window, thus reducing the work load at the end of the term. It promotes process-based learning thanks to individual feedback and an intensive support by tutors. In 2014, the Erlangen students ranked first in the subject Medical Psychology and Medical Sociology in the First Part of the Medical Exam in a country-wide comparison.

### Selected Publications


de Souza Silva MA, Lenz B, Rotter A, Biermann T, Peters O, Ramirez A, Jessen F, Maier W, Hüll M, Schröder J, Frölich L, Teipel S, Gruber O, Kornhuber J, Huston JP, Müller CP, Schäble S. Neurokinin3 receptor as a target to predict and improve learning and memory in the aged organism. Proc Natl Acad Sci U S A 2013, 110(37): 15097-15102

Easton AC, Lourdusamy A, Loth E, Toro R, Giese KP, Kornhuber J, de Quervain DJ, Papassotiropoulos A, Fernandes C, Müller CP, Schumann G: CAMK2A polymorphisms predict working memory performance in humans. Mol Psychiatry 2013, 18(8): 850-852

Gulbins E et al. Acid sphingomyelinase-ceramide system mediates effects of antidepressant drugs. Nat Med 2013, 19(7): 934-938

Ripke S et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet 2013; 45(10): 1150-1159

Donath C, Graessel E, Baier D, Bleich S, Hillemacher T. Is parenting style a predictor of suicide attempts in a representative sample of adolescents? BMC Pediatr 2014, 14: 113

Kornhuber J, Müller CP, Becker KA, Reichel M, Gulbins E. The ceramide system as a novel antidepressant target. Trends Pharmacol Sci 2014, 35: 293-304


### International Cooperations

Prof. Dr. D.B. Wildenauer, School of Psychiatry and Clinical Neurosciences University of Western Australia, Crawley: Australia

Prof. Dr. M. Barros, Institute of Pharmacology, Brasilia: Brazil

Prof. Dr. S. Trapp, Technical University of Denmark: Denmark

Prof. Dr. G. Schumann, Institute of Psychiatry, London: UK

Prof. K. Blennow, Prof. H. Zetterberg, University of Gothenburg: Sweden

Prof. B. Mroczko, Medical University of Bialystok, Bialystok: Poland

# Department of Psychiatry and Psychotherapy

## Division of Child and Adolescent Mental Health

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**Research Focus**

- Neurofeedback: Training effects on behavior and at the neurophysiological level
- Attention and inhibition processes in children with ADHD
- Neural processing of emotional and disorder specific stimuli in girls with eating disorders
- Prenatal risks for child development: FRANCES – Franconian Cognition and Emotion Studies
- Behavioral and neural consequences of prenatal trauma in an animal model
- Stress regulation in children and adolescents with anxiety disorder and/or depressive disorder

## Structure of the Division

The Division of Child and Adolescent Mental Health at the Department of Psychiatry and Psychotherapy is an independent Division of the UK Erlangen. It is subdivided in the areas research, outpatient clinic/policlinic, day hospital, and inpatient clinic. Furthermore, in cooperation with the Fürth Main Hospital, another child psychiatric day hospital is operated and professionally directed by Prof. Dr. G. Moll which was extended to include a family day care for families with children between one and four years in 2011. The clinical focus lies on: Attention deficit/hyperactivity disorder (ADHD), tic disorders, obsessive-compulsive disorders, anxiety disorders, depressive disorders, posttraumatic stress disorders, eating disorders, autistic disorders, reduced intelligence with psychiatric comorbidity, and regulation and behavior disorders in early childhood. The research projects (project leaded by: PD Dr. H. Heinrich, PD Dr. O. Kratz) aim at better understanding of developmental processes and the neurobiological basis of emotional and behavioral disorders in children and adolescents as well as gaining further insights into the neural mechanisms underlying therapeutic interventions.

## Research

### Neurofeedback: Training effects on behavior and at the neurophysiological level

Project leader: Dr. P. Studer

Neurofeedback training is a behavioral training where participants learn to gain self-control over certain brain activity patterns and thereby to better regulate their behavior. Our studies, conducted in cooperation with the Child and Adolescent Psychiatry at the University Medical Center Göttingen, significantly contributed to demonstrate the clinical effectiveness of neurofeedback (theta/beta and SCP training) as a therapeutic module in the treatment of children with ADHD. Regarding the neurophysiological mechanisms underlying the different neurofeedback protocols, we observed associations between SCP (slow cortical potentials) regulation of negativity and attentional resource allocation (increase of the contingent negative variation) in healthy adults and an increase in intracortical inhibition and facilitation after a theta/beta training. In children with ADHD, we found SCP regulation abilities to be associated with reductions in ADHD symptoms. Moreover, we developed an evidence-based neurobehavioral model of neurofeedback.

### Attention and inhibition processes in children with ADHD

Project leaders: PD Dr. H. Heinrich, PD Dr. O. Kratz

To have a more differentiated view on the neural implementation of response preparation, execution and inhibition in children with ADHD, we applied a combined neurophysiological approach, including magnetic stimulation (TMS), and event-related potentials (ERP). Results indicate deviant implementation of motor control in ADHD – due to an inhibitory deficit in the motor cortex. Both, deviant inhibitory and attentional processes seem to be characteristic for ADHD in motor control tasks.

Further investigations (ERP single trial analysis; EEG analysis of an attentive state) revealed a differential picture of processes underlying the attentional problems of these children. Among others, we observed differential patterns for different ADHD subtypes. The results may also have implications for neurofeedback training.

### Neural processing of emotional and disorder specific stimuli in girls with eating disorders

Project leader: Dr. S. Horndasch

In a pilot study, gaze behavior and central nervous and peripheral physiological responses when viewing body scheme pictures of underweight, normal weight, and overweight women were studied in adolescent girls with eating disorders (anorexia nervosa, bulimia nervosa) and typically developing girls. Eating disordered patients showed longer fixation times for unclothed body regions (visual attentional bias towards body shape-related information). At the central nervous level (event-related potentials in the EEG), anorectic patients showed largest responses for pictures of underweight women. In a further study, adolescent and adult patients suffering from anorexia nervosa and matching healthy controls were included permitting us to look at developmental effects. For the study, an assessment battery including standardized pictures of underweight, normal weight, and overweight women as well as pictures of food was developed and evaluated in healthy female adolescents. First results show differential evaluation processes of pictures of women's bodies in anorexia patients as compared to healthy controls. This evaluation bias was less pronounced in adolescent as compared to adult patients.

### Prenatal risks for child development: FRANCES – Franconian Cognition and Emotion Studies

Project leader: Dr. A. Eichler

In our longitudinal study with 200 families we investigate the cognitive, emotional, and social development of six to eight year old children. In part we focus on the problems of children exposed to prenatal risk factors.

Children were delivered between 2005 and 2007 at the Department of Obstetrics and Gynecology at the UK Erlangen and perinatal data of mothers and children were collected in the FRAMES study (FRAMES: Franconian Maternal Health Evaluation Studies, cooperation-study with the Department of Obstetrics and Gynecology and the Department of Psychiatry and Psychotherapy at the UK Erlangen).

Effects of prenatal maternal risk factors, i.e. alcohol or depression, for child development (e.g. ADHD and anxiety) were analyzed under control of relevant confounders (i.e. complications in pregnancy, actual maternal psychopathology). Data representing different levels of child adaption (behavioral, neuropsychological, neurophysiological, and neurobiological) are available. First analysis revealed that even 'subliminal' maternal alcohol consumption during pregnancy has negative consequences for their children's brain development.

### Behavioral and neural consequences of prenatal trauma in an animal model

Project leader: Dr. Y. Golub

To investigate the consequences of prenatal traumatic experience on the brain development and behavior, we established a mouse model of prenatal trauma based on the application of a single electric foot shock during pregnancy. Traumatized mothers spent less time with their offspring and showed increased anxiety levels, while this behavior went along with decreased prolactin and increased basal corticosterone levels. In a cross fostering study, we observed additive effects of prenatal trauma and postnatal environment. In cooperation with the research group of Prof. Dr. M.A. Riva (University of Milan), we showed changes in the expression of some genes in traumatized mothers and their offspring. Our results link posttraumatic changes in fear behavior and maternal care with long-term hormonal dysregulations.

### Stress regulation in children and adolescents with anxiety disorder and/or depressive disorder

Project leader: Dr. Y. Golub

In children and adolescents with anxiety and/or depressive disorder, we investigate the function of the hypothalamic–pituitary–adrenal (HPA) and the neuropeptide Y (NPY) systems under both, basal and stress conditions. Our results indicate a general up-regulation of both systems under the basal conditions and a blunted HPA-axis response to stress in children with anxiety and depressive disorder. The remission of clinical symptoms correlates with a normalization of function of both systems.

## Teaching

The teachings in the field of child and adolescent psychiatry and psychotherapy are composed of lectures, seminars, case presentations as well as block seminars. These comprise diagnostics and therapy of the clinical disorders as well as the research methods applied in this field. Year-round, students of medicine, psychology, education science, and social pedagogy are being educated and supervised. The main lecture "Child and adolescent psychiatry and psychotherapy" is attended by numerous students even though it has not yet been included in the curriculum of the Faculty of Medicine despite its immense importance for the field. However, practical training and seminar are a fixed component of the constantly very successfully evaluated lecture of the Department of Psychiatry and Psychotherapy. Moreover, the subject "Child and adolescent psychiatry and psychotherapy" is offered as a compulsory optional subject for students of medicine (clinical/preclinical term) and as an optional lecture with accompanying seminar within the course of studies in Psychology (Bachelor/Master). Since the summer term 2012, the seminar "School related psychiatric disorders" has offered as an interdisciplinary lecture for both, students and professionals, in the fields of education science, psychology, and medicine.

### Publications


Solati J, Hajikhani R, Golub Y. Activation of GABAA receptors in the medial prefrontal cortex produces an anxiolytic-like response. Acta Neuropsychiatr 2013, 25(4): 221-6

Eichler A, Glaubitz K, Hartmann L, Spangler G. Die Erfassung elterlicher Belastung mit dem Eltern-Belastungs-Screening zur Kindeswohlgefährdung (EBSK): Zusammenhänge zu Erlebens- und Verhaltensauffälligkeiten beim Kind. Z Kinder Jugendpsychiatr Psychother 2014, 42(4): 213-222

Gevensleben H, Kleemeyer M, Rothenberger LG, Studer P, Flaig-Röhr A, Moll GH, Rothenberger A, Heinrich H. Neurofeedback in ADHD: further pieces of the puzzle. Brain Topogr 2014, 27: 20-32

Heinrich H, Busch K, Studer P, Erbe K, Moll GH, Kratz O. EEG spectral analysis of attention in ADHD: implications for neurofeedback training? Front Hum Neurosci 2014, 8: 611

Heinrich H, Hoegl T, Moll GH, Kratz O. A bimodal neurophysiological study of motor control in attention-deficit/hyperactivity disorder: a step towards core mechanisms? Brain 2014, 137(Pt 4): 1156-1166

Studer P, Kratz O, Gevensleben H, Rothenberger A, Moll GH, Hautzinger M, Heinrich H. Slow cortical potential and theta/beta neurofeedback training in adults: effects on attentional processes, and motor system excitability. Front Hum Neurosci 2014, 8: 555


### International Cooperations

Prof. Dr. D. Brandeis, Dr. R. Drechsler, University of Zurich, Zurich: Switzerland

Prof. Dr. M.A. Riva, University of Milan, Milan: Italy

Dr. C. McCabe, University of Reading, Reading: United Kingdom

# Department of Psychiatry and Psychotherapy

## Division of Psychosomatic Medicine and Psychotherapy

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**Research foci**
- Psycho-oncology
- Influencing factors of migration and psychic health
- Transplantation medicine
- Somatoform disorders (persistent somatoform pain disorder and body dysmorphic disorder)
- Eating disorders and obesity

## Structure of the Division

The independent Division of Psychosomatic Medicine and Psychotherapy provides inpatient, day-care, and outpatient treatment as well as a psychosomatic liaison service. The psycho-oncologic service treating the patients of the Comprehensive Cancer Center Erlangen (CCC) is also affiliated to the Division. Clinical foci of the Division are eating disorders, adipositas, somatoform disorders including chronic pain disorders, posttraumatic stress disorder, psycho-oncology. Cooperations with other departments of the UK Erlangen demonstrate the interdisciplinary relevance of the subject psychosomatics.

## Research

### Psycho-oncology

Project managers: Prof. Dr. Y. Erim, K. Schieber, Dr. E. Morawa

Current research projects:
- Multicenter study to document the needs and demands of patients as well as the utilization of psycho-oncologic services

Cooperation study of the Comprehensive Cancer Center Erlangen

Supported by the German Cancer Aid
- Risk-adapted follow-up care in uveal melanoma

Cooperation project with the West-German Tumor Center Essen

Supported by the German Cancer Aid
- Disease management and not recognized supportive needs in oncologic patients with special consideration to a migrant background

Supported by the ELAN-program of the FAU

In addition, the following topics are being investigated within the context of dissertation projects:
- Posttraumatic growth after critical life-events during childhood: a comparison between survivors of childhood cancer, diabetes, and a normal population
- Validation of a questionnaire of patients coping with cancer
- Disease concepts in oncologic patients with a migrant background
- Resilience and fear of prognosis in female patients seeking a second opinion

Cooperation with the Department of Obstetrics and Gynecology (Prof. Dr. M. Lux).

### Influencing factors of migration and psychic health

Project managers: Prof. Dr. Y. Erim, Dr. E. Morawa

Considering the demographic development in Germany showing a continuous increase of persons with a migrant background (in 2013 20 % of the total population), research on not only specific burdens, but also resources of this group is indicated.

Current research projects deal with the prevalence of psychic disorders and mental distress in a norm population of Turkish origin (in cooperation with the Institute of Epidemiology, University of Essen); in several dissertation projects, mental disorders and disease concepts of utilization clientele with a migrant background are investigated, e.g. the investigation of the coping style in a cultural comparison of oncologic patients or patients of a general medical practice. A further study analyzes psychic burdens of Iranian patients in primary care.

### Transplantation medicine

Project manager: Prof. Dr. Y. Erim

During all phases of transplantation, the identification and treatment of patients with co-morbid psychic disorders plays a crucial role.

Studies completed have dealt with the psychosomatic evaluation and psychotherapeutic treatment of patients with ethyl toxic liver cirrhosis. In pre-surgery evaluation, the question was surveyed if additional information was gained by utilizing an ethyl glucuronide test in hair as an innovative biomarker. The influence of the transplant setting on self-reports of patients with alcoholic cirrhosis was investigated. A further study investigated the influence of psycho-educative group therapy on abstinence prior to liver transplantation. At present, in cooperation with the Department of Medicine 4 – Nephrology and Hypertension, the predictors of adherence after kidney transplantation are being investigated. Within the context of the research collaboration Emerging Fields Initiative (EFI), a catamnesis of living kidney donors is being prepared with emphasis on the experience of autonomy.

### Somatoform disorders (persistent somatoform pain disorder and body dysmorphic disorder)

Project managers: Prof. Dr. Y. Erim, Dr. I. Kollei, Dr. S. Horndasch

Etiology of chronic pain disorders

Persistent somatoform pain disorders are understood to be a chronic pain disorder that on the one hand cannot be adequately explained by an organic disease and for which, on the other hand, a recognizable emotional and/or psychosocial burden is discernible. The etiology of these disorders has as yet not been sufficiently investigated. Early childhood experiences, an uncertain attachment style, as well as altered cerebral activities (dysfunctional pain and stress processing) have been postulated as etiologic factors and are being investigated in the present study in cooperation with the Department of Neuroradiology (Prof. Dr. A. Dörfler). Both, psychometric measurements and neuro-imaging (f-MRT) are employed.

Visual perception in body dysmorphic disorder (supported by the ELAN-program of the FAU)

Body dysmorphic disorder is understood as the extreme occupation and concern with a perceived affliction in one's outer appearance. In a present ELAN-supported project, the visual body dysmorphic disorder is investigated by means of the Eye-Tracking method.

### Eating disorders and obesity

Project manager: Dr. H. Graap (in the past: Prof. Dr. M. de Zwaan, PD Dr. Dr. A. Müller until October 2011, completion of the project in 2013)

The "Research Association on Psychotherapy of Eating Disorders" (Forschungsverbund zur Psychotherapie von Essstörungen (EDNET)) was supported by the BMBF and was in progress between 2007 and 2013. Within the association, five controlled, randomized multicenter psychotherapy studies in patients with anorexia nervosa, bulimia nervosa, and eating disorders were carried out. A present intervention study investigates the effects of psycho-educative skills training in relatives of patients with eating disorders.

In the field of obesity research, the German weight control register was set up investigating psychosocial indicators supportive of long-term weight reduction. A research project on the executive function of morbid obese with and without binge eating indicated that obese persons with binge eating tend more often to unfavorable and risky decisions than obese persons without binge eating.

## Teaching

The Division of Psychosomatic Medicine and Psychotherapy is intensively involved in the curriculum of the Faculty of Medicine and participates in several cross discipline teaching efforts (Querschnittsfächer) within the curriculum of the Faculty of Medicine and also offers courses for psychology students. Medical students can choose psychosomatic medicine as a clinical elective and as an internship during their final year (clinical rotation). Furthermore, the Division provides courses in psychosomatic primary care for gynecologists. Advanced training for psychological psychotherapists-in-training is also provided. Within the context of the degree program Medical Process Management, the Division of Psychosomatic Medicine and Psychotherapy is responsible for a seminar on "Communication and Cooperation Aspects within the Health-Care System". Based on the evaluation of the medical students, the Division regularly receives high ratings for lectures and practical course.

### Selected publications


Klaus K, Rief W, Brähler E, Martin A, Glaesmer H, Mewes R. The distinction between "medically unexplained" and "medically explained" in the context of somatoform disorders. Int J Behav Med 2013, 20(2): 161-71

Kollei I, Schieber K, de Zwaan M, Svitak M, Martin A. Body dysmorphic disorder and nonweight-related body image concerns in individuals with eating disorders. Int J Eat Disord 2013, 46(1): 52-9

Erim Y, Loquai C, Schultheis U, Lindner M, Beckmann M, Schadendorf C, Senf W. Anxiety, posttraumatic stress, and fear of cancer progression in patients with melanoma in cancer aftercare. Onkologie 2013, 36(10): 540-4

Schieber K, Kollei I, de Zwaan M, Müller A, Martin A. Personality traits as vulnerability factors in body dysmorphic disorder. Psychiatry Res 2013, 210(1): 242-6

Erim Y, Beckmann M, Klein C, Paul A, Beckebaum S. Psychosomatic aspects of organ transplantation. Psychother Psychosom Med Psychol 2013, 63(6): 238-46; quiz 247-9

Morawa E, Senf W, Erim Y. Mental health of Polish immigrants compared to that of the Polish and German populations. Z Psychosom Med Psychother 2013, 59(2): 209-17


### International Cooperation

Prof. Dr. A. Helander, Karolinska Institutet and Karolinska University Hospital, Stockholm: Sweden

Prof. L.J. Kirmayer, MD, McGill University, Montreal: Canada

Prof. Dr. Dr. H.B. Rothenhäusler, MSc, Medizinische Universität Graz: Austria

# Department of Radiation Oncology

## Chair of Radiotherapy

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**Research Focus**
- Clinical Trials
- Radiation Biology
- Physical Aspects of Radiation Oncology
- Radiation Immunobiology

## Structure of the Department

The Department of Radiation Oncology offers the entire spectrum of modern radiotherapy and multimodal radiooncological therapies from one source at the highest level. Radiotherapy treatments are carried out at one of the irradiation platforms and in the division of interventional radiation therapy. The latter is one of the latest and biggest divisions for interventional radiotherapy in Germany. The treatment spectrum compasses intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT), brachytherapy with its whole spectrum of indications, intensity modulated brachytherapy (IMBT), image guided brachytherapy (IGBT), radiosurgery, deep regional hyperthermia, radiochemotherapy, palliative multimodal concepts, and supportive therapies. In 2013 a new image guided radiation system (Novalis TX) which enables volumetric intensity modulated arc therapy (VMAT) and cone beam CT was launched. In addition an innovative stereotactic body radiation therapy (SBRT) platform (vero) was installed and launched in early 2015. Clinical, biological, and 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 as well as the treatment planning department and hyperthermia unit. A total of seven senior physicians and 17 residents treat patients and are involved in running the various trials and clinical studies. Coordination of the clinical trials is carried out by the in-house clinical trials office. Besides the administration by three scientific employees, three assistant study nurses and a secretary are responsible for this work. 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 whole laboratory team consists of two associate professors, three postdoctoral fellows, three technicians as well as six Ph.D. students and numerous medical doctoral candidates. The "Medical Radiation Physics" group, headed by a W2 (associate) professor, consists of nine scientists (Ph.D.), eleven Ph.D.-students and undergraduates, and two technicians. The main scientific focus lies in respiratory and general organ motion during radiation therapy. In addition, the group is responsible for all medical physics duties of clinical radiation therapy.

## Research

### Clinical Trials

Project managers: Prof. Dr. R. Fietkau, Prof. Dr. V. Strnad, PD Dr. O. Ott, PD Dr. S. Semrau, Dr. M. Haderlein, Dr. G. Lahmer, Dr. S. Lettmaier, Dr. A. Strnad

Phase-III multicenter trials:

1. 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); funded by Deutsche Krebshilfe
2. 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);
   funded by Deutsche Krebshilfe
3. Reducing total radiation dose in the context of a simultaneous radiochemotherapy of head and neck tumors (PacCis-RCT);
   funded by Deutsche Krebshilfe
4. Pancreatic carcinoma: chemoradiation compared with chemotherapy alone after induction chemotherapy (CONKO-007);
   funded by Deutsche Krebshilfe
5. Effects of deep regional hyperthermia in patients with anal carcinoma treated by standard radiochemotherapy (HYCAN)

Phase-II trials:

6. PDR/HDR interstitial brachytherapy alone in patients with pT1/pT2 pN0 breast carcinomas after breast conserving surgery (APBI-IV)
7. 3D conformal, external partial breast irradiation in patients with pT1/2 pN0 breast carcinomas after breast conserving surgery (APBI-V)
8. Neoadjuvant chemoradiation with 5-FU (or capecitabine) and oxaliplatin combined with deep regional hyperthermia in locally advanced or recurrent rectal cancer (HyRec [multicentric])
9. Dose-painting-Image-guided interstitial brachytherapy based on HistoScanning in patients with prostatic cancer – Phase II-Study (HistoScanning)
10. Enhancement of neurocognitive functions by hippocampal sparing radiotherapy (HIPPO-SPARE 01)
11. Efficacy of dose intensified radiotherapy of spinal metastases by hypofractionated radiation and IGRT hfSRT mediated boost (SPIN-MET)
12. De-intensification of postoperative radiotherapy in selected patients with head and neck cancer (DIREKHT)

The Department of Radiation Oncology is participating in numerous externally led phase-III trials. In addition the Department is conducting many phase-I and phase-II trials.

### Radiation Biology

Project manager: PD Dr. L. Distel

1. Individual differences in the sensitivity of normal tissues to radiation are the most important determinant for the occurrence of dose-limiting side effects of radiotherapy.
   In a project run jointly with the University of Würzburg (PD Dr. T. Djuzenova), the usefulness of a bed-side test in determining the γ-H2AX phosphorylation status is compared to the established assay based on the analysis of chromosomal aberrations in peripheral blood lymphocytes. Patients with rectal and breast tumors serve as study population.
   Funded by Deutsche Krebshilfe
2. The role played by tumor infiltrating lymphocytes in determining the efficacy of a course of radiotherapy is still largely unknown.
   In a project run jointly with the Institute of Pathology at the FAU (PD Dr. M. Büttner-Herold), the role of CD4, CD8, B cells, macrophages, and the influence of regulatory T cells is studied in patients with head and neck tumors, gastric cancer, and carcinoma of the rectum.

### Physical Aspects of Radiation Oncology

Project manager: Prof. Dr. C. Bert

1. Quality assurance for hyperthermia treatments (MR spectroscopy, phantom development); ZIM-funded

2. Quantification of organ motion for prostate and bronchial tumors
3. Development of phantoms for quality assurance of treatments for intra-fractionally moving tumors;
   ZIM-funded
4. Evaluation of a fixed-anode computed tomography concept by multiphysical simulations
5. Development of a treatment plan verification method by electronic portal imaging (EPID)
6. Geometrical and dosimetric verification for interstitial brachytherapy
7. Voxel-based modeling of normal tissue complication rates for treatment planning

### Radiation Immunobiology

Project managers: PD Dr. U. Gaipl, Dr.-Ing. B. Frey

The aim of the radiation immunobiology group is to understand the relationship between local/targeted (DNA damage and DNA repair) and non-targeted/systemic (immune mediated) abscopal effects of ionizing radiation alone and especially in combination with further immune activation and to identify the underlying immune mechanisms.

The following third-party supported projects are currently handled:

1. Modulation of inflammation in inflammatory mouse models and in patients with inflammatory diseases after therapy with low dose of ionizing radiation (LDRT) or exposition to radon;
   Funded by BMBF, GREWIS network
2. Modulation of inflammation by low and moderate dose of ionizing radiation; ModInIr;
   Funded by EU, DoReMi network of excellence
3. Determination of immune and tumor markers in sera of tumor patients;
   Funded by BMBF, Leading Edge Cluster m4 Personalized Medicine and Targeted Therapies
4. Role of interaction of therapy induced dead tumor cells with dendritic cells for the induction of tumor immunity;
   Funded by DFG, GK 1660
5. Induction of anti-tumor immunity by ionizing radiation in combination with the adjuvant AnnexinA5;
   Funded by DFG

## Teaching

Apart from the traditional radiotherapy teaching sessions embedded in the course covering the related fields of medical imaging, radiotherapy treatment, and radiation protection, the Department organizes an interdisciplinary lecture series. In these series, tumors from different organs are considered from different perspectives or an interdisciplinary discussion revolving around defined tumor settings is held. In the context of this course, a database is being generated that will allow students to familiarize themselves with the interdisciplinary approach by doing clinical case studies. A course in radiation protection including practical teaching sessions for students that is recognized by the BLAEK (Bavarian State Chamber of Physicians) is held semi-annually. For students doing practical clinical work in their pre-registration year, a complementary teaching program is offered. The course "prevention, diagnostics, therapy, and after-care of cancer" was offered to the M.Sc. students of the Medical Process Management degree program. In addition we offer for students of physics and medical engineering a lecture and a practical course dealing with basics of radiation oncology and medical physics. Furthermore, lectures and seminars dealing with problems of tumor immunology are offered. The practical and theoretical training of B.Sc. and M.Sc. students takes place within the basic training "Infections Immunology" and the specialization module "Immunobiology". Lab rotations are offered for fast-track students of GK 1660.

### Selected Publications


Fietkau R, Lewitzki V, Kuhnt T, Hölscher T, Hess CF, Berger B, Wiegel T, Rödel C, Niewald M, Hermann RM, Lubgan D. A disease-specific enteral nutrition formula improves nutritional status and functional performance in patients with head and neck and esophageal cancer undergoing chemoradiotherapy: results of a randomized, controlled, multicenter trial. Cancer 2013, 119(18): 3343-53

Hecht M, Harrer T, Büttner M, Schwegler M, Erber S, Fietkau R, Distel LV. Cytotoxic effect of efavirenz is selective against cancer cells and associated with the cannabinoid system. AIDS 2013, 27(13): 2031-40

Feichtenbeiner A, Haas M, Büttner M, Grabenbauer GG, Fietkau R, Distel LV. Critical role of spatial interaction between $CD8^{?}$ and $Foxp3^{?}$ cells in human gastric cancer: the distance matters. Cancer Immunol Immunother 2014, 63(2): 111-9

Frey B, Rubner Y, Kulzer L, Werthmöller N, Weiss EM, Fietkau R, Gaipl US. Antitumor immune responses induced by ionizing irradiation and further immune stimulation. Cancer Immunol Immunother 2014, 63(1): 29-36

Rubner Y, Muth C, Strnad A, Derer A, Sieber R, Buslei R, Frey B, Fietkau R, Gaipl US. Fractionated radiotherapy is the main stimulus for the induction of cell death and of Hsp70 release of p53 mutated glioblastoma cell lines. Radiat Oncol 2014, 9(1): 89

Wölfelschneider J, Brandt T, Lettmaier S, Fietkau R, Bert C. Quantification of an external motion surrogate for quality assurance in lung cancer radiation therapy. Biomed Res Int 2014, 2014: 595430


### International Cooperations

For further information, please visit our homepage: http://www.strahlenklinik.uk-erlangen.de

### Meetings and International Training Courses

22. – 23.03.2013: Grundlagen der Brachytherapie – Interventionelle Radioonkologie, Erlangen

12. – 14.09.2013: 15. Interdisziplinäres Symposium – Interdisziplinäre Onkologie, Rothenburg

14. – 15.03.2014: Simultane Radiochemotherapie und Therapie mit Antikörpern und Small Molecules, Erlangen

28. – 29.03.2014: Grundlagen der Brachytherapie – Interventionelle Radioonkologie, Erlangen

09. – 10.10.2014: Educational Workshop Masterclass: brachytherapy in partial breast irradiation, Erlangen

15.11.2014: Jubiläums Symposium – Die Radioonkologie in den letzten 35 Jahren, Erlangen

# Department of Surgery

## Chair of Surgery

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**Research Focus**

- Evaluation of prognosis of gastrointestinal tumors
- Randomized trials for gastrointestinal tumors
- Anorectal dysfunction
- Sensitive Polyprobe-method for improved prediction of therapy response and determination of prognosis in patients with colorectal carcinoma
- Molecular mechanisms of inflammatory related angiogenesis
- Molecular mechanisms of infection related angiogenesis

## Structure of the Department

Research activities are structured into clinical research (clinical trials, clinical diagnosis, and therapy research) and molecular cell biological research. The clinical trials of the Department of Surgery are largely supervised by the Center for Clinical Studies (CCS; see own report) which efficiently initiates and monitors the clinical trials. Since its implementation, numerous trials aiming at improving cancer therapy and surgical techniques and also at establishing new surgical approaches have been conducted.
The molecular cell biological research is focus of the Division of Molecular and Experimental Surgery (AMEC; head: Prof. Dr. Dr. M. Stürzl) which was founded in 2003. The main focus of AMEC´s research is molecular oncology with particular focus on novel markers of prognosis and the molecular regulation of inflammation-associated angiogenesis in malignant and infectious diseases. In the report period, AMEC consisted of eleven scientists (four post-doctorates, seven postgraduates). Over 80 % of funding came from grants from DFG, BMBF, German Cancer Aid, IZKF, SFB, and "Emerging Fields Initiative" (EFI) of the FAU. AMEC is heading the colorectal carcinoma research group within the framework of the BMBF-core program for molecular diagnostics (see own report). Subprojects are embedded in cooperative research programs of the GK 1071 "Viruses of the immune system", the DFG clinical research group 257 "Moleculare pathogenesis and optimized therapy of chronic inflammatory bowel dieseases", the SFB 796 "Reprogramming of host cells by microbial effectors"(see own reports) and the EFI-project "CYDER: Cell Cycle in Disease and Regeneration".

## Research

### Evaluation of prognosis of gastrointestinal tumors

Project managers: Prof. Dr. Dr. h.c. W. Hohenberger, Prof. Dr. S. Merkel
Since 1978, a clinical cancer registry has been prospectively maintained for organ specific tumor documentation. At present, more than 28,000 patients are registered. The main focus is on colorectal cancer with over 12,000 documented cases. Patients are documented 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 in many patients results from an interdisciplinary cooperation of clinicians and scientists of numerous medical departments of the UK Erlangen.

### Randomized trials for gastrointestinal tumors

Project managers: Prof. Dr. Dr. h.c. W. Hohenberger, Dr. H. Golcher, Prof. Dr. J. Göhl
The Department of Surgery respectively the interdisciplinary Colorectal Cancer Centre/Modul Pancreas cancer took part in different multicenter trials about gastrointestinal tumors, inter alia "Comparison of colon-pouch versus side-to-side anastomosis respectively function and quality of life in rectal carcinoma patients", PANTER-study (perioperative chemotherapy for liver metastases in colorectal carcinoma), COMBATAC-study (HIPEC for peritoneal carcinomatosis in colorectal carcinoma). The surgical second opinion ("panel of surgeons") for the CONKO-007-trial (randomizing patients with non resectable pancreatic carcinoma) is organized by the study team, too and evaluation takes place in the daily tumor conference. Patients were screened during the interdisciplinary tumorboard for gastrointestinal tumors, assigned to the studies and further attended by the study team (e.g. timely sending of quality of life questionnaires). The trial "Neoadjuvant chemoradiation in resectable pancreatic cancer" was evaluated and published.

### Anorectal dysfunction

Project manager: Prof. Dr. K. Matzel
In 1994, the world's first sacral nerve stimulator for treatment of fecal incontinence was implanted at our Department. Since then, the method has been continuously improved. Our patients are participating in an extensive postoperative review program which for the first time allows to document long term follow-up and the sustainability of the therapeutic effects. We repeatedly run workshops on a national and international level which are dedicated to conveying innovative therapeutic methods and initiating international cooperation. Various international studies for the development and evaluation of new treatment procedures for anorectal dysfunction (e.g. constipation and incontinence), e.g. the NASHA/Dx study, have been developed and conducted.

### Sensitive Polyprobe-method for improved prediction of therapy response and determination of prognosis in patients with colorectal carcinoma

Project managers: Prof. Dr. Dr. M. Stürzl, Prof. Dr. R. Croner
The Polyprobe study is a multicentric interdisciplinary approach of the university clinics in Erlangen and Frankfurt in cooperation with the industrial partner Siemens Healthcare Diagnostics GmbH. It is the goal of the prospective study to provide new biomarkers for the initiation of combination therapy in the treatment of colorectal carcinoma.
The phase of recruitment was successfully finished by including 650 patients. The specific target of the Polyprobe project is the validation of 60 previously identified biomarkers at the mRNA level in order to predict tumor stage, survival, and response to chemo- and radiotherapy of the individual patients (predictive and prognostic molecular diagnosis, prospective diagnostics study). In this framework, a novel technical platform is used which allows automated extraction of RNA from formalin-fixed paraffin-embedded tissue (FFPE). The commercial exploitation of the validated markers will be addressed together with Siemens.

### Molecular mechanisms of inflammatory related angiogenesis

Project manager: Prof. Dr. Dr. M. Stürzl

In previous studies, the group identified the large GTPase guanylate binding protein-1 (GBP-1) as a central regulator of inflammation-associated angiostasis. GBP-1 plays an important role in colorectal carcinoma (CRC) by inhibiting proliferation, migration and invasion of tumor cells. On the molecular level this inhibition is based on the inhibition of -catenin/TCF-signal pathways and on the fact that GBP-1 leads to a remodeling of the actin cytoskeleton, respectively. In particular, the influence on migration and invasion could be explained by the actin remodeling ability of GBP-1. The clinical relevance is shown by the fact that the immune evasion of tumor cells partly depends on the loss of the ability to react to IFN-, thus losing their ability to induce GBP-1 expression. These results indicate that GBP-1 acts as a tumor suppressor protein in CRC.

### Molecular mechanisms of infection related angiogenesis

Project manager: Prof. Dr. Dr. M. Stürzl

The research on infection-associated angiogenesis focuses on the pathogenesis of AIDS-associated Kaposi's sarcoma, a tumor of endothelial cell origin which is etiologically connected with Kaposi's sarcoma-associated herpes virus (KSHV). It was systematically analyzed which of the 86 gene products of KSHV are targeted by the regulatory posttranslational modification O-GlycNAcylation. It could be shown that predominantly regulatory proteins involved in virus replication are targeted by this modification in infected cells. Moreover, experimentally induced O-GlycNAcylation was found to be associated with inhibition of virus production in infected cells. This suggests that O-GlycNAcylation mediates metabolic effects in KSHV virus replication. The validation of two computational prediction tools of O-GlcNAc sites (YinOYang 1.2 server and OGlcNAcScan) revealed the limitations of presently available methods. This is among others due to the fact that proteins of different compartments (nucleocytoplasmic, mitochondric, secretory lumen) are glycosylated on different positions guided through different signal peptides. This shows that continuous updates and further development of available databases is absolutely necessary.

## Teaching

To further deepen the acquired knowledge from the main course, we run among other measures intensive preparatory classes. In order to gain a realistic perspective of the clinical routine, small supervised groups are allowed to visit the operating theater and the intensive care unit. A bed side teaching is included in the internships. The Division of Molecular and Experimental Surgery offered in total 18 different teaching courses during the report period. Among these, a two-week cell biological ground course and a scientific project developing seminar were conducted in the degree program Molecular Medicine. Additional alternating exchange of basic researchers and medical scientists is meant to improve translational research.

### Selected Publications


Britzen-Laurent N, Lipnik K, Ocker M, Naschberger E, Schellerer VS, Croner RS, Vieth M, Waldner M, Steinberg P, Hohenadl C, Stürzl M. GBP-1 acts as a tumor suppressor in colorectal cancer cells. Carcinogenesis 2013, 34(1): 153-62

Perrakis A, Weber K, Merkel S, Matzel K, Agaimy A, Gebbert C, Hohenberger W. Lymph node metastasis of carcinomas of transverse colon including flexures. Consideration of the extramesocolic lymph node stations. Int J Colorectal Dis 2014, 29(10): 1223-9

Chudasama P, Konrad A, Jochmann R, Lausen B, Holz P, Naschberger E, Neipel F, Britzen-Laurent N, Stürzl M. Structural proteins of Kaposi's sarcoma-associated herpesvirus antagonize p53-mediated apoptosis. Oncogene 2014 Jan 27. doi: 10.1038/onc.2013.595

Ostler N, Britzen-Laurent N, Liebl A, Naschberger E, Lochnit G, Ostler M, Forster F, Kunzelmann P, Ince S, Supper V, Praefcke GJK, Schubert DW, Stockinger H, Herrmann C, StürzlM. IFN-γ-induced guanylate binding protein-1 is a novel actin cytoskeleton remodeling factor. Mol Cell Biol 2014, 34(2): 196-209

Matzel KE: Neuromodulation in an era of rising need and cost: a time for multifaceted consideration. Dis Colon Rectum 2014, 57(9): 1141-2


### International Cooperations

Prof. S. Laurberg, University of Aarhus, Aarhus: Denmark

Prof. Dr. M. Gariglio, University of Piemonte Orientale, Novara: Italy

Prof. Dr. S. Indraccolo, University of Padova, Padova: Italy

Prof. T. Holm, Karolinska Institutet, Stockholm: Sweden

Prof. Dr. M. Heikenwälder, Universitätshospital Zürich, Zurich: Switzerland

Prof. P. Quirke, Institute of molecular medicine and pathology, Leeds: UK

Prof. Dr. D. Ganem, Novartis Institutes for Biochemical Research, St Emeryville: USA

Prof. Dr. A. Nusrath, Emory University School of Medicine, Atlanta: USA

Prof. Dr. H. Stockinger, Medical University of Vienna, Vienna: Austria

Prof. Dr. A. Kuzu, Ankara University, Ankara: Turkey

### Meetings and International Training Courses

03. – 04.06.2013: 8th Advanced Course in Colorectal Cancer Surgery, Erlangen

20. – 21.06.2014: Interstim Neuromodulation Academy Colorectal Surgeons & Urologists, Fundamental Training, Erlangen

21.09.2013: Arzt-Patienten-Seminar Dickdarm- und Bauchspeicheldrüsenkrebs, Erlangen

23. – 24.06.2014: Interstim Neuromodulation Academy Colorectal Surgeons & Urologists, Fundamental Training, Erlangen

### Research Equipment

Bio-Rad Laboratories GmbH, VERSARRAY CHIPWRITER PRO

Leica, TCS-SPE

Fuji, FLA 5000

# Department of Surgery

## Division of Pediatric Surgery

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**Research Focus**

- Implementing enteral surface stimulation (EOS) in pediatric surgery
- Chest wall correction – historical development and implementation of an innovative operative concept
- Correlation between external pectus measurement and CT-bound evaluation in pectus deformities
- Development and implementation of an anal retractor for pediatric surgery
- Chronic constipation in children – clinical evaluation of influence factors and quality of life parameters

## Structure of the Division

The Division of Pediatric Surgery is a self-contained division in the Department of Surgery of the UK Erlangen. Facilities are settled down in the Department of Pediatrics and Adolescent Medicine with ward CK 4 and in the Department of Surgery with ward B 1 – 2, housing in the new building of operative medicine, closely connected to the Department of Urology.
There is also a membership in the expert-network of the Perinatal Center of Franconia, located at the Department of Obstetrics and Gyne - cology, and in the Pediatric Operative Center (KIOP). There is a close connection, including operative cooperation, to the university teaching hospitals in Bamberg, Bayreuth, Schweinfurt, and Fürth.
The medical spectrum comprises the surgical treatment of congenital malformations, especially in the thoracic, abdominal, skeletal, and integumental areas in newborn and children. Acute and chronical diseases are treated in all age groups in cooperation with the pediatrics. Strongest importance is placed on consistent after-care. Traditionally, excellent expertise is known in minimally invasive surgical treatment of chest deformities (Pectus excavatum and carinatum) and in special techniques to resolve recurrences after chest wall repair. There are outstanding experiences in minimally invasive pediatric surgery (laparoscopy, thoracoscopy, rendez-vous procedures) with high-end tissue management and wide-area indications.

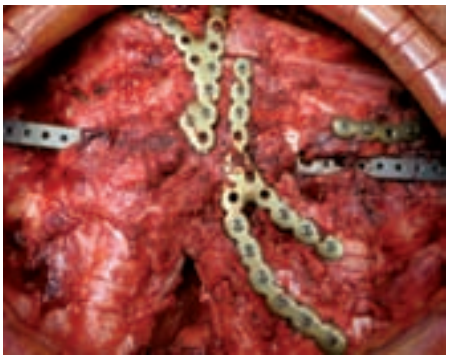
## Research

### Implementing enteral surface stimulation (EOS) in pediatric surgery

Project leader: Dr. M. Besendörfer
EOS is a low-frequency (15 – 25 Hz), long-term electrical stimulation of enteric ganglia of the nervous system. The principle finds its origin in the sacral nerve stimulation which was originally introduced by Dr. E. Tanagho (San Francisco) and was later developed furtheron by Prof. Dr. K. Matzel (Erlangen) for enteric diseases.
Its effect was first explored in urology and is now in certain forms of neurogenic urinary incontinence a therapy option. In this case, improvements of symptoms in fecal incontinence and in chronic constipated patients had been observed. Side effects were increase of the anal sphincters and an improvement in the motility of the colon. Defecation disorders in children and adolescents have a high impact and are often not taken serious and treated psychiatrically. This often leads to social isolation and developmental disorders. After several weeks of stimulation phase, a learning effect occurs, reaching a sustained reconditioning of enteral motility and pelvic floor and thus improving the quality of life. The effect of this method can be explained in part by direct stimulation of efferent nerve fibers. There is, in addition to the directly measurable, improved contraction of striated muscles of the sphincter apparatus, an improvement of sensory perception of the filling of the rectum. Furthermore we observed an increase in muscle tone of the internal anal sphincter. The cause of the afferent neuromodulation-related functional changes of sensory nerve fibers of spinal reflexes and the sympathetic and parasympathetic activity is suspected (enteral reconditioning). Due to anatomical differences in the area of the sacral bone, children are omitted from an invasive nerve stimulation (SNS). Instead, surface electrodes are glued which do not interfere with the young patients in their daily operations and in their development. By this technique, no anesthesia is needed for placing as the electrodes and the system can be performed on an outpatient basis.
Aim of the study: Treatment of the complex syndrome of childhood constipation. Initial results are very promising. Application of EOS with combined surgical/urological diseases in cooperation with the urology clinic. First patient populations are being conducted in prospective studies.

### Chest wall correction – historical development and implementation of an innovative operative concept

Project leader: J. Syed
Following the extensive research of original historical documents relating to chest wall corrections of congenital chest wall deformations, an evaluation of the operating results was carried out with respect to biomechanical aspects. Since the beginning of the 20th century chest wall corrections are made and a variety of operational procedures has been developed.
Concerning the observed long-term results and complications, especially the internal stabilization of the mobilized chest wall by metal implants has been established besides the Nuss–technique. An isolated stabilization of the sternum, as often performed, is certainly not satisfactory. By an increased radius of curvature with inverting and retracting rib attachments, the costal cartilages are considerably affected by the deformity. Thus, mobilization and subsequent stabilization of the entire chest wall widely to each side is absolutely necessary for a sufficient removal of the chest wall impression in order to address the biomechanical alignment of the chest wall tensions laterally and to prevent the power directing intrathoracically. Currently, a hybrid-method using the transsternal Erlanger bar to raise the sternum in combination with angular stable titanium plates for anatomical erection of the deformed ribs with reinsertion on the sternum turns out suitable, as has been shown in a prospective study in our interdisciplinary project group (cooperation with the Institute of Anatomy I and the Institute of Pathology) since 2010. In follow–ups multiple parameters in the biomechanical evaluation are documented. Retrosternal dislocated non-union of the ribs (stairway phenomenon), one of the major long-term complications after conventional open chest wall correction, could be excluded in all cases yet.



*Pediatric retractor: Rectosigmoid resection (M. Hirschsprung) and anal pull-through (extracorporeal anastomosis)*

### Correlation between external pectus measurement and CT-bound evaluation in pectus deformities

Project leader: Dr. S. Schulz-Drost

Pre-operative external measurement and long-term follow-up by means of a thoracic compass device in pectus deformities is a widely accepted procedure. Gold standard, however, should be the CT scan. Aim of study is the comparison of pre-operative external and CT-measurement of pectus shape and detection of feasibility to save costs and reduce radiation. Retrospectivly, data on 188 patients with pectus repairs were collected (period: 1/2009 – 9/2012; 156 pectus excavatum, 31 pectus carinatum, 1 hybrid). Patients under 15 years of age were excluded.

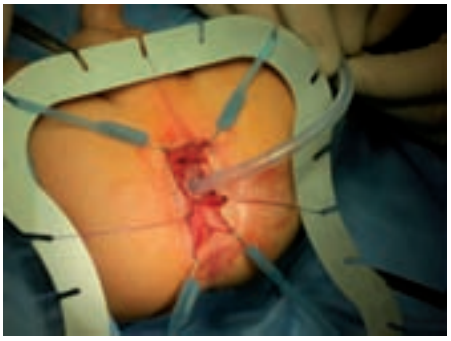
109 external compass evaluations and 152 CT-measurements came to analysis. The correlation of compass- and CT-rating was highly significant, especially in detecting the deepest point of pectus excavatum. In pectus carinatum, the Nadir and width of chest was highly significant in both techniques. No significance was shown in comparison of the sagittal depth (upper edge of sternum, Angulus Ludovici). In conclusion, the compass device measurement is feasible and reliable in evaluating the sagittal depth in pectus excavatum. This rate is the most required information in evaluating and follow-up and should be applied instead of CT evaluation. Evaluation and follow-up in pectus carinatum should be performed by means of CT scan.

### Development and implementation of an anal retractor for pediatric surgery

Project leader: Dr. P. Lux

In various interventions, such as sigma rectum resections in Hirschsprung's disease or anorectal malformations, the application of an anal retractor is necessary for the optimal exposure of the bowel segments which are to be anastomosed extracorporally via hand suturing. In the past for this purpose anal retractor systems from adult surgery were used, but were not suitable in pediatric surgery in terms of size and lack of practicability. Therefore, in collaboration with the surgical company K. Lettenbauer, Erlangen, we developed an anal retractor system which is feasible for pediatric surgery.

A laparoscopic-assisted deep rectal resection with extracorporeal anastomosis in the first year of age is only feasible with a weight not less than 6 - 8 kg. This is due to the minimized anatomical conditions in children's pelvis. The first step is the laparoscopic mobilization of the rectosigmoid portion, the intestinal segment that has been altered pathologically due to Hirschsprung's disease, with piezo-electric instruments. After the histology triggered resection of the affected bowel section, a transanal extracorporeal anastomosis is performed by hand suture. For this purpose the anal canal is optimally exposed by the designed reusable retractor system using silicone reinforced hooks. After that, the transanally everted proximal portion of the intestine is anastomosed after rerection of the distal stump according to the tube in tube principle. The splinting and protection of the anastomosis transanally is done by a large tube catheter. The retractor system ensures an atraumatic approach with superior exposure and correspondingly favorable wound healing while minimizing complications (stricture, insufficiency).



*ESCR (elastic stable chest repair): Chest wall deformity and anatomical repair (custom-made titanic implants)*

### Chronic constipation in children – clinical evaluation of influence factors and quality of life parameters

Project leader: Dr. P. Lux

Chronic constipation is a very common disease in childhood and often exhausting children and their families. Despite optimal diagnostic evaluation, no organic causes of chronic constipation such as Hirschsprung's disease can be determined. The aim of the project is using systematic evaluation of data of all previously treated patients with chronic constipation in the Erlangen pediatric surgery division, creating a database, and determining the clinical factors that significantly influence the disease and their influence on quality of life of the affected children. Following identification of the major influence factors, a parental questionnaire will be devel - oped which already allows a more accurate estimation of the severity of chronic constipation at the first presentation of patients and the influence on the subjective quality of life of the patients. Success of enteral surface stimulation is detected as well and included in the study.

## Teaching

Pediatric surgery is a self-contained surgical specialty and is presented academically as follows:

1. Curricular in the course of IMPP (general guidelines for medical studies in Germany: general and special pediatric surgery in theory and practice) in individual lectures, partly integrated in main lectures on surgery and pediatrics. Cooperative academic events in the course of technical schools at FAU (pediatric nursing, pediatric intensive care medicine, School for operational and technical assistants, physiotherapy, massage)
2. Interdisciplinary (lecture series "Emergency", seminars, boards)
3. Special (postgraduate/diploma students, practical education in phantom-courses for minimally invasive pediatric surgery in skills lab and hands-on courses). An increasing number of trainees and interns (non-local students, ERASMUS-students, students of cooperative universities) are embedded into the curriculum.

### Selected Publications


Dimova V, Horn C, Parthum A, Kunz M, Schöfer D, Carbon R, Griessinger N, Sittl R, Lautenbacher S. Does severe acute pain provoke lasting changes in attentional and emotional mechanisms of pain-related processing? A longitudinal study. Pain 2013, 154(12): 2737-2744

Kern S, Besendoerfer M, Carbon RT. Minimally invasive pullthrough (MIPT) in Hirschsprungs's disease. J Laparoendoscopic & Advanced Surg Techniques 2013, 23(12): A1-A144

Schulz-Drost S, Syed J, Besendoerfer M, Carbon RT. Sternocostal dislocation following open correction of pectus excavatum – "Stairway Phenomenon": Complication management by means of sternocowstal locking titanium plate osteosynthesis. Thorac Cardiovasc Surg 2014, 62(3): 245-252

Schulz-Drost S, Syed J, Besendoerfer M, Carbon RT. Elastic stable chest repair (ESCR) as a means of stabilizing the anterior chest wall in recurrent pectus excavatum with sternocostal pseudarthrosis: An innovative fixation device. Thorac Cardiovasc Surg 2014, Apr 21

Simon K, Schulz-Drost M, Besendörfer M, Carbon RT, Schulz-Drost S. Einsatz einer präventiven, epikutanen Unterdrucktherapie (Prevena TM) bei offener Korrektur von Deformitäten der vorderen Brustwand reduziert das Auftreten von Wundheilungsstörungen. Zentralbl Chir 2014, 139: 1-7

Agaimy A, Stachel KD, Jüngert J, Radkow T, Carbon R, Metzler M, Holter W. Malignant epithelioid peripheral nerve sheath tumor with prominent reticular/microcystic pattern in a child: a low-grade neoplasm with 18-years follow-up. Appl Immunohistochem Mol Morphol 2014, 22(8): 627-633


### Meetings and International Training Courses

09.11.2013: Pediatric Operative Center Erlangen & Perinatal Center Franconia, Expert-Meeting Prenatal diagnostics from head to toe, Erlangen

# Department of Surgery

## Division of Thoracic Surgery

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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 for chronic empyema
- Using tracking dogs in early diagnosis for lung cancer
- Imunological and molecular characterization of malignant lung tumors
- Hyperthermic intrathoracic chemotherapy after pleurectomy/decortication in pleural mesothelioma – a phase I study
- Neoadjuvant therapy of locally advanced non-small cell lung carcinoma IIIA; concurrent radiochemotherapy followed by surgery
- Trimodal therapy of malignant mesothelioma
- The value of the systematic extensive lymph node dissection in the operative treatment in non-small cell lung carcinoma

## Structure of the Division

The Division of Thoracic Surgery was founded in 2008 and is offering the complete diagnosis and therapy of lung, mediastinal, and chest diseases. Our Division is nationwide one of the first academic thoracic surgical divisions. Under the auspices of the Head, Prof. Dr. H. Sirbu, who is Extraordinarius for thoracic surgery, one consultant thoracic surgeon, four physicians in training, and a number of medical students are working at the Division of Thoracic Surgery.
In cooperation with the Departments of Medicine 1 and 5, the Department of Radiation Oncology, the Institute of Pathology, the Division of Palliative Medicine, and the Department of Nuclear Medicine, we have founded the Lung Center Erlangen.
Emphasis of our clinical activity concentrates on minimally invasive lung resections (VATS-surgery) and also on interdisciplinary therapy concepts Cisplatin for advanced lung cancer and other chest diseases. The intensive cooperation with all other oncological fields and the connection with our Comprehensive Cancer Center (CCC; see own report) assures the best therapy for our patients. The Division of Thoracic Surgery actively participates in and organizes the activities of the academic study group of the German Society of Thoracic Surgery.

## Research

**Surgical therapy of hyperhidrosis – a prospective quality control study**
Project managers: Dr. W. Schreiner, Prof. Dr. H. Sirbu, I. Mykoliuk
Videoscopic assisted thoracic sympathectomy is a widely accepted approach in the therapy of palmar and axillary hyperhidrosis. Long term postoperative results are very heterogenous. 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**
Project managers: Prof. Dr. H. Sirbu, Dr. W. Schreiner, 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 for chronic empyema**
Project managers: Dr. W. Schreiner, 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.

**Using tracking dogs in early diagnosis for lung cancer**
Project managers: Prof. Dr. H. Sirbu, Dr. M. Würfel*, Dr. P. Stapel
By using standardized collected breath samplings of patients with lung cancer, tracking dogs of the Johanniter Unfallhilfe are trained in different stages to prove if an early detection of lung cancer is possible. The main objective is to provide foundations for a technical gas analysis ("electronic nose") as well as the chemical identification of gas markers with their characteristic ratio in the different stages of cancer.
*Krankenhaus Martha-Maria, Nürnberg

**Immunological and molecular characterization of malignant lung tumors**
Project managers: Prof. Dr. H. Sirbu, Prof. Dr. S. Finotto, Dr. D.I. Trufa
The aim of this research project is to investigate 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 subpopulations, 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.

**Hyperthermic intrathoracic chemotherapy after pleurectomy/decortication in pleural mesothelioma – a phase I study**
Project managers: Dr. W. Schreiner, Prof. Dr. H. Sirbu, W. Dudek
The end point of this prospective trial is the survival and the disease free interval through the combination of the intrathoracic hyperthermic cisplatin with pleurectomy/decortication in patients with stage I pleural mesothelioma. Through radical pleurectomy/decortication, an operative tumor reduction is possible. This cytoreduction improves the efficacy of the intrathoracic chemotherapy. The combination of the intrathoracic perfusion with cisplatin and hyperthermia improves the needed cytotoxic effect locally. This trial includes patients with advanced age and co-morbidity, resectable mesothelioma masses without lymph node metastases.

**Neoadjuvant therapy of locally advanced non-small cell lung carcinoma IIIA; concurrent radiochemotherapy followed by surgery**
Project managers: Prof. Dr. H. Sirbu, Prof. Dr. R. Fietkau, Dr. W. Schreiner
In this trial, we compare the therapy concept of neoadjuvant radiochemotherapy (45Gy/

Cisplatin, Etoposide), followed by surgery with the concept of definitive radiochemotherapy in patients with locally advanced, non-small cell lung carcinoma stadium IIIA.

### Trimodal therapy of malignant mesothelioma

Project managers: Dr. W. Schreiner, W. Dudek

The trial includes patients in good clinical condition, younger than 60 years without significant co-morbidity, a resectable tumor mass, and without lymph node involvement. After neoadjuvant chemotherapy, extended operative tumor resection (pleuropneumectomy with pericardectomy and resection of diaphragma) is performed. Postoperatively, the radiotherapy of the hemithorax is added. The end point of the study is the survival and the disease free interval.

### The value of the systematic extensive lymph node dissection in the operative treatment in non-small cell lung carcinoma

Project managers: Dr. W. Schreiner, Prof. Dr. H. Sirbu, Dr. D. I. 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. In this study, we have included about 500 patients over a 20 years period.

### Pulmonary resection with parietal pleurectomy (WRPP) versus parietal pleurectomy (PP) for the treatment of primary pneumothorax

Project managers: Prof. Dr. H. Sirbu, W. Dudek

Prospective randomized multicenter clinical trial which compares two established surgical procedures (WOPP-study, funded by DFG). 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).

## Teaching

University teaching was enabled with the establishment of a professorship for thoracic surgery at the Chair of Surgery. We offer a wide thoracic surgical teaching during the main lectures, the lecture of emergency organized by the Chair of Anesthesiology, and/or lectures during hands-on training. For advanced students, we additionally offer patient based exercises on thoracic diseases.

### Selected Publications


Schreiner W, Oster O, Stapel P, Sirbu H. V. A. C. INSTILL® therapy – new option in septic thoracic surgery. Zentralbl Chir 2013, 138(1): 117-20

Barthelmeß S, Geddert H, Boltze C, Moskalev EA, Bieg M, Sirbu H, Brors B, Wiemann S, Hartmann A, Agaimy A, Haller F. Solitary fibrous tumors/hemangiopericytomas with different variants of the NAB2-STAT6 gene fusion are characterized by specific histomorphology and distinct clinicopathological features. Am J Pathol 2014, 184(4): 1209-18

Moskalev EA, Frohnauer J, Merkelbach-Bruse S, Schildhaus HU, Dimmler A, Schubert T, Boltze C, König H, Fuchs F, Sirbu H, Rieker RJ, Agaimy A, Hartmann A, Haller F. Sensitive and specific detection of EML4-ALK rearrangements in non-small cell lung cancer (NSCLC) specimens by multiplex amplicon RNA massive parallel sequencing. Lung Cancer 2014, 84(3): 215-21

Schreiner W, Semrau S, Fietkau R, Sirbu H. Oligometastatic non-small cell lung cancer--surgical options and therapy strategies. Zentralbl Chir 2014, 139(3): 335-41

Agaimy A, Koch M, Lell M, Semrau S, Dudek W, Wachter DL, Knöll A, Iro H, Haller F, Hartmann A. SMARCB1(INI1)-deficient sinonasal basaloid carcinoma: a novel member of the expanding family of SMARCB1-deficient neoplasms. Am J Surg Pathol 2014, 38(9): 1274-81

Balabko L, Andreev K, Burmann N, Schubert M, Mathews M, Trufa DI, Reppert S, Rau T, Schicht M, Sirbu H, Hartmann A, Finotto S.Increased expression of the Th17-IL-6R/pSTAT3/BATF/Rorγ T-axis in the tumoural region of adenocarcinoma as compared to squamous cell carcinoma of the lung. Sci Rep 2014, 4: 7396

# Department of Surgery

## Division of Transfusion Medicine and Hemostaseology

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**Research Focus**

- Preparation and characterization of white cell-poor platelet concentrates by apheresis
- Collection of monocytes for the generation of dendritic cells (DC)
- Preparation of dry platelet concentrates and platelet storage in additive solutions
- 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
- Platelet-derived growth factors for wound healing and angiogenesis

## Structure of the Division

The Division of Transfusion Medicine and Hemostaseology is located at the Department of Surgery of the UK Erlangen. The Head of the Division is Extraordinarius for Transfusion Medicine and Hemostaseology.

The Division of Transfusion Medicine and Hemostaseology produces pharmaceutical products from blood and has a widespread manufacturing permit from the local and the federal authorities.

The Division of Transfusion Medicine and Hemostaseology offers all laboratory methods in the fields of immunohematology and hemostaseology, organizes the depots of blood preservations and plasma derivates for the treatment of coagulation disorders, and the cord blood and stem cell bank of the UK Erlangen.

The quality management system of the Division of Transfusion Medicine and Hemostaseology is certified according to the DIN EN ISO 9001:2008 standard. Laboratories of the Division are accredited by the European Federation for Immunogenetics (EFI) and according to the DIN EN ISO 15189 standard by the National Accreditation Body (DAkkS).

## Research

### Preparation and characterization of white cell-poor platelet concentrates by apheresis

Project managers: PD Dr. J. Zingsem, Prof. Dr. J. Ringwald

Platelet apheresis processing large blood volumes to produce platelet-rich plasma has become a standard procedure. A major research focus is the preparation of extremely white cell-poor platelet concentrates making additional filtration unnecessary. Apheresis procedures were developed for producing concentrates with standardized platelet content, but containing almost no residual white cells. Another research interest is the evaluation of quality control-procedures detecting very low white cell-contaminations of cellular blood components. Additionally, the influence of different blood bags and of component volumes on the quality of stored platelets is examined.

### Collection of monocytes for the generation of dendritic cells (DC)

Project manager: 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.

### Preparation of dry platelet concentrates and platelet storage in additive solutions

Project manager: Prof. Dr. J. Ringwald

The preparation of platelet (PLT) concentrates in additive solutions attracts growing attention since there is the possibility to inactivate pathogens that contaminate cellular blood components. Such inactivation procedures presuppose the reduction of the plasma portion in platelet concentrates. Clinically, the reduction of the plasma portion in PLT components may reduce the frequency of adverse reactions, e.g. of allergic reactions. The resuspension of PLT in additive solutions requires the production of "dry platelets" – concentrates containing more than 3000 x 10e+3 per myl. For this purpose, we performed several series of PLT preparations using the TRIMA separator by Caridian. PLT concentrates in the additive solutions PAS II, PAS III, and PAS III M were compared with each other and with platelets in plasma by analyses of the in vitro quality of fresh and stored PLT concentrates.

### Clinical research related to hemostaseology

Project managers: Prof. Dr. J. Ringwald, 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

Project managers: Prof. Dr. V. Weisbach, Prof. Dr. R. Zimmermann, Prof. Dr. J. Ringwald, Prof. Dr. E. Strasser

Other research interests are the examination of antibodies against red cell antigens, the characterization of factors influencing the quality of stored red cell concentrates, and complex dysfunctions of the coagulation system.

### Mesenchymal stromal cells (MSC)

Project managers: Prof. Dr. V. Weisbach, Dr. C. Klein

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 excpected 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)

Project managers: Prof. Dr. E. Strasser, 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 of the UK Erlangen 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

Project manager: 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.

### Platelet-derived growth factors for wound healing and angiogenesis

Project manager: Prof. Dr. R. Zimmermann
Platelets contain growth factors which stimulate wound healing, angiogenesis, and possibly bone repair. Thus, these cells do not only initiate coagulation at sites of injury, but induce the processes of healing, too. A possible clinical application of these findings is the local application of concentrated platelets as a source of growth factors for wound healing and bone repair. Additionally, the phenomenon of growth factor release from activated platelets to plasma during procedures with extracorporeal circulation is a focus of research.

## Teaching

The Division of Transfusion Medicine and Hemostaseology offers lectures, seminars, and practical hands-on training for students:

- Participation in the principal subject "Laboratory diagnostics" of the German licensing regulations for physicians;
- Participation in the practical training course in surgery;
- Further lectures, seminars, and practical trainings;
- Regular seminars for the Bavarian state chamber of physicians;
- Teaching at the school for assistant medical technicians;
- Teaching for assistant medical technicians and nurses.

### Selected Publications


Breuer L, Ringwald J, Schwab S, Köhrmann M. Ischemic stroke in a patient under dabigatran treatment. N Engl J Med 2013, 368: 2440-2442

Klein C, Strobel J, Zingsem J, Richter RH, Goecke TW, Beckmann MW, Eckstein R, Weisbach V. Ex vivo expansion of hematopoietic stem- and progenitor cells from cord blood in coculture with mesenchymal stroma cells from amnion, chorion, Wharton's jelly, amniotic fluid, cord blood and bone marrow. Tissue Engineering Part A 2013,19: 2577-2585

Strasser EF, Happ S, Weiss D, Pfeiffer A, Zimmermann R, Eckstein R. Microparticle detection in platelet products by three different methods. Transfusion 2013, 53: 156-166

Zimmermann R, Krüger J, Filipovic MR, Ivanovic-Burmazovic I, Calatzis A, Weiss DR, Eckstein R. A detailed examination of platelet function inhibition by nitric oxide in platelet-rich plasma and whole blood. Clin Lab 2013, 59: 629-638

Strobel J, Antos U, Zimmermann R, Eckstein R, Zingsem J. Comparison of a new microscopic system for the measurement of residual leucocytes in apheresis platelets with flow cytometry and manual counting. Vox Sang 2014, 107: 233-238

Weiss DR, Franke D, Strasser EF, Ringwald J, Zimmermann R and Eckstein R. Von Willebrand factor, clotting factors, and clotting inhibitors in apheresis platelet concentrates. Transfusion 2014, 54: 633-639


### Meetings and International Training Courses

20.04.2013: 1. Forum Gerinnung in der täglichen Praxis, Erlangen

14.06.2013: Refresherkurs der BLÄK für Transfusionsverantwortliche und Transfusionsbeauftragte, Erlangen

08. – 09.11.2013: Fortbildungsveranstaltung der BLÄK "Qualifikation als Transfusionsverantwortlicher/Transfusionsbeauftragter", Erlangen

29.03.2014: 2. Erlanger Forum Gerinnung in der täglichen Praxis, Erlangen

15.05.2014: Refresherkurs der BLÄK für Transfusionsverantwortliche und Transfusionsbeauftragte, Erlangen

07. – 08.11.2014: Fortbildungsveranstaltung der BLÄK "Qualifikation als Transfusionsverantwortlicher/Transfusionsbeauftragter", Erlangen

# Department of Surgery

## Division of Trauma Surgery

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**Research Focus**
- Validation of a ceramic total knee replacement system
- Gait and motion analysis
- Tissue penetration of novel antibiotic agents
- Mechanisms of chondrocyte differentiation and ossification
- Cartilage regeneration and meniscus transplantation
- Magnetic resonance (MR) imaging of cartilage and joint structures
- Traumatic lesions of thoracic bone structures

## Structure of the Division

The Division of Trauma Surgery employs 16 physicians. Beside patient care, clinical and experimental research work is performed together with ten doctoral candidates, one post-doctoral scientist, and two technicians.
The different research groups work on the evaluation and development of innovative surgical methods and implants for joint replacement and treatment of skeletal lesions. Furthermore, the research focuses on basic mechanisms of cartilage and bone biology which provides the basis for the development of regenerative strategies for the musculoskeletal system. This also includes imaging and functional non-invasive methods for the analysis of musculoskeletal tissues.
The central research projects are supported by approved fundings, including the DFG and Emerging Field Initiative.
Besides the clinical and experimental research projects, the Division of Trauma Surgery is closely integrated in the "Trauma Network" of the German Society for Trauma Surgery (DGU) and is actively involved in its further development. The aim of this network is the improvement of the nationwide quality of medical care of severely injured patients by improved communication, better coordinated standards of medical care, and quality-based cooperation.

## Research

### Validation of a ceramic total knee replacement system

Project manager: Prof. Dr. F. Hennig
This study investigates the safety and clinical outcome of a novel ceramic total knee replacement system. Besides favorable tribological properties, the complete ceramic implant seems advantageous in particular for patients with known hypersensitivities against metal ions. In first one-year results, we could demonstrate an excellent clinical outcome without occurrence of any adverse events or safety concerns (such as failure or loosening).

### Gait and motion analysis

Project manager: Dr. S. Krinner
This research group focuses on a subproject of the Emerging Fields Initiative (EFIMoves) with the aim to identify the biomechanical forces that interact with the human musculoskeletal system of athletes and patients with osteoarthritis. Dynamic forces during walking, running, and climbing stairs are associated with high strain for the musculoskeletal system. The biomechanical analysis of these dynamic strains and their integration into proper situations provide the opportunity to assess strategies for reducing the loading of joints. So far, we could demonstrate that special shoe insoles could reduce the adduction moment of the knee joint, thus reducing the stress on medial knee joint structures.

### Tissue penetration of novel antibiotic agents

Project manager: Prof. Dr. F. Hennig
In this multicenter phase-I-study, we evaluated the bone penetration of the novel antibiotic agent Ceftaroline in the setting of total hip replacement surgery. The probes from the resected femoral head were analyzed by mass-spectrometry and correlated in a time-dependent manner with plasma concentrations. The yielded data support the development of novel antibiotics with improved bone-penetrating properties.

### Mechanisms of chondrocyte differentiation and ossification

Project manager: PD Dr. K. Gelse
The identification of the mechanisms of chondrocyte differentiation and endochondral ossification is one central issue to establish novel strategies for cartilage repair and osteoarthritis. Microarray analyses of osteophytic cartilage and articular cartilage identified PEDF as one of the most differentially expressed gene. PEDF is particularly expressed in terminally differentiated chondrocytes within the growth plate, osteophytes and repair cartilage. In chondrocytes, PEDF stimulates the expression of cartilage-degrading enzymes (in particular MMP13) and also induces apoptosis by FasL. These mechanisms indicate that PEDF is importantly involved in the process of endochondral ossification.

### Cartilage regeneration and meniscus transplantation

Project manager: PD Dr. K. Gelse
This project evaluated the intrinsic regeneration potential of articular cartilage with a focus on integration and chondrocyte-outgrowth from native cartilage autografts transplanted in cartilage defects in an ovine model. The cartilage autografts showed no relevant cellular outgrowth and insufficient integration with surrounding intact cartilage when transplanted into defects. Depletion of proteoglycans and cell death were detectable in the margins of the grafts. This study outlines the highly limited endogenous repair capacity of adult articular cartilage and the prerequisite of an additional cell population which may be provided e.g. by bone marrow-stimulating techniques.
A further cooperation with the Institute of Bioprocess Engineering (Faculty of Engineering) investigated the transplantation of chemically processed decellularized meniscal allografts in an ovine model. Transplanted allografts were characterized by a high biocompatibility and tightly integrated with surrounding tissue of the joint capsule without any signs of rejection. Repopulation of repair cells was observed at the surface and the meniscal basis. However, meniscal allografts only limited effect on degeneration of the articular cartilage, which could partially be ascribed to lateral extrusion of the allografts observed in this model. Chemical processing of meniscal allografts provides high biocompatibility, however, a tight bony fixation seems essential for yielding chondroprotective effects.

### Magnetic resonance (MR) imaging of cartilage and joint structures

Project manager: PD Dr. G. Welsch
This research project focuses on the evaluation of articular cartilage (repair tissues and osteoarthritis) as well as meniscal tissue by MR-imaging with the goal to validate novel biochemical MR-techniques. In experimental models, healthy articular cartilage was compared with degener-

ated articular cartilage and cartilage repair tissues induced by the microfracture technique or autologous chondrocyte transplantation. Additionally, biochemical MR-methods were used to assess the associated joint structures in a multiparametric approach. The MR-methods non-invasively attained detailed information on the composition of articular cartilage that correlated with histology. So far, "molecular" MR-imaging allowed adequate characterization of the ultrastructure of cartilage and repair tissue with visualization of the content of proteoglycans, alignment of collagen fibers, hydration status of cartilage as well as remodeling processes of repair tissues. These biochemical MR-methods allow to longitudinally visualize pathophysiological patterns and thereby serve as an early diagnostic tool, support the development of prevention strategies, and allow to monitor therapeutic approaches. In a subproject of the Emerging Fields Initiative (EFIMoves), we compare alterations in motion patterns (Parkinson Disease; knee osteoarthritis) with morphological and biomechanical changes of large joints of the lower extremity.

### Traumatic lesions of thoracic bone structures

Project manager: Dr. S Schulz-Drost

This research group focuses on the epidemiology, pathogenesis, and therapeutic options of serial fractures of the ribs and fractures of the sternum. The current treatment concepts were analyzed according to the Traumaregister DGU® and the prevalence of fractures of the ribs and sternum were determined in the cohort of severely injured trauma patients. Additionally, surgical concepts for correcting and stabilizing the chest wall were optimized based on the clini - cal relevance of instable injuries of thoracic bone structures with severely restricted respiration biomechanics. In human anatomical studies, various material combinations of plates, intramedullary splints, and transsternal metal bars were compared by external thoracic compression with respect to their stability and correction potential. In this context, surgical options for minimal invasive approaches to the chest wall were developed in order to adequately treat instable injuries of thoracic bone structures, e.g. serial fractures of the ribs.

## Teaching

The comprehensive education within the Division of Trauma Surgery comprises the traditional main lecture, the curricular practical courses, and additional integrated practical seminars, such as sewing courses and implant workshops, as well as colloquia focusing on interdisciplinary subjects. Interactive courses are also provided as an intensive training for final exams. Furthermore, the Division of Trauma Surgery offers the opportunity to participate in clinical rounds and observe in emergency wards and operation theaters.

### Selected Publications


Klinger P, Beyer C, Ekici AB, Carl HD, Schett G, Swoboda B, Hennig F, Gelse K. The Transient Chondrocyte Phenotype in Human Osteophytic Cartilage: A Role of Pigment Epithelium-Derived Factor? Cartilage, 2013, 4(3); 249-255

Pachowsky ML, Trattnig S, Wondrasch B, Apprich S, Marlovits S, Mauerer A, Welsch GH, Blanke M. In vivo evaluation of biomechanical properties in the patellofemoral joint after matrix-associated autologous chondrocyte transplantation by means of quantitative T2 MRI. Knee Surg Sports Traumatol Arthrosc 2014, 22(6): 1360-9

Schulz-Drost S, Mauerer A, Grupp S, Hennig FF, Blanke M. Surgical fixation of sternal fractures: locked plate fixation by low-profile titanium plates--surgical safety through depth limited drilling. Int Orthop 2014, 38(1): 133-9

Pachowsky ML, Werner S, Marlovits S, Stelzeneder D, Renner N, Trattnig S, Welsch GH. 3D-isotropic high-resolution morphological imaging and quantitative T2 mapping as biomarkers for gender related differences after matrix-associated autologous chondrocyte transplantation (MACT). J Orthop Res 2014, 32(10): 1341-8

Golditz T, Steib S, Pfeifer K, Uder M, Gelse K, Janka R, Hennig FF, Welsch GH. Functional ankle instability as a risk factor for osteoarthritis: using T2-mapping to analyze early cartilage degeneration in the ankle joint of young athletes. Osteoarthritis Cartilage 2014, 22(10): 1377-85

Renner N, Krönke G, Rech J, Uder M, Janka R, Lauer L, Paul D, Herz B, Schlechtweg P, Hennig FF, Schett G, Welsch G. ACPA positivity correlates with cartilage damage and proteoglycan levels in patients with rheumatoid arthritis in the hand joints. Arthritis Rheumatol 2014, 66(12): 3283-8

# Department of Urology

## Chair of Urology

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**Research Focus**
- Continuous extension of an annotated tumor tissue repository containing urologic tumors
- Systemic tumor therapy, clinical trials
- Tumor genetic research with focus on identification of biomarkers
- MRI-TRUS-fusion guides biopsies for the diagnosis of prostate cancer
- Multifactorial models in uro-tumorpathology

## Structure of the Department

UK Erlangen:
- Outpatients' clinic and pediatric urology
- Adult renal transplantation unit in cooperation with the Department of Medicine 4 (Prof. Dr. K.-U. Eckardt)
- Pediatric renal transplantation unit in cooperation with the Department of Pediatrics and Adolescent Medicine (Prof. Dr. Dr. h.c. W. Rascher)
- Uro-oncological outpatients' unit for systemic drug therapy (AURONTE) in cooperation with the Department of Medicine 5 (Prof. Dr. A. Mackensen)
- Unit for minimally invasive surgery (laparoscopic and robot-assisted surgery)

Waldkrankenhaus St. Marien gGmbH:
- Adult urology (inpatients' clinic), private insurance patients (outpatients' clinic) with a focus on endourology
- Trial documentation center

## Research

### 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). Our tissue database system is part of the Central Research Infrastructure for Molecular Pathology (CRIP). CRIP is a supervising system for the distribution of tissue samples hosted by the Institute of Biomedical Technology (IBMT) of the Fraunhofer-Gesellschaft e.V.

### Systemic tumor therapy, clinical trials

Project manager: PD 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 kidney cancer or prostate cancer:
- Registry for advanced kidney cancer
- Registry STAR – TOR
- RCC Switch 2 study
- Berat study
- Meteor XL184-308
- Principal study
- Everpro study
- marC-2 Everolimus study
- Flipper study
- Magnolia study
- Alpharadin study.

Besides this, the Department of Urology is the study centers of the PREFERE study (Evaluation of Four Treatment Modalities in Prostate Cancer With Low or "Early Intermediate" Risk).

Information about open or closed clinical trials can be found at the homepage of the urological trial registry.

### Tumor genetic research with focus on identification of biomarkers

Project manager: 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 tumor tissue repository, 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.

### MRI-TRUS-fusion guided biopsies for the diagnosis of prostate cancer

Project manager: PD Dr. B. Keck

The MRI-TRUS-fusion guided biopsy of the prostate is the advanced version of the conventional, ultrasound guided biopsy of the prostate. It combines the accuracy of multiparametric MRI imaging with the standardized and easy to perform TRUS-guided biopsy of the prostate which can be further extended by methods, such as elastography or Doppler ultrasound. A highly standardized diagnostic evaluation of the MRI images according to the PIRADS classification system is the basis for the identification of lesions suspi-

cious for harboring prostate cancer. An interdisciplinary cooperation with the Institute of Radiology provides the basis for the successful application of this diagnostic method. Current clinical trials have shown that the application of MRI-TRUS-fusion guided biopsies is able to reduce the diagnosis rate of well-differentiated, clinically insignificant prostate cancers while highly aggressive prostate cancers can be diagnosed with improved sensitivity. Nevertheless, the clinical interpretation of PIRADS class 3 lesions still poses a great challenge because these are not unanimously regarded as suspicious for a tumor. Here, the diagnostic procedure is supported by an experimental diagnostic method. Tumor-specific RNA-based biomarkers are assessed in blood serum. By combining advanced MRI-imaging and biomarker analysis, it could be possible to aid in the clinical decision if patients should undergo prostate biopsy or clinical surveillance.

### 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) 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 Department 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.

## Teaching

Medical students are taught in the lecture series of emergency medicine and specialized urological lectures. Students also conduct a practical course 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 the fields of andrology and systemic drug tumor therapy. 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 for minimally invasive surgery. In addition, practica for basic and advanced techniques in molecular urology are offered.

### Selected Publications


Hart M, Wach S, Nolte E, Szczyrba J, Menon R, Taubert H, Hartmann A, Stoehr R, Wieland W, Grässer FA, Wullich B. The proto-oncogene ERG is a target of microRNA miR-145 in prostate cancer. FEBS J 2013, 280(9): 2105-16

Keck B, Wach S, Goebell PJ, Kunath F, Bertz S, Lehmann J, Stöckle M, Taubert H, Wullich B, Hartmann A. SNAI1 protein expression is an independent negative prognosticator in muscle-invasive bladder cancer. Ann Surg Oncol 2013, 20(11): 3669-74

Kunath F, Keck B, Rücker G, Motschall E, Wullich B, Antes G, Meerpohl JJ. Early versus deferred androgen suppression therapy for patients with lymph node-positive prostate cancer after local therapy with curative intent: a systematic review. BMC Cancer 2013, 13: 131

Wach S, Nolte E, Theil A, Stöhr C, T Rau T, Hartmann A, Ekici A, Keck B, Taubert H, Wullich B. MicroRNA profiles classify papillary renal cell carcinoma subtypes. Br J Cancer 2013, 109(3): 714-22

Al-Janabi O, Wach S, Nolte E, Weigelt K, Rau TT, Stöhr C, Legal W, Schick S, Greither T, Hartmann A, Wullich B, Taubert H. Piwi-like 1 and 4 gene transcript levels are associated with clinicopathological parameters in renal cell carcinomas. Biochim Biophys Acta 2014, 1842(5): 686-90

Hart M, Nolte E, Wach S, Szczyrba J, Taubert H, Rau TT, Hartmann A, Grässer FA, Wullich B. Comparative microRNA profiling of prostate carcinomas with increasing tumor stage by deep sequencing. Mol Cancer Res 2014, 12(2): 250-63


### International Cooperations

Prof. Dr. G. Yousef, St. Michael's Hospital, Toronto: Canada

Prof. Dr. T. Ørntoft, Århus University Hospital, Århus: Denmark

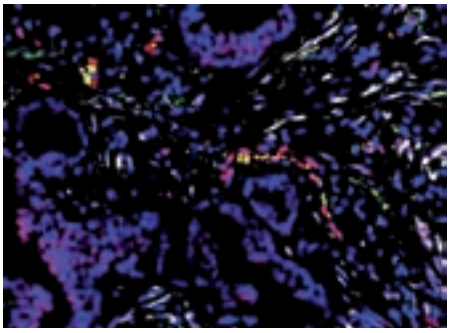
Prof. Dr. S. Subramanian, University of Minnesota Medical School, Minneapolis: USA

International Bladder Cancer Network (IBCN), Barcelona: Spain

Dr. B.S. Nielsen, Bioneer A/S, Hørsholm: Denmark

### Meetings and International Training Courses

15. – 17.05.2014: 40. Gemeinsame Tagung der Österreichischen Gesellschaft für Urologie und Andrologie sowie der Bayerischen Urologenvereinigung, Erlangen (Tagungspräsident: Prof. Dr. B. Wullich).



Visualization of a parallel miRNA in situ hybridization und immunofluorescence.
miRNA: grey; target protein: red; nuclei: blue.
Picture was produced in cooperation with B.S. Nielsen, Bioneer A/S.

# Department of Operative Dentistry and Periodontology

## Chair of Dental, Oral, and Maxillofacial Medicine – especially Operative Dentistry, Periodontology, and Pediatric Dentistry

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**Research Focus**
- Clinical fractography on dental ceramic restorations
- Residual stress profiles in veneered dental zirconia frameworks
- Tailoring of crystal alignment in dental glass-ceramic prostheses
- Study of hydrothermal degradation mechanisms in zirconium dioxide
- Material properties self-adhesive cements

## Structure of the Department

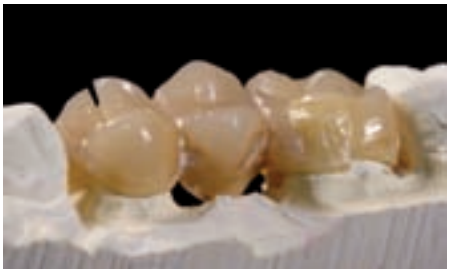
The Department of Operative Dentistry and Periodontology employs 50 staff members, including six professors and senior dentists, twelve dentists-in-training, 20 dental nurses, and four dental technicians. The Department of Operative Dentistry and Periodontology further hosts a research laboratory with seven research associates. The research is generally conducted by three clinically oriented working groups as well as one dental material, pre-clinically oriented working group. Six post-doctoral researchers, 55 dental post-graduate and graduate students, and four technical assistants are in charge of the manifold research activities in the lab section. The main focus is on dental materials research with fields of expertise in basic science of operative and periodontal treatment procedures and correlation of experimental findings with clinical outcome. Independent, pre-clinical assessment of dental materials is a further area of interest of the lab section.

## Research

### Clinical fractography on dental ceramic restorations

Project managers: Prof. Dr. U. Lohbauer, Dr. R. Belli

After the commercial launch of new dental ceramic materials, an increased incidence of intraoral fractures or chippings has been observed. The method of fractography is intended to clinically analyze failed dental restorations in order to assign 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 non-profit organization (Fracto Forum International e.V.) was founded. A first international workshop on dental fractography was successfully organized in 2014.



*Fragments of a clinically failed molar bridge.*

### Residual stress profiles in veneered dental zirconia frameworks

Project managers: Prof. Dr. U. Lohbauer, Dr. R. Belli

Clinical studies on veneered dental zirconia restorations have shown a high incidence of chipping fractures in the veneering porcelain as compared to other material combinations. In order to address this issue, the research laboratory for dental biomaterials within the Department of Operative Dentistry and Periodontology conducted several in vitro investigations to test the compatibility between veneering porcelains and zirconia. Using mechanical evaluations, the residual stress distribution generated within the glassy veneer layer was measured with regard to different thickness ratios and cooling protocols. Because the geometry of dental prostheses is complex, different geometrical forms were produced using CAD-CAM processing. Thin cross-sections were obtained for observation using the birefringence method, rendering two-dimensional distribution maps of residual thermal stresses. These results help to seek strategies that avoid residual stress development on porcelain-fused to zirconia systems and have already been successfully employed in routine fabrication protocols.

### Tailoring of crystal alignment in dental glass-ceramic prostheses

Project managers: Dr. R. Belli, Prof. Dr. U. Lohbauer

Most dental ceramics are produced from partially crystallized glass. Although these materials are hard, they are extremely susceptible to damage, especially due to the glass phase content. A strategy for strengthening these materials uses their microstructure to form reinforcing sites within the structural design. Such an approach has potential for application with lithium disilicate (LS2) glass-ceramics which contain needle-form $Li_2Si_2O_5$ crystals that deflect oncoming cracks. By press injection of the glass melt through specifically oriented injection channels, crystals are aligned in patterns that lead to high mechanical anisotropy. In natural materials, like dental enamel, such effects take place through several length-scales through the hierarchical structural arrangement within the crystals and bulk. To grasp these mechanisms in LS2 dental ceramics in the macro, micro and nano scales, respectively, the research laboratory for dental biomaterials of the Department of Operative Dentistry and Periodontology has joined forces with the Department of Materials Science (Faculty of Engineering) to investigate specific material responses using state-of-the-art mechanical testing.

### Study of hydrothermal degradation mechanisms in zirconium dioxide

Project managers: Dr. R. Belli, Prof. Dr. U. Lohbauer

Fully crystalline zirconium dioxide ($ZrO_2$) ceramics offer moderate translucency and high mechanical performance for use as an alternative to metal-based dental prostheses. The crystalline structure of $ZrO_2$ is, however, metastable at body temperature and may suffer from grain destabilization in contact with water molecules (hydrothermal degradation). This diffusion-controlled problem has been observed first in orthopedic hip implants and is discussed today as a possible degradation mechanism also in $ZrO_2$ for dental use. In dentistry $ZrO_2$ has been used for approximately 15 years mainly as infrastructure material covered with a glassy porcelain veneer which hinders its direct contact with the oral environment. However, the trend in prosthetic dentistry gravitates to monolithic structures where full-$ZrO_2$ restorations are now exposed to the wet oral environment and contact damage. The

scientific evidence regarding the mechanical behavior of ZrO2 in such conditions is very scarce and must be urgently addressed. With that in mind, the research laboratory for dental biomaterials within the Department of Operative Dentistry and Periodontology has formed research collaboration with the Prosthetic Department of the University of Espírito Santo (Brazil) to conduct a clinical investigation. Patients having single-element implants will receive customized full-ZrO2 crowns produced in the Department of Operative Dentistry and Periodontology and receive replacements after one and two years of service. The retrieved crowns will be sent to Erlangen where a thorough microstructural analysis will be conducted. This project has already been partially financed by the Bavarian University Center for Latin America and deepens research relationships with Latin-American universities.

### Material properties self-adhesive cements

Project managers: Dr. J. Zorzin, Prof. Dr. U. Lohbauer

Self-adhesive cements are novel materials for luting indirect restorations that are able to adhere without additional conditioning of the tooth structure and restorations. Of primary interest was the pH-neutralization behavior over time, hydrophilicity, and the chemical composition of these materials. The investigations demonstrated the influence of the pH-neutralization behavior on the mechanical stability, expansion, and adhesion of these materials to indirect restorative materials.

## Teaching

The main lectures of the Department of Operative Dentistry and Periodontology focus on basic science in operative dentistry and periodontology as well as on endodontology and pediatric dentistry. In the specific lectures, the most recent international scientific opinions and trends are embedded and controversially discussed, resorting to own measured data and scientific outcome of the dental materials lab. Besides the conventional lectures, the dental education is highly practically oriented. Therefore, the Department of Operative Dentistry and Periodontology has established practical block seminars in the graduate courses teaching endodontic treatment strategies (seventh term) and indirect inlay manufacturing skills (tenth term). Students as well as doctoral students are required to report in special seminars on recent scientific trends in restorative dentistry.

### Selected Publications


Lohbauer U, Belli R, Ferracane JL. Factors involved in mechanical fatigue degradation of dental resin composites. J Dent Res 2013, 92: 584-591

Belli R, Frankenberger R, Appelt A, Schmitt J, Baratieri LN, Greil P, Lohbauer U. Thermal-induced residual stresses affect the lifetime of zirconia-veneer crowns. Dent Mater 2013, 29: 181-190

Grigore A, Spallek S, Petschelt A, Butz B, Spiecker E, Lohbauer U. Microstructure of veneered zirconia after surface treatments: A TEM study. Dent Mater 2013, 29: 1098-1107

Belli R, Kreppel S, Petschelt A, Hornberger H, Boccaccini AR, Lohbauer U. Strengthening of dental adhesives via particle reinforcement. J Mech Behav Biomed Mater 2014, 37C: 100-108

Lohbauer U, Belli R, Arnetzl G, Scherrer S, Quinn GD. Fracture of a veneered-ZrO2 dental prosthesis from an inner thermal crack. Case Stud Eng Fail Anal 2014, 2: 100-106

Zorzin J, Belli R, Wagner A, Petschelt A, Lohbauer U. Self-adhesive resin cements: Adhesive performance to indirect restorative materials. J Adhes Dent 2014, 16: 541-546


### International Cooperations

Prof. G. Eliades, University of Athens (UOA), Athens: Greece

Dr. S. Scherrer, University of Geneva, Geneva: Switzerland

Prof. P.F. Cesar, University of Sao Paulo (USP), Sao Paulo: Brazil

Dr. J. Leprince, University of Louvain, Louvain: Belgium

Prof. E.W. Schubert, University of Joinville (Univille), Joinville: Brazil

Prof. J. Ferracane, Oregon Health and Science University, Portland: USA

# Department of Oral and Cranio-Maxillofacial Surgery

## Chair of Dental, Oral, and Maxillofacial Medicine – especially Oral and Cranio-Maxillofacial Surgery

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**Research Focus**
- Infection and inflammation
- Tumor research
- Biomedical technics

## Structure of the Department

The Department of Oral and Cranio-Maxillofacial Surgery is responsible for teaching oral and maxillofacial surgery, including dental surgery and dental radiology, research as well as patient care. The Department employs 17 medical doctors/dentists, one biologist and three technical assistants. Research mainly focuses on biomedical technology, infection, and inflammation as well as tumors of the head and neck. Topics of particular interest are augmentation of osseous defects by transplantation of autogenous tissues or specific bone substitutes, the pathoetiology of osteonecrosis of the jaw as well as the evaluation of therapeutic options in sites displaying compromised healing, and the identification of indicators of prognosis in patients undergoing resection of oral squamous cell carcinoma (SCC). Innovative research focuses on the evaluation and development of laser-assisted surgery. The research laboratory (S1-facility) of the Department of Oral and Cranio-Maxillofacial Surgery allows a wide range of immunohistochemical and molecular biological techniques. For experimental trials concerning bone histology and biomedical technology, a specialized facility is shared with the Department of Prosthodontics. The clinical focus is on the surgery of malformations of the head/neck and cleft lip palate in particular, oncologic and reconstructive surgery for tumors of the head and neck, orthognathic surgery, traumatology of the facial skeleton, esthetic surgery as well as dental implantology.

## Research

### Infection and inflammation

Research addresses etiology, pathogenesis, and therapeutic options in inflammatory reactions of the facial skeleton. Also the osseous regeneration of bone defects in sites displaying compromised wound healing is being investigated. A relevant focus is on the bisphosphonate-associated osteonecrosis of the jaw (BONJ).
As BONJ is restricted to craniofacial bone structures, research focuses on jaw bone specific signal transduction processes during development, bone remodeling, and disease. Cranial neural crest derived pluripotent progenitor cells are of scientific and clinical interest in experimental approaches to develop regeneration strategies in craniofacial bone structures. In addition, patient-related factors are being evaluated which may promote onset and course of bisphosphonate-associated osteonecrosis of the jaw. An animal model in pigs serves a study to answer the question whether there is an influence of bisphosphonate exposed bone in osseointegration of dental implants.
For functional and esthetic long-term success of dental implants, a sufficient amount of peri-implant hard and soft tissues is indispensable. The research especially focuses on modulation and optimization of peri-implant tissues in the context of rehabilitation of severe atrophic edentulous jaw and jaw segments with implant fixed dentures. This refers particularly to preclinical and clinical examination of new techniques and materials for the augmentation of non-space making vertical bony defects and the long-term stability of vertical bone grafts. Furthermore, research focuses on the regeneration of peri-implant soft tissues and their impact on peri-implant health.

### Tumor research

Treatment of advanced carcinoma of the oral cavity involves tumor-surgery and reconstruction of defects by using microsurgical tissue transfer. In the context of tumor recurrence or pronounced bone necrosis after irradiation, patients usually experience repeated microsurgical reconstruction. Pre-irradiated tissues contain compromised anastomosis vessels with atherosclerotic lesions and increased cellular pro-inflammatory and procoagulatoric infiltration of the vessel walls. In a clinical study the functional and morphological changes in endothelial cells and their influence on the postoperative perfusion within microvascular grafts are studied in previously irradiated versus non-irradiated patients. The postoperative perfusion of microvascular grafts is monitored using laser Doppler spectrophotometry, and intraoperative fluorescence angiography for flow measurement of graft blood flow (Zeiss surgical microscope Pentero 900 with Flow 800). To determine perioperative endothelial dysfunction, a noninvasive, ultrasonographic measurement methodology (blood flow controlled vasodilation) is performed on the patients. The aim of this research project is the improved understanding of the pathomechanic perfusion of microvascular grafts as a basis for the future application of e.g. pharmacological treatment for the reduction of perioperative complications.
In the field of cancer research another focus was set on the influence of the immune system on tumor progression. We were able to show that there is an association of histomorphological parameter with the macrophage polarization in oral SCC and in the regional lymph nodes.
According to the cancer stem cell hypothesis, a small population of cells with stem cell characteristics, so-called cancer stem cells (CSC), is responsible for the tumor genesis and progression. CSC, which were also described in SCC, are considered virtually resistant to current treatments. The aim of the current research is to determine the expression of various CSC markers in cell cultures and biopsies of SCC. The research team thus hopes to derive innovative immune and gene-specific therapies.
It has been hypothesized that the expression levels of stem cell-specific markers are increased in leukoplakia, the most common precursors of SCC of the oral cavity as compared with normal oral mucosa of healthy subjects. These changes can be attributed to the presence of cells with stem cell properties that are responsible for tumor formation. Leukoplakia of the oral cavity which increasingly has cells with stem cell properties should therefore pose an increased risk for malignant transformation. The aim of this study is to examine whether overexpression of stem cell genes in tissues indicating the development of SCC of the oral cavity in a five-year period. The aim of another project is to develop a minimally invasive method for diagnosis, prognosis, and clinical monitoring of the oral cavity SCC.

### Biomedical technics

The focus "biomedical technology" comprises research projects on regeneration of soft and hard tissues, intraoperative imaging, and laser applications. Bone substitutes promote formation of new bone in pre-existing osseous defects

by different biologic mechanisms, including inflammatory and proliferative cellular reactions. The project aims at creating, applying, and evaluating the biomimetic materials and biofunctional surfaces in implant dentistry.
In cooperation with the Bavarian Laser Center, a sensor-assisted laser system for selective bone ablation was tested in cadaver bone as well as in an in vivo setting. By connecting the Er:YAG laser to a process control for material-specific ablation, the system is able to differentiate cortical and cancellous bone as well as soft tissues. In oral and maxillofacial surgery, the selective bone ablation offers a new perspective to preserve nerval structures during surgery, such as the nervus mandibularis during osteotomy of the lower jaw. A second research approach is to transfer the system of optical tissue differentiation towards tumor tissue to allow high selective tumor resection in the future.

## Teaching

Oral and maxillofacial surgery is a part of both, medical and dental curriculum. The Chair of Oral and Cranio-Maxillofacial Surgery provides compulsory and elective courses for medical and dental students during clinical education. In clinical dentistry, these involve oral and maxillofacial surgery, dental surgery, and dental radiology. Apart from traditional methods of teaching (lectures, lectures with case demonstrations, practical training for medical and dental students), problem-based and interdisciplinary approaches are also used. Topics of interdisciplinary education include among others emergency medicine, electivum implantology for dental students (I-LECT), classes as part of the Graduate School in Advanced Optical Technologies (SAOT), and automated analysis of speech disorders in cooperation with the Chair of Pattern Recognition of the Faculty of Engineering.

### Selected Publications


Lutz R, Prechtl C, Nonhoff J, Weisel T, Damien CJ, Schlegel KA. Biofunctionalization of the implant surface with different concentrations of a synthetic peptide (P-15). Clin Oral Implants Res 2013, 24(7): 781-6

Ries J, Vairaktaris E, Kintopp R, Baran C, Neukam FW, Nkenke E. Alterations in miRNA expression patterns in whole blood of OSCC patients. In Vivo 2014, 28(5): 851-61

Wehrhan F, Amann K, Möbius P, Weber M, Preidl R, Ries J, Stockmann P. BRONJ-related jaw bone is associated with increased Dlx-5 and suppressed Osteopontin-implication in the site specific alteration of angiogenesis and bone turnover by Bisphosphonates. Clin Oral Invest 2014 Dec 3

Wehrhan F, Büttner-Herold M, Hyckel P, Möbius P, Preidl R, Distel L, Ries J, Amann K, Schmitt C, Neukam FW, Weber M. Increased malignancy of oral squamous cell carcinomas (oscc) is associated with macrophage polarization in regional lymph nodes – an immunohistochemical study. BMC Cancer 2014, 14(1): 522

Schmitt CM, Moest T, Lutz R, Neukam FW, Schlegel KA. Anorganic bovine bone (ABB) vs. autologous bone (AB) plus ABB in maxillary sinus grafting. A prospective non-randomized clinical and histomorphometrical trial. Clin Oral Implants Res 2014 Apr 15. doi: 10.1111/clr.12396


### International Cooperations

Dr. E. Felszhegy, Semmelweiss-University, Budapest: Hungary

Prof. Dr. Dr. E. Vairaktaris, University of Athens, Athens: Greece

Dr. J. Wolfaardt, Ph.D., University of Alberta, Alberta: Canada

### Research Equipment

Zeiss surgical microscope Pentero 900 with Flow 800

# Department of Orthodontics and Orofacial Orthopedics

## Chair of Dental, Oral, and Maxillofacial Medicine – especially Orofacial Orthopedics

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**Research Focus**

- Transmission of sensitive patient data by electronic media
- CBCT, MSCT, industrial MSCT, and MRI in orthodontics – A comparison of different three-dimensional imaging technologies in orthodontic issues
- Evaluation of the Frankfort Horizontal Plane to establish a reliable reference plane in CT scans
- Erlangen 3D-model analysis for cleft lip and palate newborn – long-term documentation
- Face scan – stereophotogrammetry
- Material scientific investigations
- Investigation of the reproducibility of skeletal maxillary landmarks in CT-scans
- MSCT and CBCT comparison – an in vitro study

## Structure of the Department

The Chair of Dental, Oral, and Maxillofacial Medicine – especially Orofacial Orthopedics is part of the dental departments of the FAU. Within these departments, there is a regular, biennial rotation of the spokesperson of all departments. Altogether, 25 employees are working in the Department of Orthodontics and Orofacial Orthopedics. The research is carried out by ten scientists and ten doctoral candidates. Technical assistants are not available.

The prime alignment of our research is the 3D-evaluation of dentofacial anomalies with development of practical 3D-analysis methods. Concerning this research focus, we cooperate with partners from inside and outside the FAU.

Other research projects have their focus on morphology and interdisciplinary themes, involving several disciplines of dentistry and medicine.

The clinical main emphasis is the orthodontic treatment of patients of all age groups: Babies and small children with cleft lip palates and syndrome malformation, children and adolescents with various tooth misalignments and jaw malpositions, also including craniofacial malformation, and adults with tooth misalignment and complex interdisciplinary problems. We offer an extensive spectrum of internationally accepted therapy-concepts and modern appliances for the respective age groups.

The Department of Orthodontics and Orofacial Orthopedics plays a leading role within the interdisciplinary center of cleft lip and palate of the FAU. In this interdisciplinary center, therapy concepts are continuously updated and initiated.

## Research

### Transmission of sensitive patient data by electronic media

The purpose of this study was to develop decision-making aids and recommendations for dental practitioners regarding the utilization and sharing of sensitive digital patient data. In the current environment of growing digitization, healthcare professionals need detailed knowledge of secure data management to maximize confidentiality and minimize the risks involved in both, archiving patient data and sharing it through electronic channels. Despite well-defined legal requirements, an all-inclusive technological solution does not currently exist. The need for a preliminary review and critical appraisal of common practices of data transfer prompted a search of the literature and the Web to identify viable methods of secure data exchange. A strong focus was placed on the transmission of datasets either smaller or larger than 10 MB and on secure communication by smartphone. Although encryption of patient-related data should be routine, it is often difficult to implement. Pretty Good Privacy (PGP) and Secure/Multipurpose Internet Mail Extensions (S/MIME) are viable standards for secure e-mail encryption. Sharing of high-volume data should be accomplished with the help of file encryption. Careful handling of sensitive patient data is mandatory and it is the end-user's responsibility to meet any requirements for encryption, preferably by using free, open-source (and hence transparent) software.

### CBCT, MSCT, industrial MSCT, and MRI in orthodontics – A comparison of different three-dimensional imaging technologies in orthodontic issues

Aim of this study is the development of a platform to examine the practicability of three-dimensional MRI imaging in orthodontic issues due to the statement of the German society of Orthodontics (DGKFO) on the indication of 3D-imaging and the evaluation of MRI as an alternative imaging technique to CBCT (cone beam computed tomograph), MSCT (multi slice computed tomograph), and industrial MSCT. The study is being conducted in cooperation with the Fraunhofer-Institute Würzburg.

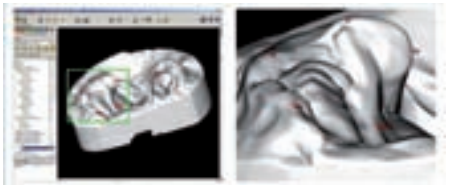
### Evaluation of the Frankfort Horizontal Plane to establish a reliable reference plane in CT scans

The review of 3D analysis in literature showed that median structures are not suitable to define valid and reliable median sagittal planes to evaluate the degree of asymmetry of facial structures. The Frankfort Horizontal Plane (FH) was already used by anthropologists to standardize anthropologic-anatomic measurements on the human skull in 19th century and shows only minor vertical deviation with high reliability, even in pronounced asymmetry of the facial bones. However, reliability of transversal direction of cephalometric landmarks is still unsatisfying and it is to be explored how substantial improvement of reliability in the transversal dimension can be achieved for future use of FH as a general reference plane. Aim of this study was to demonstrate aligner efficiency with Durancasts of the Clear Aligner System for orthodontic treatment.

### Erlangen 3D-model analysis for cleft lip and palate newborn – long-term documentation

Due to the long-term and interdisciplinary treatment of CLP (cleft lip and palate) patients, it is one of the main goals to establish a consistent and well-arranged documentation. The treatment with presurgical orthopedic appliances in Erlangen takes place in four week intervals until surgical palate closure. During this time, plaster models are made at four defined dates within the first year and later once yearly.

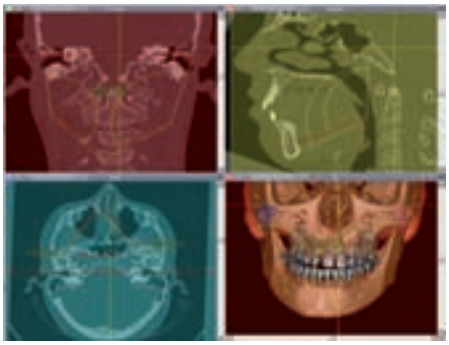
Based on our two dimensional analysis of maxillary models, a simple and clinically applicable minimal documentation analysis for linear and angular measurements on digitized models was developed (3D-Shape GmbH). The Erlangen 3D-model analysis can be applied routinely, precisely, and clinically practicable for three-dimensional documentation of changes in growth or treatment. It offers a qualification for standardized documentation and data management.



*Three dimensional measurement of maxillary casts of newborn children with unilateral cleft lip and palate.*

### Face scan – stereophotogrammetry

In the field of facial soft tissue diagnostics, our present focus is on the indirect digital measurement of these structures with three-dimensional photographs ("3D-stereophotogrammetry", face scan 3D, 3D-Shape GmbH) and the comparison of these new diagnostic procedures with conventional two-dimensional photography. Clinical relevance is given particularly for therapy planning of malocclusions and craniofacial anomalies.



*Metrical analysis of a case with craniofacial asymmetry.*

### Material scientific investigations

In order to minimize bracket failure rates during orthodontic treatment, this study investigated the bond strength of orthodontic brackets on enamel (n = 500 extracted teeth) using different bonding materials. The influence of different polymerization devices (LED light-emitting diode, QTH quartz-tungsten-halogen) and polymerization times were tested.

### Investigation of the reproducibility of skeletal maxillary landmarks in CT-scans

The skeletal landmarks anterior and posterior nasal spine are showing a high morphological variability.

Aim of the study was to verify the reproducibility of these and other cephalometric maxillary landmarks in CT-scans in the x-y-z-axis (transverse, sagittal, and vertical). For this study, the CT-examination software Voxim® was applied.

### MSCT and CBCT comparison – an in vitro study

The aim of this study was to analyze the imaging accuracy of CBCT data sets as compared with MSCT data sets in determining the exact mesio-distal width of unerupted porcine tooth germs and to compare the radiologically obtained results of width measurements with the actual mesio-distal dimension of the tooth germs. In MSCT and CBCT data sets, the largest diameter of 24 tooth germs was determined with the aid of the mesial and distal contact points. The reference method used was mesio-distal width measurement using sliding callipers after the tooth germs had been osteotomized.

## Teaching

Basic orthodontic and orthopedic knowledge is transmitted in traditional lectures by the Department of Orthodontics and Orofacial Orthopedics. Actual scientific findings are continuously integrated as well as results of own scientific work on the appraisal of MSCT and CBCT data sets. Basic knowledge in theory is systematically developed in hands-on trainings and seminars during the term and in a one-week block in the term brake to further abilities such as: Evaluating the dental and dentofacial development on the basis of dental casts, x-rays, and facial profiles and, in addition, to manufacture simple orthodontic devices (7th term).

On this basis, the main orthodontic clinical pictures are worked out in courses based on selected examples. That way, the contents of the main lectures are transferred into practice. Additionally, in a two-week program, the basic comprehension of biomechanics is applied to orthodontic materials and appliances (8th term). Skills, in particular medical interview techniques, collecting medical history, orthodontic examination and orthodontic treatment planning, are developed in small groups in further practical trainings and attendances in ortho - dontic treatment situations respectively during the 9th term.

To promote the development of practical skills, interactive e-learning materials of our own Department as well as of other institutions are available, supported by Virtual University of Bavaria (vhb).

### Selected Publications


Hofmann E, Medelnik J, Fink M, Lell M, Hirschfelder U. Three-dimensional volume tomographic study of the imaging accuracy of impacted teeth: MSCT and CBCT comparison – an in vitro study. Eur J Orthod 2013, 35: 286-294

Hofmann E, Schmid M, Sedlmair M, Banckwitz R, Hirschfelder U, Lell M. Comparative study of image quality and radiation dose of cone beam and low-dose multislice computed tomography – an in-vitro investigation. Clin Oral Investig 2014, 18: 301-11

Nkenke E, Vairaktaris E, Hanke S, Hoffmann B, Schlittenbauer T. Skeletal stability and complications in transantral maxillary distraction in patients with cleft lip and palate. J Craniofac Surg 2014, 25: 689-93

Fink M, Medelnik J, Strobel K, Hirschfelder U, Hofmann E. Metric precision via soft-tissue landmarks in three-dimensional structured-light scans of human faces. J Orofac Orthop 2014, 75: 133-43

Hofmann E, Schmid M, Lell M, Hirschfelder U. Cone beam computed tomography and low-dose multislice computed tomography in orthodontics and dentistry: a comparative evaluation on image quality and radiation exposure. J Orofac Orthop 2014, 75: 384-98

# Department of Prosthodontics

## Chair of Dental, Oral, and Maxillofacial Medicine – especially Prosthetic Dentistry

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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

## Structure of the Department

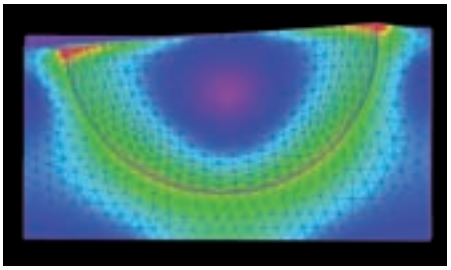
The Department of Prosthodontics is responsible for teaching undergraduate students in several areas of fixed and removable prosthodontics, dental laboratory technology, occlusion and TMJ dysfunction, dental implants, CAD/CAM technology and ceramics, as well as maxillofacial prosthodontics. The Department of Prosthodontics is staffed with 19 full-time academics with a wide range of expertise and a total of 45 employees. It is involved in several areas of research, including dental materials, biomechanics, dental implants, CAD/CAM technology, and psychogenic impact in dental problems.
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.
A future focus of research is the relationship between oral and general health in the light of the demographic change.

## Research

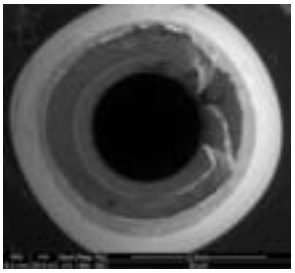
### Dental biomechanics

Project manager: PD Dr. M. Karl
Mechanical parameters of the components are decisive co-factors determining long-term treatment outcomes in implant dentistry. During the past year, an in vitro study measuring micromotion between implants and abutments was conducted using a specially designed test setup.
Clinical failures, such as fractured implants, are of great importance in this context as they allow for analyzing potential design and material related issues. Using a clinically fractured diameter reduced screw-type implant, the possibilities of fractographic analysis were shown.
Broadening the potential applications of the recently developed diagnostic tool for quantifying bone quality on the basis of intraoperative compressive testing, finite element analyses were performed simulating an acetabular cup endoprosthesis.

*In vitro test setup for measuring micromotion between implant and abutment.*



*Finite element analysis showing an acetabular cup endoprosthesis under torsional load.*



*SEM image showing the fracture surface of a clinically failed dental implant.*

### 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 dentistry

Project managers: Dr. R. Matta, B. Bergauer
In the past, quantitative assessment of biomechanical effects in vivo and intraorally required highly complex research set-ups as adequate measurement technology lacked. The aim of the research group is to establish and evaluate full-field three-dimensional (3D) optical inspection systems for clinical application in biomechanic research. The system will allow for real time quantitative depiction of biomechanical influences in the oral cavity. 3D-image correlation provides strain measurements in all dimensions which are critical for accurate strain and loading response measurements in objects. The results of these optical measurements are compatible with finite element analysis software. They facilitate verification and iteration of models that cannot be used solely to draw general conclusions regarding specific questions related to biomechanics. The system available in the Department of Prosthodontics uses photogrammetric principles. Relevant parameters for future in vivo applications were identified in current and completed studies, and first in vivo applications revealed promising results.

### CAD/CAM research laboratories

Project managers: Dr. R. Matta, B. Bergauer, G. Skibinski
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 assessing 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 analytical software programs. Since high strength oxide ceramics are applied more frequently as framework materials in dentistry, several research projects assess the clinical application and factors influencing long-term success.

## Teaching

The main focus of traditional prosthodontic education has shifted from a technically oriented towards an interdisciplinary treatment approach. Prophylaxis and biology as well as minimally invasive treatment concepts are in the focus. Clinically relevant topics are introduced into the preclinical curriculum, focusing on biologic interactions and material properties.
While theoretical knowledge remains an integral part of dental education, manual manufacture of dental restoration will be taught only exemplary.
A unique opportunity for all dentistry students at the FAU is the opportunity to participate in a three-year extra-curricular implant program. The "i.Lect" program is funded by third parties and provided in cooperation with the Department of Oral and Cranio-Maxillofacial Surgery. The i.Lect program has become an essential part of the elective and interdisciplinary education of dental students. The first students successfully passed their examinations in 2012 and started the post-graduate program (also provided in cooperation with the Department of Oral and Cranio-Maxillofacial Surgery).

### Selected Publications


Nkenke E, Agaimy A, von Wilmowsky C, Eitner S. Mandibular reconstruction using intraoral microvascular anastomosis following removal of an ameloblastoma. J Oral Maxillofac Surg 2013, 71: 1983-1992

Karl M, Krafft T, Kelly JR: Fracture of a narrow diameter Roxolid® implant – Clinical and fractographic considerations. The International Journal of Oral and Maxillofacial Implants 2014, 29(5): 1193-1196

Karl M, Taylor T: Parameters determining micromotion at the implant-abutment interface The International Journal of Oral and Maxillofacial Implants 2014, 29(6): 1338-1347

Winter W, Karl M: Basic considerations for determining the amount of press fit in acetabular cup endoprostheses as a function of the elastic bone behavior. Biomedical Engineering / Biomedizinische Technik 2014, 59(5): 413-420

Nickenig HJ, Wichmann M, Zöller JE, Eitner S. 3-D based minimally invasive one-stage lateral sinus elevation – a prospective randomized clinical pilot study with blinded assessment of postoperative visible facial soft tissue volume changes. J Craniomaxillofac Surg 2014, 42: 890-895

Nkenke E, Eitner S. Complex hemimaxillary rehabilitation with a prefabricated fibula flap and cast-based vacuum-formed surgical template. J Prosthet Dent 2014, 111: 521-524


### International Cooperations

Prof. T.D. Taylor, Prof. J.R. Kelley, Ph.D., University of Connecticut, Farmington: USA

Dr. I. Leblebicioglu, Ph.D., Universität Kayseri: Turkey

# Institute of General Practice

## Chair of General Practice

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**Research Focus**
- Clinical quality control
- Competence development in general practice trainees and medical students
- Medical decision-making in general practice
- Quaternary prevention in patient care
- Classification of diseases on primary care

## Structure of the Institute

The Institute of General Practice was founded in October 2013 as the first ordinary Chair of General Practice in Bavaria. Prof. Dr. T. Kühlein is Director of the Institute as well as Director of the Primary Care Center in Eckental (MVZ Eckental) being closely linked to the UK Erlangen. Responsible body is the Gesundheitsdienstleistungs GmbH Universitätsklinikum Erlangen, a subsidiary of the UK Erlangen. This is the first time that a German primary care center is led by an academic institution in general practice. The practice team consists of three general practitioners (GP) and five medical assistants attending to a list size of 2,500 patients per quarter. The combination of health service research and patient care is a unique concept in Germany that facilitates the implementation of innovative concepts.

As an academic institute, we have scientific expertise in the field of health service research and medical didactics. Our vision is to establish a strong primary care based on the principles of a transparent, cost-effective, and patient-oriented medicine. We want general practice to become an attractive professional field for young medical doctors. The current team working at the Institute of General Practice and responsible for research and teaching consists of four researchers (three medical doctors and one psychologist) and one team assistant. Our research focus is on clinical quality control, competence development, and on medical decision-making. Furthermore, Prof. Dr. T. Kühlein is known as an international expert in the field of quaternary prevention and classification of diseases. As representative of the WONCA (World Organization of Family Doctors), he was appointed to the advisory board of the "WHO-Family of International Classifications" (WHO-FIC) of the World Health Organization in October 2014.

## Research

### Clinical quality control

The aim of the project is to use routine data for clinical quality control. The purpose is to obtain knowledge about general practice patient care and to improve quality of care. For this reason, routine data will be extended by additional information and data. A software module will be implemented in electronic medical records to allow for additional documentation and coding of diagnoses based on ICPC-2 (International Classification of Primary Care). This should help to reveal a realistic picture of current pathways in patient care. Feedback of the results will be provided and form the basis of recommendations for an improved quality of care in the participating practices. In a first step, the software module will be implemented, tested, and fully developed to practical use in the MVZ Eckental. After that, the software system will be spread further in a large practice network (MainArzt).

### Competence development in general practice trainees and medical students

The reasons for general practice care being threatened by an acute shortage of GP are manifold. To meet this challenge, different approaches for solutions will be developed and tested in a series of research projects. To strengthen competence-based learning, strategies and methods will be assessed in the areas of medical education and vocational training with the purpose to reduce the shortage of GP by making the specialty more attractive to young medical doctors. At the same time, qualitative methods will be implemented to explore career choices in young general practice trainees and medical students. The study findings should help to improve the image of general practice and to establish funding initiatives aimed at successfully reducing the shortage of GP. First projects are funded by the Bavarian State Ministry of Health and Care, the Bavarian Association of General Practitioners, and the funding initiative Oberfranken Offensiv e.V.

### Medical decision-making in general practices

In contrast to secondary or tertiary care, prevalence of severe diseases is low in general practice. The main workload of GP compromises illnesses with vague symptoms, presented at early stages and in an undifferentiated way. To deal with diagnostic uncertainty is hence a major challenge for GP. Considering these facts, we want to investigate factors influencing medical decision-making in primary care. A series of research projects was conducted to examine the effect of tolerance of ambiguity, the importance of different symptoms in diagnostic and therapeutic processes, and how scientific evidence is taken into account. Furthermore, routine data provided by the Bavarian Association of Statutory Health Insurance Physicians (KVB) are analyzed.

### Quaternary prevention in primary care

Quaternary prevention means "an action to identify a patient at risk of over-medicalization, to protect him or her from new medical invasions, and to suggest to him or her interventions which are ethically acceptable". The purpose is to prevent patients in general practice care from overdiagnosis and overtreatment. In addition, diagnostic tests and therapeutic treatments with no or minimal beneficial effects should be identified. Quaternary prevention is seen as a central task of GP. The main purpose of our first project is to explore how GP deal with overtreatment in the German health care system.

### Classification of diseases on primary care

Since 2006 Prof. Dr. T. Kühlein has been a member of the WONCA International Classification Committee (WICC). He also became a member of the Executive Committee in 2012. The mission of WICC is to maintain and further develop classifications for primary care as for example the International Classification of Primary Care (ICPC). Recently, Prof. Dr. T. Kühlein was appointed to the WHO-FIC network, a group of international experts in the field of classification. WHO-FIC is part of the World Health Organization (WHO). Currently, two studies are run in cooperation with Radboud University in Nijmegen (The Netherlands) and Ghent University (Belgium).

## Teaching

The Institute of General Practice is responsible for the entire curricular-based education and teaching in general practice. The lecture "General Practice" is held in the first clinical term and forms the basis for a general practice elective and a three months rotation in a general practice as part of the final year (clinical rotation). Learning and transfer of practical knowledge in general practice is implemented in cooperation with 90 academic teaching practices. To maintain high levels of teaching quality, regular training events are offered to the teaching practices.

Our main concern is to establish competence-based learning in medical training, as for example the development of communication skills and medical decision-making based on scientific evidence. Both subjects are taught in elective courses.

In 2014, ten doctoral theses in medicine and three Master theses (within the degree program Medical Process Management) were supervised. Regular scientific colloquiums are held at the Institute of General Practice in which students present their projects, share experiences about their research, and are taught in scientific writing and working.

### Selected Publications


Kuehlein T, Freund T, Joos S. Patientenorientierte Medizin: Von der Kunst des Weglassens. Dtsch Arztebl 2013, 110(48): A 2312–4

Roos M, Krug D, Pfisterer D, Joos S. Professionalität in der Allgemeinmedizin in Deutschland – eine qualitative Studie zur Annäherung an das Kompetenzfeld. Z Evid Fortbild Qual Gesundhwes 2013, 107(7): 475-83

Leutgeb R, Laux G, Hermann K, Gutscher A, Szcsenyi J, Kuehlein T. Die medizinische Versorgung in einer kassenärztlichen Bereitschaftsdienstzentrale – Eine deskriptive Studie aus dem CONTENT-Projekt. Gesundheitswesen 2014, 76(12): 836-9

Leutgeb R, Szecsenyi J, Kuehlein T, Laux G. Charakteristika primärarztlicher Versorgung von Patienten außerhalb regulaerer Sprechstundenzeiten im Vergleich zur Routineversorgung. Gesundheitswesen 2014, Nov 5

Roos M, Kadmon M, Kirschfink M, Koch E, Jünger J, Strittmatter-Haubold V, Steiner T. Developing medical educators--a mixed method evaluation of a teaching education program. Med Educ Online 2014, 19: 23868

Roos M, Watson J, Wensing M, Peters-Klimm F. Motivation for career choice and job satisfaction of GP trainees and newly qualified GPs across Europe: a seven countries cross-sectional survey. Educ Prim Care 2014, 25(4): 202-10


### International Cooperations

P. Boeckxstaens MD, Ph.D., und D. Schrans, MD, Ghent University: Belgium

K. van Boven, MD, Radboud University Nijmegen: The Netherlands

Prof. M. Klinkman, MD, University of Michigan, Ann Arbor: USA

# Institute of Radiology

## Chair of Diagnostic Radiology

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**Research Focus**
- Methods of dosage reduction and biological dosimetry in medical imaging
- Functional and metabolic MRI
- Interventional radiology
- Cardiovascular imaging
- Breast imaging and gynecological radiology
- Information technology in radiology
- Experimental radiology and small animal imaging

## Structure of the Institute

The Institute of Radiology of the FAU is divided into four subsections (internal medicine, surgery, pediatric radiology, and gynecology). The staff consists of 42 medical doctors (thereof six professors and three assistant professors) and 75 radiographers/assistants (as of end of 2014). The Division of Neuroradiology is separate, but there is an intense cooperation between the institutions.

Besides providing all radiological imaging modalities, the Institute of Radiology performs a variety of interventional procedures, like imaging guided biopsies or angiographic therapies.

In cooperation with Siemens Healthcare, the Imaging Science Institute (ISI) is operated, integrating new developments in diagnostic imaging and novel IT-solutions into the clinical routine and the academic research (see own report).

Within different study groups and research projects, the clinical impact of various imaging procedures or novel technical developments is evaluated. Furthermore, experimental and preclinical studies are well-established in our scientific activities.

## Research

### Methods of dosage reduction and biological dosimetry in medical imaging

Project managers: Prof. Dr. M. Lell, Dr. M. May, PD Dr. W. Wüst, Dr. M. Brand, Prof. Dr. M. Uder

The majority of diagnostic and interventional imaging procedures in radiology are associated with exposure to ionizing radiation. CT is the major contributor to overall medical x-ray exposition. Double-strand breaks (DSB) are among the most significant radiation induced DNA damages. DSB can be detected by using an immunofluorescence microscopic technique. This sensitive detection method is based on the phosphorylation of the histone variant H2AX after DSB formation and staining with specific antibodies. Recent studies have shown a strong correlation between DSB levels and the dose deposed in blood lymphocytes of patients.

Different strategies are followed with the aim to reduce dose while maintaining diagnostic image quality. Current projects include high-pitch scanning, automated anatomy based tube voltage/tube current adaption, as well as organ based tube current adaption. Monte-Carlo-simulations provide volume data of dose distribution that allow for risk evaluation and analysis of dose reduction techniques. The influence of dose reducing approaches (e.g. risk organ based current modulation or lens protection tools) on the biological dose is investigated in patients and in biological phantom models as well. Furthermore, the potential protective effect of antioxidants/radical binding substances could be proven in vitro and in vivo. There will be further investigations on this topic.

### Functional and metabolic MRI

Project managers: Prof. Dr. M. Uder, Prof. Dr. R. Janka, Dr. M. Hammon, Prof. Dr. A. Cavallaro

With sodium MRI, we are able to measure the sodium concentration in tissue non-invasively. Research focuses lie on its further technical development, its absolute calibration, and the evaluation of different physiologic and pathophysiologic conditions.

Diffusion weighted imaging (DWI) visualizes the diffusion of free water molecules in tissue. The physiological amount of diffusion is disturbed in tissue with higher cell density particularly in tumors. The use of DWI develops continuously adding pivotal information as third pillar of MR imaging besides morphology and contrast enhancement characteristics.

In MRI, perfusion measurements without the use of contrast material are possible. For that purpose, the inflowing (arterial) spins are labeled magnetically and their concentration in the organ of interest can be measured as signal intensity. Our research focuses on determining renal perfusion.

### Interventional radiology

Project managers: Prof. Dr. M. Uder, Dr. A. Schmid, Prof. Dr. M. Lell, Prof. Dr. R. Janka

Clinical studies are performed in cooperation with the Department of Surgery (Prof. Dr. Dr. h.c. W. Hohenberger), the Division of Vascular Surgery (Prof. Dr. W. Lang), the Department of Medicine 4 (Prof. Dr. K.U. Eckardt), the Divison of Nephropathology (Prof. Dr. K. Amann), and the Departments of Medicine 1 (Prof. Dr. M.F. Neurath) and Nuclear Medicine (Prof. Dr. T. Kuwert).

Research foci include the establishment of endovascular radiofrequency ablation of sympathetic nerve fibres in renal arteries of patients with resistant hypertension and of selective internal radiotherapy and CT-guided tumor ablation techniques (irreversible electroporation, radiofrequency, and microwave). In patients with contraindication to the standard percutaneous biopsy of kidney transplants, an alternative transvenous biopsy procedure via a transfemoral approach is established.

### Cardiovascular imaging

Project managers: Prof. Dr. M. Lell, Prof. Dr. R. Janka, Dr. M. May, Dr. M. Scharf, PD Dr. W. Wüst

Close cooperation exists with the Department of Medicine 2 (Prof. Dr. S. Achenbach), the Institute of Medical Physics (Prof. Dr. W. Kemmler), the Department of Pediatrics and Adolescent Medicine, and the Divisions of Pediatric Cardiology (Prof. Dr. S. Dittrich) and Pediatric Cardiac Surgery (Prof. Dr. R. Cesnjevar).

Studies are performed to evaluate CT and MR for morphological and functional imaging of apparent coronary artery disease and to evaluate the potential of coronary CT-angiography in early diagnosis of coronary artery sclerosis in line with the "Excellenzclusteriniative", project BD-02. Furthermore, longitudinal studies to assess physiological myocardial adaptation in recreational and professional athletes using MRI and to diagnose congenital heart disease with CT and MRI are conducted.

### Breast imaging and gynecological radiology

Project managers: Prof. Dr. R. Schulz-Wendtland, PD Dr. E. Wenkel

In the breast imaging group, new methods for digital mammography are developed in cooperation with different medical systems manufacturers. On the basis of substantial experimental and clinical studies, their work includes development, implementation, and comparison of different digital mammography and ultrasound systems, including tomosynthesis, 3D and CAD (fusion- and hybridsystems). In addition, detection and volumetric analysis of tumors by mammography, (automated) ultrasound and the further characterization of breast masses by sonographic elastography are under investigation. Another main focus lies in breast MRI and the development of new MRI sequences for better differentiation between malignant and benign breast disease at 1.5T, 3T and in cooperation with the unit of experimental imaging at 7T. The research group is currently participating in the 'Spitzencluster' projects of the Medical Valley EMN BD-04 and BD-14.

### Information technology in radiology

Project managers: Prof. Dr. A. Cavallaro, Dr. P. Schlechtweg, Dr. F. Kammerer

Aims of this group in radiology include the development of new, intelligent medical databases (Medico project under the auspices of the Federal Ministry of Economics and Technology). Also, studies concerning automated segmentation, lesion detection, and characterization as well as the evaluation of mobile devices in radiology (e.g. Apple iPad) are performed.

### Experimental radiology and small animal imaging

Project manager: Prof. Dr. T. Bäuerle

Dedicated preclinical scanners are available for the imaging modalities MRT, CT, PET and SPECT for in and ex vivo studies. Focus of this research group is the establishment and optimization of innovative multimodal imaging techniques. Thereby information on the molecular, functional, and morphologic level are acquired non-invasively and correlated with the underlying pathology or pathophysiology. Examples include the investigation of experimental bone metastases, murine inflammation models (arthritis, asthma and colitis), and surgically removed tissue (hippocampi). Major aim is the translation of these methods into clinical application.

## Teaching

Besides the university 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. For students of Medicine, we always offer the possibility to 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 the degree programs of the Faculty of Medicine, including Medical Process Management and Molecular Medicine as well as as Medical Technology within the Faculty of Engineering.

### Selected Publications


Schmid A, Jacobi J, Kuefner MA, Lell M, Wuest W, Mayer-Kadner I, Benz K, Schmid M, Amann K, Uder M. Transvenous renal transplant biopsy via a transfemoral approach. Am J Transplant 2013, 13(5): 1262-71

Schwab SA, Kuefner MA, Adamietz B, Engelhard K, Keck B, Kunath F, Wach S, Wullich B, Uder M, Engehausen DG. MRI-guided core biopsy of the prostate in the supine position--introduction of a simplified technique using large-bore magnet systems. Eur Radiol 2013, 23(5): 1415-9

Schwab SA, Brand M, Schlude IK, Wuest W, Meier-Meitinger M, Distel L, Schulz-Wendtland R, Uder M, Kuefner MA. X-ray induced formation of γ-H2AX foci after full-field digital mammography and digital breast-tomosynthesis. PLoS One 2013, 8(7): e70660

Kopp C, Linz P, Dahlmann A, Hammon M, Jantsch J, Müller DN, Schmieder RE, Cavallaro A, Eckardt KU, Uder M, Luft FC, Titze J. 23Na magnetic resonance imaging-determined tissue sodium in healthy subjects and hypertensive patients. Hypertension 2013, 61: 635-640

Baccelli I, Schneeweiss A, Sinn P, Stenzinger A, Riethdorf S, Schillert A, Vogel V, Klein C, Bäuerle T, Wallwiener M, Höfner T, Sprick M, Scharpff M, Marmé F, Pantel K, Weichert W, Trumpp A. Identification of a population of blood circulating tumor cells from breast cancer patients that initiates metastasis in a xenograft assay. Nature Biotechnol 2013, 31: 539-544

Janka R, Hammon M, Geppert C, Nothhelfer A, Uder M, Wenkel E. Diffusion-weighted MR imaging of benign and malignant breast lesions before and after contrast enhancement. Röfo 2014, 186(2): 130-5


### International Cooperations

Prof. J. Titze, Vanderbilt University, Nashville: USA

Prof. W. Fahl, University of Wisconsin-Madison: USA

Prof. A. Bogdanov, University of Massachusetts Medical School: USA

Prof. D. Enzmann, University of California UCLA, Los Angeles: USA

### Meetings and International Training Courses

19. – 21.04.2013: Internationaler Fortbildungskurs Moderne Mammadiagnostik und -therapie, Erlangen

20. – 22.06.2013: MR Compact, Bamberg

14. – 15.09.2013: Mammasonokurs, Erlangen

28. – 30.10.2013: Molekulare Bildgebung 2013, Heidelberg

21. – 23.03.2014: Internationaler Fortbildungskurs Moderne Mammadiagnostik und -therapie, Erlangen

03. – 05.07.2014: MR Compact, Bamberg

27. – 28.09.2014: Mammasonokurs, Erlangen

### Research Equipment

Bruker, Clin Scan

Lorad, Selenia Dimensions Siemens, Artis mit zeego

Siemens, Inveon

Siemens, Magnetom Aera

Siemens, Magnetom Verio

Siemens, Mammomat Inspiration

Siemens, Somatom Definiton AS+

Siemens, Somatom Force

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**Research Focus**

- Clinical and experimental validation of flat-panel volume CT
- Multimodal imaging of cerebrovascular diseases
- Preoperative comprehensive imaging of epilepsy
- Functional and metabolic MR-imaging
- Holistic assessment of optical tract in glaucoma patients using diffusion tensor imaging
- Standardization of acquisition and post-processing MRI perfusion techniques (SAPP)
- Experimental neuroradiology – multimodal imaging in glioma and validation of new interventional therapies
- Simulation of hemodynamics and fluid dynamics in cerebral aneurysms

## Structure of the Division

The Division of Neuroradiology performs the neuroradiological analyses for patients of the UK Erlangen and for many patients referred from external hospitals. A special focus is the endovascular therapy of neurovascular diseases, such as acute stroke, aneurysms, stenosis of neck and brain vessels, arteriovenous malformations, and the minimal-invasive therapy of spinal pain syndromes. In the Division of Neuroradiology, a total of 42 staff members is employed. Research is performed by twelve medical doctors – six have a postdoctoral lecture qualification -, two biologists, one physicist, 16 medical technical assistants, and two study nurses.

## Research

### Clinical and experimental validation of flat-panel volume CT

The project is part of the Leading Edge Cluster Medical Valley, Network "Imaging". In cooperation with the Institute of Medical Physics, Siemens Healthcare, and the Computer Science Department 5/Pattern Recognition Lab (Faculty of Engineering), we evaluate and further develop intravenous and intraarterial flat-panel volume CT, angiographic techniques, and post-processing 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 3D visualizations in stroke patients.

### Multimodal imaging of cerebrovascular diseases

In cooperation with the Department of Neurology, we participate in several acute stroke studies. Using multimodal MR 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. Hereby, a main focus is the MR-derived patient selection for mechanical thrombectomy. Another clinical and scientific focus is the evaluation and validation of mechanical devices for revascularization strategies in acute cerebral stroke.

### Preoperative comprehensive imaging of epilepsy

In cooperation with the Epilepsy Center (Department of Neurology), we evaluate different multimodal imaging strategies in the preoperative workup of patients with focal seizures refractory for the best medical treatment. A major focus is put on high-resolution morphologic and functional MR imaging, i.e. MR spectroscopy, diffusion tensor imaging, functional MRI, perfusion- and diffusion-weighted MRI, and MR volumetry/voxel-based morphometry. Additionally, a dedicated GABA-specific MR spectroscopy sequence is used to evaluate different antiepileptic therapies.

### Functional and metabolic MR-imaging

There are several ongoing research projects in cooperation with different departments and institutes (i.e. Department of Psychiatry and Psychotherapy, Division of Child and Adolescent Mental Health, Division of Psychosomatics and Psychotherapy, Department of Medicine 3 – Rheumatology and Immunology, Department of Neurology, Institute of Physiology and Pathophysiology, Institute of Experimental and Clinical Pharmacology and Toxicology (all Faculty of Medicine), Institute of Marketing (Faculty of Business, Economics, and Law)) involving functional and metabolic MR-imaging (e.g. patients with major depressive disorders, anxiety- and eating disorders, chronic pain syndromes, and rheumatoid arthritis).

### Holistic assessment of optical tract in glaucoma patients using diffusion tensor imaging

In cooperation with the Department of Ophthalmology and Computer Science Department 5/Pattern Recognition Lab (Faculty of Engineering), we evaluate diffusion tensor imaging (DTI) using 3 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, first results indicate that DTI can distinguish at an early stage between different forms of glaucoma that require diverse treatment.

### Standardization of acquisition and post-processing MRI perfusion techniques (SAPP)

Broad clinical application of cerebral MR perfusion is limited due to heterogeneous MR protocols used in the investigations published up to date and due to limited size of study collectives. Therefore an international, prospective, blinded crossover multicenter trial lead by the Division of Neuroradiology was designed in cooperation with Bayer AG und four international centers (Mailand/Italy, Upsala/Sweden, Ontario/Canada, and Los Angeles/USA). In a first step, the research team developed a standardized MR-perfusion protocol. As next step, a large database will be generated based on sequence and contrast media parameters. Collected data will be investigated by means of technical and radiological parameters and clinical outcome.

### Experimental neuroradiology – multimodal imaging in glioma and validation of new interventional therapies

In cooperation with the Department of Neurosurgery, the Preclinical Imaging Platform Erlangen (PIPE; Institute of Radiology), and the Department of Nuclear Medicine, we evaluate multimodal imaging and new therapy strategies in experimental brain gliomas, using micro-CT, high-field MRI, and micro-PET. Additionally, using an elastase-induced and a surgical aneu-

rysm model, we evaluate different imaging techniques such as flat-panel volume CT, conventional CT, MRI, and angiography as well as new materials and techniques for endovascular treatment and follow-up.

### Simulation of hemodynamics and fluid dynamics in cerebral aneurysms

In cooperation with the Computer Science Department 5/Pattern Recognition Lab (Faculty of Engineering), Siemens Healthcare, and the Institute of Fluid Mechanics (Faculty of Engineering), we evaluate the hemodynamic and fluid dynamics in cerebral aneurysms and malformations. A special focus is put on the effects of different endovascular therapies using different endovascular microimplants, such as stents and coils. In the medium-term, we intend to develop and clinically implement a software-platform used by endovascular radiologists.

## Teaching

The Division of Neuroradiology is involved in training medical students. We offer a variety of lectures and practical courses, partially in cooperation with the Departments of Neurology, Neurosurgery, Ophthalmology, Psychiatry and Psychotherapy, the Institute of Radiology (all Faculty of Medicine), Institutes of Computer Science, Medical Engineering (Faculty of Engineering). In addition, we participate in lectures of neuroanatomy and neuroendocrinology. We furthermore train physicians (in training) in neuroradiology and general radiology and contribute to the vocational training program for radiological technicians.

### Selected Publications


Struffert T, Ott S, Kowarschik M, Bender F, Adamek E, Engelhorn T, Gölitz P, Lang S, Strother CM, Dörfler A. Measurement of quantifiable parameters by time-density curves in the elastase-induced aneurysm model: first results in the comparison of a flow diverter and a conventional aneurysm stent. Eur Radiol 2013, 23(2): 521-7

Gölitz P, Struffert T, Lücking H, Rösch J, Knossalla F, Ganslandt O, Deuerling-Zheng Y, Dörfler A. Parametric color coding of digital subtraction angiography in the evaluation of carotid cavernous fistulas. Clin Neuroradiol 2013, 23(2): 113-20

Saake M, Breuer L, Goelitz P, Ott S, Struffert T, Dörfler A. Flat detector computed tomography angiography with intravenous contrast application: feasibility for visualization of cerebral arterial vasculature. J Neuroimaging 2013, 23(3): 414-20

Sehm T, Fan Z, Weiss R, Schwarz M, Engelhorn T, Hore N, Dörfler A, BuchfelderM, Eyüpoglu IY, Savaskan NE. The impact of dietary isoflavonoids on malignant brain tumors. Cancer Med 2014, 3(4): 865-77

Schmidt MA, Mennecke A, Michelson G, Dörfler A, Engelhorn T. DTI analysis in patients with primary open-angle glaucoma: impact of registration on Voxel-Wise statistics. PLoS One 2014, 9(6): e99344

Struffert T, Hauer M, Banckwitz R, Köhler C, Royalty K, Dörfler A. Effective dose to patient measurements in flat-detector and multislice computed tomography: a comparison of applications in neuroradiology. Eur Radiol 2014, 24(6): 1257-65


### International Cooperations

Prof. C. Strother, University of Wisconsin, Madison: USA

Dr. A. Bose, Lenox Hill Hospital New York: USA

Prof. Dr. I. Wanke, Prof. Dr. D. Rüfenacht, Neuroradiologie Hirslanden, Zürich: Switzerland

Prof. Dr. A. El-Rafei, Ain Shams University, Cairo: Egypt

Prof. Dr. M. Essig, University of Manitoba, Winnipeg: Canada

### Meetings and International Training Courses

01. – 02.03.2013: Workshop "Advanced Neuro-MRI", Erlangen

06. – 07.03.2013: Workshop "Innovations in Interventional Neuroradiology", Erlangen

09. – 10.04.2013: Workshop "Zerebrale Aneurysmatherapie", Erlangen

29.06.2013: Kursus "Update Neuroradiologie", Update Neurologie 2013, Karlsruhe

03. – 04.07.2013: Workshop "Innovations in Interventional Neuroradiology", Erlangen

23. – 24.10.2013: Workshop "Advanced Neuro-MRI", Erlangen

24. – 25.10.2013: Workshop "Innovations in Interventional Neuroradiology", Erlangen

06. – 07.11.2013: Workshop "Zerebrale Aneurysmatherapie", Erlangen

21. – 22.02.2014: Workshop "Advanced Neuro-MRI", Erlangen

25. – 26.03.2014: Workshop "Innovations in Interventional Neuroradiology", Erlangen

13. – 14.05.2014: Workshop "Zerebrale Aneurysmatherapie", Erlangen

03.12.2014: Kursus "Neuroradiologie", Update Neurologie und Psychiatrie, Düsseldorf

### Research Equipment

Siemens, 3 Tesla Magnetom TimTrio MRI

Siemens, 1.5 Tesla Magnetom Aera MRI

Siemens, Somatom Definition AS+; 128 multidetector CT

Siemens, Axiom Artis dBA; biplane Flat panel Angiography with integrated CT option

Siemens, Siemens Axiom Artis zeego; robot-mounted monoplane Flat panel Angiography with integrated CT option (OP-Standard)

# Medicine

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## Aims and Structure

In the winter term 2013/2014, 2,366 students were enrolled in the degree program of Medicine (among them 190 students in the 1st term) and in the summer term 2014 2,448 students studied Medicine at the FAU (among them 189 students in the 1st term). The percentage of women studying Medicine decreased as compared to the winter term 2012/2013 by 1.3 %. In the winter term 2013/2014, 59.7 % of the enrolled students were female and in the summer term 2014, there were 59.1 % female students.
According to statistics of the FAU, 6.7 % of the students enrolled in the degree program Medicine were foreigners (winter term 2013/2014); in the summer term 2014, the percentage of foreigners studying Medicine in Erlangen was 7.1 %.
Applicants for this degree program are chosen according to the criteria of the "Stiftung für Hochschulzulassung" (foundation for higher education admission, the successor of ZVS) through the corresponding online platform. Applicants for the degree program Medicine are able to improve their chances of receiving a place at the FAU by participating in the so-called "Test für medizinische Studiengänge" (test for medical degree programs). Taking the test is, however, optional. Applicants who decide to take the test get a chance to improve their grade of their higher education entrance qualification (Abitur).

## Online-Evaluation

Each term, courses offered within the degree program are evaluated online by the students with the help of the online evaluation platform EvaSys. The results of this evaluation are presented by the Dean for Student Affairs in the faculty council where they are discussed once per term. A major part of the state funds is distributed in the UK Erlangen according to the results of the online evaluation. Each term the students vote for the best lecturers and monetary sums are awarded to the department or institute to which the winner belongs. It is noteworthy that teaching awards are financed by the achievement-oriented funds allocation (LOM). Departments and institutions whose instructors perform best in the online evaluation receive grants for good teaching performance. The best three instructors of the clinical part of the degree program (terms 5 – 10) Medicine receive grants of 5,000, 3,000, and 2,000 EUR, respectively. For the degree programs Dentistry, Molecular Medicine, and Medical Process Management, the best instructors receive 5,000 EUR each. Instructors in the pre-clinical or theoretical part of the degree program (term 1 – 4) receive certificates only as grants cannot be awarded due to cameralistic accountancy they belong to. Additionally, the departments that offer the top ten classes according to the student's evaluations are awarded a total of 165,000 EUR. A class can, however, only be taken into account for a grant if at least 20 % of the students have participated in its evaluation.

## Skills Lab PERLE

The Skills Lab PERLE offers students an opportunity to practice medical examination skills with the help of well-trained student-tutors and doctors. Students can practice about 30 different skills, e.g. auscultation, catheterization, tak - ing blood with the help of artificial arm-models, lumbar puncture, suturing, examination of nervous system as well as of eye and ear, preparation for clinical electives (Famulaturen) and the practical year (Praktisches Jahr). Skills Lab PERLE, fully funded by student fees, is a visible enrichment of the medical education in Erlangen. Courses can be attended by all students during the term. Additionally, PERLE offers special courses during the lecture free time. In addition, practicing in PERLE within the frameworks of the Introduction into Clinical Medicine (EKM) course is a part of the Medicine curriculum.

## Medical State Examination

In the study year 2013/14, the Medicine students in Erlangen achieved very good results in the First Medical State Examination (first part of the physician exam). According to the statistics of the German Institute for Medical and Pharmaceutical Examination Questions (IMPP), the examination results of the Medicine students in Erlangen have been ranking among the top results of the medical departments in Germany for many years. In the winter term 2014/15, the Medicine students have achieved the best results in Bavaria in the Second State Examination and have reached a remarkable fourth place in the general ranking of Germany.

# Dentistry

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## Aims and Structure

Approximately 110 students are educated each year in the degree program Dentistry, despite the fact that facilities within the departments of dentistry were originally designed to accommodate a maximum enrollment of 100 students. The overall amount of time dedicated to curriculum teaching and examinations at dentistry school is quite considerable, given the extensive role played by practical training, as compared to what is the case with students taught in Medicine. New licensing regulations for the practice of dentistry have been formulated, but are not likely to go into effect for a foreseeable future. The fact that new licensing regulations to practice medicine are already in effect has resulted in a clear separation of the training provided in Dentistry from the training provided in Medicine.

As in the preclinical/theoretical phase of the degree program Medicine, the calculation of admission figures for the departments of dentistry is based on a ratio of students to clinical academic teaching staff. These parameters are considerably less favorable for dentistry students than for medical students (for instance, in terms of the amount of supervision and support provided to students during clinical internships where they are required to treat patients, there is an average ratio of six students per academic staff member in the departments of dentistry as opposed to somewhere between three and six students per academic staff member in the degree program Medicine; academic credit factors for internships are 0.3 for dentistry students as opposed to 0.5 for medical students).

The number of students admitted by the university has been constant for the last years, there is no increase resulting from lawsuits. Under the conditions offered by LOM, a performance-based funding scheme, finances for teaching the curriculum for the degree program Dentistry have improved. Under this scheme the financing of staff positions, whether academic or non-academic (the latter also essential to ensure a good training environment), can be guaranteed on a long-term basis. Teaching evaluation is part and parcel of the training program at the departments of dentistry. The results are used in the process of updating and restructuring our curriculum with a view of achieving steady improvement in the quality of teaching.

The departments of dentistry are equipped with high-quality technical systems in sufficient numbers so that they have no trouble satisfying the demands and needs that arise in connection with dentistry training. National and international quality comparisons show that our standards are very good. All the necessary prerequisites are given for our students to receive modern, clinically oriented training in the field of dentistry.

# Molecular Medicine

**Speaker**
Prof. Dr. rer. nat. Michael Wegner

**Coordination**
Dr. rer. nat. Inga Ebermann

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## Aims and Structure

The consecutive bachelor/master degree program Molecular Medicine combines the subjects of experimental medicine and the approaches of molecular biology, biochemistry, and genomics. This degree program acknowledges the fact that boundaries which traditionally separated biomedical disciplines have long lost their meaning. The Faculty of Medicine offers a future-oriented degree program for medical scientists interested in research careers in industry, academics, and administration. Nationwide, this degree program Molecular Medicine is met by an extraordinary interest. Each academic year 37 students are admitted out of 800 – 1,000 applicants.

## Objectives

The advances in biomedical research continually change our knowledge and understanding of basic biological mechanisms and disease-induced alterations, reflected in new and improved therapies. The consecutive B.Sc./M.Sc. degree program Molecular Medicine addresses the necessity to teach both, medical and bioscientific contents. The interdisciplinary curriculum aims at preparing our students for the challenges of medical research and enables them to become independent researchers.
The B.Sc. degree program spans six terms in which a solid education in all basic disciplines of Molecular Medicine is achieved. The core curriculum in Molecular Medicine is mainly taught by preclinical and theoretical institutes and the NFZ. The first academic year focuses on the basic sciences that are taught by the Faculty of Sciences (physics, inorganic/physical/organic chemistry). The preclinical aspects are the focus of the second year, while pathology and experimental therapy conclude the curriculum in the last year. The B.Sc. degree program ends with a scientific thesis.
The main goal of the consecutive two year master degree program is to convey a deeper understanding of science by working with original publications and extended practical training.
Whereas the B.Sc. curriculum teaches the basics of single disciplines, the M.Sc. degree program focuses on interdisciplinary topics which are taught by the Institutes of Biochemistry, Physiology and Pathophysiology as well as the Departments of Neurology and Psychiatry and Psychotherapy, respectively. The Master degree program ends with a thesis of six month. Another focus of the theoretical part of the degree program is molecular imaging. This module represents another scientific strength of Erlangen, as it puts the degree program at the interdisciplinary junction between basic science and industrial application.
The first year students in Molecular Medicine are welcomed by an annual symposium, introducing them to the degree program and the Faculty of Medicine of the FAU. In recent years, these symposia have encountered an extraordinary interest among the new students. Moreover, students are offered support by an academic mentoring program. The mentors are recruited among the lecturers involved in the B.Sc. degree program, ensuring easy communication between students and the lecturing staff. The participation of student representatives in the study committee ensures the active involvement and participation of the students in the further development of the degree program.

## Applications, development of student numbers, and implementation of the degree program

Potential applicants are introduced to the degree program Molecular Medicine by the advisory service of the Faculty of Medicine, the central advisory service of the FAU, as well as by brochures and the internet homepage. At present, half of the students enrolled in Molecular Medicine are in-state students from Bavaria, while the other half originate from other German states or are international students. This situation demonstrates the nationwide attractiveness of our study program. Having asked students for their alternative choices in case they would not have been admitted to Molecular Medicine, most students listed medicine, biochemistry, or biotechnology.
Presently, more than 30 applicants compete for one admission slot in Molecular Medicine. For several years, the admission requirements for the degree program have been constantly at the highly selective grade point average of 1.4. Admission procedures follow federal and state regulations (Bayerische Hochschulzulassungsverordnung).
Accordingly, 90 % of admissions are based on the average grade point of the general qualification for university entrance (Abitur), while another 10 % of admissions are granted based on a waiting period. Following the guide lines from the Bologna declaration, the B.Sc./M.Sc. Molecular Medicine is characterized by close-meshed and course-related exams which are continuously documented in an electronic management system. In the Master degree program, the higher portion of practical courses allows an individualized curriculum. The first two months of the third M.Sc. term are intended as a "mobility window" to facilitate the integration of international internships and industrial placements.

## Perspectives

The degree program Molecular Medicine offers the opportunity to join a high-quality doctoral program at the FAU. Graduates may enroll in a doctoral program (Dr. rer. nat.) offered in collaboration with the Faculty of Sciences. The degree program Molecular Medicine enables its students to successfully contribute to scientific and practical work in medical research, laboratory diagnostics, and medical biotechnology. A variety of occupational fields in industry, private laboratory, and public institutions are available to the graduates of Molecular Medicine. Industrial employment options include research and development as well as production and quality control, marketing, or administration. Private laboratories, hospitals, and authorities depend on university graduates experienced in molecular diagnostics, DNA and protein diagnostics for medical and biotechnological applications.
The degree program Molecular Medicine has already proven its concepts through successful professional and academic careers of its graduates which currently have positions in national and international research institutions (e.g. assistant professor at Harvard Medical School) and in industry (e.g. Novartis or Roche). Graduates of the first generation are already holding professorships.

# Medical Process Management

**Speaker**
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## Aim of the degree program

About five million people are employed in the German healthcare system, with two third of them working as healthcare professionals in one of 30 different professions. Of the remaining employees who do not treat nor care for patients, there is still a substantial part that needs medical knowledge and good understanding of the healthcare system in the daily, professional life. The master's degree program Medical Process Management (MPM) conveys medical basics and health competencies, know-how of quality and process management, and advanced knowledge of information technologies in the healthcare system. Aims of the degree program are an elevated patient's benefit and increased added value in the patient-centered care with both, effective and efficient processes.

## Structure and contents

MPM is a non-consecutive M.Sc. degree program. It is designed as a full-time, attendance study program that comprises at least three terms plus the period for writing the master's thesis. The degree program starts in the winter term only. For successful completion of the degree program, 120 ETCS credit points must be obtained.
This degree program provides medical knowledge, deep proficiencies of the German healthcare sector, and the effects of different healthcare systems on people's health status. Beyond that, the curriculum offers broadly diversified insights into business process management and the information technology with regard to medical sciences as well as the healthcare sector. Additionally, fundamental questions are dealt with concerning evidence based medicine, quality and risk management, pharmaceutical business operations, hospital and supply management, strategic management, and psychology of communication. In this way, the degree program connects medicine and healthcare to business process management and information technology. Strengthening patient-orientation, improving the quality of medical care, and increasing efficiency in the healthcare sector are the topics that make up the curriculum's key focus.

## The situation of the students

In the first place, the master's degree program addresses applicants who hold an above-average bachelor's degree in computer sciences, engineering, economic, or social sciences. Beyond that, students with a related, appropriate background or work experience in the healthcare sector will be permitted. In the reporting period, 150 students applied each year for admission to the MPM degree program (80 % female). Half of the applicants were admitted. However, after initiation of the qualification assessment exam in summer 2014, the rate of students who accepted the university place rose from 40 % in 2013 to 65 % in 2014. This means that the sixth year contains 30 students, whereas the seventh year comprises 50 students. Besides the diversity of the lessons described above, we also focus on the students' needs. As the majority of the students work alongside the degree program, its length can be organized flexibly between three and six terms. Upon that, we established a four-days-week during the lecture periods in the first and third term and appropriate occupation is credited as study internship with up to 15 ECTS. Due to the different bachelor degrees of the students, we cope with the individual state of knowledge by offering four additional modules. With these, the students can substitute up to 20 ECTS of either redundant or less interesting lectures of the curriculum (75 ECTS). The master thesis (30 ECTS) can be conducted at one of the three faculties that are involved in the MPM degree program as well as in external institutions – with an additional supervisor of the university. Each year elects a female and male term speaker who represent the interests of the cohort and who have a seat in the study committee. The results of the lecture evaluation are presented to students and lecturers and are subsequently discussed to develop measures for optimizing the lessons.

## Profile and Perspectives

The master's degree program is characterized by its pronounced inter-professional interconnectedness of the lectures which guarantees the successful imparting of the necessary knowledge and skills. More than 100 professors, physicians, scientists, lecturers, and guest lecturers are engaged in about 30 lectures. Most of these people represent professions and disciplines of the healthcare supply: Medicine, care, engineering, administration, industry, and healthcare management industry. MPM is a "highly application-oriented" degree program – therefore the topics innovation, leadership, management, and change play a pivotal role. The competence to link the theoretical knowledge to practical experience can only be acquired in companies themselves during internships, study-related occupation, and the master thesis.
MPM is more than just a new master's degree program: It is an innovative approach to tackle the challenges faced by healthcare systems in industrialized countries. No other university in Germany offers a comparable program. The degree program is geared towards the growing demand the healthcare market displays for specialists with analytical expertise in medical issues. Among other things, graduates are capable to analyze, plan, implement, and evaluate processes which take place in an interinstitutional and interprofessional realm. They are thus qualified, for instance, to work as process managers in hospitals and surgeries, as case managers for health insurances, and as network managers for healthcare networks. Furthermore, graduates are able to work for companies belonging to the pharmaceutical and medical engineering industry. The same applies to consulting companies, IT manufacturers and healthcare management organizations. So far, graduates have consistently been able to quickly gain ground on the labor market, having found very good jobs in the healthcare system.

# Logopedics

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## Aims and Structure

With the adoption of the 'Gesetz zur Einführung einer Modellklausel in die Berufsgesetze der Hebammen, Logopäden, Physiotherapeuten und Ergotherapeuten' (act introducing a model degree program in the laws on the professions of midwives, speech and language therapists, physiotherapists and occupational therapists), the B.Sc. degree program Logopedics was established at FAU in the winter term 2011/2012. The degree program has been met with great interest nationwide. Out of 300 applicants, 16 students are admitted every year.
The main objective of the Bachelor's degree program Logopedics is to combine teaching, research and practical application. Academic teaching builds on current research which is essential for practical application. Practical application and research complement each other. Research findings are applied to meet the needs of everyday working life. Research leads to practical application while problems arising in practice provide direction for research. In this way, the independent logopedics research tradition is developed further.
The German law on the profession of speech and language therapists 'Gesetz über den Beruf des Logopäden' and the job training and examination regulations define the practical aspect of the degree program. One third of the course is devoted to practical training. The degree program focuses on therapy training and practical work which is reflected in the following modules:

- practical sessions where students observe and carry out therapy under supervision
- disorder-specific training
- patient-oriented training
- collaboration with partners
- placements.

The practical stages of the degree program will prepare students for a successful start in their careers as therapists and provide a basis for their continued professional development. The students learn how to cope with the demands of working life in a responsible manner. They are encouraged to embrace new challenges and evaluate them critically. To this end, students prepare therapy sessions for which they receive support from their teachers as part of their educational supervision. The therapy sessions are then analyzed together with other students and teachers. This process focuses on the questions as to how clinical and therapeutic skills can be acquired and how research findings can be used in speech and language therapy. Such a form of training is essential to obtain evidence-based practical skills.
The degree program Logopedics comprises two degrees:

- the professional title 'staatlich anerkannte/r Logopäde/Logopädin' (state-approved speech and language therapist) awarded upon successful completion of the state professional examination (staatliches Berufsexamen) in the sixth term,
- the B.Sc. in Logopedics awarded upon successful completion of the degree program, the Bachelor's thesis, and the colloquium.

The degree program received accreditation from the accreditation agency Agency for Quality Assurance (AQAS) in 2013.

## Objectives

This degree program aims at conveying the theoretical basis as well as professional expertise in diagnostics, therapy, and counseling in the area of speech and language therapy. It enables its students to treat their patients independently and with profound scientific knowledge. It is a full-time degree program that is completed after seven terms. Graduates are awarded a B.Sc. degree.

## Application Procedure

The general higher education entrance qualification (allgemeine Hochschulreife) / subject-specific university entrance qualification in social studies or health studies is required for admission to the degree program. Application procedures follow the 'Verordnung über die Zulassung zu den öffentlichen Berufsfachschulen für Logopädie' (regulation on admission to state vocational schools for speech therapists) of 19 December 2005. A preselection of applicants is conducted by drawing lots.

## Perspectives

Speech and language therapists diagnose and treat problems such as communication and swallowing disorders and counsel patients and their relatives. Within their field, speech and language therapists work independently and assume responsibility for their work.
Potential occupational areas for speech and language therapists are in the health care sector, e.g. in hospitals, rehabilitation centers, centers for speech therapy, their own practices, or as freelancers. Furthermore, they may find employment within the fields of teaching, science, or research. The regulations governing the profession will be amended after the end of the model period to acknowledge the B.Sc. and the professional title of state-certified speech and language therapist as equal qualifications.

*Lip strength measurement*

*Voice formation and training*

*Lecture (explaining the larynge with the help of a model)*

# Interdisciplinary Center for Clinical Research (IZKF)

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## Aims and Structure

The Interdisciplinary Center for Clinical Research (IZKF) is a central structure of research development at the Faculty of Medicine. Its mission is to improve the overall quality of clinical research at the Faculty of Medicine, to stimulate interdisciplinary research, to advance the careers of young scientists, and to foster the acquisition of extramural funds. It was established in 1996 under the major topic "Inflammatory Processes: Etiopathogenesis, Diagnostics, and Therapy". During the first eight years (1996-2004) it received regressive funding from the BMBF within the program "Health related research 2000". Since 2004 it has been fully funded by the Faculty of Medicine within the UK Erlangen and the FAU. The initial scientific focus on inflammation research could be further developed to also accommodate all other focal research areas and interdisciplinary fields of the Faculty without sacrificing this distinctive topic. This allows nearly all institutions of the Faculty of Medicine to file applications with IZKF. IZKF activities can be subdivided into three major areas:

### Research Grants

The IZKF offers research grants which cover a 30 month period and include one graduate student, one technician, and consumables. Project leaders are expected to have an active publication record and own external funding. Preliminary results should yield the promise of a successful transfer of the project into external funding after the three years term. Innovative and original ideas and concepts are especially valued; the same applies to the clinical relevance and interdisciplinary approaches. Starting in 2015, call for proposals will take place in a 2-year-period. From now on a higher funding for consumables can be provided.
If project leaders apply for external funding at the end of the project, funding for another six months is provided. Given the fact that IZKF funding starts at an early phase of a project, it can be considered as a high risk funding program. It is nevertheless reassuring that most of the projects are successful and thus likely to be transferred into extramural funding. In this context it seems noteworthy that nearly half of the project leaders raise more extramural funds than they receive intramurally by IZKF.
76 % out of 86 % of the 2010 approved projects submitted successfully a subsequent project proposal.
In addition, five projects from the project cohort of 2013 submitted proposals to external funding agencies that have already been approved.

### Core Facilities and Supporting Activities

Modern molecular technologies such as genomics, proteomics, and advanced molecular imaging require very expensive and sophisticated instrumentation and are methodologically very demanding. Core facilities or units are centralized platforms that offer access to these modern methods and technologies to a broad user spectrum. Core units also make sure that smaller groups and those with other methodological focus get access to these technologies. They also ensure that students get direct access to these modern developments. The IZKF offers an initial funding of core facilities covering up to five years. Supporting activities include the "Visiting Professor Program" and a biennial international scientific meeting.
Apart from the external funding, the publication output is of importance. Various parameters are used to evaluate the performance of the IZKF in advancing clinically oriented research at the Faculty of Medicine. Scientific publications and academic success of young scientists are the most obvious and straightforward parameters. Furthermore, patents, scientific prizes, and offers of professorships are relevant parameters. In 2013, the 47 running projects altogether published 60 original articles with a cumulative impact factor (IF) of 406.823. The high quality of many of these publications is reflected in eight publications with an IF > 10.

### Career Development

Support and development of young scientists has been a central goal of the IZKF since its inception. Two positions for junior research groups housed in the NFZ offer an attractive career development opportunity for outstanding young scientists with a training in medicine or natural sciences, a strong background, and reputation in one of the Faculties' main research fields. Over a period of up to six years, each junior research group receives funding for the group leader, one postdoctoral and one postgraduate scientist, one technical assistant, and consumables. The group of Prof. Dr. J. Titze works on "Immune system as regulator of volume and blood pressure" and the group of Prof. Dr. B. Winner on "Modeling neurodegenerative diseases using stem cells". A third group focused on the subject "Molecular Oncogenesis" is currently being established.
In addition, the IZKF supports six positions for a laboratory rotation and 18 MD-thesis scholarships. Since 2014, improved conditions are valid following the funding height of the DFG.
Since 2009 the IZKF in collaboration with the ELAN-Fond has offered starting grants to young postdoctoral physicians and scientists up to 35 years of age without previous significant external funding. Candidates should have a visible publication record and projects should be based on an original idea with first tangible results. Project aids include a position for a technician or a doctoral student and consumables for 2,5 years. After this time it is expected that successful projects submit an external grant application. To offer physicians an improved compatibility of their research activities and clinical requirements, the IZKF from now on provides an exemption up to twelve months full-time or 24 months part-time.

# Preclinical Experimental Animal Center (PETZ) at the Franz-Penzoldt-Center (FPZ)

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## Aims and Structure

The Preclinical Experimental Animal Center (PETZ) belongs to the Faculty of Medicine and is a facility at the Franz-Penzoldt-Center (FPZ) that serves as a state-of-the-art experimental animal facility for basic and preclinical research. The facility resources are primarily meant for users belonging to the Faculty of Medicine, but also offer state-of-the-art and appropriate animal housing with directly associated experimental facilities for other research groups and associations.
The Center is a research-oriented animal facility that provides for customers a modern infrastructure and specific-pathogen-free conditions for preclinical animal experiments. The center offers various research related services, e.g. import of transgenic mouse strains via embryo transfer as well as veterinary advice and supervision for surgical or toxicological studies on large or small animals. Already as early as the time of project application, the team of the PETZ provides competent references in all areas of the application processes and related questions regarding experimental strategy.
With its infrastructure, the PETZ supports effective and optimized science and enables translational medical research in a controlled, standardized environment most appropriate for each of the species. Our center represents a professional and reliable partner on the way from the scientific idea and the consecutive ways ultimately resulting in benefits for the human patients.

## Research

The superior goal of the PETZ is the continuous implementation of the principles of reduction, replacement, or refinement (3R's) in experimental research with animals as well as the responsibility of constant optimization of the housing conditions to the benefit of both, animal welfare and quality of scientific results. Central functions of the PETZ are:
– providing a responsible and ethical animal treatment in accordance with the local and national law authorities,
– optimizing and standardizing processes in animal housing,
– implementing a modern quality assurance,
– assuring continuous professional development of the scientific and technical personnel, providing state-of-the-art research facilities,
– establishing and providing core units especially in the area of animal phenotyping in order to assure an effective and standardized application in this highly specialized technical field.
The PETZ provides statutorily regulated areas of operation such as e.g. housing and experimental rooms that meet the safety levels for genetically modified organisms S1 and S2, and the biological safety levels (BSL) for infectious agents BSL I and BSL II. We take care that the experimental work within the facilities is carried out in accordance with the legal regulations of the German Infection Protection Act, Pharmaceuticals Act, Chemicals Act, and Medical Products Acts.
At the beginning of 2015 a variety of different research projects representing over 85 working groups are realized in the PETZ. These researchers originate from 43 institutes, academic chairs, or departments. The majority of these working groups belong to the Faculty of Medicine.

## Teaching

The PETZ team organizes qualifying professional development courses in laboratory animal science (e.g. courses according to FELASA B criteria), offers the opportunity to learn animal experimental techniques and functions as a training company (Ausbildungsbetrieb) for the recognized occupation requiring formal training "laboratory animal technician" which is certified by the chamber of industry and commerce (IHK). The Center is a competent venue for surgical trainings in students' education as well as in the professional development of experienced practitioners. It places a priority on being a family friendly institution and implements the principles of gender equality in its processes and management to help its staff achieve a work-life-balance.

# Center for Clinical Studies (CCS Erlangen)

**Speaker**
Prof. Dr. med. Dr. h.c. Wolfgang Rascher

**Managing Director**
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## Aims and Structure

In 2008, CCS Erlangen was founded as a service unit shared by the Faculty of Medicine of the FAU and the UK Erlangen. From an organizational point of view, it is affiliated with the UK Erlangen as one of its central facilities. Its tasks comprise:

1. provision of counseling and support to members of the Faculty of Medicine and staff of the UK Erlangen for the conception, planning, conduct, and analysis of clinical studies, taking into account the relevant legal and regulatory requirements;
2. support to the UK Erlangen for fulfilling the rights and duties of the sponsor in clinical studies;
3. administration of the insurance for participants in clinical studies;
4. administration of the clinical studies database of the Faculty of Medicine;
5. organization of educational events on all aspects of clinical studies.

Since its inception, CCS Erlangen participated in about 350 clinical research projects of members of the Faculty of Medicine and staff of the UK Erlangen. These comprise several multinational clinical studies in Europe and the USA as well as three projects involving the first administration to humans of novel medicinal products (first-in-man trials).

CCS Erlangen divides into the areas of study management and clinical monitoring, quality management, and pharmacovigilance.

## Counseling and Support for Clinical Studies

### Counseling

Each year, CCS Erlangen provides a broad range of counseling services, especially in the preparatory phase of clinical studies. The main focus is on so-called investigator-initiated trials (IIT), planned and conducted by members of the Faculty of Medicine and staff of the UK Erlangen. CCS Erlangen evaluates the feasibility of the research project from an economic and organizational perspective as well as its adherence to the relevant legal and regulatory requirements. All counseling services are provided free of charge.

### Study management and clinical monitoring

Prior to clinical study start, CCS Erlangen offers various services, ranging from the generation of the study protocol to obtaining approval from competent authorities and endorsement of the study protocol by ethics committees. This includes multicenter and multinational clinical research projects.

During the conduct of the clinical study, CCS Erlangen provides clinical monitoring, if requested by the sponsor or the project leader.

### Quality management

Institutions which assume sponsor responsibilities in clinical studies are required to follow standard operating procedures (SOP). The section quality management within CCS Erlangen helps identify and develop the relevant SOP.

If requested by the sponsor or the project leader, CCS Erlangen performs audits of study sites or other institutions involved in a clinical study to assess their compliance with regulatory requirements. On request, CCS Erlangen provides advice and guidance for inspections by the regulatory authorities.

### Pharmacovigilance

For clinical studies subject to AMG (Medicinal Products Act) or MPG (Medical Devices Act) and sponsored by the UK Erlangen, CCS Erlangen ensures the documentation and timely notification of serious adverse events according to legal and regulatory requirements. For this task, CCS Erlangen uses a dedicated and certified database.

### Administration of the insurance for participants in clinical studies

CCS Erlangen administers the insurance for participants in clinical studies initiated by members of the Faculty of Medicine and staff of the UK Erlangen. This comprises obtaining insurance offers and accompanying the project until its conclusion.

## Research

### Clinical studies database of the Faculty of Medicine

The clinical studies database serves to present the clinical research efforts of the Faculty of Medicine. It contains prospective interventional clinical studies which may be listed according to predefined criteria, providing a survey of the clinical research activities.

### Education

At the request of the Faculty of Medicine, CCS Erlangen in collaboration with the Institute of Clinical Pharmacology and Clinical Toxicology has currently conducted more than 30 educational events for investigators, coordinating investigators, and staff involved in clinical studies. Along with conveying the relevant legal and regulatory requirements, the sessions focus on practical aspects and recommendations which may have a major impact on the feasibility and timely recruitment of clinical studies. Currently more than 600 physicians from the UK Erlangen and the associated academic teaching hospitals have attended the courses.

# Comprehensive Cancer Center Erlangen-EMN

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## Aims and Structure

The Comprehensive Cancer Center Erlangen – European Metropolitan Region Nürnberg (CCC ER-EMN) is an interdisciplinary center of excellence established to coordinate medical care, research, and teaching. For patients, relatives, physicians, and scientific researchers, the CCC ER-EMN is the central contact for all questions connected to cancer diseases.
The center organizes further education and training courses on topics in oncology and coordinates research projects. In addition, the CCC ER-EMN runs a free tumor consultancy service for patients and their relatives.
Nationwide, there are currently only 13 institutions as leading centers for cancer research and treatment, sponsored by German Cancer Aid.
The CCC ER-EMN was founded in December 2007 as the Erlangen University Cancer Center by members of staff at the UK Erlangen and the Faculty of Medicine at the FAU. In January 2013, a cooperation agreement with Bamberg Hospital (Sozialstiftung Bamberg) and Bayreuth Hospital (Klinikum Bayreuth, GmbH) was established. All three sites have oncological centers certified in accordance with the German Cancer Society criteria.
Under the aegis of the CCC ER-EMN, there is a total of 13 certified organ cancer centers and 25 interdisciplinary tumor conferences which are responsible for optimized patient care and multidisciplinary development of clinical pathways according to the most up-to-date standards.

### Interdisciplinary treatment based on a clear plan

At the CCC ER-EMN institutions, all types of cancer are diagnosed and treated as gently and effectively as possible using the most advanced modern technologies. Specially trained nurses and psychologists are there to assist patients during the treatment phase. Due to the high level of research activity at the CCC ER-EMN, patients have access to innovative therapeutic approaches.
All treatment decisions are taken jointly by the experts in each specialty, at meetings known as "tumor conferences."

### Aims of the CCC ER-EMN

– Interdisciplinary and inter-organizational optimization of care for oncology patients;
– Interdisciplinary and inter-organizational support for cancer research at the level of clinical research, epidemiological research, translational research, and basic research;
– Support for regional collaboration in the field of tumor diagnosis, treatment, and follow-up care together with other hospitals — particularly university teaching hospitals, specialist oncology practices, specialist physicians and family doctors, hospices, and rehabilitation facilities;
– Support for interdisciplinary and inter-organizational teaching in oncology;
– Recruitment of highly talented junior staff for clinical care and research.

## Research

If possible, patients are treated in the framework of clinical studies. This means that they directly benefit from clinical progress and can be treated in accordance with the highest safety standards in the context of clinical trials. Links with the Center for Clinical Studies (CCS) at UK Erlangen and with the study coordination offices at the cooperating hospitals are available for this purpose.
Patient care and clinical research at UK Erlangen are supported by a structured IT approach. This consists mainly of the electronic patient file system Soarian™ and the data warehouse tool Cognos™. Supplementary to these IT systems, there are commercial IT solutions for cancer registry, trial management, and biobanking. Data for cancer patients at CCC ER-EMN are documented in two clinical cancer registries in the Gießener Tumordokumentationssystem (GTDS). This enables scientists in the field of cancer research to analyze disease courses and investigate and develop improved treatments. Research on biomaterials forms the basis for new discoveries. For this purpose, a biomaterials bank has been set up for tumor tissue, tissue from healthy controls, and also body fluids (e.g. pleural effusions, urine, etc.) as well as DNA from tumor patients and control individuals. These biomaterials are used with the consent of the patients involved and enable the development of investigational methods at the highest scientific standards to pursue major research goals — speeding up medical progress with new discoveries and the development of new forms of treatment. The core units "tissue based automated RNA and DNA diagnostics" and "cell line construction" have been respectively will be set up at the CCC ER-EMN.
There are currently major translational research groups for six different tumor entities at the CCC ER- EMN: breast cancer, leukemia and lymphoma, lung cancer, melanoma, renal cell cancer, and colorectal cancer. Approaches for other tumor entities are also being pursued.

## Teaching

The center offers physicians, private medical practices, and hospitals the opportunity to receive further training in the various fields involved in oncology and to consult with experts in difficult treatment cases. In addition, the CCC ER-EMN provides a series of lectures for physicians and scientists in the field of cancer research as well as a further training program in oncology for family practitioners.

# Emil-Fischer-Center (EFC)

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## Aims and Structure

The Emil Fischer Center (EFC) aims at promoting and implementing research and educational projects involving pharmaceutical sciences, food chemistry, and molecular medicine. This interdisciplinary center constitutes an association of eight chairs from the Faculty of Medicine and the Faculty of Science. The EFC includes the full and associate professors of the Institute of Biochemistry and the Institute of Experimental and Clinical Pharmacology and Toxicology (Faculty of Medicine) and of the chairs of Pharmaceutical Chemistry, Pharmaceutical Technology, Food Chemistry, and Bioinorganic Chemistry (Faculty of Science).
The EFC promotes collaborative research between its members and operates the core unit "Bioanalytics" as well as several basic technical facilities. The EFC represents its members vis-à-vis third parties, coordinates interdisciplinary fund-raising activities and serves as a platform for cooperation with partners from the pharmaceutical and food industries. The interdisciplin - ary training of post-graduates is accomplished by the associated Emil-Fischer-Graduate School (EFS). At the end of 2014, the EFC was evaluated positively by the University and was granted increased support.

## Research and Teaching

The EFC studies biomedically relevant target proteins which are controlled by biologically active substances including drugs, second messengers, and food constituents. The elucidation of ligand-target protein interactions enables the rational design of new drugs. In addition, the signal transduction mechanism of target proteins, their physiological and pathophysiological role in the mammalian organism and modifications by posttranslational mechanisms are studied. By combining the individual expertise of the EFC members, several interdisciplinary research initiatives have been successfully established. Research and teaching activities at the EFC are supported by the Emerging Fields Initiative of the FAU, the SFB 796, the GK 1071 and 1910, the BMBF, the European Union, and the Elite Network of Bavaria.
One aim of the EFC is the coordination of interdisciplinary teaching activities between pharmacy, food chemistry, and molecular medicine. A main focus is the organization and development of the "Emil Fischer Graduate Program in Pharmaceutical Sciences and Molecular Medicine (EFS)". This program was established several months after foundation of the EFC and includes currently 54 graduate students. In addition, the EFC provides the platform for the EFS lecture series.
Instrumental analysis at the EFC is based on the following major equipment:
– three LC-ion trap-MS,
– two LC-triple quadrupol-MS/MS,
– one MALDI-TOF-MS,
– one SELDI-TOF-MS,
– two NMR 360 and 600 MHz,
– one CD spectrometer,
– one confocal laser microscope (Zeiss LSM 5),
– NMR for small animals (4,7 Tesla),
– equipment for microinjection and electroporation,
– real-time PCR devices,
– various electrophysiological setups, and
– a computer cluster.

# Erlangen Center for Infection Research (ECI)

**Speaker**
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(Faculty of Sciences)

**Scientific Coordinator**
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## Aims and Structure

The Erlangen Center for Infection Research (ECI) was founded as an interdisciplinary center of the FAU on July 28, 2010. The ECI is a consortium of more than 30 professors and lecturers and their research groups which belong to the Faculty of Medicine (MF), the Department of Biology, the Department of Chemistry and Pharmacy, or the Department of Chemistry and Bioengineering (all Faculty of Sciences, NF). Infectious disease research is one of the key research areas at the FAU and the UK Erlangen.
The ECI focuses on the analysis of the pathogenesis of infections in order to improve the prevention, diagnosis, and therapy of infectious diseases in the long run. Accordingly, the ECI aims at providing a close scientific interaction between medical doctors in the clinics (e.g. specialists for infectious diseases, dermatology, hematology, and oncology) as well as microbiologists, virologists, infectious disease immunologists, pathologists, clinical pharmacologists, pharmaceutical, organic, and inorganic chemists, and bioengineers. The necessity for an interdisciplinary and interfaculty cooperation and for combining the diverse scientific strength and know-how in the area of infection research becomes particularly apparent whenever novel anti-infectives, vaccines, or therapeutics for the treatment of immunopathological processes during chronic infections are to be developed. The broad spectrum of expertise of the ECI members in medicine and science will serve to open up new fields of research, such as the design and analysis of redox-active metal compounds for the therapy of infections and chronic inflammatory processes.
The organizational structure of the ECI comprises an executive board of five scientists (Prof. Dr. S. Backert (NF; speaker), Prof. Dr. C. Bogdan (MF), Prof. Dr. J. Eichler (NF), Prof. Dr. T. Harrer (MF), Prof. Dr. T. Stamminger (MF)), a steering committee – consisting of the members of the executive board and five additional faculty members (Prof. Dr. A. Baur (MF), Prof. Dr. A. Burkovski (NF), Prof. Dr. B. Fleckenstein (MF), Prof. Dr. I. Ivanovic-Burmazovic (NF), and Prof. Dr. R. Lang (MF)) – as well as the members' assembly.

## Research

According to its central tasks and aims, the ECI functions as a platform for innovative research ideas to initiate new collaborative applications for extramural research grants. Scientists of the ECI are currently involved in multiple research projects including three ongoing collaborative research centers (SFB 643, SFB 796, SFB/TRR 130), several research training groups (GK 1660, GK within SFB643, and SFB 796), an Emerging Field Initiative of the FAU as well as in a new collaborative research center of the FAU (SFB 1181 "Checkpoints for Resolution of Inflammation", designated speaker: Prof. Dr. G. Schett). The initiation of new research consortia in the area of infectious diseases and microbial pathogenesis at the FAU remains the primary goal of the ECI.

## Teaching

The researchers of the ECI participate in a number of courses for students and as well as in research seminar series. These include not only the interdisciplinary infectious disease and immunology course for medical students (Q4 series), but also the invitation of national and international infectious disease researchers for guest lectures.

### Selected lectures

07.03.2013, Dr. Bernd Lepenies, MPI of Colloids and Interfaces Department of Biomolecular Systems, Berlin
"Towards novel carbohydrate-based adjuvants and immunomodulators: from glycan arrays to murine studies"

12.07.2013, Prof. Dr. J. Solnick, Center for Comparative Medicine, University of California, USA
"Tuning the host inflammatory response: plasticity in the *Helicobacter pylori* type IV secretion system"

18.10.2013, Prof. Dr. E. Grohman, Division of Infectious Diseases, University of Freiburg
"Type IV Secretion in *Enterococcus faecalis:* molecular insights in DNA transport"

21.02.2014, Prof. Dr. M. Rohde, Helmholtz-Zentrum für Infektionsforschung, Braunschweig
"The "In" and "Out" of Strepcocci Infections"

02.04.2014, PD Dr. H. Antelmann, Institute for Microbiology, University of Greifswald
"Oxidative stress responses in Gram-positive bacteria and the role of bacterial thiol-redox buffers"

03.06.2014, M. Krendel, Ph.D., SUNY Upstate Medical University, Syracuse, NY, USA
"Myosin 1e is a dynamic actin-membrane linker that regulates cell adhesion"

26.06. 2014, Prof. Dr. S. Wessler, Division of Microbiology, Paris-Lodron University of Salzburg, Austria
"Targeting E-cadherin: Functional role of HtrA in *Helicobacter pylori* pathogenesis"

12.09.2014, Prof. Dr. P. Sutton, The Royal Children's Hospital, Parkville, Australia
"How the host protects itself against *Helicobacter pylori*-associated disease"

17.12.2014, Prof. Dr. Y. Yamaoka, Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine, Japan
"Molecular epidemiological studies for *Helicobacter pylori* infections"

# Imaging Science Institute (ISI)

**Speaker**
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## Aims and Structure

The Imaging Science Institute (ISI) was founded in 2005 as a cooperation project between Siemens Healthcare and the Institute of Radiology of the FAU. Its location within the UK Erlangen allows optimizing modern imaging systems to improve quality and efficiency of diagnostic analysis as well as treatment methods. The ISI provides the prerequisites to transfer new developments regarding imaging methods and data-processing systems into the clinical setting. Aside from scientific activities, the ISI provides training courses for users and technicians to operate new hard- and software services in the field of biomedical imaging. Moreover, the ISI is also a platform in which other medical centers and the public can get familiar with the latest developments regarding research and application of state-of-the-art medical imaging techniques. Aside from the acquisition of scientific findings, medical professionals and decision-makers working in public health all over the world will learn about quality improvement and opportunities to minimize costs by employing novel technologies. Within the eight years since its establishment, roughly 20,000 people from all over the world have visited the ISI Erlangen, among them numerous leaders of medical centers as well as representatives of public healthcare systems and politicians.

**ISI partners:**
– Siemens AG
– Fujitsu Technology
– Medtron
– Medrad, INC.
– Barco
– Federal Ministry of Economics and Technology
– BMBF
– Medical Valley EMN e.V.

## Research

A wide variety of studies are currently being conducted at the ISI. The research field comprises not only the optimization of current imaging methods, but also methods for future systems. Large-scale projects, such as the "Medico Project" conducted under the auspices of the BMBF, or the currently running project "Data intelligence for clinical solutions" are designed to develop new and intelligent medical databases. With the aid of such programs it will be possible to restructure medical information in a more intelligent way in order to provide fast and reliable assistance via internet search during the diagnostic and therapeutic decision-making processes in the future. In addition, the ISI plays a pivotal role in the activities of the leading-edge cluster "Medical Valley EMN", sponsored by the BMBF.
Many patients are examined every day using the technologies available at ISI. Importantly, a sufficiently high number of regular imaging examinations performed daily at the ISI guarantee relevant research results. Furthermore, the ISI optimizes medical devices and explores their potential for further applications. Ideas for novel imaging methods and new medical devices are developed in close collaboration between clinical users and developers or technicians from the medical industry. As a result of this collaboration, jointly-owned patents are filed on a regular basis which attests to the innovative strength and extensive expertise of the ISI Erlangen.

**Research Foci (selection):**
- Breast MRI
- Sodium MRI and metabolic imaging
- Electronic data management
- Musculoskeletal imaging
- Cardiovascular imaging

**Teaching and advanced training**
Offering a wide range of courses and workshops for physicians, technicians, engineers, and radiographers, the ISI enjoys a very high national and international reputation owing to the professional competence of the course instructors and the excellent training conditions. Since the founding of the ISI in 2005, more than 10,000 people have already participated in advanced training courses.

# Interdisciplinary Center for Aging Research (ICA)

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## Aims and Structure

Since its foundation in 2003, the Interdisciplinary Center for Aging Research (ICA; formerly known as Interdisciplinary Center of Gerontology – ICG) has been active in the fields of biological, medical, psychiatric, psychological, behavioral, humanistic, economic, and technological aging research. The ICA initiates and supports interdisciplinary collaboration on aging research at the FAU. The ICA is also actively collaborating with communal institutions of medical care and with nursing homes of the region. Currently the ICA has 29 members from four different faculties and five associated institutions.

## Research

Research of the members of the ICA focuses predominantly on health promoting intervention and prevention in the domains of nutrition, physical activity, and social environment. Each area of research addresses social, institutional, technological, and environmental conditions and their effects on physical health, autonomy, and personal responsibility.

### Field of Research: Nutrition

Quantity and quality of our daily diet are of major importance for health, functionality, and well-being until very old age. With increasing age, an adequate nutrition is, however, often impaired by numerous age-related changes of the health and living situation. In addition, physical activity, psychological, and social factors play important roles. Within the framework of the 'Theo and Friedl Schöller Foundation Professorship of Clinical Nutrition in the Elderly', the relation between different aspects of nutrition and physical as well as mental functionality in very old age was studied in interdisciplinary projects. In addition, nutritional problems and aspects of nutritional care in older persons with dementia living in private households and nursing homes were studied. Independent from the place of living, an increasing prevalence of malnutrition and of risk factors for malnutrition with deteriorating health and general status as well as between malnutrition and functionality could be demonstrated.

### Field of Research: Physical Activity

Targeted promotion of physical activity can improve function, activities, and participation in the course of life and thus help to maintain independence and autonomy. The aim of physical-activity-related interventions is to induce long-term commitment to physical activity. Applied in rehabilitation, such a behavior-oriented exercise therapy (BET) leads to improved body functions and pain coping competencies and less work incapacity days in patients with chronic back pain (project: PASTOR; VBT in der VMO). Physical activity-related interventions in the elderly lead to positive effects on physical functioning (muscle strength, balance), the risk of falls, the risk of dementia, and cognitive performance (projects: F.i.A.T, GESTALT I and II; Sturzprävention im Alter, PREFALL and PREFALLID DEDIPAC sedentary behavior; SPRINNT – Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies; FORMOSA Project, WB-EMS in older women with sarcopenic obesity). An important aspect of longterm changes in physical activity behavior is the affective attitude towards physical activity (project: KASPADI). The dissemination of physical activity interventions can successfully be realized via internet-delivered interventions for various indications (projects: Rückenwind (low back pain), ms-intakt, PACE, FatEx (multiple sclerosis)). A further area of research lies on motor control, especially after injuries or in persons with neurological conditions and/or movement/gait disorders (e.g. Parkinson´s disease, project Stable). Besides the individual level, organizational and political aspects play a central role in physical activity promotion for the elderly. In order to expand and optimize offers, improving both, internal capacities (e.g. staff training, goal definition, and resource allocation) as well as cross-organizational and intersectoral networks in and between sport, healthcare, and social care organizations, is essential. Important means to these ends include structured planning processes and networking between researchers, practitioners, and policymakers (projects: CAPITAL4HEALTH, MOVE). Of special interest to gerontology are assets and barriers for the integration of evidence-based, structured interventions for the prevention of dementia into providers' routines (project: GESTALT I). An important focus of this research are difficult-to-reach target groups, such as socially disadvantaged and sedentary older people (projects: GESTALT and GESTALTkompakt).

### Field of Research: Social Relations

Beyond dispute the quality of an efficient social network plays a major role in maintaining health and a prolonged time of independent living in old age. For example, positive social relationships substantively contribute to improved health and longevity as well as to reduced risks of dementia and frailty. There is also some preliminary evidence suggesting that the association of physical activity and nutrition partly depends on the quality of social and family resources. The situation of care-giving relatives with its resulting burdens, challenges, and risks is also of great importance. Additional projects analyze the situation of family caregivers, particularly with respect to the potentials of psychoeducation of family caregivers. Another focus of research is directed on the living conditions and quality of life of seniors living in institutions of residential care, concentrating mainly on aspects of social interaction between residents, relatives, and staff.
Interdisciplinary and comprehensive research approaches focus on questions of prevention and interventions strategies with regard to dementia and age-related frailty. Additional nonclinical research is centered round the possibilities of assistive technology for supporting mobility and independent living in later life (e.g. EMN-Moves).

## Teaching

The majority of the ICA-members is engaged in the interdisciplinary course offerings of the master's program in gerontology (M.Sc.). Some courses are realized in close cooperation with the associated members of the ICA, especially those related to gerontological practice. A series of lectures (Q7 – medical science of aging) focusing on geriatric and ethical topics are organized by numerous members of the ICA at the Faculty of Medicine.
Furthermore, the ICA operates a collective graduate program "gerontology" which provides structured lecturing and special workshops for doctoral students in gerontology as well as in psychology, psychiatry, and sport sciences.

# Interdisciplinary Center of Ophthalmic Preventive Medicine and Imaging (IZPI)

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## Aims and Structure

The "Interdisciplinary Center of Ophthalmic Preventive Medicine and Imaging" (IZPI) was founded to increase the intensity and the efficiency of cooperation projects between the Faculties of Medicine and Engineering of the FAU in the field of preventive medicine. The aim is to improve the conditions of research and the public communication of the arising results.
In the scientific areas medical imaging, pattern recognition, and preventive medicine, there was already scientific excellence in the Faculties of Medicine and Engineering. Embedded in the main research focus "Medical Technology" of the FAU, the IZPI should help to enforce and to improve the scientific excellence in these topics.
The most important purpose of IZPI is the development of novel diagnostic methods in the area of preventive medicine. The goal is to develop new technologies for early detection of risk factors or symptoms of diseases.
Thus, the areas of interest of IZPI are
(1) development of novel technologies and
(2) improvement of well-established technologies by optimizing image acquisition, analysis, and medical prediction.
The analysis of medical images and data comprises all processes which lead to a medical interpretation or a transformation of the medical image in a symbolic description. To extract relevant risk factors from a given medical image, there is the necessity to develop an effective model of the disease. The model will allow elute relevant information from a given image.

## Research

IZPI researchers from the Faculties of Medicine and Engineering cooperate within third-party funded projects of the Center of Excellence for Medical Technology "Medical Valley EMN e.V." and the School of Advanced Optical Technologies "SAOT" (compare own reports).

### Third-party funded projects of the Center of Excellence for Medical Technology "Medical Valley EMN e.V."

IZPI scientists work on two projects of the "Medical Valley EMN e.V" which deal with telemedical applications in ophthalmology.
(1) Telemedical LowCost-Fundus Camera System: The goal of this project (A04) is the development and clinical validation of a low cost telemedical system for threshold countries for early detection of diabetic retinopathy, hypertensive retinopathy, and glaucoma. We succeeded in generating high-resolution images of the retina by using Superresolution Technology. In 2012 four peer-reviewed articles were published and two patents were accomplished.
(2) E. Atlas: The goal of this project (A02) is the development of novel technologies to run an interactive image database, fully accessible by mobile communication technology. We succeeded in platform-independently publishing of the data base Atlas of Ophthalmology with 6,000 reference images for iOS (Apps iPhone, iPad) and for Windows 8 (Apps for Tablets with Windows 8). In 2012 seven peer-reviewed articles were published.

### Third-party funded projects of the School of Advanced Optical Technologies (SAOT)

Several IZPI researchers work on third party funded projects of the SAOT:
(1) 3D-Vision: Within two Ph.D.-projects, a gesture-controlled, interactive system is developed, enabling the measurement and training of the stereo vision capacity. We began a tight cooperation with the University of Kunming (province Yunnan, China), leading in 2012 to a Visiting Professorship.
(2) MR-DTI imaging of the visual tract: A novel MRI-method (Diffusion Tensor Imaging, DTI) and image pattern analysis allows to quantify the integrity of axons of the cerebral part of the optic tract. By this method, it becomes possible to detect unknown causes of vision impairment. In 2012 four peer-reviewed articles were published.

## Teaching

IZPI researchers give lectures within several interdisciplinary frameworks of the Faculties of Medicine and Engineering. At the Faculty of Medicine, the lecture "retinal microangiopathy as early marker of cardio-vascular diseases" is given as well as lectures for students of the degree program "Medical Engineering". The overall concept of these lectures which are called "Biological and Technical Vision" is to link mechanisms of human vision with the vision of machines. For students of "Medical Engineering", we offer the lectures "Biological and Technical Vision" and "Medical Applications of Photonics". In addition, a weekly colloquium "Biological and Technical Vision" is offered to students of the Faculties of Medicine and Engineering.

# Interdisciplinary Center for Health Technology Assessment and Public Health (IZPH)

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## Aims and Structure

"Networking across scientific borders" is the unique selling proposition of the Interdisciplinary Center for Health Technology Assessment and Public Health (IZPH). The IZPH is a multidisciplinary research center involving different faculties of the FAU: The primary objective of the Center is to merge medical, economical, and social sciences and management in order to advance research in public-health and resolve current health care challenges of the aging society.
Within the Nürnberg Metropolitan Region, the IZPH bundles all relevant stakeholders of the health care industry, i.e. medical professionals (doctors, hospitals trusts, outpatient sectors), the different statutory health and care insurance providers, health technology providers (global operating companies, like Siemens Healthcare, and pharmaceutical manufacturers), as well as patients and their family members.

## Research

The research focus of the Center is driven by its previous interdisciplinary research in the field of public health and takes special interest in issues of Health Technology Assessment (HTA) and market access, health promotion and preventive medicine, and federal health monitoring.
During the report period, the Center performed a number of large-scale studies addressing research topics as need of care and resource use in chronically ill patients (dementia, cancer, and stroke) as well as assessment of health care services funded externally with three million EUR.
With its emphasis on Health Technology Assessment (HTA) and market access, health promotion and preventive medicine, and federal health monitoring, the Center acts as the scientific platform for outcomes research at the FAU and as the main regional promoter.

## Teaching

Members of the IZPH provide interdisciplinary lectures and courses in the field of public health, such as health economics, health system research, health promotion, and prevention. Special focus is also given to lectures on public health issues for students of the Faculty of Business, Economics, and Law and to the interdisciplinary Master degree program "Medical Process Management" (M.Sc.; compare own report).

# Medical Immunology Campus Erlangen

**Speaker**
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**Scientific Coordinator**
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## Aims and Structure

The Medical Immunology Campus Erlangen, an interdisciplinary center at the Faculty of Medicine of the FAU, was founded in March 2009 in order to provide a common organizational platform to scientists from all areas of immunobiology and clinical immunology. Since then, several institutes, clinics, clinical divisions, and research groups of the UK Erlangen, the Faculties of Medicine and Sciences of the FAU, the Fraunhofer Institute for Integrated Circuits IIS, and the Max Planck-Institute for the Science of Light have been integrated into the Campus. The Medical Immunology Campus Erlangen organizes scientific seminars and lectures, promotes the research of its members by public relation activities, develops teaching concepts for immunology in the Bachelor's and Master's degree programs of Molecular Medicine, and coordinates the participation in competitive federal funding initiatives. By bundling the available scientific resources in the field of immunology, the Campus is dedicated to strengthen the research focus Immunology and Infection Research of the Faculty of Medicine and, in the long run, to enable the founding of a non-university institution (i.e. Leibniz Institute) for translational immunology and immunotechnology. Three times a year, the Campus publishes a Newsletter on exciting publications, honors, and awards of the Campus' more than 80 members.

## Research

Medical Immunology Campus Erlangen researchers investigate the basic mechanisms of the development, composition, function, and deficiencies of the immune system. By translating the results into clinical approaches, new and personalized methods for the prevention, diagnostic, and therapy of infectious, autoimmune, and inflammatory diseases as well as for neoplasias are developed.
During the reporting period, the scientists of the Medical Immunology Campus Erlangen succeeded in setting up a new immunological research association under FAU-leadership (SFB-Transregio 130 "B cells: Immunity and Autoimmunity", Speaker: Prof. Dr. L. Nitschke) and prolonging three already existing immunological research consortia funded by the DFG (SFB 643 "Strategies of cellular immune intervention", Speaker: Prof. Dr. G. Schuler; GK 1660 "Adaptive Immunity", Speaker: Prof. Dr. H.-M. Jäck; Clinical Research Group KFO 257 "Chronic intestinal inflammation", Speaker: Prof. Dr. C. Becker and Prof. Dr. M. Neurath; see own reports).

## Teaching

The members of the Medical Immunology Campus Erlangen are involved in teaching medical students and students of the Bachelor's and Master's degree programs of Molecular Medicine at the Faculty of Medicine as well as students of the life science programs at the Faculty of Sciences. Furthermore, the Campus promotes scientific exchange by hosting national and international speakers of a broad, interdisciplinary range of topics at the weekly Immunological Colloquium. The annual Joachim Kalden Lecture was initiated by the Medical Immunology Campus Erlangen in order to honor outstanding researchers with substantial impact on immunological research, such as the director of the Deutsches Rheuma-Forschungszentrum Berlin, Prof. Dr. A. Radbruch, in 2013 and the director of the Clinical Department of Pathology, Medical University Vienna, Austria, Prof. Dr. D. Kerjaschki, in 2014.

### Lectures

Scientists of the Medical Immunology Campus Erlangen organized the 27th Annual Conference of the European Macrophage and Dendritic Cell Society which took place in Erlangen from 10 - 12 October 2013. Almost 300 scientists from 18 different countries attended this conference. In 2013 and 2014, the Medical Immunology Campus Erlangen organized 60 research colloquia with distinguished national and international guest scientists. The following compilation is a selection of the complete list which can be viewed at the homepage of the interdisciplinary center.

15.01.2013 Prof. V. Sexl, Veterinärmedizinische Universität Wien
"Nk cell dependent tumor surveillance – STATs in the spotlight"

12.04.2013 Prof. E. Vivier, Centre d'Immunologie de Marseille-Luminy
"Natural Killer cells, Innate lymphoid cells and Innate Imumnity"

11.06.2013 Prof. C. Ardavin, National Center for Biotechnology, Madrid
"Production of type I interferon by inflammatory dendritic cells in response to *Candida albicans* infection"

02.07.2013 Prof. S. Jonjic, School of Medicine, University of Rijeka, Kroatien
"Expression of NKG2D ligand RAE-1 by mouse cytomegalovirus enhances virus immunogenicity and vaccine efficacy"

14.10.2013 Dr. G. Shakhar, Weizman Institute of Science, Revohot, Israel
"Insights from live 2-photon imaging of tumors"

17.12.2013 Dr. H. Wardemann, Max Planck Institute for Infection Biology, Berlin
"Single cell analysis of B cell repertoires"

06.02.2014 Prof. B. Stockinger, National Institute for Medical Research, London
"Environmental triggers of inflammatory immune responses"

06.05.2014 Prof. M. Kopf, Institute of Molecular Health Sciences ETH Zürich
"Alveolar macrophage development and function in respiratory viral infection"

08.05.2014 Assoz. Prof. Dr. P. Stoitzner, Innsbruck Medical University
"Skin dendritic cells in tumor immunity: interesting targets for immunotherapy?"

20.05.2014 Prof. F. Randow, MRC Laboratory of Molecular Biology, Cambridge
"Autophagy in host-pathogen interactions"

24.06.2014 Prof. W. Kastenmüller, University of Bonn
"Pathogen defense in the lymph node – from innate to adaptive immunity"

08.07.2014 Prof. Dr. S. Ehl, Centrum für Chronische Immundefizienz, Universitätsklinikum Freiburg
"New lessons from human genetic disorders of T cell immunity"

20.10.2014 Dr. P. Murray, St. Jude Children's Research Hospital, Memphis
"Amino acid metabolism links immunoregulation and immune pathology"

25.11.2014 Prof. B. Becher, University of Zürich
"How T cells instruct myeloid cells in tissue inflammation!"

09.12.2014 Prof. S. LeibundGut-Landmann, Institute of Microbiology, ETH Zürich
"Interleukin-17-mediated host defense against fungal infection"

# Medical Technology Test and Application Center (METEAN) of the Fraunhofer Institute for Integrated Circuits IIS

**Speaker**
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## Aims and Structure

Intention and main focus of METEAN is to combine the research competence in biomedical engineering of the Fraunhofer IIS with the clinical expertise of regional partners from industry, research institutes, and specifically the UK Erlangen in a synergistic way to exchange ideas for technical solutions considering the medical and clinical needs and hence providing and opening perspectives for innovative and market-oriented products. METEAN is located at the Faculty of Medicine inside facilities of the UK Erlangen and hosts technical and medical scientists. A tight involvement of the project partners from clinics, academics, and industry into the research and development activities allows an active participation into the strategic, programmatic, and process-related orientation of METEAN.

## Research

### Computer assisted microscopy

The analysis of cells and tissues by means of microscopy has been established as a standard within microbiology, virology, and immunology and is the diagnostic reference method for histopathology. The research goal of subproject A4 within the SFB 796 (compare own report) is the conception and development of generic image analysis methods that are capable to provide solutions for many similar applications in analysis of fluorescent micrographs.
In cooperation with the Institutes of Pathology and Anatomy, a web based education system using digital virtual slides of histopathological samples has been established. This platform is also used for multi-center studies in cooperation with the Institute of Neuropathology. For such projects, digital slide scanners for bright-field and fluorescent scanning are available in the METEAN facilities. The scanning of different samples as well as scientific counseling with respect to automated image analysis are part of the cooperation and service possibilities for the UK Erlangen as well as for external partners.

*Zeiss AxioScan.Z1*

### Decision support systems

The research and development tasks in the field of "Computer-assisted Diagnosis" (CAD) are focused on the development of "intelligent" systems for computer based detection, analysis, and interpretation of lesions depicted in various medical imaging modalities (endoscopy, colposcopy, mammography). Improved early detection of dysplastic tissue within screening programs as well as an objective differential diagnosis are the main functional purposes of the developed CAD-technology. Within the context of the BMBF-supported project "KoloPol", image processing methods are developed for the automated detection of polyps in colonoscopic sequences. In cooperation with the UK Erlangen and the Bayreuth Medical Center, a reference image data collection is generated. Based on these images, data algorithms for detection and classification of malignant lesions are developed and evaluated. Using such methods, gastroenterologists can potentially be supported in the process of colon screening.

### Analysis and wireless transfer of biosignals of the respiratory and cardiovascular systems

In order to detect and extract therapy-relevant parameters for hemodynamic monitoring, novel methods for continuous non-invasive acquisition of biosignals of the respiratory and cardiovascular system are investigated in cooperation with the Departments of Medicine 4 and Anesthesiology, and the Max-Schaldach Chair for Medical Technology. A crucial part of this research concentrates on the development of a laboratory prototype which can be applied to the human body for continuous non-invasive long-term acquisition of the central arterial blood pressure under daily standard conditions. A further research goal concentrates on the mathematical modeling of the arterial pulse wave. The information-theoretical characterization of the interaction between the respiratory and the cardio-vascular system yields insights about the physiological-pathophysiological aspects of the bidirectional influence and regulation of these systems.
Goal of the project "KARDIKOM Wireless", funded by the BMBF, was a tight monitoring of patients with cardiac risk constellations for both, stationary and home care monitoring. After optimization towards a micro-system, the portable vital-sensor system (developed earlier within the project SOMATEK) was certified as medical class II product. Based on this sensor system, two observer studies were conducted in cooperation with the Department of Internal Medicine of the Heidelberg University Hospital and the local Department of Anesthesiology. In Heidelberg, the "KARDIKOM Wireless" system was tested with respect to clinical use and its integration into a patient data management system, whereas the focus of investigation in Erlangen has been the user acceptance and suitability for home care monitoring.

## Teaching

Within METEAN facilities, students of medical and applied informatics, biomedical technology and electronic devices, physics and mathematics of the FAU as well as of the regional universities of applied sciences are educated and qualified through assignments and supervision of internships, bachelor- and master theses. Additionally, scientists from the Fraunhofer IIS are involved in various lecture units of the Faculties of Medicine and Engineering.

# Nikolaus-Fiebiger-Center of Molecular Medicine (NFZ)

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## Aims and Structure

The NFZ is a research institution of the Faculty of Medicine. The center harbors the two Chairs of Experimental Medicine I and II (Molecular Pathogenesis Research and Molecular Tumor Research, respectively), a Division of Molecular Immunology as part of the Department of Medicine 3, a division of the Chair of Genetics of the Faculty of Sciences, as well as two junior research groups of the IZKF of the Faculty of Medicine. Additionally, lab space is provided to rotating clinical research groups. The intention of the research center is to strengthen biomedical research within the Faculty of Medicine by stimulating cooperations between basic and clinical researchers and by giving young clinicians the opportunity to carry out competitive biomedical research projects, benefitting from the infrastructure of a modern research center.

Research Units:
– Chair of Experimental Medicine I (Molecular Pathogenesis Research)
  Prof. Dr. T. Brabletz
– Chair of Experimental Medicine II (Molecular Oncology)
  Prof. Dr. J. Behrens
– Department of Medicine 3 – Rheumatology and Immunology - Division of Molecular Immunology
  Prof. Dr. H.-M. Jäck
– Department of Biology - Division of Genetics (Faculty of Sciences)
  Prof. Dr. T. Winkler
– Junior Research Groups of the IZKF
  • Group 2: PD Dr. J. Titze
  • Group 3: PD Dr. B. Winner
– Clinical Research Groups
  • Prof. Dr. A. Bozec (Department of Medicine 3 – Rheumatology and Immunology)
  • Prof. Dr. J. Winkler (Department of Neurology)
  • PD Dr. J. Beier (Department of Plastic and Hand Surgery)
  • Dr. G. Krönke (Department of Medicine 3 – Rheumatology and Immunology)
  • PD Dr. M. Stock (Department of Medicine 3 – Rheumatology and Immunology)
  • PD Dr. K. Gelse (Department of Surgery - Division of Trauma Surgery)

## Research and Teaching

The main research topics at the NFZ comprise different aspects of molecular pathology including tumor biology, immunology, neurobiology, and genetics. The Chair of Experimental Medicine I has been vacant since October 2012 and was filled with Prof. Dr. T. Brabletz in May 2014.

The NFZ is well equipped with modern research facilities required for cell and molecular biological research including animal facilities and offers a variety of biochemical, immunological, and cell biological seminars, guest lectures, and common graduate student seminars.

# Translation Research Center (TRC)

**Speakers**
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## Aims and Structure

In 2014 the Translational Research Center (TRC) with an exemplary concept and infrastructure was opened at the Faculty of Medicine of FAU. The newly established research building enables physicians and basic scientists to collaborate closely and develop novel approaches for diagnosing and treating diseases. Areas of expertise covered in the center include aspects of inflammation-, tumor-, kidney-, heart-, and circulation research.
The concept for the TRC was developed in 2007 in preparation for a competitive call for novel research centers according to § 91 b Section 1 No 33 GG, and received a positive evaluation through the German Council of Science and Humanities ("Wissenschaftsrat"). A central approach of the TRC is a highly efficient and flexible use of laboratory space. The research modules have a uniform floor plan. All laboratory areas are linked to a central middle zone which harbors multiuser equipment in order to ensure easy access and efficient utilization of advanced technologies. Several core units complement the infrastructure and provide a broad array of specialized methodologies. These include a central isotope area that for example enables to generate markers used for innovative imaging techniques, a biobank for sample storage, processing, and analysis of blood and urine of patients, and a cutting edge unit for immune monitoring of patients. All research areas are connected with an open structure to facilitate intense interaction. To this end, a central communication area was created for all personnel.

*Translational Research Center – Western view of the building*
*(Photo: UK Erlangen)*

## Research

The TRC assembles research groups of the Departments Internal Medicine, Dermatology, Nuclear Medicine, and Surgery, and of the Institute of Pathology in one building. Approximately one quarter of laboratory space is temporarily allocated for projects initiated by newly established principal investigators. In addition, the center will contribute to national and international networks in translational research, based on current and future collaborations of the participating scientists.
The research goals of the TRC focus on diseases that play a central role for patient care of the participating institutions. Research topics include the regulation of cardiac and renal development, disturbances in calcium metabolism, novel therapeutic targets in inflammatory bowel disease, angiogenesis, vascular activation and endothelial transmigration in tumors, certain aspects of tumor- and transplantation immunology, immunomodulation of angiogenesis, and the relevance of hypoxia and inflammatory processes for renal diseases. Research on specific pathogenic processes that play a role in the development of various diseases affecting different organ systems provides overarching synergies. For example different mechanisms of endothelial activation are being studied by five research groups within the TRC, including the studies of tumor angiogenesis, metastasis formation, transendothelial migration, and development and progression of atherosclerosis. Immune reactions are being addressed in the context of angiogenesis, tumor therapy, and as a pathogenic driver of inflammatory bowel disease, kidney disease, and atherosclerosis. The establishment of a zebra fish unit expands the methodological spectrum and will allow additional joint research strategies. Another innovative, interdisciplinary approach includes the analysis of extracellular vesicles which function as intercellular communication units.


*Opening Ceremony of the TRC (24 October 2014) (from left) Prof. Dr. K.-U. Eckardt (Director of the Department of Medicine 4 – Nephrology and Hypertension and Project Manager of the TRC), Prof. Dr. Dr. h.c. H. Iro (Medical Director of the UK Erlangen), Dr. F. Janik (Mayor of Erlangen), Prof. Dr. Dr. h.c. J. Schüttler (Dean of the Faculty of Medicine), Dr. L. Spaenle (Bavarian Minister of Science), D. Maußner (Leading construction manager of the state-owned building department Erlangen-Nürnberg), J. Herrmann (Bavarian State Minister of the Interior, for Building, and Transport), S. Müller (Parliamentary State Secretary to the Federal Minister of Education and Research), and Prof. Dr. K.-D. Grüske (President of the FAU)*
*(Photo: UK Erlangen)*

# Central Institute of Medical Engineering (ZiMT)

**Speaker**
Prof. Dr.-Ing. Joachim Hornegger

**Corporate Executive Committee**
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## Aims and Structure

Medical technology is one of the scientific focuses of the FAU. Almost 100 scientists and lecturers are working in this sector linked together in the Central Institute of Medical Engineering (ZiMT). The coordination of responsibilities of numerous cooperation partners as well as international visibility are the important core areas of ZiMT. It is an organizational unit which sharpens the biomedical engineering profile of the FAU and improves the general conditions for interdisciplinary collaboration in the diversified research area of healthcare engineering.
Head of ZiMT is an interdisciplinary joint team, consisting of Prof. Dr. J. Hornegger (Faculty of Engineering), Prof. Dr. Dr. h.c. J. Schüttler (Faculty of Medicine), and Prof. Dr. B. Fabry (Faculty of Sciences). On an operative level, ZiMT is managed by Dr. K. Höller and T. Zobel.

## Research

After the positive decision on the competition "cluster of excellence" of the BMBF for the Center of Excellence for Medical Technology "Medical Valley EMN e.V.", ZiMT, Siemens and Medical Valley have succeeded to set one more milestone regarding research in medical technology: As part of the 8th European Union Research Program Horizon2020, the European Institute of Innovation and Technology (EIT) has extended its focus to "Healthy Living and Active Ageing". ZiMT has been representing the interests of FAU and Medical Valley EMN e.V. in numerous Europe-wide consortia meetings and work groups of the applying consortium "InnoLIFE" from 2012 to 2014.
Using about 80 million Euro in funding for the next seven to 15 years, the aim of the European consortium is to connect excellent medical research networks. Within those networks, the objective of joint projects is to promote creative entrepreneurship, develop joint innovations for healthy living and active aging, and leverage the Europeans to more health, improved well-being, and higher productivity.
Finally, "InnoLIFE" was awarded winner of the bidding "Healthy Living and Active Aging" (EIT Health) by EIT on December 9, 2014. Now, FAU and Siemens Healthcare are two of the Europe-wide 50 core partners. Medical Valley EMN e.V. and Fraunhofer IIS also participate as associate members. With a total venture volume of more than two billion Euro, thereof up to 700 million Euro for funding, EIT Health is one of the biggest publicly funded initiatives in the field of healthcare worldwide.

## Teaching

At the FAU, the relevance of "healthcare engineering" as a scientific focus is not only visible in research, but also in the educational sector. The bachelor and master programs of healthcare engineering were able to show very high numbers of applications right from the start and are until today with 720 enrolled students one of the largest study programs at the Faculty of Engineering. The constantly high amount of students and the goal of having as few students dropping out as possible were the reasons for the introduction of a procedure of determining aptitudes for healthcare engineering. Despite the extra effort, this procedure enables to offer a valuable individual advisory service before the start of a study program.
In particular, courses such as computer science, electrical engineering, electronic engineering, information technology, mechanical engineering, material engineering as well as chemical and biological engineering are embedded in the program of healthcare engineering.
Another outstanding feature about the healthcare engineering program is the high percentage of female students which is more than 50 %. Until today, no other engineering study program has reached those numbers. The master program in healthcare engineering which has been existing since winter term 2011/2012 offers three different specializations: Medical electronics (electrical engineering), medical imaging and data processing (informatics), and medical instrument and production engineering and prosthetics (mechanical and material engineering).
At the end of 2012, the bachelor as well as the master study program have been internationally certified as an act of quality assurance. Compared to other study programs at the FAU, the healthcare engineering programs were the only ones being certified without any specific additional requirements. This confirms the feasibility of the program and its clearly defined and valid goals, which can be realized with the existing concept using the organizational and infrastructural setting at the FAU.

## 3-D Imaging in Medicine

With the goal of internationally promoting the excellent position in the fields of science, research, and development of our country and strengthening the cooperation with recognized centers of excellence in the field of healthcare engineering throughout the world, the BMBF had launched an initiative to advertise Germany as an excellent research location. Under the motto "Germany – Land of Ideas", an attempt is being made to enlargen the visibility of Germany's attractiveness and its research environment attractiveness in important target countries in order to initiate new sector-specific cooperations. Workshops, multiplier events, partnering events, lectures, and presentations at conferences and meetings were organized. BMBF has selected eight participants for initial support that highlight its ideals and goals. Under the auspices of ZiMT and the topic "3-D Imaging in Medicine – Cutting Edge Research in Germany's Medical Valley", the partners conducted workshops abroad with the aim of establishing international graduate schools and cooperations. Erlangen as a highly innovative location offers unique opportunities for young scientists in the field of medical 3-D imaging.
The expansion of study and research cooperation to internationally attractive and recognized institutions – i.e. the Stanford University, the Johns Hopkins University, and Harvard Medical School, USA – and economically important partners, like Brazil and China, have already been established. Also, student exchange programs with the above mentioned partners as well as an international oriented graduate school with the Peking University and the FAU have been realized.

ZiMT
ZENTRALINSTITUT FÜR MEDIZINTECHNIK

# Collaborative Research Center 643: Strategies of Cellular Immune Intervention

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## Aims and Structure

The SFB 643 "Strategies of cellular immune intervention" has been existing since July 2004. By the end of 2012, the third funding round (2013 – 2016) was approved by the DFG. The goal of the SFB 643 is the successful implementation of immunological knowledge in treatments that are based on a manipulation of the immune system, i.e. on immune intervention. Immune therapeutic approaches to treat tumors and infectious diseases require the enhancement or stimulation of the immune response. Conversely, innovative treatments of inflammatory diseases, including autoimmune diseases, allergic diseases, and transplantation reactions call for novel and improved immunosuppressive strategies. The SFB 643 is conceptually structured in three closely interconnected project areas: A) basic immunology, B) immune intervention in animal models, and C) therapeutic applications.

## Research

Several representative projects will be described shortly.

Prof. Dr. U. Schubert investigates the role of the ubiquitin proteasome system (UPS) for antigen presentation via the MHC class I (MHC-I) pathway.

PD Dr. U. Schleicher and Prof. Dr. C. Bogdan are focused on natural killer (NK) cells and their effector functions in the immune response against the intracellular parasite Leishmania with the aim to elucidate the mechanism leading to the activation of NK cells.

Prof. Dr. D. Dudziak will translate the strategy concept of in vivo "antigen targeting" of dendritic cells (DC) into the human system. Thereby, the work focuses on the production of antigen-conjugated antibodies to analyze T cell responses in tissue culture and the characterization of DC in human tissues. These data will be important for an eventual implementation into the clinic to optimize vaccination.

Prof. Dr. F. Nimmerjahn focuses on antibodies which are essential for defending the body against invading pathogens and show promising results in the therapy of human tumors. In depth knowledge about the cell types involved in phagocytosis and ADCC reactions in vivo is the basis for the generation of novel therapeutic strategies aiming at modulating these reactions.

Prof. Dr. M. Herrmann focuses on the immune modulation by apoptotic cells, necrotic cells, and annexins. Apoptotic cells are considered to be only weakly immunogenic because of their swift recognition and clearance by phagocytes and can even be tolerogenic. The exposure of immature glycoproteins and the phospholipid phosphatidylserine represent signals for the phagocytosis of dead (necrotic) and dying (apoptotic) cells, respectively.

Prof. Dr. L. Nitschke studies the newly developed sialic acid derivatives as high-affinity ligand analogs for CD22, a B cell receptor-associated inhibitory co-receptor, in order to therapeutically manipulate B cells. CD22 can interact with the CD22 ligands on bone marrow endothelial cells which might control the homing of circulating mature B cells and plasma cells into the bone marrow. The therapeutic potential of these modified derivatives will be explored as a novel therapeutic tool to treat patients with multiple Myeloma.

In the long run, Prof. Dr. A. Steinkasserer aims at developing new vaccination strategies for patients with tumors by direct in vivo targeting of DC. The human CD83 promoter complex which is only active in mature DC, is an ideal candidate for transcriptional targeting of mature DC and will set the stage for next generation in situ vaccination strategy that should be particularly effective and safe as it for the first time assures selective antigen expression in mature DC while avoiding expression in tolerogenic immature DC. This approach will be combined with transductional DC-targeting using anti-DEC-205 modified adenoviral vectors and nanoparticles.

Prof. Dr. J. Siebler and Prof. Dr. M. Neurath deal with the transcriptional regulation and pathogenetic relevance of the IL-28/IL-29 cytokine system in colitis and colitis associated colon carcinoma. Thereby, the transcriptional regulation of the IL-28/IL-29 cytokine gene expression will be investigated using murine T cells. The functional role of IL-28/IL-29 for the immunopathogenesis of colitis and colitis-associated colon carcinoma will be characterized in vivo using murine models.

PD Dr. B. Schuler-Thurner, PD Dr. N. Schaft, Dr. J. Dörrie, and Prof. Dr. G. Schuler aim at developing new and innovative immunotherapies based on DC especially for the treatment of patients with cancer (melanoma as a prime model). Several clinical phase I-trials have already been conducted using peptide-loaded DC and now an additional clinical study was concluded that used DC which have been electroporated with defined RNA encoding the tumor associated antigens MAGE-3, MelanA, and Survivin. In addition, new and advanced antigen loading strategies have been developed using RNA electroporation.

The ability to adoptively transfer T cells to treat cancer is in the focus of Prof. Dr. A. Mackensen. In initial studies the efficacy of adoptive T cell transfer therapies for the treatment of patients with metastatic melanoma has been shown. Effective cell therapy demands in vivo persistence and/or expansion of the transferred TAA-reactive T cells and homing to the tumor. Several strategies will be developed to enhance proliferation, migration, and persistence of infused tumor-reactive T cells. These approaches could improve the efficacy of adoptive T cell therapy for cancer. In the current funding period the adoptive transfer of CMV/EBV-multi-epitope-specific T cells will be tested in a clinical trial in stem cell transplanted patients.

Prof. Dr. T. Winkler and Prof. Dr. M. Mach are concentrating on the adoptive transfer of memory B cells as a new cell based therapy for infection with Cytomegalovirus after transplantation. Support of the patient's immune defense against the virus is a major goal in transplantation medicine. Memory B cell transfer provided long-term protection from the lethal course of the infection that was invariably seen in immunodeficient animals. This provided the experimental rationale for a cell based strategy to support the humoral immune response to effectively combat infectious pathogens in severely immunodeficient hosts. A first in man clinical trial using adoptively transferred memory B cells in stem cell transplanted patients has been started within the current funding period.

# Collaborative Research Center 796: Reprogramming of Host Cells by Microbial Effectors

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## Aims and Structure

The long-term goal of the SFB 796 "Reprogramming of host cells by microbial effectors" which started in January 2009 is the understanding of the molecular and ultimately structural basis of pathogen-host interactions as well as the development of novel strategies for immunization and intervention. In order to achieve this goal, interactions between known microbial effector proteins (e.g. bacterial type III secretion machines, viral transport proteins) and host cell structures will be characterized on the molecular level. Furthermore, new virulence factors will be identified and their role during pathogenesis will be studied.
The SFB 796 which was initiated by the Faculty of Sciences has an interfacultary structure. Groups of the Faculty of Medicine and the Faculty of Sciences as well as of the Fraunhofer Institute for Integrated Circuits (IIS) are involved in the collaborative research. Although the individual research goals of the bio-medical and plant-oriented groups might appear different at first (improved prevention and therapy versus pathogen-resistant and high-yielding crop plants), the underlying basic concepts in pathogen-host interactions are expected to be rather similar, rendering a comparative approach highly appealing. Thus, we expect that the comparative investigation of the reprogramming of central cellular processes (e.g. ubiquitin-mediated protein degradation, vesicular trafficking) in several pathosystems (human and plant pathogenic viruses and bacteria) will enable us to identify general themes that we expect to extend also to pathogens not studied within the SFB 796. To reach the long-term goal, the SFB 796 incorporates closely cooperating scientists with complementary expertise, as well as a core unit to study structure-function relationships. Presently, the SFB 796 harbors 16 different projects that can be divided into three subgroups that are interconnected:

A) structural basis of molecular interactions,
B) reprogramming of cellular processes, and
C) replication structures and transport processes.

## Research

**Subgroup A: Structural basis of molecular interactions**
Structure-function relationships of already known effector proteins and their interactions with specific cellular targets will be studied in subgroup A. Linear sequence motifs mediating protein-protein interactions are widely used by pathogenic organisms to reprogram cellular processes. The elucidation of the structural requirements for the promiscuity is the focus of several projects of this sub-area.

**Subgroup B: Reprogramming of cellular processes**
The focus of subgroup B is the elucidation and detailed understanding of mechanisms used by microbial effectors to reprogram cellular processes, including selected signal transduction pathways, intrinsic immune responses, targeted protein turnover, and the primary metabolism.

**Subgroup C: Replication structures and transport processes**
The focus of subgroup C is the question as to how microbial effectors use, and partially convert, cellular structures for successful microbial colonization and replication.
How viral and bacterial proteins modify the cellular transport is the focus of several projects of this subgroup.

**Central project (Z)**
Crucial methods for generating novel insight are provided by the central project (Z). The central project will reach into all research areas by offering an integrated and state-of-the-art technology platform supporting all groups of the SFB 796.

# Priority Program 1468: Osteoimmunology – IMMUNOBONE – A Program to Unravel the Mutual Interactions between the Immune System and Bone

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## Aims and Structure

The interdisciplinary project "Osteoimmunology – IMMUNOBONE – A Program to Unravel the Mutual Interactions between the Immune System and Bone" (SPP 1468 – IMMUNOBONE) is a priority program to unravel the mutual interactions between the immune system and bone. SPP 1468 – IMMUNOBONE has been funded by the DFG for the first funding period of three years with a total volume of 7.3 million EUR. At the beginning of 2013, SPP 1468 – IMMUNOBONE has been positively evaluated for a second funding period for additional three years. The interdisciplinary consortium consists of 20 groups of 15 different research institutions of osteologic orthopedics, rheumatology, and immunology.

## Research

Osteoimmunology is an interdisciplinary research field investigating the interactions between immune and bone cells. It is assumed that both systems communicate with each other and that their interplay has an influence on diseases like osteoporosis and arthritis. Initial insights about the interaction between bone and the immune system were recognized 15 years ago by the discovery of a protein termed Receptor Activator of NF-κ B Ligand (RANKL). It was shown that molecules on the surface of immune cells influence bone homeostasis. Within SPP 1468 – IMMUNOBONE, we identified several molecular mechanisms and essential cellular interactions between inflammatory cells, cytokines, and bone cells. The findings improved knowledge of the pathogenesis of bone diseases triggered by inflammatory processes. On the other hand these findings form the basis to develop innovative therapy approaches for treatment of rheumatic inflammatory diseases. The significant results of the project groups in Erlangen can be summarized as follows:
A control mechanism of the adaptive immune system for bone resorption which is relevant for treatment of inflammatory diseases could be described. The group in Erlangen has shown that immune activating drugs increase the number of bone resorbing cells and that immune suppressive drugs which are prescribed for the treatment of inflammatory diseases reduce bone resorbing cells.
Different antibodies could be identified which show a strong and specific effect on osteoclast-mediated bone resorption by patients with rheumatoid arthritis. Particularly Fc-receptor activation plays a relevant role in the stimulation of osteoclastogenesis. Experimental investigations showed that the osteoclastogenesis is influenced by antibodies directly which bind to Fc-receptors on bone resorbing osteoclasts. These data about factors which control inflammation as well bone development emphasize the interactions between the immune system and bone.
During all inflammatory and renewal processes immune cells meet pathogens and human dying cells. The blockade of an enzyme in macrophages named 12/15 lipoxygenase (12/15-LO) leads to disturbed disposal of dying cells and results in autoimmune reactions. It is assumed that this mechanism takes place in all types of tissue in the human body and can be an approach to develop new therapies combating inflammatory diseases.
Furthermore, research within the consortium has revealed new clinical approaches to characterize human bone structure. Additional data showed that the nuclear receptor PPARβ/δ is a key player for bone homeostasis. Within SPP 1468 – IMMUNOBONE, RANKL could be identified to develop insulin resistance apart from its essential role within bone homeostasis. All the results show that diverse interactions between the immune and skeletal system exist which are clinically relevant. The results mentioned are just a part of the more than 70 scientific articles published within SPP 1468 – IMMUNOBONE.

## Teaching

The head of the research group is involved in the traditional teaching program (lectures, seminars, practica) covering all subjects in the field of medicine and molecular medicine as well as the Ph.D./MD programs for basic and translational research.

# BMBF Leading Edge Cluster "Center of Excellence for Medical Engineering – Medical Valley EMN e.V."

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## Aims and Structure

Following its application as a "Center of Excellence for Medical Engineering", the Medical Valley EMN was announced on 26 January 2010 as one of five winners in the Leading Edge Cluster Competition sponsored by the BMBF. The decisive, unique selling feature of the Medical Valley EMN Leading Edge Cluster is the common objective among all industrial and academic cluster partners: Interdisciplinary, research-based further development of products, services, and solutions that help to verifiably improve the effectiveness and efficiency of healthcare.
As part of an accompanying evaluation the implementation of the cluster strategy as well as the progress in achieving the stated objectives are reviewed regularly. In total, 45 leading edge cluster projects are making a vital contribution for reaching the objectives. Within ten exemplary selected projects, the respective contribution to increase the efficiency of health care was estimated. In total there is a German wide potential for reduction in health expenditure of more than EUR 1.4 billion per year without diminishing the quality of health care. The products and services developed in these projects are very competitive due to their level of innovation and thus likely to gain market share. The estimated sales potential of some of the products and services is almost 2.9 billion EUR in the period 2015 – 2020. The project ideas have already led to more than 40 granted patents and additional 80 patent applications. Project results were published in over 350 publications.

## Research

To further consolidate its leading position in the global market, the Medical Valley EMN cluster is generating innovative excellence in its core research areas of diagnostic imaging, intelligent sensors, treatment systems, and ophthalmology, as well as horizontal innovations for product and process optimization, a subject with broad application.

### Diagnostic imaging

The use of innovative diagnostic imaging technologies results in earlier detection of disease and therefore in less invasive, more cost-effective treatment. Diagnostic imaging is equally important for optimizing minimally invasive interventions and determining the effectiveness of treatment. The diagnostic imaging core research area includes projects many of which were performed in cooperation with the Department of Obstetrics and Gynecology, the Institute of Radiology, the Department of Otorhinolaryngology, and the Department of Medicine 1.

### Intelligent sensors

In conjunction with communication and information technologies, intelligent sensors can contribute significantly to reduce costs in the health system. Within the projects in this core research area, miniaturized sensor modules are being developed that can reliably measure vital care-related data, such as breathing and circulation parameters, in mobile situations outside hospitals. The modules help optimize the treatment of different illnesses with rapidly growing patient numbers, such as heart insufficiency. The following project of the Department of Medicine 2 is associated with this core research area: "Home monitoring of patients with cardiac insufficiency to avoid decompensation and reduce hospitalization rates".

### Treatment systems

Most of the research projects in this area are being carried out in cooperation with the Department of Anesthesiology, the Institute of Experimental and Clinical Pharmacology and Toxicology, the Department of Psychiatry and Psychotherapy, the Institute of Medical Informatics, Biometry, and Epidemiology, the Chair for Technical Thermodynamics, and the Department of Medicine 1. The projects are designed to increase personalization and safety in drug therapy, prove treatment with anti-infective drugs to be more efficient and economic, and develop innovative procedures for early diagnosis and safe treatment.

### Ophthalmology

Among diseases of the eye, defective vision such as presbyopia, cataracts, glaucoma, and age-related macular degeneration are by far the most prevalent and economically significant diseases. Together with the Department of Ophthalmology, leading technological companies who operate on a global basis within the Medical Valley EMN cluster are developing laser applications for refractive surgery, artificial lenses, and diagnostic systems in a number of Leading Edge Cluster projects.

### Horizontal innovations for product and process optimization

In addition to the core technology research areas, horizontal innovations for product and process optimization are also being generated in the Leading Edge Cluster. With the participation of the Interdisciplinary Center for Public Health, the "ProHTA" project is creating models to simulate the effect of new technologies on the quality of care as well as on direct and indirect costs. At the same time it is supporting the search for potential efficiency levers for new technologies and products.

INVENTED IN GERMANY
MEDICAL VALLEY
Europäische Metropolregion Nürnberg
GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

# BMBF-Network "Clinics and Pathophysiology of Osteophytes and Ankylosis (ANCYLOSS)"

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## Aims and Structure

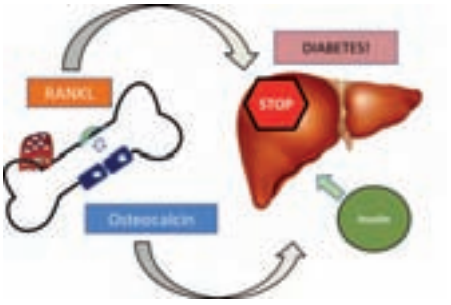
The ANCYLOSS consortium is funded within the BMBF framework "scientific networks of musculoskeletal diseases". The project was designed to investigate the molecular mechanisms and clinical impact of osteophytes (new bone formations) in joint diseases, such as osteoarthritis (OA), psoriasis arthritis (PsA), and ankylosis spondylitis (AS). The project has been funded with a total amount of 1.5 million EUR by the Deutsches Zentrum für Luft- und Raumfahrt (DLR; national aeronautics and space research center) for the first period (three years) in 2010. Within the six different work packages, the expertise were bundled from different scientific fields, such as bone biology, lipid metabolism, molecular biology, genetics, animal models, imaging, and clinical research. Three of these projects (WP 1 – 3) concentrate on the pathophysiology of osteophyte formation and joint ankylosis, the other three projects (WP 4 – 6) are more clinically orientated and determine biomarkers as well as imaging tools to better visualize osteophytes.

## Research

Primary goals of this collaborative project are to understand the mechanisms of osteophyte formation in degenerative and inflammatory rheumatic disease as well as to build concepts and strategies to therapeutically interfere with the onset and progression of such lesions. ANCYLOSS is the first consortium which pursues research on osteophytes by using an interdisciplinary approach. Hitherto the scientific concepts in rheumatic diseases focused on disease aspects such as inflammation, pain, and functional impairment, but did not sufficiently target the structural aspects of rheumatic diseases. The interdisciplinary structure of the project also facilitates the translation of results from laboratory into clinical research. This implementation is achieved by different strategies: Genetic and biomarkers studies will optimize prediction of osteophyte formation and high-resolution imaging will improve the detection of osteophyte formation. The ANCYLOSS consortium focuses the mechanistic and clinical aspects of musculoskeletal diseases and specifically the mechanisms relevant to the crosstalk between inflammation, bone, and the adipose tissue.
One of the exciting findings of the ANCYLOSS project was the observation that diabetes constitutes an independent risk predictor for severe joint diseases. By using a well-documented prospective epidemiological cohort of healthy individuals (Bruneck cohort), we could show that diabetes is associated with later development of severe osteoarthrosis resulting in joint replacement surgery. Importantly, this association was independent from the two other major risk factors for osteoarthrosis, i.e. age and weight. Since its foundation, the consortium has pub - lished 34 scientific publications and contributed to improve know-how about musculoskeletal diseases.

## Teaching

The interdisciplinary research is particularly suitable for the education of young scientists. The research group leaders supervise basic as well as clinically oriented theses in medicine and biology. The results of the interdisciplinary research will be rapidly implemented in lectures and advanced training courses (medicine/molecular medicine/medical physics) in order to raise interest among young scientists to join this project.




ANCYLOSS

DLR Project Management Agency

# BMBF Core Program "Molecular Diagnostics"

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## Aims and Structure

Molecular medicine has gained a significant increase in scientific and technological knowledge in the past years. The present challenge is to transfer available knowledge of basic research into clinical application. In this framework, the development of reliable diagnostic and prognostic markers for a powerful molecular diagnostics is still at the very beginning for many diseases. One of the major bottlenecks is the validation of potential biomarkers. Therefore, an improved connection of the results of basic research with clinical findings from well characterized patient cohorts is expected to significantly foster the development and validation of novel markers for individualized treatment in the future. The BMBF has established the core program Molecular Diagnostics to address this point. The primary goal of this program is to support molecular diagnostic research in Germany and to transfer results from basic research to clinically available and economically exploitable products or processes.

## Research

A research group headed by Erlangen on colorectal carcinoma was sponsored between the years 2009 – 2014. World-wide more than 945,000 colorectal carcinomas (CRC) are newly diagnosed per year, and 492,000 patients die of them. The goal of the study was the validation and diagnostic application of RNA expression profiles in order to predict the tumor stages and the responses to standard therapies of colorectal carcinoma. The project was sponsored by the BMBF and an industrial partner with a total of two million EUR. Within the frame of this proj - ect, different institutes and departments of the clinical centers in Erlangen, Frankfurt, and Bochum in cooperation with clinics in Cologne and Schwabach together with Siemens Healthcare Diagnostic Products GmbH were cooperating. It was a specific clue of this study that all investigations were exclusively carried out on routinely acquired paraffin-embedded and formalin-fixed material. This will foster the spread and commercial exploitation of the potential test in the future. The major innovative components for the project were established in previous studies by members of the consortium.

(1) Predictive and prognostic relevant marker signatures were identified through performing extensive transcriptome analysis on fresh tissues of colorectal carcinomas. Different marker signatures were detected which highly significantly identify metastatic tumor stages (Prof. Dr. R.S. Croner, Department of Surgery) and predict angiogenesis-related survival (Prof. Dr. Dr. M. Stürzl, Department of Surgery), as well as responses to chemotherapy (Prof. Dr. W. Brückl, Department of Medicine 1) and radiochemotherapy (Prof. Dr. C. Rödel, PD Dr. F. Rödel, Clinical Center Frankfurt).
(2) The industrial partner of the consortium has established a technology for the isolation of RNA from formalin-fixed, paraffin-embedded tissues which are acquired from routine pathological procedures. In this process, the RNA is isolated by silicate-coated magnetic beads which bind nucleic acids with high affinity. Based on this simple, but efficient purification principle, the extraction of RNA from tissue sections could be fully automated. The process has been optimized so that one thin section of a tumor tissue is sufficient to extract RNA amounts sufficiently high enough for quantitative RT-PCR analyses of the expression of more than 1,000 different genes (Polyprobe-test). Siemens Healthcare Diagnostic Products GmbH has established this key technology at the UK Erlangen and in addition has provided the required equipment for the procedure in the course of the cooperation. In the project, 61 different molecular markers which have been identified in previous studies were validated in an independent patient cohort. Currently, three markers have been identified from previous analysis (n = 80 CRC) which correlate significantly with metastasis in independent retrospective (n = 82 CRC) and prospective (n = 203 CRC) patient cohorts. During further analysis of 177 cases, these three markers showed a significant correlation with survival during a five year follow-up period. Up to the end of the funding period, the predictive power of the Polyprobe-test for determination of the tumor stage (primary endpoint) and the prediction of response to standard therapy (secondary endpoint) will be evaluated. In the course of an ongoing follow-up period (36 months after the end of patient recruitment), it will be investigated whether the established biomarker signatures can also predict disease free survival or total cancer-related survival in the recruited patients. The study is carried out in a prospective manner. 650 patients have been successfully recruited and the expression of all 61 marker genes has been analyzed. Accordingly, this study is one of the largest studies on this subject worldwide.

# Bavarian Research Network „Induced Pluripotent Stem Cells (ForIPS)“

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## Aims and Structure

The Bavarian Research Network ForIPS has the major and long-term goal to establish human cellular disease models and novel intervention strategies for sporadic and chronic disorders of the brain with the current focus on sporadic Parkinson's disease (PD). The first task of the ForIPS consortium is to establish a biobank for human induced pluripotent stem cells (IPS) of Parkinson's disease patients and healthy controls at the UK Erlangen including the implementation of important quality controls in terms of genomic and transcriptional stability as well as the development of non-integrating reprogramming strategies. Reprogramming of mature cells of the body into so called "induced pluripotent stem cells" represents one of the most innovative biomedical developments in recent years (Nobel Prize in Medicine, 2012). Using this technology, connective tissue cells of patients are obtained and reprogrammed to the stage of pluripotency. As a result, patient specific stem cells are generated and in the framework of ForIPS further differentiated to neurons. Using this technology, ForIPS is able to generate IPS-derived neurons from affected patients. These cells may serve as a cellular model for the analysis of individual disease mechanisms, in particular with regard to the individually underlying pathogenesis of the patient, thus enabling the development of new treatment strategies.

## Research

The Bavarian Research Network ForIPS focuses on the most prevalent neurodegenerative movement disorders of Western industrial countries, the sporadic Parkinson's disease, first described by James Parkinson in 1817. This disorder is characterized by specific motor deficits such as bradykinesia, rigidity, tremor, and postural instability. Throughout the disease course, in particular, however, in the premotor stage, non-motor symptoms such as hypoosmia, autonomic dysfunction, disturbed gut mobility, and cognitive deficits are observed. The goal of ForIPS network is, based on PD-derived cells, to characterize the molecular and cellular mechanisms which are crucial for the etiology for the disease. To this aim, ForIPS provides the individual projects with primary skin fibrobiasts or with IPS. The projects, headed by Prof. Dr. A. Reis (FAU) and Prof. Dr. M. J. Riemenschneider (UK Regensburg), are analyzing the genetic and epigenetic stability and alteration of IPS and its cellular derivatives. The scientific questions of other projects are covering in particular functional studies on neural cells and focusing on neuronal compartments such as neurites and synapses (Prof. Dr. J.H. Brandstätter, Prof. Dr. J. Winkler, FAU), on intracellular organelles such as mitochondria (Dr. D. Vogt-Weisenhorn, Prof. Dr. W. Wurst, TU Munich), on intraneuronal mechanisms such as autophagia (PD Dr. J. Klucken, Prof. Dr. D.C. Lie, FAU) as well as on proteins such as TAU (Dr. S. Schwarz, Prof. Dr. G.U. Höglinger, TU Munich). In addition, the project of Prof. Dr. M. Wegner (FAU) is focusing on the generation of enteric nervous tissue, in particular in the light, that the gut may be one of the first sites for the onset of Parkinson's disease. The functional assessment of astrocytes, underlying specific Parkinson-associated neurodegenerative processes, will be examined by Prof. Dr. M. Götz (LMU Munich; deputy speaker). The inflammatory interplay between neuronal and glial cells is the major task of the project of ForIPS of Dr. I Prots and Prof. Dr. B. Winner (IZKF Research Group FAU), whereas Prof. Dr. F. Edenhofer (JMU Würzburg) aims at developing transgene-free reprogramming strategies and at studying age-dependent processes in cell culture models of Parkinson's disease. Furthermore, *in situ* reprogramming strategies of pericytes and the differentiation of IPS to specific striatal interneurons are developed in the project of Dr. M. Karow (LMU Munich) and Prof. Dr. B. Berninger (JGU Mainz). Based on the common source of patient-derived cells, there is a high interaction within the research network, furthermore a long-lasting biobank of IPS with its cellular derivatives is established at the UK Erlangen. Novel technologies in life sciences such as the IPS-technology are positioned in our society and raise important ethical questions which are covered by two projects in particular focusing on the internal and public discussion as well as on aspects of biopatenting and commercialization (PD Dr. A. Manzeschke, TTN Munich, Prof. Dr. P. Dabrock, FAU).

## Teaching

The research network ForIPS, coordinated by Dr. R. Lederer together J. Burczyk (FAU), is undergoing large efforts in activities for the education and training of young undergraduates, graduate students, as well as postdoctoral fellows. By offering seminars at the UK Erlangen, the participating scientists are enabled to learn the technology of human IPS, thus standardizing the cell culture models and transferring this technology to all other Bavarian sites. In addition, two Ph.D. seminars with different topics in stem cell biology and neurodegeneration took place in 2014. In July 2015, an international symposium is planned at the Carl-Friedrich-von-Siemens-Foundation (Munich) with numerous outstanding national and international speakers.

# Bavarian Immunotherapy Network (BayImmuNet): Adoptive Immunotherapy

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## Aims and Structure

Immunotherapy – the therapeutic interference with the human immune system – is one of the most important cornerstones of modern medical research. One of the current challenges is the translation of innovative therapy approaches from the laboratory into clinical application. In the area of immunotherapy – particularly antibody therapy and cellular therapy – Bavaria has excellent scientific teams and, consequently, a high degree of scientific potential. Many of the projects carried out by those teams are already at a stage in which rapid translation into clinical application can be expected. However, on the part of the university hospitals there is an investment bottleneck that is preventing rapid and efficient translation into clinical application. The Bavarian Immunotherapy Network (BayImmuNet), a unique network established by the Bavarian state government in 2008 with a start-up financing of ten million EUR, has set itself the goal of achieving faster translation of new approaches in immunotherapy into clinical application. Five clinical research groups were established at the universities of Erlangen, Regensburg, Würzburg, and München (LMU and TU München).

## Research

Realization that cellular immune reactions, mediated primarily by activated T-lymphocytes recognizing defined antigens, are responsible for the rejection of tumors in experimental models has led to multiple attempts to develop effective immunotherapies for the treatment of cancer patients based on stimulating T cell reactivity against cancer antigens.
Recent success using adoptive transfer of tumor-specific T cells has fueled optimism that this approach may find a place as a targeted therapy for some human cancers. Furthermore, it is well established that the curative potential of allogeneic bone marrow transplantation (BMT) is due to immunocompetent donor T cells inducing potent antineoplastic effects against host tumor cells, the "graft versus tumor" (GvT) reaction.
However, GvT reactions are mostly associated with the graft-versus-host disease (GvHD) which is the major cause of morbidity and mortality after allogeneic BMT.
This project aims at developing new strategies for the priming, selection, and expansion of antigen-specific effector T cells (CTL) under the guidelines of good manufacturing procedures (GMP) that will be used for adoptive T cell therapy in patients with solid and hematologic malignancies. CTL generated with peptide-pulsed antigen presenting cells are often peptide reactive, but not reactive with tumors that express the gene of interest due to low level expression or impaired antigen processing by the tumor cells.
To circumvent this, we will focus on an approach of full-length proteins or overlapping peptides to generate T cell lines with a broader antigenic repertoire. The focus of another clinical study will be on the comparative analysis of different chemotherapeutic strategies for the induction of lymphopenia before adoptive T cell transfer.
Changing the equilibrium of various immune cell populations may result in a selective advantage being given to adoptively transferred T cells. Successful accomplishment of the aims could yield a new treatment option for patients with certain types of cancer, particularly malignant melanoma and hematologic diseases after allogeneic BMT.
The new building housing the Center for Internal Medicine (INZ) provides clean-rooms within the Department of Medicine 5 – Hematology and Oncology for the cGMP compliant production of cellular products. A clinical phase I study investigating the prevention of CMV/EBV reactivation with CMV/EBV specific T cells as „Advanced Therapy Medicinal Product (ATMP)" in patients after allogeneic stem cell transplantation was initiated in 2014. The study is currently recruiting and involves six centers throughout Germany. The study is funded by the BayImmuNet consortium.

## Teaching

The pricincipal investigators of BayImmuNet are involved in the teaching program (lectures, seminars, practica) covering all subjects in the field of medicine and molecular medicine and the Ph.D. and MD program for basic and translational research.

# German Chronic Kidney Disease (GCKD-Study): National Cohort Study on Chronic Kidney Disease

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## Aims and Structure

Chronic kidney disease is an increasing health problem, affecting approximately 10% of the population. The burden of morbidity and mortality associated with chronic kidney disease derives from progression to end stage renal disease with requirement of dialysis. Patients suffering from chronic kidney disease have a disproportionate risk of cardiovascular diseases including myocardial infarction and stroke.
However, the course of progression of kidney and cardiovascular disease in the setting of renal disease is highly variable and factors determining progression and complication rates are to a large extend unknown.
The number of randomized controlled trials in nephrology lags behind all other medical disciplines.
To address these questions, the FAU is coordinating a large prospective observational cohort study in Germany including the cooperation with the universities of Aachen, Berlin, Freiburg, Hannover, Heidelberg, Innsbruck, Jena, München, Regensburg, and Würzburg and a network of approximately 200 nephrologists from different regions all over Germany.
The study aims at gaining important insights on the heterogeneity of disease courses in observing a large number of patients over a long period of time, opening ways for a more deliberate and focused application of existing diagnostic and therapeutic procedures, and developing novel and more effective therapies.
The GCKD Study is funded by the KfH Foundation of Preventive Medicine and the BMBF.

## Research

A total of 5,217 patients with impaired kidney function have been included and will be observed over a period of up to ten years. With this number of patients, the GCKD study represents the largest prospectively followed cohort of patients with chronic kidney diseases worldwide. Observations on the course of the disease, symptoms, and complications will be correlated with genetic information and findings from bioanalytical approaches in blood and urine samples applying modern biostatistical methods of data analysis. A large central biobank has been established in Erlangen. The study aims at establishing valid associations between biomarkers affecting the disease progression and opening insights to the question why patients with kidney disease have a tremendously increased risk and disposition of cardiovascular diseases, including elevated blood pressure, myocardial infarction, and stroke.
Another research focus is placed on the implications and consequences of kidney impairment on general health and quality of life. These findings on disease course and associated complications will open ways for a more deliberate and focused application of diagnostic and therapeutic procedures, improve the overall prognosis, and help to postpone or avoid onset of dialysis.

*Picture of the biobank at the TRC.*

# Clinical Research Unit 257: Molecular pathogenesis and optimized therapy of chronic inflammatory bowel disease (CEDER)

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## Aims and structure

The Clinical Research Unit 257: CEDER (KFO 257) was established in 2012 at the UK Erlangen and has since been supported by the DFG. Topics of the research center are the molecular pathogenesis and optimized treatment of inflammatory bowel diseases (IBD; Ulcerative Colitis and Crohn's disease).
Ulcerative colitis and Crohn's disease are prototypes of recurrent chronic inflammation of the intestine. Research in recent years has led to the realization that both, environmental and genetic factors and a misdirected activation of the intestinal immune system to the intestinal flora, are key pathogenetic factors for the development of these diseases. The aim of KFO 257 is to develop and evaluate concepts for the pathogenesis of chronic IBD in order to develop new diagnostic and therapeutic approaches for the clinical management of these diseases. This translational research approach will be conducted in a close interaction between clinically and scientifically active IBD specialists and experienced basic scientists in Erlangen. For example, innovative approaches to influence angiogenesis, mucosal healing, and aberrant immune responses are developed and evaluated experimentally. In addition, methods are established to improve individualized diagnosis and therapy of IBD and the molecular mechanisms of action of established therapies are being researched. Should KFO 257 succeed in developing preclinical therapy concepts, testing in clinical trials will be sought. In the years 2013 and 2014, KFO 257 had two positions to allow rotation of clinicians into laboratories.
On September 24th, 2013 a meeting was held at Schloss Weissenstein in Pommersfelden in which the project leaders presented and discussed their scientific results. On 27th and 28th October 2014, KFO 257 was re-evaluated by an international advisory committee of the DFG. In this evaluation, the Commission of Experts strongly praised the dynamic development of the center and the excellent research achievements and recommended funding for additional three years. It was emphasized that KFO 257 currently represents the leading center for IBD in Germany. In addition, the reviewers were impressed by the promotion of the clinical and young scientists. Nine out of ten newly proposed projects were recommended for funding.

## Research

In 2013/2014 KFO 257 was structured into seven projects (TP):

- TP 1: Mechanisms of cytokine-mediated immune pathogenesis of IBD.
  Project managers: Prof. Dr. C. Becker/PD Dr. J. Mudter (Department of Medicine 1)
- TP 2: Functional analysis of the immunomodulator sCD83 in the pathogenesis and therapy of inflammatory bowel disease.
  Project managers: Prof. Dr. A. Steinkasserer/ Dr. M. Lechmann (Department of Dermatology, Division of Immune Modulation)
- TP 3: Role of the Wnt/-catenin signaling pathway in IBD.
  Project manager: Prof. Dr. J. Behrens (Chair of Experimental Medicine II )
- TP 4: Immune regulation of angiogenesis in IBD.
  Project managers: Prof. Dr. M. Stürzl/Dr. M. Waldner (Department of Surgery/Department of Medicine 1)
- TP 5: Analysis of the molecular mechanism of action of cyclosporin A in ulcerative colitis.
  Project managers: Dr. B. Weigmann/Prof. Dr. R. Atreya (Department of Medicine 1)
- TP 6: Characterization and expansion of regulatory T cells to establish a cell-based therapy of IBD.
  Project managers: Prof. Dr. M.F. Neurath/Prof. Dr. G. Schuler (Department of Medicine/Department of Dermatology)
- Central project: Project to coordinate the scientific program of the KFO 257.
  Project managers: Prof. Dr. C. Becker/PD Dr. J. Mudter (Department of Medicine 1)

## Teaching

Seminars on IBD:

- Immune pathogenesis and treatment of inflammatory bowel disease
- Molecular Medicine
- Molecular mechanisms of tumor development in the intestine
- Physiology and pathophysiology of the gut
- Seminar internal medicine, pathophysiology of IBD
- Academic research in medicine: insights into current clinical-immunological research and dissemination of methodologies knowledge

Current scientific literature (Topic: Research publications on IBD)
Research progress seminar (Topic: Current research findings of KFO 257)

### Meetings and International Training Courses

– 13.04.2013 Doctor-Patient-Seminar IBD
– 19.07.2013 Training for doctors IBD
– 15. – 16.11.2013 training for doctors IBD
– 23.11.2013 Doctor-Patient-Seminar IBD
– 11.12.2013 training for doctors IBD
– 28.03.2014 training for doctors IBD
– 31.05.2014 Doctor-Patient-Seminar IBD

*Meeting of the Clinical Research Unit*

# Research Unit 832: Regulators of Humoral Immunity

**Speakers**
Prof. Dr. rer. nat. Thomas Winkler
(Faculty of Natural Sciences)
Prof. Dr. rer. nat. Hans-Martin Jäck
(Faculty of Medicine)

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## Aims and Structure

Since 2008, the DFG has been sponsoring a new interdepartmental research unit (FOR) with the main topic of "Regulators of the Humoral Immune Response" and granting a total volume of two million EUR for it. Seven scientists from the Institute for Biology (Faculty of Sciences, three projects) and the UK Erlangen (Faculty of Medicine, four projects) are participating in the research unit. Five of the eight participating project leaders which include both, biologists and clinicians, are residing at the NFZ. In close cooperation, the seven projects research the molecular circuits that are involved in the control and regulation of antibody-producing B-lymphocytes. Cell-culture and mouse models are employed. Meetings on a regular basis (such as at the monthly B cell Club), a mutual concept for the education of doctoral students analogous to the program of the expired GK 592 ("Lymphocytes: Differentiation, Activation, and Deviation"), the participation in supervisory commissions for doctoral students, as well as scientific colloquia (B cell retreat) additionally promote the mutual scientific objective.

## Research

The B cell is at the center of attention of FOR 832. During its maturation in the bone marrow, the genes for the antibody molecules are assembled by rearranging the corresponding DNA segments. This process creates millions of B cells, all of which produce a different type of antibody. This molecule is either directed at a specific pathogen or at a molecular structure that generally signals an attack. The mature B cell initially carries its antibody to the cell surface, thus allowing detecting an appropriate signal. In this case, the B cell is activated in the peripheral lymphatic organs and releases large amounts of soluble protective antibodies into the blood. FOR 832 concentrates on these complex regulatory processes during the maturation and activation of B cells.

On the one hand, congenital disorders of the complex differentiation schema can lead to immune deficiencies – which means to a special susceptibility to conditions ranging from infectious diseases to life-threatening immune defects. However, excessive and misdirected immune responses, such as those of allergies and autoimmune diseases, are caused by disorders in the regulation of the immune response. In autoimmune patients, the immune system frequently develops antibodies that react to structures of their own body instead of pathogens. The research unit directs the focus of its work towards the clarification of such undesirable developments. The approach of the research unit is initially focused on fundamental research because it will only be possible to develop new types of therapy through a better understanding of the molecular circuits and complex cell-cell interactions in the immune defense that is imparted by the antibody.

At the present time, an efficient humoral immune response cannot be adequately reconstructed "in the test tube". The high degree of complexity and the multitude of cellular and molecular interactions between B cells and other cells of the immune system require studies on the living organism, on both tissue sections and cells that have been isolated from the suitable animal models through appropriate cell-sorting methods. Consequently, one experimental focus of FOR 832 is the use of the mouse as an animal model for the humoral immune response. The research of the previous years has clearly demonstrated that the processes of antibody formation occur in a very similar manner in mice and humans. The possibility of using and also establishing "genetically tailored" mouse models here in Erlangen will be employed by the research unit, for better understanding molecular and cellular processes during the humoral immune response that cannot be specifically investigated in either the cell cultures or the human being.

## Teaching

All project leaders are actively integrated into the supervision of the respective doctoral students as members of the doctoral supervisory commissions. All members of the research unit are also actively involved in public relation (such as the Long Night of the Sciences and supervision of seminar theses for high school students).

# Research Unit 894: Fluid Mechanical Basis of the Human Voice

**Speaker**
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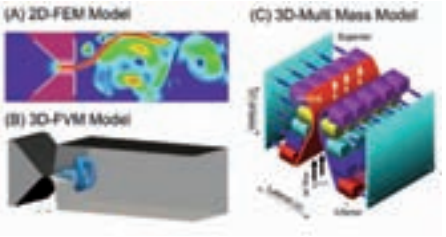
## Aims and Structure

Participating Institutions:
Division of Phoniatrics and Pediatric Audiology, Chair of Applied Mathematics II, Chair of Sensor Technology, Institute for Process Technology and Machinery, Institute of Fluid Mechanics (all FAU);
Institute of Mechanics and Fluid Dynamics (TU Bergakademie Freiberg);
Institute of Mechanics and Mechatronics (Vienna University of Technology).
Funding period was 01/2008 – 12/2013.
Voice production within the larynx is still not entirely understood, neither in normal nor in pathological voice. The goal of the interdisciplinary research unit (FOR) 894 is to substantiate knowledge of normal and pathological vocal fold dynamics and of the resulting acoustic signal. Human voice is the result of a complex process comprising fluid dynamics coupled with moving elastic tissue. Analyzing such complexities necessitates different modeling approaches. Therefore, departments from different research fields are working together to derive a better picture of the entire voice origination process. The different suggested models allow a review and verification of the results and assumptions. In the international fluid dynamics and voice research community, different approaches are still applied and discussed on their own. Hence, FOR 894 is performing pioneer research. To coordinate and lead the interdisciplinary group, the DFG established a W2-professorship on Computational Medicine. Prof. Dr.-Ing. M. Döllinger is the scientific head of FOR 894.
During the funding period, FOR 894 published more than 50 journal articles and more than 130 conference contributions. Five members of the FOR were appointed to professorships, further two members were granted the title apl. Professor. Two members obtained the postdoctoral qualification showing the ability to lecture and do research at professorial level. More than 20 medical doctoral theses and nine technical doctoral theses were completed within the FOR.

## Research

The strategy of FOR 894 is the application of different experimental and numerical models, yielding a comprehensive description of voice production. The bases for the models are endoscopic high speed digital video recordings from both, healthy and pathological subjects. At the Division of Phoniatrics and Pediatric Audiology, biomechanical models are fitted to the recorded dynamics for receiving quantitative information on the severity of diseases.
For analyzing fluid mechanical causalities, an air driven physical model has been developed representing a realistic model of human voice production. Vocal folds consisting of a silicon mixture are set into vibration and allow to experimentally analyze the entire chain of fluid-structure-acoustic interaction. The material parameters of the synthetic vocal folds are adapted to human laryngeal tissue by numerical optimization algorithms (Institute of Applied Mathematics II). The model enables the variation of pressure, air flow, and elongation of the synthetic vocal folds (Chair of Sensor Technology). Hence, impacts on dynamics and acoustics can be observed and analyzed. However, irregularities cannot be separated regarding their cause and resulting effect.
To investigate predefined clinical observed irregularities and their impact on voice quality, a water driven model was developed by the group from Freiberg. Here, the fluid dynamics are easier to observe due to the increased time scale. This model is especially appropriate for observing eddy induced acoustics.
The experimental work is supplemented by a numerical 2d-finite element method model and a 3d-finite volume model. Thus, fluid volume as well as mechanical induced acoustics can be analyzed directly. However, due to the complexity, these models cause high computational costs.
By these approaches the different acoustic sources can be investigated and analyzed. In the future, conclusions for medical conservative as well as surgical treatments will be driven, based on the cause-and-effect chain.




*The three by the group developed and applied numerical models.*

## Teaching

The participating groups in FOR 894 supervise mathematical, technical, and medical theses as well as interdisciplinary master theses and student research projects. The principal investigators of the different projects are involved in lectures in three different Faculties (Medical, Engineering, and Sciences).

# Research Unit 1228: Molecular Pathogenesis of Myofibrillar Myopathies

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## Aims and Structure

The DFG has been funding the multilocation research unit (FOR) 1228 since November 2009. This FOR aims at clarifying the molecular processes that lead to progressive skeletal muscle and cardiac damage in myofibrillar myopathies. FOR 1228 combines the scientific expertise of physicians, biologists, and biochemists and is composed of 13 distinguished groups from the universities of Erlangen, Bonn, Bochum, Köln, Heidelberg, Ulm, and Vienna. After a positive evaluation in July 2012, FOR 1228 was granted a second funding period until November 2015. The financial support of the DFG sums up to 3.6 million EUR for a six year term of funding.

## Research

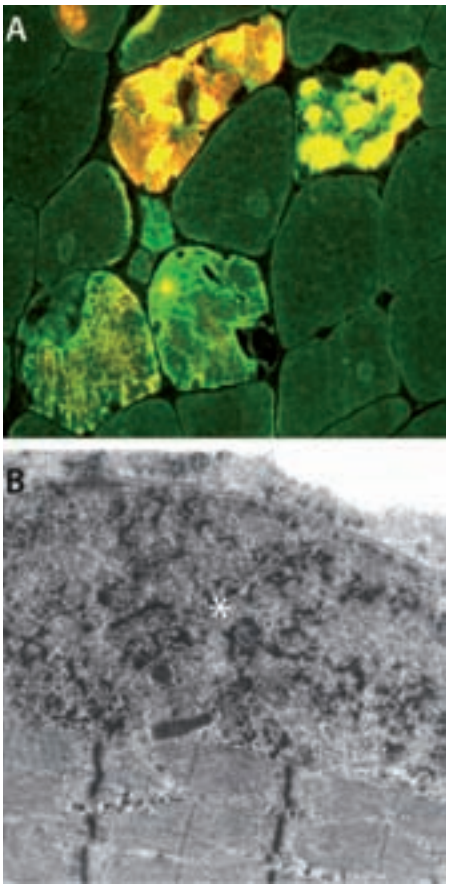
Myofibrillar myopathies (MFM) are progressive and devastating diseases of human skeletal and cardiac muscles that often lead to premature death. MFM are histopathologically characterized by desmin-positive protein aggregates and myofibrillar degeneration. While about half of all MFM are caused by mutations in genes encoding sarcomeric and extra-sarcomeric proteins (desmin, filamin C, plectin, VCP, FHL1, ZASP, myotilin, and B-crystallin, BAG3, DNAJB6), the other half of these diseases is due to still unresolved gene defects. During the first funding period, FOR 1228 has made substantial contributions to our current understanding of the molecular pathogenesis of desminopathies, plectinopathies, filamin C-, FHL1- and VCP-related MFM. Major joint achievements have been the establishment and validation of MFM-related animal and cell models, the adaptation and refinement of laser microdissection and proteomic analysis of pathological protein aggregates and biochemical approaches to address molecular pathways contributing to the pathogenesis of MFM. In the second funding period, FOR 1228 will focus on the following major goals:

1) Characterization of individual and shared disease mechanisms in myofibrillar myopathies due to pathogenic desmin-, plectin-, filamin C-, and VCP-mutations;
2) Systematic analyses of disease-specific cell and animal models;
3) Validation of cell and animal models for pharmacological treatment strategies;
4) Proteomic characterization of the composition of pathological protein aggregates in skeletal muscle biopsies from patients with genetically proven MFM-causing gene mutations and mouse models;
5) Identification of novel candidate genes that cause human myofibrillar myopathies by laser dissection microscopy followed by proteomic analysis and genomic DNA sequencing;
6) A multi-scale approach addressing biomechanical properties of MFM in myoblasts, myofibers, and whole muscles.

FOR 1228 offers the unique opportunity to unravel the molecular "MFM sequence" that leads to pathological protein aggregation and progressive muscle damage. Currently no causative or ameliorating therapy is available for MFM. The joint work of FOR 1228 will therefore not only provide deeper mechanistic and preclinical insight into the pathogenesis of MFM, but also aims at paving the way to novel targeted treatment concepts. As translational approach we will therefore study the therapeutic effect of drugs and compounds that directly target pathological protein aggregation processes. In addition, gene replacement strategies by AAV-mediated gene transfer will be evaluated.

## Teaching

The participating groups of FOR 1228 are supervising Ph.D. and/or medical theses. The principal investigators of individual projects are also actively participating in the teaching of students in the field of medicine, molecular medicine, biology, and biochemistry.




*Visualization of pathological protein aggregates in a diagnostic skeletal muscle biopsy from a patient with genetically confirmed desminopathy.*
*A) Double-immunofluorescence labelling of pathological protein aggregates (yellow) using antibodies against desmin and alphaB-Crystallin.*
*B) Ultrastructural demonstration of granulofilamentous protein aggregates (*) in direct vicinity to myofibrils.*

# Integrated Research Training Group 130: B cells and beyond

**Speaker**
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## Aims and Structure

The DFG has been supporting the SFB Transregio 130 (TRR 130) "B cells: Immunity and Autoimmunity" since 2013. The intercity research consortium assembles B Cell Immunologists from the Faculties of Medicine and Sciences of the FAU as well as the Albert-Ludwigs-University Freiburg, the Charité Berlin, the Deutsches Rheuma-Forschungszentrum, the Max Planck Institute for Infection Biology, und the Universitätsmedizin Göttingen to better understand the function and dysfunction of B cells. To train highly skilled and internationally competitive immunologists and to foster interactions within and between the four participating locations, an integrated GK (IRTG) with a strong research and training program as well as mentoring and career development concept has been established within the TRR 130. Common retreats, lab rotations within the TRR 130, and the annual B Cell Winter School provide an ideal platform for an intensive exchange between principle investigators and doctoral students within and between the four participating locations.

## Research

B cells are an important part of the human immune system. When pathogens invade the body, B cells are activated and differentiate into so-called plasma cells that produce pathogen-fighting antibodies. Scientists of the TRR 130 examine the mechanisms that control the activation of B cells and the production of antibodies. In particular, scientists of this consortium will elucidate in detail how B cell responses are triggered, how B cells learn to remember pathogens (the so-called immunological memory), and how plasma cells manage to produce high affinity antibodies for long periods of time. A second scientific topic of the TRR 130 is to understand how B cells with autoreactive antigen receptors are activated to produce autoantibodies that attack the body´s own tissue. Autoantibodies can be involved in the pathogenesis of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, or multiple sclerosis. The scientists of this consortium aim at broadening the general knowledge of B cell and antibody-mediated autoimmune diseases with the long-term goal to develop new therapeutic strategies against these diseases.

## Teaching

The training program of the IRTG will be based on four pillars: research, education, mentoring, and career development. Each Ph.D. student will be supervised by a thesis advisory committee. It consists of the supervisor and two additional group leaders of the TRR 130. The annual B Cell Winter School provides a platform for the Ph.D. students to present their research in front of a larger audience and to discuss the progress of their Ph.D. thesis. Each of the four participating locations offers a bi-weekly jour fixe where doctoral students can discuss relevant literature, research results and new methods with the local TRR 130 investigators. A student exchange program allows optional visits in laboratories within the TRR 130 to broaden the range of methods of the Ph.D. students, foster exchange, and promote cooperation between the participating locations.
Science and professionally relevant workshops (e.g. presentation of industrial occupational fields beyond academia, scientific writing skills or the analysis of scientific results) are offered on site by each city or centrally for all Ph.D. students. To develop their organizational skills, the doctoral students are encouraged to organize their own meetings, contribute in the design of the educational program, and participate in the IRTG steering committee. To improve the Ph.D. students' national and international networks and to discuss their projects in a broader context, Ph.D. students have the possibility to participate at network meetings with other GK and organize the international TRR 130 symposium and the bi-annual international GK symposium. To promote public awareness about the importance of immunological research, the IRTG-Ph.D. students also participate in local public relations projects. Finally, the IRTG covers the costs to attend scientific congresses and the various immunology schools of the "Academy of Immunology" within the German Society for Immunology.


# Integrated Research Training Group within SFB 643: Strategies of Cellular Immune Intervention

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## Aims and Structure

The GK is integrated in the SFB 643 "Strategies of Cellular Immune Intervention". It will train the doctoral candidates to become highly qualified scientists. With a structured educational and support program, it will prepare purposefully for the job. Our offer to the students includes a bi-weekly regular meeting, workshops on communication and GMP-production, project-related workshops that allow students to spend time in labs outside of Erlangen. Additionally, each student gets the chance to gain organizational skills, build up scientific networks, and discuss their research with internationally recognized scientists. Finally, the close supervision of the students by three faculty members streamlines and focuses each research project and thus facilitates the completion of the thesis in a timely manner.

## Research

The SFB 643 "Strategies of Cellular Immune Intervention" has been existing since July 2004 and is currently in its third funding period. The goal of the SFB 643 is the successful implementation of immunological knowledge in treatments that are based on a manipulation of the immune system, i.e. on immune intervention. Immune therapeutic approaches to treat tumors and infectious diseases require the enhancement or stimulation of the immune response. Conversely, innovative treatments of inflammatory diseases, including autoimmune diseases, allergic diseases, and transplantation reactions, call for novel and improved immunosuppressive strategies.

The research program is conceptually structured in three closely interconnected project areas:

**Project area A:**
Basic immunology

**Project area B:**
Immune intervention in animal models

**Project area C:**
Therapeutic applications

## Teaching

We believe that our structured mentoring and education program will not only result in better trained doctoral students, but will also make them independent scientists early in their career. Our goal is based upon the following mentoring and educational units: Every graduate student will be accompanied by a support commission. It consists of the direct supervisor and two part-project-leaders of the SFB 643. In a bi-weekly regular meeting the candidates discuss literature, methodical problems, and their own research-data. Internal Report-Symposia and Network-Meetings with other topically relevant and external GK will train the candidates to present their research in front of a larger council. Workshops imparting the following skills are held: Knowledge of the different industrial occupational fields and the improvement of the students' presentation and scientific writing skills. The SFB 643 emphasizes on translating experimental data into clinical practice. Therefore, courses will be offered that deal with the GMP-production of cell based medicine and medical auxiliary material, quality management, certification, and accreditation. Project-related courses, optional visits in external laboratories over the course of several months within the trainee program, and a guest speaker program teach the candidates how to take personal responsibility, establish international networks, and discuss their research projects with international scientist.
We have experienced that especially the intensive scientific exchange does not only educate the candidates to the better, but also helps them to become independent scientists very early in their career. By including the support commission and an intense exchange between the candidates and their mentors, "wrong directions" are detected at an early stage and the education of the candidates is streamlined.

# Integrated Research Training Group within Collaborative Research Center 796: Erlangen School of Molecular Communication

**Speaker**
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## Aims and Structure

The GK "Erlangen School of Molecular Communication" forms part of the SFB 796 "Reprogramming of Host Cells by Microbial Effectors", an interdisciplinary cooperation of groups from the Faculty of Medicine and the Faculty of Sciences of the FAU as well as the UK Erlangen and the Fraunhofer Institute of Integrated Circuits. The GK offers an attractive doctoral program, primarily for students of the natural sciences, but also for medical students. There is a strong emphasis on lively scientific exchange and interdisciplinary work. This is promoted by annual retreats, an engaging series of seminars and a mentoring program. As a special feature, the GK now offers a fast track program. Outstanding students will be given the opportunity to replace the two-year master degree by a one-year curricular phase, thus starting their doctoral studies more quickly.
First funding period: 2009 – 2012
Prolongation: 2012 – 2016

## Research

The strong focus on interdisciplinary research at the GK "Erlangen School of Molecular Communication" is both, attractive and challenging. The research within the SFB 796 aims at investigating the dynamic interplay between microbial effectors (viruses and bacteria) and their host cells. This is achieved by examining both, the intrinsic response of plant and mammalian cells and the microbial host cell manipulation at the molecular and cellular level. This research raises the question whether similar structures and mechanisms have developed in the heterogenic host/pathogen interactions during evolution. These general themes may be extended to other pathogens not investigated within the SFB initiative.

### Project area A: Structural basis of molecular interactions

Research in project area A focuses on structure/function relationships of previously identified effector proteins and their interactions with specific cellular targets. Major topics include investigation of the HIV regulatory Vpr protein, of HIV mimetic molecules, structural analyses of the potyvirus with plant chaperones, and the development of bioinformatic tools for the prediction of protein-protein interactions.

### Project area B: Reprogramming cellular processes

The focus of project area B is the detailed elucidation of mechanisms used by microbial effectors to reprogram cellular processes, including selected signal transduction pathways, intrinsic immune responses, targeted protein turnover, and the primary metabolism. Research objects range from viral pathogens (herpesvirus saimiri, herpes-simplex virus 1, human cytomegalovirus) to bacterial pathogens of plant and human cells (Xanthomonas campestris, Corynebacterium diphtheriae).

### Project area C: Replication structures and transport processes

Project area C focuses on the question of how microbial effectors use and partially convert cellular structures for successful colonization and replication. A number of different types of host/pathogen interactions are also investigated in this area, namely the role of molecular chaperones during virus replication and spreading in plants, the structure and function of the nuclear egress complex of the human cytomegalovirus, the influence of the vesicles transport in plants by type III effectors from X. campestris as well as the development of new methods for the expression analysis of Salmonella-virulence proteins.

## Teaching

The GK offers structured research training in internationally renowned laboratories. Each doctoral student is supervised by two experienced scientists: The principal investigator of the relevant SFB project and another SFB member. The training program is complimented by scientific and method lectures. Graduate students are given the opportunity to choose the topics for the GK seminars according to their own requirements and were also given responsibility for one session within the first international conference of the SFB in October 2011. Acquisition of soft skills is an important part of the individual development of the students and will support their scientific work and future career. With this in mind, a number of tailor-made workshops are organized to improve presentation and communication skills and writing techniques. In addition to these courses, further training in specific techniques or methods, such as statistics or fluorescence microscopy, are also provided on student request.

*Retreat of the integrated research training group within SFB 796 at Kloster Banz.*

*Confocal Laserscanning Microscopy of macrophage infections with pathogenic corynebacteria.*

# Research Training Group 1071: Viruses of the Immune System

**Speaker**
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## Aims and Structure

The Research Training Group 1071 "Viruses of the Immune System" (GK 1071) provided an internationally oriented, structured training mainly for Ph.D., but also for MD students. It was based on an established interdisciplinary cooperation among scientists of the Faculty of Medicine and the Faculty of Sciences at the FAU. The special feature of the GK 1071 was an integrated exchange program with Harvard Medical School (HMS). Students holding a diploma or master degree in life sciences or molecular medicine from Erlangen joined the laboratory of a participating Harvard faculty member and, upon completion of their thesis, graduated as Dr. rer. nat. from FAU. Joint retreats provided an intense exchange between students and faculty members from Erlangen and Boston. This direct interaction enforced the mentoring program and enabled the students to gain insight into the everyday life at one of the leading research institutions. The resulting internationalization enhanced the Ph.D. projects and the professional perspectives of the students.
Second funding period: 2009 – 2013.

## Research

The scientific focus of the GK 1071 was on the interface of virology and immunology. Research projects mainly concentrated on two groups of persisting lymphotropic viruses, herpesviruses, and retroviruses. They are clinically relevant as causative agents of human tumors and AIDS. Research topics included the basis of AIDS pathogenesis and viral oncology as well as therapy and prophylaxis of viral infections. Thus, this network contributed to the research focus on infectiology/immunology at the Faculty of Medicine.

**Section A: Viral immunodeficiency**
Projects in this field investigated the interactions of Human Immunodeficiency Virus (HIV) with its host cells as well as with other viruses. They contributed to the definition of mechanisms relevant to pathogenesis and of potential targets for therapeutic intervention.

**Section B:**
**Basis of Prevention and Therapy**
Humoral, cellular, and innate immune responses to viruses were the main topic of projects in this section. They improved the understanding of immunological processes controlling infection and suggested novel strategies for specific prevention and therapy.

**Section C: Lymphotropic tumor viruses**
This research field covered various aspects of viral oncogenesis. The viruses investigated induce various forms of lymphoma which are relevant as human diseases or as model systems for lymphocyte growth transformation.

## Teaching

Our program strived for a comprehensive, internationally oriented graduate training that fosters both, scientific and personal skills of the Ph.D. students. To this end, their research projects were accompanied by a mentoring program. Early independence was supported by mandatory research reports at the retreats and by student travel funds that allowed for participation in scientific conferences. Personal development was further boosted by activities mediating complementary skills for a career in science or industry. Among these were an autonomous student seminar, workshops on presentation and writing techniques as well as the organization of scientific and public-oriented events. Particularly, the 4th International GK Symposium in Erlangen was realized in 2013 together with students of other GK. Members of GK 1071 furthermore contributed to the Long Night of the Sciences in 2013.

*(Cartoon by I. Niemann, Institute of Clinical an Molecular Virology)*

# Research Training Group 1660: Key Signals of Adaptive Immune Response

**Speaker**
Prof. Dr. rer. nat. Hans-Martin Jäck

**Coordination**
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## Aims and Structure

Since October 2010, the DFG and Bavaria have been supporting the first doctoral Fast-Track program that was established at a German university.
To increase the attractiveness of our program and to recruit the best students, we have developed an innovative doctoral pilot program for undergraduates with a bachelor's degree which will lead to the Dr. rer. nat. in 4.5 years. The program also accepts nine doctoral students with a master's or diploma degree (associated graduates). In addition, we have developed a doctoral training program for six talented medical students. The doctoral students with a bachelor's degree will first pass through a 1.5-year training program where they will receive intensive training in immunology and related disciplines, participate in three research-oriented laboratory rotations (including one at an external laboratory), and attend communication and soft skill workshops. After the training period, they will start their thesis with one of the participating mentors. The main objective of this new training program is to teach and foster young scientists in the field of adaptive immunity. Based on an excellent evaluation by external reviewers, the DFG has decided in May 2014 to continue funding for a second funding period with 3.5 million EUR for 4.5 years.

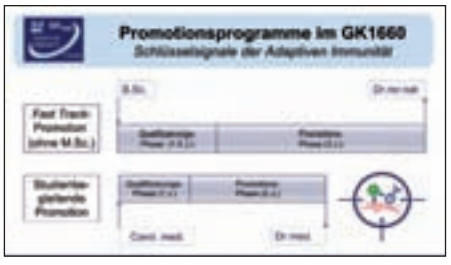
## Research

Our research program focuses on the molecular analysis of three cell populations (dendritic cells, B cells, and T cells) which will contribute to our fundamental understanding of how the adaptive immune response works under physiologic as well as pathophysiologic conditions. The main research focus concentrates on the identification of intra- and extracellular signaling factors that control the activation as well as the interaction of these cell types. Beyond the molecular analysis of these three cell types in mouse model systems, the role of these signals in autoimmunity and inflammatory disease will be investigated.
To achieve this goal, we have recruited 20 research groups headed by internationally recognized experts in the field of the biology of dendritic cells, B cells, and T cells from nine institutes and clinical departments at the FAU. All supervisors have external funding and are experienced in graduate training.

## Training

During their theses, the doctoral graduate and medical students will participate in the successfully tested core events and activities of the expired GK 592:
1. A bi-weekly doctoral regular meeting organized by the students,
2. Subject-specific as well as interdisciplinary workshops,
3. Research symposia and network meetings with members of other external training grants,
4. External laboratory visits,
5. And the guest speaker seminar series.
The students will also organize seminars and workshops for the public and high school. The doctoral students will be mentored by a three-member thesis advisory committee. To internationally position our doctoral students, they will organize the 5th International GK Symposium on "Regulators of Adaptive Immunity" in 2016.

Our research and innovative training concept will not only lead to a reduction in the time required to finish a doctoral program, but it will also provide a high-quality training environment for young scientists at an internationally competitive level.

# Emil Fischer Graduate Program of Pharmaceutical Sciences and Molecular Medicine (EFS)

**Speaker**
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## Aims and Structure

It is the aim of the Emil Fischer graduate program to provide young researchers pursuing their doctoral thesis in an interdisciplinary environment with key qualifications required for a successful career in drug target research and drug development. Main areas of interest are the identification and characterization of target proteins, signal cascades, drugs, and mechanisms of action and related bioanalytical techniques.

The program is supported by members of the following chairs of the Faculties of Sciences and Medicine:

- Chair of Bioinorganic Chemistry
- Chair of Biochemistry and Molecular Medicine
- Chair of Biochemistry and Pathobiochemistry
- Chair of Clinical Pharmacology and Clinical Toxicology
- Chair of Pharmacology and Toxicology
- Chair of Food Chemistry
- Chair of Physiology
- Chair of Clinical Nuclear Medicine
- Chair of Pharmaceutical Biology
- Chair of Pharmaceutical Chemistry
- Chair of Pharmaceutical Technology.

In 2011, the chairs of Organic and Pharmaceutical Chemistry at Regensburg University were integrated in the graduate program. Based on the graduate program, a DFG-funded research training group ("Medicinal chemistry of selective GPCR ligands", GRK 1910) could be established in 2013.

## Research and Teaching

The graduate program provides a framework of activities, including seminars and counseling, in order to allow the Ph.D. students to acquire interdisciplinary skills that reach far beyond the particular topic of their Ph.D. thesis. Throughout the graduate program, all Ph.D. students are independently counseled by a mentor and a co-mentor. Interdisciplinary seminars provide insights into the research topics and methods of the other groups of the Emil Fischer Center. The Ph.D. students are actively involved in the selection of seminar topics. Additional lectures by high profile speakers from other institutions are organized on a regular basis. The scientific training is complemented by training in soft skills required in the academic environment as well as in industry. Regular "research days" are held to provide an opportunity for the Ph.D. students to present and discuss their methods and data in an interdisciplinary framework.
Since the start of the program in December 2008, over 99 Ph.D. students have enrolled in the program. Until February 2015, already 48 candidates successfully completed the program with a Ph.D. and a program certificate.

# Erlangen Graduate School in Advanced Optical Technologies (SAOT)

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## Aims and Structure

In November 2006, the Erlangen Graduate School in Advanced Optical Technologies (SAOT) was established in cooperation with the Faculty of Medicine at the FAU within the framework of the excellence initiative of the German federal and state governments to promote science and research at German universities. Funding was reapproved for another five years in November 2012. SAOT offers a structured, internationally oriented (working language English) and interdisciplinary education program to doctoral candidates. It is hosted by the Faculties of Engineering, Sciences, and Medicine and is embedded into an international network of distinguished experts in their respective fields of optical technologies. The scientific topics SAOT focuses on are optical metrology, optical material processing, optics in medicine, optics in communication and information technologies, optical materials, and systems and computational optics.

## Research

Intensive research work is carried out in each of the SAOT topics which are partly overlapping. This in particular is true for the topic "Optics in Medicine" which can be considered to form an application field of the other topics. It is inherently interdisciplinary, covering e.g. optical diagnostics as well as optical therapy and surgery. The further development of optical techniques in medicine demands an intensive and comprehensive exchange and collaboration between the different disciplines involved. The topic "Optics in Medicine" deals with the fundamental functioning principles of the human body, its organs and tissues under the exposure of optical radiation covering a broad field of frequencies and light strengths. These detailed investigations of the interaction of light and tissue promote the development of improved diagnostics, therapy, and surgery techniques. Moreover, technical specifications are defined which will serve as the basis for future development and engineering of bio-optical sensors and apparatuses for medical applications. To reach these objectives, the Clinical Photonics Laboratory (CPL) and an associate professorship for functional imaging in medicine (Prof. Dr. M. Waldner, Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology) were established within SAOT. CPL is equipped with a worldwide unique apparatus pool for the comprehensive characterization of optical properties of biological tissues. CPL runs several collaborations with international institutes and medical and clinical research institutes of the FAU. To intensify the interdisciplinary and international collaborations, SAOT routinely organizes international workshops. The "Postdoctoral Medical Research Center" which has been established in 2013 and which is supported by SAOT with personnel, allows doctoral candidates from SAOT and postdocs from the Faculty of Medicine to work together on joint interdisciplinary research projects.

## Teaching

During the terms, SAOT offers standard lectures which are related to the application of optical technologies in medicine. Special SAOT activities related to the educational program comprise seminars, workshops, and academies. Outstanding scientists from international leading institutions are invited to give an one hour talk on specialized themes at the SAOT seminar. Workshops usually last up to three days, e.g. the past workshops on "Retina image processing" and "Advanced Optical Methods for Diagnostics, Assessment, and Monitoring of Clinical Therapy and Surgery". The program includes several speakers of leading international research institutions who contribute with a talk to a major subject. During the weeklong academies which take place outside Erlangen twice a year, the doctoral candidates are in charge of contributing to the success of the formed group work on a specific focus or have to give short presentations on the activities in their own field. Additionally, participation in the entrance academy which is organized once a year is mandatory for all SAOT doctoral candidates. At the end of this academy, they have to pass the entrance examination which covers all scientific topics of SAOT.

# Cord-Michael Becker-Prize

**Speaker**
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## Aims and Structure

Since 2013, the Faculty of Medicine and the Research Foundation of Medicine award the Cord-Michael Becker-Prize for outstanding doctoral research in molecular medicine.
With this award the Research Foundation honors Prof. Dr. C.-M. Becker who developed and institutionalized the research-oriented degree program Molecular Medicine at the FAU. The prize is endowed with 5,000 EUR. It is awarded to graduates of all programs in Molecular Medicine for an outstanding doctoral thesis and aims at encouraging talented young researchers to pursue a scientific career. The prize is awarded on a yearly basis in a ceremony organized by the Faculty of Medicine.

## Awardees of 2013 and 2014

In 2013, Dr. A. Bill was awarded the first Cord-Michael Becker-Prize for her thesis entitled "Cytohesins are cytoplasmic ErbB receptor activators". Dr. A. Bill received her diploma in Molecular Biomedicine from the Rheinische Friedrich-Wilhelms-Universität Bonn. Afterwards, she pursued her Ph.D. at the LIMES Institute, also at the University of Bonn where she studied the role of cytohesins in cell growth. She could show that these proteins bind to ErbB receptors and are necessary for their activation in cell growth and cell differentiation. She further observed that cytohesins are overexpressed in lung cancer and that inhibition of cytohesins by a specific inhibitor reduced the growth of cancer cells. Her findings may lead to the development of new cancer therapies and have been published in the renowned research journal Cell. Dr. A. Bill currently works at the Novartis Institute for Biomedical Research in Cambridge, Massachusetts, USA.

*Award ceremony 2013:*
*(left to right) Prof. Dr. Dr. h.c. J. Schüttler, Dr. A. Bill, Prof. Dr. B. Fleckenstein*
*(Photo: Faculty of Medicine FAU)*

In 2014, the second Cord-Michael Becker-Prize was awarded to Dr. L.N. Sachs (Ph.D.) for his thesis entitled "The role of CD151 and integrin $\alpha 3\beta 1$ in the pathophysiology of kidney and skin". After his diploma studies in Molecular Medicine at the FAU, Dr. L.N. Sachs performed his Ph.D. at the Netherlands Cancer Institute in Amsterdam. He studied specific cell adhesion complexes that play a crucial role in physiological processes as different as ultrafiltration of the kidney and tumorigenesis of the skin. He elucidated the functions of the integrin $\alpha 3\beta 1$ and its partner molecule tetraspanin CD151. These two proteins are part of cell-cell and cell-matrix contacts between epithelial cells of the kidney (glomerular podocytes) and of the skin (epidermial ceratinocytes). Dr. L.N. Sachs currently works at the Hubrecht Institute for Developmental Biology and Stem Cell Research in Utrecht, The Netherlands.

*Award ceremony 2014:*
*(left to right) Prof. Dr. C.-M. Becker, Prof. Dr. B. Fleckenstein, Dr. L.N. Sachs and wife, Prof. Dr. A. Sonnenberg, Prof. Dr. h.c. J. Schüttler*
*(Photo: Faculty of Medicine FAU)*

# ELAN Program for Supporting Clinical Research and Teaching

**Speaker**
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## Aims and Structure

The ELAN program was designed according to the guidelines of the National Science Council and the Conference of Ministers of Cultural Affairs to support clinical research and teaching. A total of 1.3 million EUR annually is devoted to fund projects for limited periods of time, taking into account the previous work done by the respective researchers. Decisions on the distribution of funding are made by a committee of Faculty members consisting of seven professors from various clinical and preclinical departments, the Dean of the Faculty, the medical director, and the chairman of the research advisory board. Main purposes of the program are to financially support research projects, promote innovative didactic models, and internationalize clinical teaching as well as its evaluation.

## Funding

First and foremost, funding is provided for projects of highly qualified young investigators and newly established groups. Besides this, pilot projects are supported and financial gaps in ongoing investigations are bridged ("standard program"). The best young investigators are additionally supported by the so-called "first-time-applicant program", initiated and financed in cooperation with the IZKF. It is intended to enable as many qualified investigators as possible to raise further funding from external grant providers. The standard program provides short-term support for personnel and operational costs for six to twelve months. In the "first-time-application-program", an extension of up to 30 + 6 months is possible. From mid-1998 until the end of 2014, a total of 917 grant applications were received (2013: 37, 2014: 54), coming from virtually all clinical departments. The numbers of grant proposals from the respective departments are proportional to both, their sizes and research activity, although to a different extent. The average funding per project was about 40,000 EUR in both years in the standard program and about 107,000 EUR in the "first-application-program". The total amount of funding requested was 1.3 million EUR in 2013 and 1.9 million EUR in 2014. The total amount of granted money in the standard program oscillated around 1.3 million EUR annually, reflecting the total available resources. External peer review of grant proposals is required for funding requests above 20,000 EUR. Besides the scientific excellence of the project, the committee also considers compliance with other prime goals of the ELAN program in its funding decisions, e.g. initial funding for new research groups or young investigator support.

The grant applications reflect the impact of the research foci immunology and infection research (one third to one quarter) and the growing focus tumor research (18 to 23 %). Neurosciences (15 %) and others (20 %) remained nearly unchanged; renal and vascular research decreased from 10 to 5 %.

An evaluation of the program shows that the average time span from approval to the end of the project is two years. It takes an additional 2-3 years to have a paper resulting from a project accepted or to obtain a subsequent funding from external parties. Therefore, the final evaluation can be done 4-5 years after granting.

More than 90 % of grant applications of 2010 are completed. 55 % of grants resulted in an accepted publication and led to external funding amounting to more than two million EUR, thus indicating a higher income than investment. Parental leave, change of jobs, or lack of feedback to the ELAN fund account for missing reports and/or a lack of results in terms of publications or external funding. The web-based application and management system launched in 2012 will help to increase the feedback by an automatic reminder function.

In conclusion, the ELAN program has successfully stimulated high quality research projects from all clinical departments. This emphasizes the value of this program as a tool to dynamically improve clinical research within the Faculty of Medicine.

# Advancement of Women and Gender Research Promotion

**Speaker**
Prof. Dr. med. Kerstin Amann

**Deputies**
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Prof. Dr. (TR) Yesim Erim

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## Aims and Structure

The women's representative of the Faculty of Medicine was placed at the disposal of academic staff of the FAU and UK Erlangen. In October 2007, the Executive Board of the FAU and the Faculty of Medicine concluded the first target agreement to support women in science. On 20th March 2013 the second target agreement has been signed, including targets for 2017:

- Increase in the number of habilitated women from 22 % (2009/2011) to 25 % (2017);
- Increase in the number of female W2-Professors within the Faculty from 11 % (2011) to 15 % (2017)
- Increase in the number of female W3-Professors within the Faculty from 2 % (2011) to 8 % (2017)
- Increase in the number of female senior doctors from 16 % (2011) to 20 % (2017).

## Mentoring program – ARIADNEmed

Project coordinator: Dr. M. Zirngibl
Part of the target agreement is the installation of a mentoring program called ARIADNEmed. It was launched in 2008 at the Faculty of Medicine. The core of the program is an individual mentoring/coaching of young female scientists by experienced female and male professors, focusing on strategic questions regarding career development, leading to the implementation of concrete steps, and resulting in career moves. The mentoring is combined with a seminar program on relevant career topics, such as funding, work-life-balance, bibliometry, and coaching for appointment processes.
15 Mentees (seven physicians, six natural scientists, one psychologist, and one pedagogue) participate in the current round which started in October 2013. The mentees are supervised by 15 female/male mentors. The round ends after 18 months in May 2015. A new round will start in May 2015 after the current round has ended.

## Headhunting

Headhunting was established to invite qualified female scientist to apply for vacant professor calls in order to try to raise the number of female professors (applicants for professor calls).

## Gender Mainstreaming

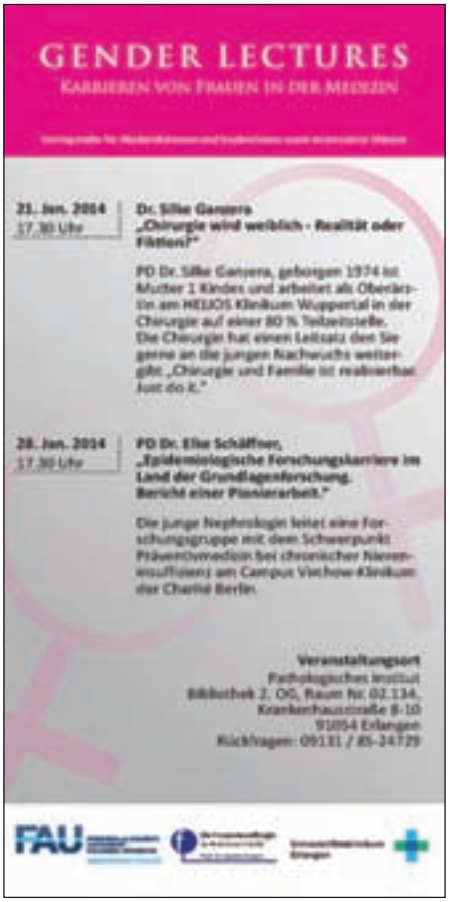
Additionally ARIADNE mentees are involved in the appeal committee in a subject-oriented consulting manner. To make appointment processes more transparent, in addition to the woman's representative one further female expert is elected in the appointment committee, so that a minimum of two women are part of the appointment committee. Furthermore, a member of the Senate of the University monitors the committee in order to achieve a consequent, systematic, and consistent integration of gender aspects during appointment process.

## Gender Lectures

The woman's representative introduced the "Gender Lectures". Female scientists who serve as role models are invited as guest speakers and can hopefully ease the path to decide for a scientific university career. Each term, two female guest speakers from the medical sector who serve as role models are invited to give a 30 – 40 minutes lecture.

## Travel grants and scholarships

Talented postdoctoral researchers can apply for financial support to attend scientific conferences. The so called travel grant can be applied for once a year. Each person can obtain the grant three times at the most. Prerequisite is an active participation in the particular conference, e. g. a poster contribution. In 2013 and 2014, 13 out of 18 applications were supported which amounts to a total funding of 9,675 EUR.

# Research Foundation of Medicine

**Speaker**
Prof. Dr. med. Werner G. Daniel

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Donations account:
Stadt- und Kreissparkasse Erlangen
IBAN: DE69 7635 0000 0000 0620 00
BIC: BYLADEM1ERH

## Aims and Structure

The Research Foundation of Medicine at the UK Erlangen was founded in December 2007 by an initiative of professors of the UK Erlangen and the Faculty of Medicine of the FAU. The initial capital stock of almost 150,000 Euro was given by 36 founder members – mainly directors of departments and institutes, but also other persons, like the mayor of the city of Erlangen – out of their personal assets. The Research Foundation is intended to be a permanent and stable means of financing in particular medical research, independent from public funding and support. Thus, former patients, alumni, and other patrons can support with their donations individual projects as well as certain medical disciplines or clinics, and also medical research at the UK Erlangen in general. Model for our initiative was the long-lasting, successful culture of foundations at the universities in the USA.

## Goals

The Research Foundation of Medicine at the UK Erlangen pursues four main goals:

- Advancement of research in all fields of basic and clinical sciences in medicine,
- Advancement of training and further education of students, physician, and scientists,
- Promotion of the public health care system, especially in the fields of prevention and early diagnosis of disease, and
- Benevolence within the medical care of patients in need.

## Development

The Research Foundation of Medicine provides attractive honors and stimulations for sponsors: donators of 10,000 EUR or more are listed on a special table of honor placed in the main entrance hall of the UK Erlangen, with a fostering sum of 100,000 EUR it becomes possible to establish an own self-named foundation within the Research Foundation of Medicine, and in certain cases a lecture hall may be named after a particularly generous sponsor (e.g. the "Rudolf-Wöhrl-Hörsaal" in 2009 and in 2013 the "Ernst-Freiberger-sen.-Hörsaal" named after the father of Ernst Freiberger jun., a most generous businessman and patron who donated 500,000 EUR, particularly for research projects in neurology). Due to the innovative model of the Research Foundation of Medicine, many generous sponsors could be found during the last years. In addition, an appeal to donate not yet changed Deutsche Mark to the Research Foundation of Medicine (and receive the donation receipt on the calculated Euro sum) contributed to the successful development. This campaign continues. Thus, between 2011 and 2014 the Research Foundation of Medicine was able to distribute approximately 2.8 million EUR for various projects. This high amount became possible also by a "Matching-Funds" concept, established by the UK Erlangen in 2011. The UK Erlangen increases all financial supports given by the Research Foundation of Medicine by additional money out of the clinic income that is subject to income tax. The "Matching-Funds" program has also stimulated the willingness of donators for funding immensely. This concept is successfully practiced in other countries, as e. g. USA and Great Britain.

The Research Foundation of Medicine at the UK Erlangen has meanwhile supported numerous projects. This is true for many clinical and basic research projects as well as for the "Erlanger Medizinische Bürgervorlesung", a series of 12 – 14 lectures on up-to-date medical topics, initiated in 2007 and addressed each term to interested citizens. During the last 17 terms, the "Erlanger Medizinische Bürgervorlesung" has reached an audience of approximately 50,000 persons and was awarded the Erlanger Medizinpreis 2012. Numerous lectures were also broadcasted by television (BRalpha and ARDalpha). For the third time, the Research Foundation of Medicine – together with the Faculty of Medicine – has given the Jakob-Herz-Prize to an outstanding researcher in the field of medicine: In 2013 Prof. Sir P.J. Ratcliffe, Oxford, England, was the awardee. Since 2013, the Research Foundation of Medicine and the Faculty of Medicine award the Cord-Michael Becker-Prize for an outstanding doctoral research study in Molecular Medicine. In 2013, the prize was received by Dr. A. Bill (Bonn and Harvard) and in 2014 by Dr. L.N. Sachs (FAU and Netherlands Cancer Institute/University of Amsterdam). The Research Foundation of Medicine also awards each year a prize for the best dissertation study (thesis) in the field of clinical and basic research, respectively. In 2013, Dr. Dr. T. Huth (Institute of Physiology and Pathophysiology) and Dr. Dr. R. Lutz (Department of Oral and Cranio-Maxillofacial Surgery), and in 2014, Dr. W. Kustermann (Department of Pediatric and Adolescent Medicine) and Dr. B. Abels (Department of Radiation Oncology) were awarded this prize for their outstanding theses.

*Ceremonial act on the occasion of the naming of the Ernst-Freiberger-sen.-lecture hall*
*(from left to right) Prof. Dr. Dr. h.c. H. Iro, Prof. Dr. K.-D. Grüske, Prof. Dr. Dr. h.c. S. Schwab, E. Freiberger (jun.), J. Herrmann, Prof. Dr. Dr. h.c. J. Schüttler, Prof. Dr. B. Fleckenstein, Prof. Dr. W.G. Daniel*
*(Photo: UK Erlangen)*

*Donation of the charitable Manfred-Roth-foundation to finance the "Manfred-Roth-scholarship (NORMA) for food and nutrition research" (4th June 2014)*
*(from left to right) Prof. Dr. W.G. Daniel, K. Schink, Dr. W. Polster, Prof. Dr. Y. Zopf, Prof. Dr. M.F. Neurath*
*(Photo: UK Erlangen)*

# Jakob-Herz-Prize

**Speaker**
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## Aims and Structure

Since 2009, the Faculty of Medicine of the FAU together with the Research Foundation of Medicine has been awarding the Jakob-Herz-Prize for medical research. This prize is named after Prof. Dr. J. Herz, the famous physician from Erlangen and the first Jewish professor in Bavaria. The award is granted for outstanding scientific success in the whole field of theoretical and clinical medicine. Both, individual achievements in research as well as lifetime achievements, can be honored. The prize is awarded biannually in the course of a ceremony organized by the Faculty of Medicine. This ceremony includes a talk given by the laureate.
Adequate candidates can be recommended by all professors of the Faculty of Medicine. The committee of the Jakob-Herz-Prize consists of the professors of the commission for research and young academics within the Faculty of Medicine who evaluate the proposed candidates. The final decision is made by the faculty council. The prize comprises the amount of 10,000 Euro, a certificate, and a medal with the portrait of Jakob Herz.

## History and Funding

This prize has been designed in honor of the prominent physician and researcher from Erlangen, Prof. Dr. J. Herz (1819-1871). Prof. Dr. J. Herz was among the leading instructors of pathological anatomy and surgery of his time and is considered the founder of surgical anatomy. In 1869, Prof. Dr. J. Herz was appointed full professor in the kingdom of Bavaria. At this time he had already been honorary citizen of Erlangen for two years. Prof. Dr. J. Herz died in 1871 as a consequence of his tireless commitment to his patients and to science. His larger than life memorial at the Hugenottenplatz in Erlangen was destroyed by the Nazis. During the National Socialism, his native town Bayreuth removed a memorial plaque at his birthplace and renamed streets which were previously named after him. Therefore, the religious persecution did not end for the Jewish physician, scientist, and philanthropist with his death. It was only in 1983 that the citizens of Erlangen regretted the destructions dating from the Third Reich and installed a new memorial at the corner Universitätsstraße/Krankenhausstraße. This memorial can be regarded as a compensation for the destroyed one and shows the following sentence: "We remember Jakob Herz to whom citizens of Erlangen erected and destroyed a memorial". In 2000, the president of FAU at that time, Prof. Dr. G. Jasper, unveiled a bronze memorial plaque in honor of Jakob Herz at the Hugenottenplatz.

In 2013, the Faculty of Medicine elected the renowned scientist Prof. Sir P.J. Ratcliffe from Oxford for the Jakob-Herz-Prize. Prof. Sir P.J. Ratcliffe studied medicine in Cambridge. After obtaining his doctorate, he did his specialty training in internal medicine and nephrology. In 1996, he was appointed Professor of Renal Medicine at the University of Oxford. He has been Nuffield Professor and Head of the Department of Internal Medicine in Oxford since 2004. The Faculty of Medicine honored his accomplishments regarding the discovery and characterization of the ubiquitous cellular oxygen mechanism which cells use to register changes in oxygen supply and to control the transcription of hypoxia-induced genes. Besides cellular adaptation to reduced oxygen concentrations, this mechanism also affects complex processes such as cell division and immunological processes. Prof. Sir P.J. Ratcliffe's findings provide a basis for new therapeutic approaches for tumor and cardiovascular diseases.

*(from left to right) Prof. Dr. Dr. h.c. J. Schüttler, Prof. Sir P.J. Ratcliffe, Prof. Dr. K.-D. Grüske*
*(Photo: R. Windhorst)*

# Johannes and Frieda Marohn-Foundation

**Speaker**
Prof. Dr. med. Dr. med. dent. Dr. h.c. Friedrich W. Neukam

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## Aims and Structure

According to the founders' will, the purpose of the Johannes and Frieda Marohn-Foundation is the promotion of innovative projects of the Faculty of Medicine of the FAU, serving diagnosis, prevention, and therapy of diseases in general. Projects dealing with diseases in the field of gastroenterology, including all liver and pancreatic diseases inclusive diabetes, cancer, and medical data bases shall be supported preferentially. The founders explicitly have stated that the purpose of the Foundation can be adapted to other modern developments and needs of medical research taking place at the Faculty of Medicine.

According to the rules of the Foundation, five members of the Faculty of Medicine have to be elected for a three year period as members of the scientific board of the Foundation. Five additional members of the Faculty of Medicine have to be elected to replace members of the scientific board in case of time conflicts or conflicts of interest.
Only clearly defined, relevant scientific projects will be funded. Grants can be used for personnel, equipment, consumables as well as for cooperation costs between scientific and clinical departments.
Grant applications should be sent to the chairperson of the scientific committee. The rules of the Foundation are available at the secretariate of the Johannes and Frieda Marohn-Foundation.

**Accepted projects**
**(Time of funding 2013 – 2014)**

| Financial year | Budget | Number of accepted applications |
|---|---|---|
| 2013 | 286,660.83 € | 7 = 194,998.00 € |
| 2014 | 256,996.08 € | 5 = 127,325.00 € |

**Finalized projects**
**(Time of funding 2013 – 2014)**

| Number of projects | Number of publications | Continued funding by other foundations* |
|---|---|---|
| 11 | 18 | 3 |

** DFG = two projects*
*Other foundations = one project*
*Eight projects could not obtain further financial support.*

*Frieda Marohn*

*Johannes Marohn*

# Further Foundations for Research Support

In addition to the ELAN program, the Research Foundation of Medicine, and the Johannes and Frieda Marohn Foundation, more than 20 different foundations and endowments are established at the Faculty of Medicine and support research projects at different levels. Furthermore, there are donations to the Faculty of Medicine (e.g. Dr. Jahn donation, Elise Pittroff donation). Science supporting foundations are of particular relevance for the research progress.

The most important foundations either managed by FAU or closely connected to the Faculty of Medicine are presented below.

The **Dr. Fritz Erler Fund** supports medical research at FAU, especially in surgical disciplines. In 2013, a research project received a grant of 36,000 EUR. Furthermore, every three years, a reputed physician engaged in meritorious surgical medicine is awarded the Dr. Fritz Erler Research Award. The next call will be published in 2015.

The **Gottfried and Lieselotte Naumann Fund** rewards special achievements in ophthalmology, especially contributions to clinical ophthalmopathology and microsurgery of the eye. Every four years, a prize is given to an extraordinary researcher. The **Ernst-Muck** and **Dr. Valentin Aplas Foundations** also support ophthalmology research.

The **Dr. Norbert Henning Foundation** endows a biannual prize for extraordinary accomplishments in gastroenterology research.

The **Dr. Kurt and Margarete Groß Donation** supports specific achievements in cardiology, cardiac-physiology, or cardiac surgery. In 2013 and 2014, several research projects were supported with 39,000 EUR in total.

The **Ria Freifrau von Fritsch Foundation** endows a prize for young investigators in cancer research. In 2013, the prize was awarded to PD Dr. D. Mougiakakos (Department of Medicine 5) for his work on "Mitochondria as target structures for cancer therapy in chronic lymphocytic leukemia".

Both, the **Angelika and Helmut Trunk-Foundation** and **Sofie Wallner Foundation,** also support cancer research. The Sofie-Wallner-Foundation endows yearly awards for gifted medical students with a special interest in oncology, enabling them to spend time in biomedical research laboratories abroad. In 2013, J. Kleemann, V. Weyerer and A. Hösl received the prize; the 2014 awardees were K. Völkl, F. Hohmann, and K. März.

Research projects in environmental medicine can be supported by the **Adolf Rohrschneider Foundation.**

The **Johanna Prey Foundation** supports research in the field of Alzheimer's disease, especially by giving grants for doctoral and master theses. In 2013, the grant was awarded to J. Weinbeer (Department of Psychiatry and Psychotherapy).

The **Dr. Ernst and Anita Bauer Foundation** is an independent foundation based in Nürnberg. Its aim is to support gifted young physicians originating from the Middle Franconian area. Awards for outstanding research results, benefits for doctoral theses, postdoctoral qualifications, and research projects as well as grants to stay in a foreign laboratory are given by this foundation.

The **Luise Prell** and the **Fritz and Maria Hofmann Foundations** recognize outstanding master and diploma theses. K. Schödel and B. Häberle received the Fritz and Maria Hofmann Prize in 2013 and 2014, respectively. The Luise Prell prize was awarded to B. Ettle in 2013 and to S. Menges in 2014.

The **Thiersch Prize** is awarded annually for the best and most concise postdoctoral qualification (Habilitation). In 2013, PD Dr. R. Linker (Department of Neurology) was awarded with the Thiersch-Preis for his outstanding habilitation dissertation. PD Dr. C. Zweier (Institute of Human Genetics) was awarded this prize in 2014 for her habilitation dissertation.

The **Staedtler Prize,** provided by the **Staedtler-Foundation**, honors outstanding doctoral theses (awardees 2013 and 2014: C. Steinmann, Division of Psychosomatics and Psychotherapy, and S. Eckl, Department of Cardiac Surgery, respectively). The Staedtler-Foundation furthermore provides generous support for research project, amounting to 430,000 EUR in 2013 and 2014.

The **Novartis foundation** supports young investigators at our Faculty of Medicine.

The **Foundation for Teaching at the Faculty of Medicine** was founded to support and improve the education and training of medical students and training of young physicians.

The central university administration of FAU, Division F3 – Körperschaft und Stiftungen, provides further details upon request.

# Physico-Medical Society Erlangen

**Managing Committee**
Prof. Dr. med. Christian Bogdan (Chairman)
Prof. Dr. h.c. Willi A. Kalender, Ph.D. (Vice Chairman)
Prof. Dr.-Ing. Dr. rer. med. Ulrich Hoppe (Secretary)
Prof. Dr. med. Thomas Pasch (Treasurer)
Prof. Dr. med. Dr. h.c. Karl-Heinz Plattig (Past Treasurer)

**Contact**
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## Aims and Structure

The Physico-Medical Society Erlangen (PMSE), also known as Societas physico-medica Erlangensis, was founded on March 20th, 1808, in order to exchange "ideas, observations, and experiences between all the areas of natural sciences and medicine". These first statutes and articles, defined in the year 1808, are still valid; by amendment of the statutes in 1990, the technical disciplines have also been admitted. On June 18th, 2008, the PMSE celebrated its 200th birthday in a ceremony at the castle of the FAU. In the year of the 200th birthday of the PMSE, the Medical Society which had separated from the PMSE in 1958 after the 150th birthday celebration of the Societas physico-medica Erlangensis merged again with the PMSE.
As of February 5th, 2015, the Society has 365 members inside and outside Germany, with 15 of them being honorary members. Once per year the Society holds a members´ assembly upon invitation by the council.
Every term the Society holds three to four regular meetings with scientific lectures. These are primarily given by invited national and international scientists, but also by members of the PMSE. According to its primary goal, i.e. to promote the scientific exchange between different fields of research, the PMSE preferentially invites guest speakers with outstanding interdisciplinary research approaches and achievements.
From 1984 to 2012, eleven volumes of reports were published, each of them consisting of four single issues. Beside scientific papers, the reports contain recent outstanding academic speeches, for example inaugural or farewell speeches, addresses on the occasion of honorary promotions and the annual graduation ceremony of the Faculty of Medicine of the FAU.

**Lectures**

09.01.2013
Prof. Dr. h.c. W.A. Kalender, Ph.D.
Institute of Medical Physics, FAU
"Concepts for High-Resolution Low-Dose CT of the Breast"

06.02.2013
Prof. Dr. med. N. Suttorp
Infektiologie und Pneumologie, Charité Universitätsmedizin Berlin
"Die Immunität der Lunge verstehen, um die Therapie der Pneumonie zu verbessern"

11.07.2013
Prof. Dr. med. E. von Mutius
Dr. von Haunersches Kinderspital der LMU München
"Schutz vor Asthma und Allergien im bäuerlichen Umfeld"

18.06.2014
Prof. Dr. J. Guck
Biotechnology Center, Technische Universität Dresden
"Soft Matters – Mechanics in Biology and Medicine"

16.07.2014
Prof. Dr. med. B. Beck Schimmer
Institut für Anästhesiologie, Universitätsspital Zürich
"Magnetic nanoparticles: one step closer to the bedside?"

# Selection of Honors and Prizes

## 2013

### Sicca-Sponsorship Award of the German Professional Association of Ophthalmologists
**Daniel B. Abrar and Valerian Altersberger**
Chair of Anatomy II

### Honorary doctorate of the Yeni Yüzyil University Istanbul
**Prof. Dr. med. Yusuf Ziya Akcetin**
Department of Urology

### Sponsorship Award of the Rolf-and-Hubertine-Schiffbauer-Foundation
**PD Dr. med. Philipp Bahrmann, MHBA**
Institue for Biomedicine of Aging

### Löffler-Frosch-Medal of the Society for Virology
**Prof. Dr. med. Walter Doerfler**
Institute of Clinical and Molecular Virology

### AGNP-Research Award for Research in Psychopharmacology
**Dr. Dipl.-Ing. Oliver Welzel, PD Dr. Teja W. Groemer**
Department of Psychiatry and Psychotherapy

### Science Award of the Saxon Society of Ophthalmologists
**Dr. med. Ulrike Hampel**
Chair of Anatomy II

### Honorary doctorate of the Huazhong University of Science and Technology, Wuhan, China
**Prof. Dr. med. Raymund Horch**
Director of the Department of Plastic and Hand Surgery

### Honorary doctorate of the Faculty of Medicine of the University of Crete
**Prof. Dr. med. Dr. h.c. Heinrich Iro**
Director of the Department of Otorhinolaryngology – Head and Neck Surgery
Medical Director of the UK Erlangen

### Carol-Nachman-Medal of Wiesbaden
**Prof. Dr. med. Dr. h.c. Joachim Robert Kalden**
former Director of the Department of Medicine 3 – Rheumatology and Immunology

### Pauwels-Medal of the German Society for Orthopedics and Orthopedic Surgery (DGOOC)
**Prof. Dr. h.c. Willi A. Kalender, Ph.D.**
Institute of Medical Physics

### Gray Medal of the International Commission on Radiation Units & Measurement (ICRU)
**Prof. Dr. h.c. Willi A. Kalender, Ph.D.**
Institute of Medical Physics

### Telemed Award
**Ines Leb, M.Sc.**
Chair of Medical Informatics

### Award for "Research on Medical Care and Epidemiology of Mental Disorder" of the German Association for Psychiatry, Psychotherapy, and Psychosomatics (DGPPN)
**PD Dr. rer. biol. hum. Katharina Luttenberger**
Department of Psychiatry and Psychotherapy

### Enrico Greppi Award 2013 of the Italian Society for the Study of Headaches (SISC)
**Kristin Seiler, Judith Nusser, Prof. Dr. Karl Messlinger, Prof. Dr. Winfried Neuhuber**
Student of Medicine at the FAU, Institute of Physiology and Pathophysiology, Director of the Institute of Anatomy I

### Full Member of the Scientific Class, Sudeten German Academy of Science and Art
**Prof. Dr. med. Dr. h.c. Karl-Heinz Plattig**
Institute of Physiology and Pathophysiology

### Bavarian Cultural Award
**Dr. med. Julia Reinfelder**
Department of Nuclear Medicine

### Karl-Heinrich-Bauer-Medal of the German Cancer Society
**Prof. Dr. med. Rolf Sauer (professor emeritus)**
Department of Radiation Oncology

### Member of the German National Academy of Sciences Leopoldina
**Prof. Dr. med. Dr. h.c. Jürgen Schüttler**
Director of the Department of Anesthesiology

### German Pain Award
**Dr. med. Reinhard Sittl**
Department of Anesthesiology

### Dentsply-Sponsorship Award of the German Society for Stomatology
**Dr. med. Manuel Weber**
Department of Oral and Cranio-Maxillofacial Surgery

## 2014

**Theodor-Frerichs-Award of the German Society for Internal Medicine (DGIM)**
**Prof. Dr. med. Raja Atreya**
Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology

**Science Award of the German Society for Aesthetic Plastic Surgery**
**PD Dr. med. Justus P. Beier**
Department of Plastic and Hand Surgery

**Award of the European League Against Rheumatism (EULAR)**
**Dr. med. Christian Beyer and David Simon**
Department of Medicine 3 – Rheumatology and Immunology

**Award for Good Teaching at Bavarian Universities**
**Dr. med. Georg Breuer**
Department of Anesthesiology

**Fritz-Acker-Award (German Cardiac Society)**
**Prof. Dr. med. Robert Cesnjevar**
Head of the Division of Pediatric Surgery

**Rehder-Poster-Award**
**Dr. med. Stephan Dürr**
Department of Otorhinolaryngology – Head and Neck Surgery

**Honorary Member of the Polish Society of Nephrology**
**Prof. Dr. med. Kai-Uwe Eckardt**
Director of the Department of Medicine 4 – Nephrology and Hypertension

**Justinus-Kerner-Award of Weinsberg**
**Prof. Dr. med. Dipl. Psych. Frank Erbguth**
Department of Neurology

**Honorary Member of the European Skull Base Society Gold Medal Award**
**Honorary Member of the German Society for Computer and Robot Assisted Surgery**
**Prof. Dr. med. Rudolf Fahlbusch**
Former head of the Department of Neurosurgery

**Award of the German Cancer Aid**
**Prof. Dr. med. Dr. h.c. Werner Hohenberger**
Director of the Department of Surgery

**Honorary Doctorate of the Hannover Medical School**
**Prof. Dr. med. Dr. h.c. Joachim Robert Kalden**
Former Director of the Department of Medicine 3 – Rheumatology and Immunology

**Glocker-Medal**
**Prof. Dr. h.c. Willi A. Kalender, Ph.D.**
Director of the Institute of Medical Physics

**Federal Cross of Merit on the Bond (Bundesverdienstkreuz am Bande)**
**Prof. Dr. med. Elke Lütjen-Drecoll**
Chair of Anatomy II

**Vincenz-Czerny-Award of the German Society for Hematology and Oncology**
**PD Dr. med. Dimitrios Mougiakakos**
Department of Medicine 5 – Hematology and Oncology

**Toshiba-Research Award**
**Daniel Paulus and Prof. Dr. rer. med. Harald H. Quick, Dipl.-Ing.**
Institute of Medical Physics

**Life Time Award of the Narayana Institute of Vascular Science**
**Prof. Dr. med. Dieter Raithel**
Department of Surgery

**Federal Cross of Merit on the Bond (Bundesverdienstkreuz am Bande)**
**Prof. Dr. rer. nat. Dr. med. habil. Helga Schüssler**
Adjunct professor of Medical Radiology

**Carol-Nachman-Medal of Wiesbaden**
**Prof. Dr. med. Gerd Weseloh, a. D.**
Division of Orthopedic Rheumatology

**Junior-Award of the German Society for People with Muscular Diseases**
**Dr. rer. nat. Lilli Winter**
Institute of Neuropathology

**Frank-Majewski-Award**
**PD Dr. med. Christiane Zweier**
Institute of Human Genetics

# International Mobility of Scientists

## Visiting Scientists *

### Department of Anesthesiology

- Project title: Nonlinear mixed effect modeling for population analysis in pharmacometrics
  Project managers: Prof. Dr. Dr. H. Schwilden, Dr. H. Ihmsen
  Huacheng Liu, M.M., from China (2014)
- Project title: Population analysis in pharmacokinetic/-dynamic modeling
  Project managers: Prof. Dr. Dr. H. Schwilden, Dr. H. Ihmsen
  Dr. T. Saari from Finland (2011 – 2013)

### Institute of Anatomy – Chair of Anatomy II

- Project manager: Prof. Dr. F. Paulsen
  Prof. Dr. E. Eppler from Switzerland (2014 – 2015); visiting professor, funded by Gender and Diversity
- Project title: In vitro Analysen zur Oberflächenadhäsion von Meibozyten
  Project manager: Prof. Dr. F. Paulsen
  Dr. N. Asano from Japan (2012 – 2013)

### Department of Ophthalmology

Project title: Die Entwicklung elektrophysiologischer Techniken, um Sehbahnen in der gesunden und erkrankten Netzhaut funktionell zu charakterisieren
Project manager: Prof. Dr. J. Kremers
C. Martins and M. Jacob from Brazil (2014 – 2015)

### Department of Otorhinolaryngology – Head and Neck Surgery Division of Phoniatrics and Pediatric Audiology

Project title: Strömungsphysikalische Grundlagen der menschlichen Stimmgebung (Humboldt-Stipendium)
Project manager: Prof. Dr. M. Döllinger
Prof. Dr. L.P. Fulcher from the USA (2013)

### Department of Medicine 3 – Rheumatology and Immunology

- Project title: Östrogen in der Knochenentwicklung
  Project manager: Prof. Dr. G. Schett
  Dr. C. Engdahl from Sweden (2014 – 2016)
- Project title: Glycosylierung von Autoantikörpern
  Project manager: Prof. Dr. M. Herrmann
  Prof. Dr. R. Bilyy from the Ukraine (2014)
- Project title: NETose durch Nanodiamanten
  Project manager: Prof. Dr. M. Herrmann
  Prof. Dr. Y. Zhao from China (2013 – 2014)

### Institute of Clinical Microbiology, Immunology, and Hygiene

Project title: Histological characterization of skin biopsies from patients with cutaneous leishmaniasis before and after treatment with pharmaceutical sodium chlorite
Project manager: Prof. Dr. C. Bogdan
Dr. F.A. Mahfuz from Afghanistan (2012 – 2013)

### Department of Nuclear Medicine

Project title: Emerging Field – Neurotrition: Quantitative PET imaging of DAT in rats
Project manager: Prof. Dr. O. Prante
PD Dr. P. Cumming from Germany (LMU München; 2013)

### Institute of Pathology

- Project title: LBH589-induced DAPK activation triggers apoptosis and autophagy in human colon tumor cells
  Project manager: Prof. Dr. R. Schneider-Stock
  M. Gandesiri from India (2009 – 2013)
- Project title: Negative regulation between DAPK and STAT3 in intestinal epithelial cells under TNF-stimulus
  Project manager: Prof. Dr. R. Schneider-Stock
  S. Chakilam from India (2009 – 2013)
- Project title: Interplay of DAPK signalling pathway with LIMK/cofilin complex in TNF-induced apoptosis in HCT116 colorectal cancer cells
  Project manager: Prof. Dr. R. Schneider-Stock
  J. Ivanovska from Serbia (2009 – 2013)
- Project title: Clinical potential of Thymoquinone in colorectal cancer: identification of molecular targets and efficacy in combination therapy
  Project manager: Prof. Dr. R. Schneider-Stock
  C. El Baba from the Lebanon (2011 – 2014)

### Institute of Experimental and Clinical Pharmacology and Toxicology

Project title: Catechins as constituents of green tea as mediators of transporter-mediated drug-drug interactions
Project manager: Prof. Dr. M.F. Fromm
Dr. S. Misaka from Japan (2012 – 2014)

### Institute of Physiology and Pathophysiology

Project title: Senior External Expert im EFI Medicinal Redox Inorganic Chemistry
Project manager: Prof. Dr. P. Reeh
Prof. Dr. A. Babes from Romania (2013 – 2014)

### Department of Operative Dentistry and Peridontology

- Project title: Residual stresses in dental bilayer ceramic structures
  Project manager: Prof. Dr. U. Lohbauer
  M. Wendler from Chile (2013 – 2017)
- Project title: Y-TZP/MWCNT-COOH nanocomposite development for application. Characterization and Aging
  Project manager: Prof. Dr. U. Lohbauer
  L. Hian from Brazil (2013)
- Project title: Mechanical characterization and fatigue resistance of novel Ormocer matrix composites
  Project manager: Prof. Dr. U. Lohbauer
  L. Mingori from Brazil (2014 – 2015)

## FAU Scientists going abroad *

### Department of Anesthesiology

- Project title: Novel therapeutic approach to post-brain injury pain
  Project manager: Prof. Dr. Dr. h.c. J. Schüttler
  PD Dr. A. Tzabazis, Dr. A. Eisenried at the Stanford University (USA)

### Department of Psychiatry and Psychotherapy Division of Child and Adolescent Mental Health

Project title: Reward processing in the brain of those at risk of eating disorders
Dr. S. Horndasch with Dr. C. McCabe in England (2013 – 2014)

### Department of Neurology Division of Molecular Neurology

Project title: Assessing the myelinogenic potential of oligodendrocytes in a cell culture model of multiple system atrophy
B. Ettle with Prof. Dr. F.H. Gage in the USA (2014 – 2015)

* Duration of stay at least three months.

# Doctorates Theses, Board Qualifications, Additional Qualifications, Habilitations*

## Institute of Anatomy
Chair of Anatomy I

### Doctorate Theses 2013

**Sommer, Daniel,** Dr. med. dent.: Exzitatorische enterische Co-Innervation von quergestreifter Muskulatur im Mäuseösophagus
**Afsah, Maryam,** Dr. med.: Typsierung der quergestreiften Muskulatur im menschlichen Ösophagus

### Doctorate Theses 2014

**Kramer, Kerstin,** Dr. med.: Quantitative evaluation of neurons in the mucosal plexus of adult human intestines
**Mayr, Lucia,** Dr. med.: Untersuchung der neuronalen Strukturen im Bereich des Hiatus oesophageus
**Hübsch, Marco,** Dr. med.: Muskarinische Azetylcholinrezeptoren im Ösophagus der Maus: Fokus auf intraganglionäre laminäre Endigungen (IGLEs)
**Horling, Lena,** Dr. med.: Lokalisation und Verteilung von CGRP-Rezeptoren im Ösophagus der Maus

### Habilitation 2014

**Jabari, Samir,** PD Dr. med.: Veränderungen des enterischen Nervensystems – immunhistochemische Untersuchungen zur Pathogenese des Chagas-Megakolons

## Institute of Anatomy
Chair of Anatomy II

### Doctorate Theses 2014

**Beron, Jan Martin,** Dr. med.: Nachweis und Charakterisierung des Oberflächenproteins PLUNC (Palate, Lung, and Nasal Clone Protein) an der Augenoberfläche und Bedeutung für das Trockene Auge
**Stengl, Christina,** Dr. med. dent.: Nachweis der Surfactantproteine A,B,C und D im Epithel der humanen Gingiva sowie deren Quantifizierung in gesundem und pathologisch verändertem Speichel

### Habilitation 2013

**Bräuer, Lars,** PD Dr. rer. nat.: Extrapulmonale Surfactant Proteine

### Board Qualification 2013

**Tektas, Ozan,** Dr. med.

### Additional Qualification 2014

**Scholz, Michael,** PD Dr. rer. nat. Dr. habil. med.: Master of Medical Education (MME)

* Postdoctoral qualification showing ability to lecture and do research at professorial level

## Institute of Biochemistry – Emil-Fischer-Center
Chair of Biochemistry and Molecular Medicine

### Doctorate Theses 2013

**Wittmann, Astrid,** Dr. med.: Etablierung eines Reportergenassays zur Untersuchung des Promotors der GABAC-Rezeptoruntereinheit rho 2

## Institute of Biochemistry – Emil-Fischer-Center
Chair of Biochemistry and Pathobiochemistry

### Doctorate Theses 2013

**Vogl, Michael,** Dr. rer. nat.: Interaktion des HMG-Box Transkriptionsfaktors Sox10 mit Chromatin-modifizierenden und transkriptionsrelevanten Komplexen während der terminalen Differenzierung myelinisierender Glia-Zellen

### Doctorate Theses 2014

**Hornig, Julia,** Dr. rer. nat.: Analyse transkriptioneller Netzwerke während der Oligodentrozyten-Differenzierung und zentralnervöser Myelinisierung in der Maus
**Paul, Mandy,** Dr. rer. nat.: The role of transcription factors Sox4 and Sox11 in mouse heart development

## Institute of Biochemistry – Emil-Fischer-Center
Professorship of Bioinformatics

### Doctorate Theses 2013

**Kristin, Kaßler,** Dr. rer. nat.: Exploring Stability, Dynamics, and Interactions of Microbial Effectors and Host Proteins: A Computational Approach

## Institute of Physiology and Pathophysiology
Chair of Physiology

### Doctorate Theses 2013

**Holom, Vigdis,** Dr. med.: Temperature-dependent neuronal regulation of arterial blood flow in rat cranial dura mater
**Kankel, Jennifer,** Dr. med.: Differential effects of low dose Lidocaine on C-fiber classes in humans
**Sixt, Marie-Luise,** Dr. med.: Der CGRP-Rezeptor-Antagonist Olcegepant wirkt im spinalen trigeminalen Nucleus
Vierow, Verena, Dr. rer. biol. hum.: Untersuchungen zur zerebralen Verarbeitung von Jucken und Schmerz

### Doctorate Theses 2014

**Feistel, Stephan,** Dr. med. dent.: Hemmung der Aktivität spinaler trigeminaler Neurone durch den CGRP-Rezeptorantagonisten MK-8825 während der Infusion von Nitroglycerin
**Nusser, Judith Isabel,** Dr. med.: Immunhistochemische Darstellung von löslicher Guanylatzyklase und CGRP im Ganglion trigeminale der Ratte – Veränderungen nach Vorbehandlung mit Glyceroltrinitrat
**Seiler, Kristin,** Dr. med.: Wirkung von Glyceroltrinitrat auf die Expression der CGRP-Rezeptorkomponenten CLR und RAMP1 im Ganglion trigeminale der Ratte – eine immunhistochemische Untersuchung
**Vogelgsang, Rebekka,** Dr. med.: Funktionelle Magnetresonanztomographie-Studie zum Einfluss des Opioid-Antagonisten Naltrexon auf histaminerges und nicht-histaminerges Jucken

### Board Qualification 2013

**Lampert, Angelika,** Prof. Dr. med.

## Institute of Cellular and Molecular Physiology
Chair of Physiology (Systems Physiology)

### Doctorate Theses 2013

**Kustermann, geb. Foltz, Wibke,** Dr. med.: N-Acetylcystein verhindert den elekrtischen Umbau und reduziert die zelluläre Hypertrophie in epikardialen Myozyten von ratten mit Aorta ascendens Stenose
**Söll, Daniel,** Dr. med.: Funktionelle Charakterisierung der V348M-Mutation des epithelialen Natriumkanals (ENaC)

### Doctorate Theses 2014

**Korbmacher, Judit,** Dr. med.: Funktionelle Charakterisierung von Mutationen des epithelialen Natriumkanals (ENaC) bei Patienten mit atypischer Zystischer Fibrose
**Krappitz, Matteus,** Dr. med.: Aktivierung des humanen epithelialen Natriumkanals (ENaC) durch Plasmin und Cathepsin-S

### Habilitation 2014

**Härteis, Silke,** PD Dr. rer. nat. Dr. habil. med.: Regulation des humanen epithelialen Natriumkanals (ENaC) durch Proteasen

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

### Doctorate Theses 2014

**Krieger, Christoph,** Dr. med.: Ausbildungszufriedenheit und Zukunftsperspektiven von Medizinstudenten am Beispiel der Universität Erlangen-Nürnberg

### Habilitation 2013

**Korinth, Gintautas,** PD Dr. med.: Experimentelle Studien zur Hautresorption und Metabolismus von chemischen Arbeitsstoffen

## Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Pharmacology and Toxicology

### Doctorate Theses 2014

**Oppel, Pascal,** Dr. med.: Untersuchungen zum Schmerzmittelgebrauch im Breitensport

### Habilitation 2013

**Renner, Bertold,** PD Dr. med.: Experimentelle und klinische Aspekte der Schmerztherapie mit selektiven und nicht-selektiven Cyclooxygenase-Inhibitoren

### Habilitation 2014

**Herrmann, Stefan,** PD Dr. rer. nat.: HCN Kanäle und deren Bedeutung bei kardialer Rhythmogenese und Nozizeption

## Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Clinical Pharmacology and Clinical Toxicology

### Doctorate Theses 2013

**Geldmacher, Fabian,** Dr. med.: Charakterisierung der Dimethylarginin-Dimethylaminohydrolase-2-Knockout-Maus

### Doctorate Theses 2014

**Klatt, Sabine,** Dr. rer. nat.: In vitro-Untersuchungen zur Bedeutung von hepatischen Aufnahme- und Effluxtransportern für Arzneimittelinteraktionen mit oralen Antidiabetika

## Institute of Medical Informatics, Biometry, and Epidemiology

Chair of Medical Biometry and Epidemiology

### Doctorate Theses 2013

**Potapov, Sergej,** Dr. rer. biol. hum.: Improving the split criteria for classification trees and ensemble methods

### Doctorate Theses 2014

**Keller, Andrea,** Dr. rer. biol. hum.: Evaluation des saisonalen Effekts auf die Diagnoserate kutaner maligner Melanome
**Schwitulla, Judith,** Dr. rer. biol. hum.: Polysensibilisierung gegen Kontaktallergene – klinische und demographische Risikofaktoren

## Institute of Medical Informatics, Biometry, and Epidemiology

Chair of Medical Informatics

### Doctorate Theses 2013

**Beyer, Alexander,** Dr. med.: Vergleich der Prozessabläufe in Krankenversorgung, Registerdokumentation und Klinischer Forschung als Basis der Konzeption einer Single-Source IT-Infrastruktur
**Ries, Markus,** Dr. rer. biol. hum.: Konzeption und Aufbau eines Single-Source Tumordokumentationsablaufs am Comprehensive Cancer Center Erlangen-Nürnberg

### Doctorate Theses 2014

**Kraus, Stefan,** Dr. rer. biol. hum.: Wissensbasierte Funktionen zur Unterstützung der Therapie auf Intensivstationen
**Köpcke, Felix,** Dr. rer. biol. hum.: Wiederverwendung elektronisch verfügbarer Behandlungsdaten für die Rekrutierung von Patienten in klinische Studien

## Institute of Medical Physics

Chair of Medical Physics

### Doctorate Theses 2013

**Althoff, Felix,** Dr. rer. biol. hum.: Systemdesign und Patientenlagerung bei der dedizierten Brust-Computertomografie
**Braun, Harald,** Dr. rer. biol. hum.: Strategies for simultaneous whole-body PET/MR hybrid imaging with continuous table motion
**Gayetskyy, Svitlana,** Dr. rer. biol. hum.: Bildgebende Charakterisierung und Quantifizierung der Angiogenese bei Arthritis mittels µCT im Mausmodell
**Hendrych, Ronny,** Dr. rer. biol. hum.: Interaktive Filterung großer Volumendaten in der dedizierten Brust-CT
**Lowitz, Torsten,** Dr. rer. biol. hum.: Strukturuntersuchung am Knie mit quantitativer CT zur Arthrosediagnostik
**Peetz, Alexander,** Dr. rer. biol. hum.: Steuerungskonzept für einen dedizierten Brust-CT-Scanner
**Petrasek, Carina,** Dr. rer. biol. hum.: Einfluss der Reizintensität eines 16-wöchigen Ausdauertrainings auf den kardiovaskulären Risikofaktor Homocystein bei untrainierten Männern – Ergebnisse aus der RUSH-Laufstudie
**Wicklein, Julia,** Dr. rer. biol. hum.: Entwicklung eines Verfahrens zur Online Geometrie- und Bewegungskorrektur von C-Bogen CT Systemen
**Ziegler, Susanne,** Dr. rer. biol. hum.: Simultaneous PET/MR Hybrid Imaging: Phantom Measurement Strategies

### Doctorate Theses 2014

**Brehm, Marcus,** Dr. rer. biol. hum.: Dose-efficient high temporal resolution motion-compensated reconstruction of 4D CBCT data
**Flach, Barbara,** Dr. rer. biol. hum.: Rekonstruktion mit Vorinformation für die Niedrigstdosis-CT-Fluoroskopie in der Interventionellen Radiologie
**Hofmann, Christian,** Dr. rer. biol. hum.: Iterative Reconstruction in Clinical CT
**Lück, Ferdinand,** Dr. rer. biol. hum.: Einfluss von Formfiltern auf Dosis und Bildqualität für Brust-CT
**Schilling, Harry,** Dr. rer. biol. hum.: Datenübertragungskonzepte für ein Brust-CT

## Institute of the History of Medicine and Medical Ethics

Chair of the History of Medicine

### Doctorate Theses 2014

**Salzner, Marina,** Dr. med. dent.: Jüdische Zahnärzte in Nürnberg und Fürth im Nationalsozialismus. Leben und Schicksal
**Schmidt, Cornelia Marlene,** Dr. med.: Bernhard Nathanael Gottlob Schreger (1766-1825). Leben und Werk

## Institute of the History of Medicine and Medical Ethics

Professorship for Medical Ethics

### Doctorate Theses 2014

**Echinger, Karolina,** Dr. med.: Schwangerschaft in Grenzsituationen – Die "Erlanger Fälle" 1992 und 2007

## Nikolaus-Fiebiger-Center of Molecular Medicine

Chair of Experimental Medicine II (Molecular Oncology)

### Doctorate Theses 2013

**Brauburger, Katharina,** Dr. rer. nat.: Funktionelle und molekulare Charakterisierung von Amer3: ein neuer Regulator des Wnt/ß-Catenin-Signalwegs

### Doctorate Theses 2014

**Bernkopf, Dominic,** Dr. rer. nat.: Differential regulation of Wnt-ß-catenin signaling by Axin and Conductin/Axin2

## Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

Chair of Orthopedics and Orthopedic Surgery

### Doctorate Theses 2013

**Hemmer, Stefan,** Dr. med.: Hüftbehandlung bei Morbus Perthes mit der Varisierungsosteotomie – Langzeitergebnisse nach 18 Jahren

## Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

Division of Orthopedic Rheumatology

### Doctorate Theses 2014

**Hotfiel, Thilo,** Dr. med.: Die Bedeutung der Kniestreckfähigkeit für die plantare Druckverteilung

**Gräfin von Keller-Schmitt, Julia,** Dr. med.: Vergleichende Messung des plantaren Spitzendrucks im Nachwuchs-Leistungsfußball mittels dynamischer Pedobarographie
**Kluger, Anna Katharina,** Dr. med.: Introduction of a neutral shoe to assess reference values for dynamic pedobarography

## Institute for Biomedicine of Aging
Chair of Internal Medicine (Geriatrics)

### Doctorate Theses 2013

**Bollwein, Julia,** Dr. rer. biol. hum.: Ernährung und Gebrechlichkeit bei zu Hause lebenden Senioren im Raum Nürnberg

### Doctorate Theses 2014

**Kieswetter, Eva,** Dr. rer. biol. hum.: Ernährungszustand, Funktionalität und Mortalität häuslich gepflegter Senioren – Ergebnisse einer multizentrischen Untersuchung in Deutschland

### Habilitation 2013

**Bahrmann, Philipp,** PD Dr. med.: Altersabhängige Diagnostik beim nicht ST-Streckenhebungsinfarkt
**Singler, Katrin Franziska Isolde,** PD Dr. med.: Risikostratifizierung und Besonderheiten des geriatrischen Patienten in der Notfallmedizin

## Department of Anesthesiology
Chair of Anesthesiology

### Doctorate Theses 2013

**Brügel, Jacob,** Dr. med.: Retrospektive Vergleichsuntersuchung zu verschiedenen Anästhesieverfahren bei der Anlage von tension-free-vaginal tapes (TVT)
**Wiegner, Maria,** Dr. med.: Untersuchungen zur klinischen Validierung eines neuartigen, nicht linearen Schwingkreissensors zur Detektion eines Herzkreislaufstillstandes

### Doctorate Theses 2014

**Frank, Georg,** Dr. med.: The partial μ-opioid receptor agonist buprenorphine potently inhibits voltage gated Na+ channels in a local anesthetic like manner
**Weiß, Marina,** Dr. med.: Frühdetektion der arteriellen Hypotonie bei geburtshilflicher Spinalanästhesie mit Pulsoximetrie und kontinuierlicher nicht-invasiver Blutdruckmessung
**Westhoff, Claudia,** Dr. med.: Anästhesiologisches Vorgehen bei orthopädischen Eingriffen bei Patienten mit Duchenne-Muskeldystrophie: Eine Übersicht von 232 Fällen

### Board Qualification 2013

**Albermann, Matthias,** Dr. med.
**Bauer, Katharina,** Dr. med.
**Eisenried, Andras,** Dr. med.
**Rohde, Doris,** Dr. med.
**Rüth, Tobias,** Dr. med.
**Singler, Boris,** Dr. med.
**Wilken, Verena,** Dr. med.
**Wintzheimer, Simone,** Dr. med.

### Board Qualification 2014

**Alt, Christina,** Dr. med.
**Freund, Robert,** Dr. med.
**Heinrich, Sebastian,** Dr. med.
**Korder, Stephan,** Dr. med.
**Krajinovic, Ljubica,** Dr. med.
**Lamprecht, Christoph,** Dr. med.
**Leiner, Bernhard,** Dr. med.
**Weidinger, Cornelia,** Dr. med.

### Additional Qualification 2013

**Birkholz, Torsten,** PD Dr. med.: Intensive Care Medicine
**Brugger, Florian:** Emergency Medicine
**Eisenried, Constanze,** Dr. med.: Emergency Medicine
**Fischer, Jonas:** Emergency Medicine
**Gold, Andreas,** Dr. med.: Emergency Medicine
**Korder, Stefan,** Dr. med.: Emergency Medicine
**Moritz, Andreas,** Dr. med.: Emergency Medicine
**Petzoldt, Marlen:** Emergency Medicine
**Weller, Konrad,** Dr. med.: Emergency Medicine

### Additional Qualification 2014

**Eiche, Christian:** Emergency Medicine
**Hüttl, Stefan:** Emergency Medicine
**Hunsicker, Alexander,** Dr. med.: Intensive Care Medicine
**Ludwig, Stefanie,** Dr. med.: Special Pain Therapy
**Mauer, Christoph,** Dr. med.: Emergency Medicine
**Schmidt, Christian:** Emergency Medicine
**Schmitt, Christopher,** Dr. med.: Intensive Care Medicine
**Siegle, Michaela:** Emergency Medicine
**Stuhlfelder, Konstanze,** Dr. med.: Emergency Medicine
**Sturm, Tanja:** Emergency Medicine
**Weiß, Benjamin,** Dr. med.: Emergency Medicine
**Weith, Thomas:** Emergency Medicine

## Department of Anesthesiology
Division of Palliative Medicine

### Doctorate Theses 2014

**Vogt, Carola,** Dr. med.: Ethische Fragestellungen in der Palliativmedizin – eine qualitative Beobachtungsstudie

### Habilitation 2013

**Stiel, Stephanie,** PD Dr. rer. medic.: Möglichkeiten und Grenzen qualitativer und quantitativer Assessments von Schwerstkranken und Sterbenden

### Additional Qualification 2014

**Christensen, Britta:** Palliative Medicine
**Köhler, Heike:** Palliative Medicine

## Department of Cardiac Surgery
Chair of Cardiac Surgery

### Doctorate Theses 2013

**Eckl, Sebastian,** Dr. med.: Die Kombination von Clopidogrel und Everolimus verhindert die Ausbildung der Transplantatarteriosklerose

### Doctorate Theses 2014

**Pantele, Siegrun,** Dr. med.: Die MitroFix-Prothese – eine neue Option im Bereich der Mitralklappenrekonstruktion
**Pizon, Marek,** Dr. med.: Bedeutung der epikardialen Ablation bei begleitendem Vorhofflimmern für den Spiegel des Atrialen Natriuretischen Peptides und die Vorhoffunktion in sechsmonatiger Nachbeobachtung. Prognostiziert der präoperative ANP-Spiegel die Ergebnisse der Ablation?
**Rahimilaleh, Farokh,** Dr. med.: Postoperatives Follow-up und Langzeitergebnisse nach einer Mitralklappenrekonstruktion

## Department of Dermatology
Chair of Skin and Veneral Diseases

### Doctorate Theses 2014

**Glöckler, Anne,** Dr. med. dent.: Proteinkontaktdermatitis: Untersuchung von Häufigkeit und Prädispositionsfaktoren im Kollektiv der Hautklinik Universitätsklinikum Erlangen und des Informationsverbundes Dermatologischer Kliniken (IVDK) 1998-2008
**Güll, Ina,** Dr. med.: Bedeutung der Heparinallergie im Kollektiv der Hautklinik Universitätsklinikum Erlangen (1999 – 2009)
**Streiff, Laura,** Dr. med.: Calcitonin zur systemischen Therapie der progressiven Sklerodermie – eine Verlaufsbeobachtung mit Patientenbefragung

### Habilitation 2013

**Renner, Regina,** PD Dr. med.: Chronische Wunden Beeinflussungsfaktoren und mathematische Beschreibung des Heilungsverlaufs

### Habilitation 2014

**Lechmann, Matthias Johannes,** PD Dr. rer. nat.: CD83 und TSLP als Modulatoren der Immunantwort

## Department of Dermatology
Division of Immune Modulation

### Doctorate Theses 2014

**Burkard, Miriam,** Dr. rer. nat.: Podocytes as non-hematopoietic professional antigen-presenting cells
**Eckhardt, Jenny,** Dr. rer. nat.: Soluble CD83 (sCD83) and Thymic stromal lymphopoietin (TSLP): Modulators of the Immune System
**Kreiser, Simon,** Dr. rer. nat.: Analyses of a CD83-expressing regulatory murine T cell population

**Heilingloh, Christiane Silke,** Dr. rer. nat.: Modulations of the CD83 molecule on mature dendritic cells by herpes virus infection

### Habilitation 2014

**Lechmann, Matthias Johannes,** PD Dr. rer. nat.: CD83 und TSLP als Modulatoren der Immunantwort

## Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology

Chair of Internal Medicine I

### Doctorate Theses 2013

**Franke, Julia,** Dr. med.: Untersuchungen zur Entwicklung von Depression und Angststörungen bei Hashimoto-Thyreoiditis
**Gottfried, Angelina,** Dr. med.: Langzeiterfolg der endoskopischen Ballondilatation im Vergleich zu operativen Verfahren bei der Therapie von Morbus Crohn bedingten Darmstenosen
**Hashimi, Zarlasht,** Dr. med.: Etablierung eines hepatozytenspezifischen siRNA-Transfektionssystems zur gezielten Therapie viraler Hepatitiden und assoziierter Folgekrankheiten
**Kersten, Sven,** Dr. med.: Auswertung einer palliativen systemischen Chemotherapie mit Gemcitabin und hochdosiert 5-Fluorouracil als 24h-Infusion bei Patienten mit metastasierten Karzinomen des Gallenwegssystems

### Habilitation 2013

**Zopf, Steffen,** PD Dr. med.: Epigenetische Modulation in der Therapie gastrointestinaler Tumoren

### Habilitation 2014

**Fuchs, Florian Siegfried,** PD Dr. med.: Neue Verfahren zur endobronchialen Diagnostik von Lungenerkrankungen
**Ganslmeyer, Marion,** PD Dr. med.: Epidemiologische Entwicklung und neue therapeutische Ansätze zur Behandlung des HCC
**Görtz, Rüdiger Stephan,** PD Dr. med.: Acoustic Radiation Force Impulse (ARFI) – Elastometrie der Leber
**Weigmann, Benno Johannes,** PD Dr. rer. nat.: Analyse von molekularen Transkriptionsfaktoren in entzündlichen Darmerkrankungen
**Wirtz, Stefan Joachim,** PD Dr. rer. nat.: Cellular and molecular aspects of cytokine functions in inflammatory diseases – Studies about the role of IL-27, IL-33 and IL-35 in the context of infection and inflammation

### Board Qualification 2013

**Atreya, Raja,** Prof. Dr. med.
**Görtz, Rüdiger Stephan,** PD Dr. med.
**Hildner, Christine,** Dr. med.

### Board Qualification 2014

**Egger, Cornelia,** Dr. med.
**Hagel, Alexander,** Dr. med.
**Quast, Stefan,** Dr. med.

### Additional Qualification 2013

**Wildner, Dane,** Dr. med.: Gastroenterology

### Additional Qualification 2014

**Albrecht, Heinz,** Dr. med.: Gastroenterology
**Zopf, Steffen,** PD Dr. med.: Gastroenterology
**Zirlik, Sabine,** Dr. med.: Palliative Medicine

## Department of Medicine 2 – Cardiology and Angiology

Chair of Internal Medicine II

### Doctorate Theses 2013

**Barthel, Thomas,** Dr. med.: Einfluss von Statinen auf die Expression von TGF-ß1, VAR-1, Eotaxin3 und MIG als inflammatorische Trigger humaner hochgradig stenosierter und verkalkter Aorterklappen
**Gnutzmann, Daniel,** Dr. med.: Growing Cardiospheres and Cardiosphere Derived Cells and Characterization thereof by FACS Analysis
**Kronfeldner, Helmut,** Dr. med.: Kultivierung und Charakterisierung von potentiellen kardialen Progenitorzellen
**Rieger, Andreas,** Dr. med.: Einfluss von Statinen, Niereninsuffizienz, Chlamydia pneumoniae-Infektion und Toll-like-Rezeptordefekten auf die Maturation und Funktion Dendritischer Zellen bei der Atherogenese im Mausmodell
**Wörner, Anja,** Dr. med.: Zelluläre und hämodynamische Mechanismen der Entstehung von atherosklerotischen Plaques an Gefäßbifurkationen und die vermehrte Destabilisierung fortgeschrittener Läsionen an der proximalen Plaque-Schulter

### Doctorate Theses 2014

**Lutter, Christoph,** Dr. med.: Einfluss der Mikrostrukturierung von Stentoberflächen auf die Stentendothelialisierung
**Nothhaft, Matthias,** Dr. med.: Einfluss von mikrostrukturierten Oberflächen auf die Hämokompatibilität und Funktionalität von Stents
**Rost, Marie-Charlotte,** Dr. med.: Quantifizierung der Infarkttransmuralität nach akutem Myokardinfarkt mittels echokardiographischer Funktionsparameter in körperlicher Ruhe
**Schiessl, Susanna,** Dr. med. dent.: Volumetrie epikardialen Fetts in kontrastverstärkten und nativen Datensätzen der kardialen Computertomographie

## Department of Medicine 3 – Rheumatology and Immunology

Chair of Internal Medicine III

### Doctorate Theses 2013

**Albrecht, Andreas,** Dr. med.: The structural basis of MRI bone erosions: an assessment by microCT
**Aschenberg, Sophie,** Dr. med.: Catabolic and anabolic periarticular bone changes in patients with rheumatoid arthritis: a computed tomography study on the role of age, disease duration and bone markers
**Dandorfer, Stefan,** Dr. med.: Differences in the Patient´s and the Physician´s Perspective of Disease in Psoriatic Arthritis
**Derer, Anja,** Dr. rer. nat.: Die Funktion von RSK2 und IL-36 in synovialen Fibroblasten und entzündlicher Arthritis
**Finzel, Stephanie,** Dr. med.: Die hochauflösende periphere quantitative Computertomografie (High-resolution peripheral quantitative CT, hr-pQCT): Neue Einblicke in die Arthritis 213
**Grötsch, Bettina,** Dr. rer. nat.: Role of the AP-1 transcription factor Fra1 in B cell development and activation
**Mühlbauer, Carolin,** Dr. med.: Charakterisierung der knöchernen sowie synovialen Veränderungen bei Daumensattelgelenksarthrose
**Ruiz-Heiland, Gisela,** Dr. rer. biol. hum.: Signalwege des inflammationsgetriebenen Umbaus von Knochen und Gelenken. Analyse der Effekte einer Modulation der Wingless- und Hedgehog Signalwege auf die experimentelle Arthritis
**Scherbel, Carina,** Dr. rer. nat.: The Role of the Nuclear Receptor PPARb/d in the regulation of Wnt-Signaling and Bone Homeostasis
**Weingärtner, Simon,** Dr. med. dent.: Pomalidomide is effective for prevention and treatment of experimental skin fibrosis
**Zerr, Pawel,** Dr. rer. nat.: Evaluation neuer molekularer Ansätze für die Behandlung der Fibrose

### Doctorate Theses 2014

**Englbrecht, Matthias,** Dr. rer. biol. hum.: Interaktion von körperlicher Funktion und emotionalem Befinden bei Patienten mit rheumatoider Arthritis und deren Auswirkung auf die empfundene Krankheitsaktivität und die Anwendung von Strategien zur Situationsbewältigung
**Herz, Barbara,** Dr. med.: Osteitis and synovitis, but not bone erosion, is associated with proteoglycan loss and microstructure damage in the cartilage of patients with rheumatoid arthritis
**Ipseiz, Natacha,** Dr. rer. nat.: The role of the nuclear receptor Nr4a1 as mediator of the anti-inflammatory effects of apoptotic cells
**Krämer, Marlene,** Dr. med.: Inhibition of H3K27 histone trimethylation activates fibroblasts and induces fibrosis
**Lin, Neng-Yu,** Dr. rer. nat.: Die Rolle der Autophagie in der Knochenremodellierung
**Reis, Petra,** Dr. med.: Krankheitsverarbeitung und Lebensqualität bei Patienten mit primären systemischen Vaskulitiden
**Schauer geb. Schorn, Christine,** Dr. rer. nat.: Mechanisms of monosodium urate induced inflammation

### Habilitation 2013

**Stock, Michael,** PD Dr. rer. nat.: Neue Gene in Entwicklung und Pathogenese des Skeletts

### Habilitation 2014

**Krönke, Gerhard,** PD Dr. med.: Die Rolle von Lipidoxidationsprodukten in der Pathogenese chronisch-entzündlicher Erkrankungen

## Department of Medicine 4 – Nephrology and Hypertension

Chair of Internal Medicine IV

### Doctorate Theses 2013

**Bauernschubert, Philipp,** Dr. med.: Eingeschränkte Vasodilatation retinaler Widerstandsgefäße bei Patienten mit essentieller Hypertonie
**Breyer, Johannes,** Dr. med.: Bedeutung von Rho-Kinasen für das Genexpressions- und Migrationsverhalten mikrovaskulärer Endothelzellen
**Hummel, Diana,** Dr. med.: Dihydropyridine calcium antagonists are associated with increased albumiuria in treatment-resistant hypertensives
**Schuster, Iris,** Dr. med.: Prospektive Studie über die Endothelfunktion renaler Gefäße bei hypertensiven Patienten mit Diabetes mellitus Typ 2

### Doctorate Theses 2014

**Jagusch, Lisa,** Dr. med.: Eine gestörte Angiogenese unterscheidet einen malignen von einem nicht-malignen Verlauf der experimentellen renovaskulären Hypertonie
**Jobst-Schwan, Tilman,** Dr. med.: Die endozytotische Aufnahme des antiapoptotischen Proteins Survivin wird im proximalen Tubulus der Niere durch Megalin vermittelt

### Habilitation 2013

**Ott, Christian,** PD Dr. med.: Erfassung der Endothelfunktion beim vaskulären Risikopatienten
**Ritt, Martin,** PD Dr. med.: In vivo Untersuchungen früher Veränderungen in der retinalen Mikrozirkulation: Assoziation mit kardiovaskulären Risikofaktoren und –indikatoren sowie hämorheologischen Parametern

### Habilitation 2014

**Weidemann, Tilman Alexander,** PD Dr. med.: Gewebsspezifische Funktionen der Hypoxie-induzierbaren Transkriptionsfaktoren – Untersuchungen in vitro und in vivo mit genetischen Modellen

### Board Qualification 2013

**Bock, Dieter,** Dr. med.: Internal Medicine and Nephrology
**Dahlmann, Anke,** Dr. med.: Internal Medicine and Nephrology
**Forster, Christian,** Dr. med.: Internal Medicine and Nephrology
**Moye, Brigitte,** Dr. med.: Internal Medicine and Nephrology
**Raabe, Andrea,** Dr. med.: Internal Medicine
**Schödel, Johannes,** Dr. med.: Internal Medicine

### Board Qualification 2014

**Arrenberg, Aliki,** Dr. med.: Internal Medicine and Nephrology
**Herbst, Larissa,** Dr. med.: Internal Medicine
**Kistner, Iris,** Dr. med.: Internal Medicine
**Moye, Brigitte,** Dr. med.: Internal Medicine
**Ott, Christian,** PD Dr. med.: Internal Medicine and Nephrology
**Pfau, Anja,** Dr. med.: Internal Medicine
**Weidemann, Tilmann Alexander,** PD Dr. med.: Internal Medicine and Nephrology

## Department of Medicine 5 – Hematology and Oncology

Chair of Hematology and Oncology

### Doctorate Theses 2013

**Bösl, Karina,** Dr. med.: Die Rolle der Natürlichen Killerzellen bei der spezifischen T-Zellantwort im Rahmen der Tumorimmunität
**Britting, Sabine,** Dr. rer. nat.: Induktion und Charakterisierung einer T-Zellantwort gegen das uveale Melanom
**Feulner, Julian,** Dr. med.: T Lymphocytes Can Be Effectively Recruited for Ex vivo and In vivo Lysis of AML Blasts by a Novel CD33/CD3-Bispecific BiTE Antibody Construct
**Heinrich, Stefan,** Dr. med.: Zytotoxische Funktion von T-Lymphozyten gegen Melanomzellen nach in vitro Stimulation mit einem Melanoma chondroitin sulfate proteoglycan (MCSP)xCD3 bispezifischen Antikörper
**Schauenberg, Philipp,** Dr. med.: Aktivitäts- und Verlaufsparameter unter neu initiierter Therapie mit Antagonisten gegen Tumornekrosefaktor alpha: Infliximab, Etanercept und Adalimumab im Vergleich

### Doctorate Theses 2014

**Mayer, Friederike,** Dr. med.: Der Einfluss natürlicher Killerzellen auf die Tumorimmunität in einem Doxorubicin-abhängigen murinen Vakzinierungsmodell
**San Nicoló, Katja,** Dr. med.: Retrospektive Analyse zur Überprüfung der Wirksamkeit von Antibiotika-beschichteten zentralvenösen Venenkathetern bei hämatologischen Patienten

### Habilitation 2013

**Mougiakakos, Dimitrios,** PD Dr. med.: Die redox-assoziierte Immunregulation und ihre Implikationen für maligne und entzündliche Erkrankungen

### Habilitation 2014

**Kremer, Anita,** PD Dr. med.: HLA Klasse II restringierte Antigene in Graft-versus Leukämie Effekt und Graft-versus-Host Erkrankung nach allogener Stammzelltransplantation

### Board Qualification 2014

**Weidinger, Martina,** Dr. med.

## Department of Neurology

Chair of Neurology

### Doctorate Theses 2013

**Lins, Anna,** Dr. med.: Diagnostischer Wert der Verteilung der regionalen Hirnperfusion im SPECT bei verschiedenen Demenzformen mittels reduktionistischer Analyse prinzipieller Komponenten
**Machold, Kristin,** Dr. med.: Experimentelle Ansätze zur Anwendung von Granulocyten-Kolonie stimulierendem Faktor als Therapie bei intrezerebaler Blutung an der Ratte
**Stark, David,** Dr. med.: Hypertone Kochsalzlösung bei erhöhtem intrakraniellen Druck aufgrund einer schweren akuten zerebrovaskulären Erkrankung – Untersuchung
**Türk, Matthias,** Dr. med.: Dopaminerge Differenzierung addulter humaner hippocampaler Stammzellen

### Doctorate Theses 2014

**Beuscher, Vanessa,** Dr. med.: Induktion zytoprotektiver Mechanismen als Schutz für Endothelzellen gegenüber einer Schädigung durch 7-Ketcholeserol
**Herfurth, Kirsten,** Dr. rer. biol. hum.: Vergleichende Sprachlateralisation und Lokalisation mittels funktioneller Magnetresonanztomographie und Magnetenzephalographie in der präoperativen Diagnostik der pharmako-resistenten Epilepsien, validiert am Wada-Test
**Lang, Johannes,** Dr. med.: S100B als Marker für Lewy-Körper-Erkrankungen: Eine Fall-Kontroll-Studie mit Bestimmung von Einzelbasen-Polymorphismen und Serum- und Liquorwerten
**Möbius, Cornelia,** Dr. med.: Prognose des ischämischen Schlaganfalls in der älteren Bevölkerung: Evaluation des SPAN-100-Index
**Olmes, David-Gerhard,** Dr. med.: Beteiligung der adulten Neurogenese bei schizophrenen Psychosen
**Stadler, Peter,** Dr. med.: Altersabhängige Effekte aggressiv bewerteter Musik auf die autonome Arousal-Antwort
**Ullah, Jasmin,** Dr. med.: Sensitivität und Spezifität von Pyramidenbahnzeichen – Die besondere Bedeutung von Clauss und Babinski

### Habilitation 2013

**Derfuß, Tobias,** PD Dr. med.: Die Rolle von Antikörpern bei der Pathogenese der Multiplen Sklerose
**Waschbisch, Annette,** PD Dr. med.: Mechanismen der Immunregulation bei entzündlichen Erkrankungen des Muskels und des Zentralnervensystems

### Board Qualification 2013

**Intravooth, Tassanai,** Dr. med.
**Kiphuth, Ines,** Dr. med.
**Nickel, Florian,** Dr. med.
**Stallforth, Sabine,** Dr. med.

### Additional Qualification 2013

**Köhrmann, Martin,** PD Dr. med.: Geriatrics/Intensive Care Medicine
**Olmes, David-Gerhard,** Dr. med.: Emergency Medicine
**Seifert, Frank,** PD Dr. med.: Geriatrics/Intensive Care Medicine

## Department of Neurology
Division of Molecular Neurology

### Doctorate Theses 2013

**May, Verena,** Dr. rer. nat.: Zelluläre Plastizität im zentralen Nervensystem bei Synukleinopathien

### Doctorate Theses 2014

**Kalis, Johannes,** Dr. med. dent.: Korrelation der Riechfunktion und des Bulbus-olfactorius-Volumens mit der motorischen Einschränkung beim idiopathischen Parkinson-Syndrom
**Kalis, Nina,** Dr. med. dent.: Korrelation des Bulbus-olfactorius-Volumens mit der Riechfunktion in der Frühdiagnose des idiopathischen Parkinson-Syndroms
**Pöhler, Anne-Maria,** Dr. rer. nat.: The autophagy-lysosomal-pathway in aggregation, release, and toxicity of alpha-synuclein

## Department of Neurosurgery
Chair of Neurosurgery

### Doctorate Theses 2014

**Fan, Zheng,** Dr. rer. biol. hum.: Der Einfluss von Dexamethason bei tumorassoziierten Degenerations- und Angiogeneseprozessen

## Department of Nuclear Medicine
Chair of Clinical Nuclear Medicine

### Doctorate Theses 2013

**Menges, Mareen,** Dr. med.: I-131 SPECT/CT in the Follow-up of Patients with Differentiated Thyroid Carcinoma

### Doctorate Theses 2014

**Beck, Michael,** Dr. med.: Anwendung des 3D-Ultraschalls in der Diagnostik von Schilddrüsenknoten – Vergleich mit dem konventionellen 2D-Ultraschall
**Bennewitz, Christian,** Dr. med.: Computer-aided evaluation of the anatomical accuracy of hybrid SPECT/spiral-CT imaging of lesions localized in the neck and upper abdomen
**Sumer, Johannes,** Dr. med.: SPECT/CT in Patients with Lower Back Pain after Lumbar Fusion Surgery

### Habilitation 2013

**Schmidt, Daniela,** PD Dr. med.: Bedeutung der SPECT/CT als neues bildgebendes Verfahren für die Diagnostik beim Schilddrüsenkarzinom

## Department of Obstetrics and Gynecology
Chair of Obstetrics and Gynecology

### Doctorate Theses 2013

**Ellmann, Stephan,** Dr. med.: PTEN als Modulator von Östrogenrezeptor- und Tyrosinkinase-Signalwegen in Brust- und Endometriumkarzinomzellen unter Tamoxifenbehandlung
**Heim, Stefanie,** Dr. med.: Komplikationsrate, Patientenzufriedenheit und therapeutische Möglichkeiten der Vakuumsaugbiopsie
**Hofmiller, Bettina,** Dr. med.: Vergleich von Laparoskopischer Suprazervikaler Hysterektomie und Totaler Laparoskopischer Hysterektomie
**Meindl, Nicole,** Dr. med.: Auswirkungen von humanem Seminalplasma auf die Kontraktilität des extrakorporal-perfundierten, nicht-schwangeren Schweineuterus unter dem Einfluss von Progesteron
**Polier, Astrid,** Dr. med.: Kombination von RAD001 und Chloroquin zur Behandlung von Brustkrebs – eine Analyse der zellulären und molekularen Mechanismen
**Schölch, Daniel,** Dr. med.: Porcine uterus cryopreservation: An analysis of contractile function using different uterotonics
**Tänzer, Thorsten,** Dr. med.: Einflussfaktoren von Ärztinnen und Ärzten auf die Indikation unterschiedlicher Therapieoptionen in der kurativen und palliativen Situation von Patientinnen mit eine Mammakarzinom – Ergebnisse der Gut Informieren – Gemeinsam Entscheiden! Studie
**Thieme, Franziska,** Dr. rer. biol. hum.: Analyse verschiedener humaner endogener retroviraler Hüllgene in Karzinomen des Ovariums und Endometriums

### Doctorate Theses 2014

**Binder, Katja,** Dr. med.: Mustererkennung in digitalisierten Mammografien im Rahmen einer Fall-Kontroll-Studie
**Dietl, Anna Katharina,** Dr. med.: Schwangerschaft, Geburt und fetalem Outcome bei fortgeschrittenem maternalen Alter
**Gaaß, Kathrin,** Dr. med.: Zusammenhang zwischen mütterlicher Bindung, postpartaler Depression und kindlichen Entwicklungsauffälligkeiten bis zum 18. Lebensmonat
**Lotz, Laura,** Dr. med.: Does stimulation with human gonadotropins and gnrh agonist enhance and accelerate the developmental capacity of oocytes in human ovarian tissue xenografted into scid mice?
**Reiß, Marion,** Dr. med. dent.: Können Gewicht und Gewichtsperzentile bei Geburt bereits im frühen 2. Trimenon vorhergesagt werden? Eine prospektive Studie mit neuen Ultraschall- und Fruchtwasserparametern
**Sauer, Stephanie,** Dr. med.: Die Rolle der Stop-mutation im ERV3-1-Hüllprotein bei hypertensiven Schwangerschaftserkrankungen und Minderansprechen auf eine In-vitro-Fertilisationsbehandlung
**Seidl-Ertel, Janine,** Dr. med.: Dokumentationsaufwand einer Patientin mit einem Mammakarzinom von der Primärdiagnose bis zum Follow-up und den verbundenen Ressourcen

### Habilitation 2013

**Faschingbauer, Florian,** PD Dr. med.: Fetales Monitoring mittels pränataler Sonografie
**Schrauder, Michael,** PD Dr. med.: Molekulare Marker für Diagnostik und Prognose beim Mammakarzinom

### Habilitation 2014

**Heusinger, Katharina,** PD Dr. med.: Mammografische Dichte in Prävention, Früherkennung und Behandlung des Mammakarzinoms
**Jud, Sebastian,** PD Dr. med.: Neue Bildgebungsverfahren und Bildanalyse-Methoden in der Frauenheilkunde
**Mehlhorn, Grit,** PD Dr. med.: Untersuchungen von präinvasiven und invasiven Läsionen des weiblichen Genitaltraktes

### Board Qualification 2013

**Hein, Alexander,** Dr. med.
**Heusinger, Katharina,** Dr. med.
**Hildebrandt, Thomas,** Dr. med.

### Board Qualification 2014

**Fahlbusch, Christine,** Dr. med.
**Strahl, Olga,** Dr. med.

### Additional Qualification 2013

**Löhberg, Christian,** PD Dr. med.: Gynecological Oncology

### Additional Qualification 2014

**Faschingbauer, Florian,** PD Dr. med.: Special Obstetrics and Perinatal Medicine
**Hautmann, Simone,** Dr. med.: Gynecological Exfoliative Cytology
**Hüttner, Nina,** Dr. med.: Naturopathic Methods
**Renner, Stefan,** Prof. Dr. med.: Special Obstetrics and Perinatal Medicine

## Department of Ophthalmology
Chair of Ophthalmology

### Doctorate Theses 2013

**Steinhäuser, Mareike,** Dr. med.: Einfluss einer Optical Coherence Tomograph-gesteuerten Referenzebene auf die semiautomatische Glaukomdiagnose des Heidelberg Retina Tomo- graphen- ein Methodenvergleich

### Doctorate Theses 2014

**Kreißel, Jacqueline,** Dr. med. dent.: Aufbau eines digitalen Managementsystems für Gewebeproben (Biobank)
**La Mancusa, Antonia,** Dr. med.: Muster-Elektroretinogramme während des Eiswassertests bei Glaukompatienten und Normalprobanden
**Rudolph, Michael,** Dr. med.: Corneal Higher-Order Aberrations after Descemet's Membrane Endothelial Keratoplasty

### Habilitation 2014

**Sel, Saadettin,** PD Dr. med: Genexpressionsanalyse während der Retinogenese

## Department of Otorhinolaryngology – Head and Neck Surgery
Chair of Otorhinolaryngology

### Doctorate Theses 2013

**Beck, Biancamaria,** Dr. med.: Verteilung magnetischer Nanopartikel in einem Arterienströmungsmodell in Abhängigkeit der Magnetfeldstärke und der Partikelgröße – Vorarbeiten für das genetische Drug Targeting
**Tratz, Erika,** Dr. med.: Auditory Event-Related Potentials to Single Words and Sentences in Normal Hearing Adults
**Walter, Markus,** Dr. med. dent.: Context Dependent Auditory Thresholds Determined by Brainstem Audiometry and Prepulse Inhibition in Mongolian Gerbils

### Habilitation 2013

**Bohr, Christopher,** PD Dr. med.: Dreidimensionale Analyse der Stimmlippendynamik
**Psychogios, Georgios,** PD Dr. med.: Prognostische Faktoren bei Oropharynxkarzinomen

## Department of Otorhinolaryngology – Head and Neck Surgery
Division of Phoniatrics and Pediatric Audiology

### Doctorate Theses 2013

**Bartke, Betina Eva Katrin,** Dr. med. dent.: Perzeptive und maschinelle Stimm- und Sprechanalyse bei chronischer Laryngitis und T1-Stimmlippenkarzinomen
**Gleißner, Harald,** Dr. med. dent.: Validität der Elternfragebögen FRAKIS und ELAN bei der Vorsorgeuntersuchung U7
**Hüttner, Björn,** Dr.-Ing.: Biomechanical Analysis Methods for Substitute Voice Production
**Luegmair, Georg,** Dr.-Ing.: 3D Reconstruction of Vocal Fold Surface Dynamics in Functional Dysphonia
**Rogal, Marcin,** Dr. med. dent.: Analyse akustischer Phonationssignale bei in vitro Halbkehlkopfexperimenten
**Seiferlein, Eva,** Dr. med. dent.: Zusammenhang zwischen der Krankheitsverarbeitung und der subjektiven Einschätzung der stimmbezogenen Lebensqualität von Patienten nach Entfernung von T1- und T2-Larynxtumoren

### Doctorate Theses 2014

**Hempel, Eric,** Dr. med.: In vitro Experimente am Kehlkopfpräparat: Einfluss der Änderung der Adduktionskräfte und des subglottalen Druckes auf die 3D-Stimmlippenbewegung und die Akustik
**Kersting, Jan,** Dr. med. dent.: Erhebung und statistische Auswertung einer Kontrollgruppe zur Validierung der automatischen Verständlichkeitsanalyse durch Spracherkennungssysteme
**Mathies, Dorothea,** Dr. med.: Deformationseigenschaften der Epithelschicht von humanen Stimmlippen anhand von Hemilarynxexperimenten
**Prudil, Stefan,** Dr. med. dent.: Dreidimensionale Stimmlippenbewegungen im exzidierten Schweinemodellkehlkopf
**Reiß, Franziska Elisa,** Dr. med. dent.: Selbst- und Fremdbewertung der Stimmqualität nach Larynxteilresektion
**Reuter, Anne,** Dr. med.: 3D – Schwingungsanalyse künstlicher Stimmlippen
**Schmarje, Anne,** Dr. med. dent.: Retrospektive Analyse der Stimmbewertung bei Patienten mit funktioneller Dysphonie
**Schulz, Aneliya,** Dr. med. dent.: Validierung eines automatischen Sprechanalyseverfahrens mit Sprechproben von Kindern und Jugendlichen mit einer isolierten Gaumenspalte
**Xue, Ning,** Dr.-Ing.: Automated Model-Based Semantic Registration of Multimodal MR Image Data

### Board Qualification 2013

**Bohr, Christopher,** Prof. Dr. med.

## Department of Pediatric and Adolescent Medicine
Chair of Pediatrics

### Doctorate Theses 2013

**Dawood, Yousif Louay,** Dr. med.: Verifikation von im plazentaren Genarray identifizierten, endokrinen Biomarkern für intrauterine Wachstumsrestriktion in vivo und deren Regulation durch Hypoxie in plazentaren Zellen in vitro
**Dinkel, Christina,** Dr. med.: Die Bedeutung des Integrins alpha 8 beta 1 für die Zellaktivierung in der Pathogenese der Fibrose
**Fährmann, Nina,** Dr. med.: Intrauterine Wachstumsrestriktion der Ratte: Charakterisierung hormoneller Einflüsse am Modell der duktalen Morphogenese der pubertären Brustdrüse
**Jobst, Eva,** Dr. med.: Metabolische Programmierung des renal-intrinsischen Leptin-Neuropeptid Y-Systems mit renalem Funktionsverlust nach postnataler Hyperalimentation
**Nitz, Alexandra,** Dr. med.: Prospective evaluation of cisplatin- and carboplatin-mediated ototoxicity in paediatric and adult soft tissue and osteosarcoma patients
**Yang, Xiaojun,** Dr. med. dent.: Untersuchung der neuronalen Differenzierungsfähigkeit eines aus CD133-positiven humanen Nabelschnurblutzellen gewonnenen Stammzellklons

### Doctorate Theses 2014

**Kaiser, Agnes,** Dr. med.: Die Rolle der antimikrobiellen Peptide und des E-Cadherins in der Pathogenese der Nekrotisierenden Enterokolitis
**Lendzian, Lisa,** Dr. med.: Rolle des TGF-ß Systems in der Lungenentwicklung nach intrauteriner Wachstumsrestriktion in der Ratte
**Madeja, Julia,** Dr. med.: Untersuchungen zum Längenwachstum bei Kindern mit CHARGE-Syndrom
**Pichl, Carolin,** Dr. med.: Untersuchung zum Kohlenhydrat- und Lipidstoffwechsel bei Kindern und Jugendlichen mit einem Adrenogenitalem Syndrom mit 21-Hydroxylase-Defekt (AGS)
**Reif, Fabian,** Dr. med.: Dopplersonographische Flussmessungen der Blutströmung in den Vertebralarterien bei Neugeborenen mit Erhebung von Normwerten der Flussgeschwindigkeiten, Übersicht über krankhafte Blutströmungen der hirnstammversorgenden Arterien und Häufigkeit anatomischer Varianten der Vertebralarterien in einem Normalkollektiv

### Board Qualification 2013

**Fahlbusch, Fabian,** Dr. med.
**Kusnik, Stefan,** Dr. med.

### Board Qualification 2014

**Freund, Johanna,** Dr. med.
**Hammersen, Johanna,** Dr. med.
**Leyh, Jörg**
**Marek, Ines,** Dr. med.
**Menendez-Castro, Carlos,** Dr. med.
**Wolf, Paul,** Dr. med.

### Additional Qualification 2013

**Galiano, Matthias,** Dr. med.: Pediatric Nephrology

### Additional Qualification 2014

**Chada, Martin,** Dr. med.: Pediatric Oncology and Hematology
**Fahlbusch, Fabian,** Dr. med.: Sonografie DEGUM I
**von Goessel, Heiko,** Dr. med.: Pediatric Oncology and Hematology
**Naumann-Bartsch, Nora,** Dr. med.: Pediatric Oncology and Hematology
**Nögel, Stephanie,** Dr. med.: Pediatric Neurology

## Department of Pediatric and Adolescent Medicine
Division of Pediatric Cardiology

### Habilitation 2013

**Glöckler, Martin,** PD Dr. med: Therapeutischer Nutzen neuer Computertomografie-Techniken in der Kinderkardiologie
**Zartner, Peter,** PD Dr. med.: Entwicklung und Anpassung der Herzschrittmacher- und Defibrillator Therapie an die Erfordernisse bei Kindern und Jugendlichen mit angeborenen Herzfehlern

## Department of Plastic and Hand Surgery
Chair of Plastic Surgery and Hand Surgery

### Doctorate Theses 2013

**Kleinmann, Judith,** Dr. med.: Immunhistochemische Analysen des Musculus rectus abdominis Lappen am Schweinemodell unter extrakorporaler Perfusion
**Rother, Ulrich,** Dr. med.: Die mikrochirurgische Ausbildung in einem großen rekonstruktiven Zentrum

### Doctorate Theses 2014

**Strobel, Leonie,** Dr. med.: Optimization of bone tissue engineering concepts – The effects of biomaterials, growth factors and culture conditions on the osteogenic capacity of bone cells

## Department of Psychiatry and Psychotherapy

Chair of Psychiatry and Psychotherapy

### Doctorate Theses 2013

**Bausch, Michaela,** Dr. med.: Gegensätzliche Auswirkungen von Depression und Antidepressive auf die Verarbeitungsgeschwindigkeit und die Fehlerquote
**Beck, Johannes,** Dr. med.: Aktivität der sezernierten sauren Sphingomyelinase im Blutplasma von alkoholabhängigen Patienten und ihr Verlauf im Entzug
**Bode, Jens,** Dr. med.: Die Aktivität der sauren Sphingomyelinase wird im Zellkulturmodell durch Zelldichte reguliert
**Düchs, Christina,** Dr. med.: Schlaganfallpatienten nach stationärer neurologischer Rehabilitation der Phase B und C: Durchführung von Heilmittelbehandlungen und Arztkontakte in einem Langzeitverlauf von 2,5 Jahren nach Entlassung
**Dygon, Dominika,** Dr. med.: Einfluss einer Serie hochfrequenter repetitiver Transkranieller Magnetstimulation auf Stimmung und affektive Symptome bei gesunden männlichen Probanden
**Friedrich, Kerstin Anne,** Dr. med.: Einfluss einer Serie hochfrequenter repetitiver Transkranieller Magnetstimulation auf kognitive Parameter bei gesunden männlichen Probanden
**Kießlinger, Jens Harro,** Dr. med.: HERPUD – Homocystein-inducible endoplasmic reticulum-resident ubiquitin-like domain member protein mRNA-Expression und Promotormethylierung bei Patientinnen mit Anorexia nervosa und Bulimia nervosa
**Lins, Anna,** Dr. med.: Diagnostischer Wert der Verteilung der regionalen Hirnperfusion im SPECT bei verschiedenen Demenzformen mittels reduktionistischer Analyse prinzipieller Komponenten
**Mühlbacher, Markus,** Dr. rer. nat.: Computer-aided methods for predicting and analyzing drug localisation and mambrane permeability using moleccular properties
**Satt, Florian,** Dr. med.: Die Auswirkungen verschiedener genetischer Polymorphismen auf die Tagesschläfrigkeit beim Menschen
**Schilling, Nicole,** Dr. med.: Aktivität der Enzyme Monoaminoxidase A und Monoaminoxidas B im Serum depressiver Patienten
**Schipper, Theresa,** Dr. med.: Diagnostischer Wert der Liquorbiomarker Aß42, Gesamt-Tau-Protein und Phospho-Tau für die Alzheimer-Demenz in der klinischen Routinediagnostik
**Schulz, Hans-Jürgen,** Dr. med.: Einfluss medizinischer und psychologischer Faktoren auf den Erfolg stationärer geriatrischer Rehabilitation
**Söhngen, Carmen,** Dr. med.: Sind für den C1-Stoffwechsel relevante Polymorphismen mit Hyperhomocysteinämie und DNA Hypermethylierung bei Alkoholabhängigkeit assoziiert?
**Veh, Katharina,** Dr. med.: Geschlechterunterschiede in der kortikalen Repräsentation der glücklichen und unglücklichen Liebe
**Viegas, Reena,** Dr. med.: Untersuchung zur Reliabilität und Validität eines neu entwickelten Leistungstests zur Erfassung fundamentaler Alltagsaktivitäten von Demenzkranken im Pflegeheim
**Wunschel, Michael,** Dr. med.: Untersuchung der DNA-Methylierung als pathogenetischer Faktor der Schizophrenie am Sox-10- und Reelinpromotor mit der RT-PCR und genomweit mit Hilfe der MS-RDA

### Doctorate Theses 2014

**Bacher, Alina,** Dr. med.: Einfluss selektiver Serotonin-Wiederaufnahme-Hemmer auf die Aktivität der sauren Sphingomyelinase, Expression der Tryptophan-Hydroxylase 2 und Expression des Methyl-CpG-Binding-Domain Protein 1 bei gesunden männlichen Probanden
**Elm, Cornelia,** Dr. med.: Veränderungen im Geruchssinn von Morbus-Crohn-Patienten
**Eska, Kathrin,** Dr. rer. biol. hum.: Prädiktoren der Institutionalisierung bei Demenzpatienten im leichten und mittelschweren Stadium: eine prospektive Untersuchung im 4-Jahres-Zeitraum
**Fuchs, Kathrin,** Dr. med.: Charakterisierung der Ceramidase-Aktivität im Plasma gesunder und alkoholabhängiger Probanden
**Marquardt, Michael,** Dr. med.: Psychotherapie und Religion: Eine aktuelle Erhebung unter fränkischen Psychotherapeuten
**Schaller, Gerd,** Dr. med.: Einfluss einer Serie hochfrequenter repetitiver transkranieller Magnetstimulationen auf periphere BDNF Spiegel bei gesunden männlichen Probanden
**Seiler, Kristin,** Dr. med.: Wirkung von Glyceroltrinitrat auf die Expression der CGRP-Rezeptorkomponenten CLR und Ramp1 im Ganglion trigeminale der Ratte – eine immunhistochemische Untersuchung
**Wielopolski, Jan,** Dr. med.: Aktivitätsverhalten depressiver Patienten in verschiedenen Stadien der Erkrankung

### Habilitation 2013

**Luttenberger, Katharina,** PD Dr. rer. biol. hum.: Neuropsychologische Diagnostik und nicht medikamentöse Therapie bei degenerativen Demenzen

### Habilitation 2014

**Grömer, Teja Wolfgang,** PD Dr. med.: Synaptischer Vesikeltransport in Gesundheit und Krankheit

### Board Qualification 2013

**Burger, Pascal,** Dr. med.
**Fischer, Lisa Marie,** Dr. med.
**Schaller, Gerd,** Dr. med.
**Zimmermann, Rüdiger,** Dr. med.

### Board Qualification 2014

**Grömer, Teja,** Dr. med.
**Rotter-Neubert, Andrea,** Dr. med.
**Spitzer, Philipp,** Dr. med.
**Wielopolski, Jan,** Dr. med.

### Additional Qualification 2014

**Müller, Helge,** Dr. med.: Certificate Geropsychiatric Care
**Müller, Helge,** Dr. med.: Qualification "Expert in Traffic Medicine"
**Spitzer, Philipp,** Dr. med.: Primary Addiction Treatment

## Department of Psychiatry and Psychotherapy

Division of Child and Adolescent Mental Health

### Habilitation 2013

**Kratz, Oliver,** PD Dr. med.: Aufmerksamkeits- und Inhibitionsprozesse bei Kindern und Jugendlichen mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) und deren pharmakotherapeutische Modulation

### Board Qualification 2013

**Wieland, Ann-Kristin,** Dr. med.

### Board Qualification 2014

**Kleehaupt, Eva,** Dr. med.

## Department of Psychiatry and Psychotherapy

Division of Psychosomatics and Psychotherapy

### Doctorate Theses 2013

**Brandl, Christina,** Dr. rer. biol. hum.: Executive functions in obese patients with and without regular binge eating
**Zitarosa, Dino,** Dr. rer. biol. hum.: Belastungen, unerfüllte Bedürfnisse und Expressed Emotion bei Angehörigen von Erwachsenen mit Anorexia nervosa und Bulimia nervosa

## Department of Radiation Oncology

Chair of Radiotherapy

### Doctorate Theses 2013

**Auer, Judith,** Dr. med.: Untersuchungen zur individuellen Strahlenempfindlichkeit von Brustkrebspatientinnen
**Kraus, Florian,** Dr. med.: Wirkung von Hyperthermie und ionisierender Strahlung auf Fibroblasten, Lymphozyten und lymphoblastoide Zellen
**Schmidt-Heck, Silke,** Dr. med.: Prognostische Bedeutung des mittleren Abstandes zwischen regulatorischen T-Zellen und Memory T-Zellen und deren Dichten bei Kopf-Hals-Tumoren
**Weiss, Eva-Maria,** Dr.-Ing.: Ex vivo Inaktivierung autologer Tumorzellen mittels hydrostatischen Hochdrucks zur Generierung eines Ganzzell-basierenden Tumor-Vakzins

### Doctorate Theses 2014

**Barth, Cécile,** Dr. med.: Prognostische Bedeutung der Dichte und des mittleren Abstandes zwischen regulatorischen T-Zellen und Killer-T-Zellen bei Kopf-Hals-Tumoren
**Hoppe, Philipp,** Dr. med.: Individuelle Empfindlichkeit gegen Strahlen- und Chemotherapeutika induzierte Apoptose und Nekrose von Entzündungszellen im Blut von Tumorpatienten
**Körber, Jana,** Dr. med.: Variabilität der vorbestehenden und unreparierten DNA Doppelstrangbrüche in Lymphozyten bei Patienten mit Rektumkarzinom
**Kühlwein, Alexander,** Dr. med. dent.: Untersuchung der Seneszenz in Normalgewebszelllinien im Vergleich zur Apoptoseinduktion
**Miederer, Alexander,** Dr. med.: Untersuchung zur spezifischen Strahlenempfindlichkeit humaner Fibroblasten im Röntgenenergiebereich verschiedener spektraler Zusammensetzung
**Stenger, Sarah,** Dr. med.: Prognostische Bedeutung der Häufigkeit und des Abstandes zwischen regulatorischen T-Zellen und Memory T-Zellen beim Rektumkarzinom
**Weiss, Stefanie,** Dr. med.: Gesundheitsbezogene Lebensqualität bei Patienten mit Rektumkarzinom unter neoadjuvanter Radiochemotherapie
**Wenger, Barbara,** Dr. med.: PML-nukleäre Bodies nehmen mit dem Alter ab und haben zusätzlich eine gestörte Stressantwort bei älteren Menschen
**Zühlke, Mirjam,** Dr. med.: Einfluss der F-18-Fluorodeoxy-Glukose-Positronenemissionstomographie auf die Vorhersage des Therapieansprechens des lokal fortgeschrittenen Rektumkarzinoms nach neoadjuvanter simultaner Radiochemotherapie

### Habilitation 2014

**Semrau, Sabine,** PD Dr. med.: Strategien zur Optimierung der Radio-Chemotherapie bei soliden Tumoren

### Additional Qualification 2013

**Richter, Andreas,** Dr. rer. nat.: Medical Physics Expert

### Additional Qualification 2014

**Lahmer, Godehard,** Dr. med.: Hygienebeauftragter Arzt
**Reichensperger-Goertzen, Claudia,** Dr. med.: Medical Quality Management

## Department of Surgery

Chair of Surgery

### Doctorate Theses 2013

**Barthelmann, Susanne Karin,** Dr. med.: Endoprothetische Versorgung des Kniegelenks bei primärer Gonartherose-Analyse und Diskussion von 180 implantierten Oberflächenersatzprothesen vom Typ Scorpio
**Berrens, Norbert,** Dr. med.: Erstversorgung traumatischer Notfallpatienten durch den Notarzt
**Bingold, Joachim,** Dr. med.: Raumbelastung während zahnärztlicher Lachgassedierung
**El Chafchak, Jamal,** Dr. med.: Trochanteric-Gammanagel-Titan versus Trochanteric-Gammanagel-3. Eine retrospektive Studie
**Hein, Carolin,** Dr. med.: Ergebnisse und Verlauf von Kindern mit operierter Ösophagusatresie der Jahre 1994 – 2006
**Heinrich, Johanna,** Dr. med.: Die histomorphometrische Analyse der axialen Vaskularisation im AV-Loop Modell des Schafes: Ergebnisse einer tierexperimentellen Untersuchung
**Kaminski, Thomas,** Dr. med.: Der perioperative Verlauf von sTREM-1 als Prognosefaktor für postoperative Infektionen
**Kunold, Claudia,** Dr. med.: Lipidmodifizierte Tumorbiologie – Der Einfluss von Fettsäuren auf das Wachstum von Novikoffhepatomen
**Müller-Bergh, Larissa,** Dr. med.: Prognostische Wertigkeit von Faktor VIII, Von-Willebrand-Faktor-Antigen und Ristocetin-Cofaktor beim kolorektalen Karzinom
**Nuding, Anna,** Dr. med.: Lebertransplantation bei alkohol-toxischer Leberzirrhose
**Oppelt, Konrad,** Dr. med.: Einfluss der Fingerposition auf das Rupturverhalten des Ringbandsystems der Beugesehnen der Finger und die dabei auftretenden Kräfte im Kadavermodell
**Ostler, Nicole,** Dr. rer. nat.: Interferon-induced guanylate-binding protein-1 is a novel actin cytoskeleton remodeling factor
**Pfeifer, Eva,** Dr. med.: Eine retrospektive Nachuntersuchung zum Vergleich minimalinvasiv anterolateral implantierter Hüfttotalendoprothesen mit dem lateralen Standardzugang nach Bauer und dem hinteren Zugang nach Moore
**Schlechtweg, Alessandra,** Dr. med.: Morphologische Veränderungen im Oberen Sprunggelenk bei Höchstleistung im Spitzensport
**Stäber, Silke,** Dr. med.: Vergleichende Analyse prädiktiver und prognostischer Faktoren zwischen Patienten < 50 Jahre versus > 50 Jahre mit kolorektalem Karzinom – Eine Untersuchung des Erlanger Patientenkollektivs mit 1990 Patienten
**Thurau, Sandra,** Dr. med.: Lebensqualität und Sportfähigkeit nach Implantation einer Oberflächenersatzprothese am Hüftgelenk
**Urbaniak, Aleksandra,** Dr. med.: Klinische Ergebnisse der Perkutanen Transluminalen Angioplastie bei chronisch kritischer Beinischämie vom Unterschenkeltyp
**Vassos, Nikolaos,** Dr. med.: Prognostische Bedeutung von Expression von beta 1 Integrin in kolorektalen Lebermetastasen
**Zepnik, Felicitas,** Dr. med.: Evaluation des peri- und postoperativen Verlaufs bei der minimalisierten Erlanger Trichterbrustkorrektur nach Hümmer

### Doctorate Theses 2014

**Bochskanl, Wennemar,** Dr. med. dent.: Analyse der regulatorischen T-Zellen in Monozytapheresen gesunder Blutspender
**Caemmerer, Martin,** Dr. med. dent.: Analyse von T-Zellen in Stammzellkonzentraten aus Plazentarestblut
**Chudasama, Priya,** Dr. rer. nat.: Systematic analysis of anti-apoptotic activities of KSHV proteins using chip-based high-throughput transfection approaches
**CUI, Zhe,** Dr. med.: Long term outcome of the sacral nerve stimulation
**Hammon, Katrin,** Dr. med.: Ausprägung des HPA -1, -2, -3, -4, -5 und -15 Systems bei türkischen und deutschen Blutspendern
**Hausmann, Annekathrin,** Dr. med.: Gezielte Infektprävention bei Katheterverfahren zur postoperativen Schmerztherapie
**Heu, Franziska,** Dr. med.: Pilotstudie zum Einfluss einer Low-Level Lasertherapie auf die lokale Perfusions- und Oxygenierungssituation bei gesunden Personen
**Hohnheiser, Frederike,** Dr. med. dent.: Chirurgische Therapie von Karzinomen des Kolon transversum und der linken Flexur mit und ohne Erhalt des Kolon ascendens: Postoperative Komplikationen, Prognose und Lebensqualität
**Jenzer, Maximilian,** Dr. med.: Validierung und Regulation von Zielgenen einer GBP-1-assoziierten antiangiogenen Immunreaktion in Tumorendothelzellen aus dem kolorektalen Karzinom 2014
**Pohl, Johann,** Dr. med.: Neuroendokrine Tumore des Pankreas – eine Untersuchung an 82 operierten Patienten
**Schaal, Ute,** Dr. rer. biol. hum.: The role of Axin2 in colorectal cancer
**Selder, Doris,** Dr. med.: Rückverlagerung von protektiven Ileostomata: Früh- versus Spätverschluss. Eine nicht randomisierte monozentrische Pilotstudie
**Weber, Thomas,** Dr. rer. nat.: Accelerating drug evaluation by preclinical imaging: Monitoring pharmacodynamic and -kinetic activities of therapeutic antibodies in cancer xenograft models to improve treatment strategies

### Habilitation 2014

**Perrakis, Aristotelis,** PD Dr. med.: Indikationswandel in der Tumor- und der Transplantationschirurgie der Leber
**Schellerer, Vera Simone Angela,** PD Dr. med.: Molekularbiologische Charakterisierung des desmoplastischen Gewebes beim kolorektalen Karzinom
**Schildberg, Claus,** PD Dr. med.: Das aktuelle Spektrum der Magenchirurgie

### Board Qualification 2014

**Perrakis, Aristotelis,** PD Dr. med.
**Vassos, Nikolaos,** Dr. med.

## Department of Surgery

Division of Transfusion Medicine and Hemostaseology

### Doctorate Theses 2013

**Brenner, Lukas,** Dr. med.: Auswirkung der Transportdauer und Transporttemperatur des Plazentarestblutes auf die Qualität der hämatopoetischen Zellen in daraus hergestellten kryokonservierten Stammzellpräparationen

**Stützer, Tobias,** Dr. med.: Von-Willebrand-Faktor (vWF), Faktor-VIII-Spiegel sowie frei und zellulär in Thrombozyten zirkulierende Wachstumsfaktoren der Angiogenese bei Patienten mit Colon-Karzinom in verschiedenen UICC-Stadien

### Doctorate Theses 2014

**Born, Lena,** Dr. med.: Verträglichkeit von Leukozytapheresen bei Patienten mit Malignen Melanom
**Braun, Timm,** Dr. med.: Frühzeitige Bestrahlung leukozytendepletierter Erythrozytenkonzentrate in der additiven Lösung SAG-M aus zwei Blutspendediensten am Tag +3
**Burk, Samaya,** Dr. med.: Optimierung des Buffy-Coat-Volumens bei Leukozytapheresen
**Niemeyer, Nicole,** Dr. med.: Orale Antikoagulation und Reisen: Reisegewohnheiten und reiseassoziierte Komplikationsraten oral antikoagulierter Patienten
**Rudolph, Pamela,** Dr. med.: Das Reiseverhalten von Patienten mit Hämophilie A und B – Ergebnisse einer multizentrischen Fragebogenstudie

### Habilitation 2014

**Weiß, Dominik,** PD Dr. med.: Die thrombogenen Eigenschaften des Gefäßendothels und seiner unmittelbaren Umgebung

## Department of Surgery

Division of Trauma Surgery

### Doctorate Theses 2013

**Ranft, Tilo,** Dr. med. dent.: Drei-Jahres-Ergebnisse vorderer Kreuzbandplastikfixationen mittels RIGIDFIX® Cross Pin System unter Verwendung autologer Sehnentransplantate

### Doctorate Theses 2014

**Cipa, Franziska,** Dr. med.: Vergleich von Osteophytenknorpel und hyalinem Gelenkknorpel – Unterschiede auf molekularer und zellulärer Ebene
**Meier, Eva,** Dr. med.: Untersuchung einer neuartigen primären Knietotalendoprothese aus Keramik – biomechanische Tests und erste klinische Ergebnisse
**Stapel, Philipp,** Dr. med.: Beurteilung der Lebensqualität und körperlichen Belastbarkeit von erwachsenen Trisomie 21-Patienten mit operativ korrigiertem und nicht korrigiertem atrioventrikulärem Septumdefekt

### Board Qualification 2013

**Langenbach, Andreas,** Dr. med.

### Additional Qualification 2013

**Schulz-Drost, Stefan,** Dr.med.: Special Accident Surgery
### Additional Qualification 2014
**Welsch, Götz,** Dr. med.: Special Accident Surgery

## Department of Urology

Chair of Urology

### Doctorate Theses 2013

**Holzer, Kerstin,** Dr. med.: Auswertung von Häufigkeitsverteilungen und Korrelationen, der Proteine Hdm2, P53, P63, P14ARF und P16INK4a im invasiven Harnblasenkarzinom an digitalisierten Tissue Mikroarrays – eine experimentelle Arbeit

### Doctorate Theses 2014

**Al-Janabi, Omar,** Dr. rer. nat.: Die Untersuchung und Charakterisierung von Biomarkern im Nierenzell- und Prostatakarzinom
**Teichgräber, Ina Maria,** Dr. med.: Über die Wirksamkeit der oralen Pentosanpolysulfat-Therapie (SP54) in der Behandlung der Chronisch Interstitiellen Cystitis

### Board Qualification 2013

**Harlander-Weikert, Eva,** Dr. med.

### Board Qualification 2014

**Kunath, Frank,** Dr. med.
**Richterstätter, Mario,** Dr. med.
**Rogenhofer, Michael,** Dr. med.

### Additional Qualification 2013

**Hirsch, Karin,** Dr. med.: Fellow of the European Academy of Pediatric Urology; FEAPU
**Kunath, Frank,** Dr. med.: Fellow of the European Board of Urology; FEBU

### Additional Qualification 2014

**Kunath, Frank,** Dr. med.: Master of Health Business Administration, MHBA

## Department of Operative Dentistry and Peridontology

Chair of Dental, Oral, and Maxillofacial Medicine – especially Operative Dentistry, Periodontology, and Pediatric Dentistry

### Doctorate Theses 2013

**Dippold, Christoph,** Dr. med. dent.: Approximale Kastenelevationstechnik – Einfluss auf die marginale Adaptation von Kompositinlays
**Hösl, Michael,** Dr. med. dent.: Linearer Schrumpf zahnärztlicher Komposite – ein neues lichtoptisches Verfahren
**Kecskes, Valeria,** Dr. med. dent.: Analyse der apikalen Dichtigkeit von Wurzelkanalfüllungen unter Verwendung der Wurzelkanalfüllpasten Hybrid Root Seal und Activ GP Sealer in Kombination mit vier verschiedenen Obturationstechniken
**Marali-Djame-Khiabani, Mina,** Dr. med. dent.: Dichtigkeitsanalyse der koronalen Verbundzone adhäsiv inserierter Glasfaserstifte – eine Langzeitstudie

### Doctorate Theses 2014

**Albrecht, Florian,** Dr. med. dent.: Evaluation der adhäsiven Leistungsfähigkeit eines innovativen Schichtkonzepts
**Birner, Marion,** Dr. med. dent.: Bakteriendichtigkeit des Wurzelkanalsealers GuttaFlow Cuttable platziert mit vier verschiedenen Techniken
**Mangal, Munisha,** Dr. med. dent.: Polish Retention and related material parameters of provisional crown and Bridge materials
**Nowroth, Veronika,** Dr. med. dent.: Untersuchungen zur Haftkraft von Befestigungssystemen an Faserstiften unter dem Einfluss der Alterung
**Schlick, Carolin,** Dr. med. dent.: Zur Eignung von dentalen Kompositen für den direkten Höckerersatz im Seitenzahnbereich – eine Abrasionsstudie

### Habilitation 2014

**Taschner, Michael,** PD Dr. med. dent.: Adhäsive restaurative Zahnheilkunde in vitro und in vivo

### Additional Qualification 2014

**Holzner, Anna-Louisa,** Dr. med. dent.: Curriculum Endodontics
**Koch, Andreas,** Dr. med. dent.: Curriculum Implantology

## Department of Oral and Cranio-Maxillofacial Surgery

Chair of Dental, Oral, and Maxillofacial Medicine – especially Oral and Maxillofacial Surgery

### Doctorate Theses 2013

**Kwon, Yeeun,** Dr. med. dent.: Bewertung der Bedeutung von MAGE-A Expressionsanalysen zur Einschätzung des Risikos der malignen Transformation von Leukoplakien

### Doctorate Theses 2014

**Kaufmann, Christina,** Dr. med. dent.: Retrospektive Analyse der mikrovaskulär gestützten Rekonstruktion an der Mund-, Kiefer- und Gesichtschirurgischen Klinik über einen Beobachtungszeitraum von 6 Jahren
**Köpple, Markus,** Dr. med. dent.: Vergleichende tierexperimentelle Studie dreier verschiedener Implantatsysteme mit unterschiedlichen Oberflächenmodifikationen
**Mitsimponas, Konstantinos,** Dr. med.: Der mikrovaskulär anastomosierte Skapula-/Paraskapulalappen als ein zuverlässiger Rekonstruktionsverfahren im Kopf- Hals Bereich: Eine retrospektive Analyse von 130 Rekonstruktionen, die in einem Zeitraum von 5 Jahren in einer Mund-, Kiefer- und Gesichtschirurgischen Klinik durchgeführt wurden
**Rapp, Anja,** Dr. med. dent.: Parodontaler Status der Zähne im Spaltbereich nach sekundärer und tertiärer Osteoplastik bei Lippen-, Kiefer-, Gaumenspalten

**Wahabzada, Hommeira,** Dr. med. dent.: Knochenaugmentation mittels periimplantärer Elevation des ortsständigen Periosts

### Habilitation 2013

**Stockmann, Philipp,** PD Dr. med. Dr. med. dent.: Bisphosphonat-assoziierte Knochennekrosen des Kiefers

### Habilitation 2014

**Wehrhan, Gunther Falk,** PD Dr. med. Dr. med. dent.: Spezifische Signaltransduktion der Regeneration kraniofazialer Gewebe

## Department of Orthodontics and Orofacial Orthopedics

Chair of Dental, Oral, and Maxillofacial Medicine – especially Orofacial Orthopedics

### Doctorate Theses 2013

**Neupert, Jasmin,** Dr. med. dent.: Morphometrische Betrachtung der Mandibula klinisch symmetrischer Patienten – eine CT-Studie
**Teufel, Lisa,** Dr. med. dent.: Metrische und volumetrische Vermessung der Manibula bei Patienten mit einseitigen Lippen-Kiefer-Gaumenspalten – eine CT-basierte Studie

### Habilitation 2013

**Hofmann, Elisabeth,** PD Dr. med. dent.: Evaluierung impaktierter Zähne mittels Mehrschichtspiral- und Dentaler digitaler Volumentomographie – Strahlenbelastung und Bildqualität

### Board Qualification 2013

**Fink, Martin,** Dr. med. dent.

### Board Qualification 2014

**Hirschinger, Veronika,** Dr. med. dent.
**Spitzl, Caroline,** Dr. med. dent.

## Department of Prosthodontics

Chair of Dental, Oral, and Maxillofacial Medicine – especially Prosthetic Dentistry

### Doctorate Theses 2013

**Röder, Anja,** Dr. med. dent.: Anwendbarkeit photogrammetrischer Messtechniken zur quantitativen Erfassung von Mikrobewegungen dentaler Minischrauben
**Speer, Anne,** Dr. med. dent.: Vergleichende klinische Studie zur Wirksamkeit von Akupunktur beim Cranio-Mandibulären-Schmerzsyndrom (CMS/CMD) unter einem Elektromyographie (EMG) – Monitoring
**Wenzel, Kerstin,** Dr. med. dent.: Mundgesundheitsbezogene Lebensqualität, Depression und Mundhygiene eine Längsschnittstudie mit drei Messzeitpunkten am Beispiel eines mehrmonatigen militärischen Auslandseinsatzes

### Doctorate Theses 2014

**Baumgart, Christina,** Dr. med. dent.: Untersuchungen zu biomechanischen Eigenschaften des Kieferknochens
**Schittenhelm, Birgit,** Dr. med. dent.: Einfluss verschiedener Befestigungsparameter auf die Spannungsentwicklung verschraubter und zementierter Implantatrestaurationen

### Habilitation 2013

**Göllner, Matthias,** PD Dr. med. dent.: Photogrammetrische Messtechnik zur Quantifizierung von Mikrobewegungen oraler Strukturen

## Institute of Clinical and Molecular Virology

Chair of Clinical Virology

### Doctorate Theses 2013

**Bolduan, Sebastian,** Dr. rer. nat.: Virale Interferenz am Beispiel der Wechselwirkung der Zelloberflächenrezeptoren Tetherin und NTB-A mit dem regulatorischen HIV-1 Protein Vpu
**Eißmann, Kristin,** Dr. rer. nat.: Mechanismen der GBV-C vermittelten Hemmung der HIV-1-Replikation
**Scherer, Myriam,** Dr. rer. nat.: Antagonisierung zellulärer Abwehrmechanismen durch das IE1-Protein des humanen Cytomegalovirus
**Schmeiser, Cathrin,** Dr. rer. nat.: Studies on two essential viral proteins forming the core nuclear egress complex of human cytomegalovirus
**Setz, Christian,** Dr. rer. nat.: Regulation der Proteinstabilität durch virale und zelluläre Abbausignale und deren Einfluss auf die MHC-I Antigenpräsentation
**Spindler, Nadja,** Dr. rer. nat.: Funktionelle und strukturelle Charakterisierung von Antikörpern gegen das Glykoprotein B des Humanen Cytomegalovirus
**Vogel, Benjamin,** Dr. rer. nat.: Herpesvirus saimiri: Episomal replication timing, cell tropism and human NK cell transformation

### Doctorate Theses 2014

**Bootz, Anna,** Dr. rer. nat.: Die Rolle von Fc gamma-Rezeptoren bei der humoralen Immunantwort gegen das Cytomegalovirus
**Hahn, Friedrich,** Dr. rer. nat.: Funktionelle Charakterisierung des HIV-1 p6 Gag-Proteins
**Mann, Melanie C.,** Dr. rer. nat.: The interplay between the viral oncoprotein Tax and the transcription elongation factor ELL2
**Schuster, Philipp,** Dr. rer. nat.: Die Rolle Plasmazytoider Dendritischer Zellen in der Koordination der Immunreaktion gegen Herpes simplex Virus Typ1
**Webel, Rike,** Dr. rer. nat.: Protein kinase pUL97 of human cytomegalovirus – functional specification of three individual isoforms
**Wiegers, Anna,** Dr. rer. nat.: Humane neutralisierende Antikörper gegen das Glykoprotein B des humanen Cytomegalovirus

### Habilitation 2013

**Reil, Heide,** PD Dr. rer. nat. Dr. med.: Die Interferenz zwischen dem GB Virus C (Hepatitis G Virus) und Immundefizienzviren

## Institute of Clinical Microbiology, Immunology, and Hygiene

Chair of Microbiology and Immunology of Infection

### Doctorate Theses 2013

**Friedrich, Diana,** Dr. rer. nat.: Hypertonizität und Entzündung
**Jebran, Ahmad-Fawad,** Dr. med.: In vivo und in vitro Wirkung von pharmazeutischem Natriumchlorit bei der kutanen Leishmaniose
**Niedzielska, Magdalena,** Dr. rer. nat.: The role of DUSP16 and DUSP9 in the Innate Immune System

### Doctorate Theses 2014

**Eckart, Rita,** Dr. rer. nat.: Charakterisierung der anti-apoptotischen Aktivität des Coxiella burnetii Typ IV Effektorproteins AnkG
**Klingenbeck, Leonie,** Dr. rer. nat.: Manipulation of host cell apoptosis by Coxiella burnetii type IV secretion system effector proteins CaeA and CaeB
**Wenzel, Jens,** Dr. rer. nat.: Regulation of TLR-induced macrophage responses by cytoskeleton-associated phosphaproteins

### Habilitation 2014

**Jantsch, Jonathan,** PD Dr. med.: Regulation der Immunantwort und Infektionsabwehr durch periphere Milieufaktoren

## Institute of Human Genetics

Chair of Human Genetics

### Doctorate Theses 2013

**Götz, Manuela,** Dr. med.: Identifizierung von Genen für mentale Retardierung: Mutationsscreening im GRIK2-Gen und Analyse von Kandidatengenen bei unbalancierter Transkokation der(14)t(14;20)(q32.33;p13)
**Hofmann, Kristin,** Dr. rer. nat.: Aufklärung seltener humaner Entwicklungsstörungen mittels molekularer Karyotypisierung
**Jeschke, Jana,** Dr. rer. nat.: Analyse genomweiter Veränderungen der DNA Methylierung in Brustkrebs zur Identifizierung von Biomarkern für die Prognose und Mechanismen der Tumorgenese
**Kraft, Michael,** Dr. rer. nat.: Molekulargenetische Charakterisierung konstitutioneller chromosomaler Translokationen zur Positionsklonierung krankheitsverursachender Gene
**Röthel, Kristina,** Dr. med.: Analyse des Gens CLIP2 als Kandidatengen für mentale Retardierung
**Zweier, Markus,** Dr. rer. nat.: Aufklärung der mentalen Retardierung beim 5q14.3q15 Mikrodeletionssyndrom

### Doctorate Theses 2014

**Gregor, Anne,** Dr. rer. nat.: Identifizierung und Charakterisierung genetischer Ursachen bei Mentaler Retardierung
**Nelkenbrecher, Claudia,** Dr. rer. nat.: Molekulare Analysen zur Funktion von SPOC1 (PHF13) in der epigenetischen Regulation der Spermatogenese mit Hilfe eines Spoc1-/--Mausmodells

### Habilitation 2013

**Zweier, Christiane,** PD Dr. med.: Klinische, genetische und funktionelle Charakterisierung mentaler Retardierung

## Institute of Neuropathology

Chair of Neuropathology

### Doctorate Theses 2013

**Stangl, Regina,** Dr. med.: Mutationsanalyse von Axin2/Conductin bei Patienten mit Hypophysenadenomen und Kraniopharyngeomen
**Türk, Matthias,** Dr. med.: Dopaminerge Differenzierung adulter humaner hippocampaler Stammzellen

### Doctorate Theses 2014

**Stache, Christina,** Dr. rer. nat.: Molekulare und zelluläre Grundlagen des Wachstumsverhaltens humaner Kraniopharyngeome

## Institute of Pathology

Chair of General Pathology and Pathological Anatomy

### Doctorate Theses 2013

**Görgens, Jennifer,** Dr. med. dent.: Einflussfaktoren auf die Rezidivrate beim DCIS

### Doctorate Theses 2014

**Daniels, Marc,** Dr. med.: Molekulares, immunhistochemisches und Risikospektrum gastrointestinaler Stromatumore

### Board Qualification 2014

**Strehl, Johanna,** Dr. med.

## Institute of Pathology

Division of Nephropathology

### Doctorate Theses 2013

**Frank, Christina,** Dr. med.: Effekte verschiedener Therapiekonzepte auf kardiovaskuläre Veränderungen bei Systemischem Lupus erythematodes im Tiermodell

### Doctorate Theses 2014

**Burkhardt, Miriam,** Dr. rer. nat.: Podozyten als nicht-hämatopoetische Antigen-präsentierende Zellen
**Danizcek, Carolin,** Dr. med.: Einfluss von sGC-Stimulator BAY 41-2272 auf kardiovaskuläre Veränderungen bei experimentellem Diabetes mellitus der Spraque-Dawley-Ratte

## Institute of Radiology

Chair of Diagnostic Radiology

### Doctorate Theses 2013

**Dudek, Anna,** Dr. med.: Biochemische Bildgebung der lumbalen Bandscheibe mittels MRT unter Routinebedingungen bei 1.5 Tesla: Untersuchung der Reliabilität und Korrelation von T2- und T2*-Messungen unter Optimierung von MRT-Akquisitionsparametern

### Doctorate Theses 2014

**Kappey, Hanna,** Dr. med.: Der Effekt von Calyculin A auf die Dephosphorylierung des Histons -H2AX nach der strahleninduzierten Entstehung von DNA-Doppelstrangbrüchen in menschlichen Blutlymphozyten
**Knott, Michael,** Dr. med.: Ist die limitierte Zwei- und Drei-Schicht Perfusion der Ganzhirn-Perfusion zur Indikationsstellung einer Thrombolyse im erweiterten Zeitfenster bei akuter zerebraler Ischämie gleichwertig?
**Schiessl, Susanna,** Dr. med. dent.: Volumetrie epikardialen Fetts in kontrastverstärkten und nativen Datensätzen der kardialen Computertomographie
**Schröder, Tim,** Dr. med.: Einfluss einer neuen Software für CT-gesteuerte Biopsien auf Zugangswinkel, Effektivität und Komplikationsrate

### Habilitation 2013

**Heinrich, Marc,** PD Dr. med.: Kontrastmittel-induzierte Nephropathie
**Meier-Meitinger, Martina,** PD Dr. med.: Ansätze zur Verbesserung der Diagnostik von Brusttumoren

### Habilitation 2014

**Wüst, Wolfgang,** PD Dr. med.: Kardiale Bildgebung mit CT Techniken

### Board Qualification 2013

**Kammerer, Ferdinand,** Dr. med.
**Kramer, Manuel,** Dr. med.
**Melzer, Katja,** Dr. med.
**Schwab, Ina,** Dr. med.

### Board Qualification 2014

**Brand, Michael,** Dr. med.
**Eller, Achim,** Dr. med.
**Kratz, Susanne,** Dr. med.
**Prause, Sabine-Selin,** Dr. med.
**Saake, Marc,** Dr. med.
**Wüst, Wolfgang,** Dr. med.

### Additional Qualification 2014

**Schlechtweg, Philipp,** Dr. med.: Medical Quality Management

## Institute of Radiology

Division of Neuroradiology

### Doctorate Theses 2013

**Hempel, Susanne,** Dr. med.: Veränderung der fraktionellen Anisotropie bei glaukomatöser Optikusatrophie. Eine Untersuchung am 3 Tesla MRT

### Doctorate Theses 2014

**Knott, Michael,** Dr. med.: Ist die limitierte Zwei- und Drei-Schicht Perfusion der Ganzhirn-Perfusion zur Indikationsstellung einer Thrombolyse im erweiterten Zeitfenster bei akuter zerebraler Ischämie gleichwertig?
**Strauss, Catharina,** Dr. med.: Evaluation der Messmethoden für die Größenbestimmung von Vestibularis-Schwannomen. Korrelation der präoperativen Volumetrie mit den operativen Therapieergebnissen

### Habilitation 2014

**Gölitz, Philipp Ulrich,** PD Dr. med.: Innovative Anwendungen der Flachdetektor-CT zur nichtinvasiven und funktionellen Diagnostik zerebrovaskulärer Erkrankungen

### Board Qualification 2013

**Dietzel, Matthias,** Dr. med.

### Board Qualification 2014

**Lücking, Hannes,** Dr. med.

# In Memoriam

## 2013

**Prof. Dr. med. Manfred Kessler**
retired Director of the Institute of Physiology and Cardiology

## 2014

**Prof. Dr. rer. nat. Dr. h.c. Nikolaus Fiebiger**
former President of the FAU

# Personnel Index

**Publisher**
Faculty of Medicine
of the Friedrich-Alexander-Universität
Erlangen-Nürnberg
Krankenhausstr. 12, 91054 Erlangen
Tel.: 09131-8523708, Fax: 09131-8523704

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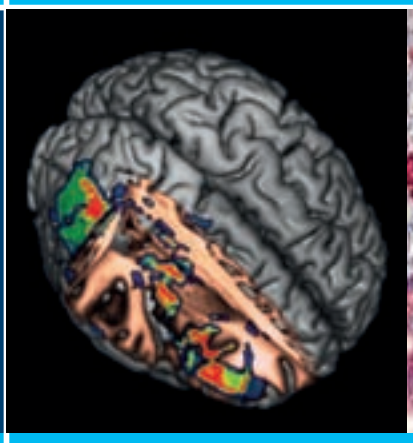
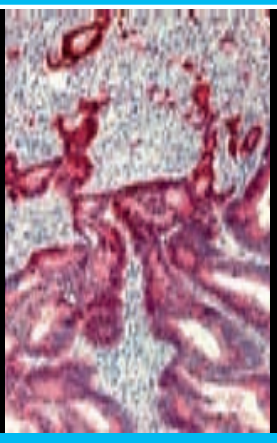
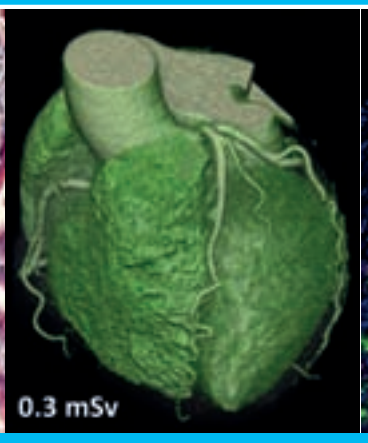
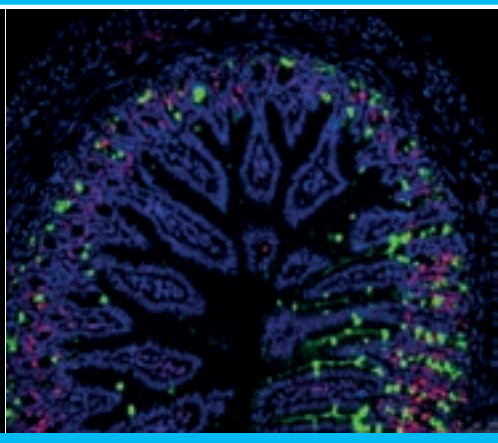
**Setting/Processing/Printing**
Druckhaus Haspel
Willi-Grasser-Str. 13a, 91056 Erlangen
Tel.: 09131-9200770, Fax: 09131-9200760
das@druckhaus-erlangen.de

**Cover**
The cover shows the Translation Research Center (TRC; © UK Erlangen) as well as figures of research projects within the Faculty of Medicine.



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