

# Research Report 2017

Faculty of Medicine







# **Research Report 2017**

## **Faculty of Medicine**

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Every other year, the Faculty of Medicine presents its institutes, departments, divisions, degree programs and all research facilities and projects established in the Faculty and their respective performance within the last two years in a lively and clear format. As Dean of the Faculty of Medicine, I am very happy that the time has come to present these achievements and performances by means of our new research report.

This time, I wish to point out the new research networks and projects that could be established at our Faculty within the last two years. These new projects further strengthen the core research areas of the Faculty of Medicine:

- The collaborative research center 1181 "Checkpoints for resolution of inflammation" has been funded by the DFG since July 2015 and investigates the molecular mechanisms involved in the resolution of inflammation. The main focus is on why resolution of inflammation fails in chronic inflammatory diseases which are characterized by chronic inflammation of the inner surfaces of the body, usually having serious health implications for its patients. (*Infection and immunology research*)
- The research training group 2162 "Neurodevelopment and vulnerability of the central nervous system" is characterized by a close collaboration of scientists from different faculties of the FAU with a focus on neurosciences. (*Neurosciences*)
- The clinical research group 257 "Molecular pathogenesis and optimized therapy of chronic inflammatory bowel disease" was positively evaluated and will be further funded by more than 4.8 million Euro. This sum doubles the extent of funding and acknowledges the research activities so far undertaken by the scientists from the Department of Medicine 1. (*Infection and immunology research*)
- The research network METARTHROS "Metabolic impact on joint and bone diseases", funded by the BMBF, examines the causes and interrelationships of metabolic (e.g. obesity and diabetes mellitus) and inflammatory (e.g. rheumatism and arthrosis) diseases. (*Infection and immunology research*)
- Scientists from FAU, the Goethe University Frankfurt, and the University of Regensburg jointly investigate the development of colorectal cancer within the research group „Cell Plasticity in Colorectal Carcinogenesis" (FOR 2438). (*Tumor research*)
- How likely do patients develop cancer again after a tumor has been surgically removed? This is the central question of the new research project „MeEVIR – Melanoma, Extracellular Vesicles, and Immune Response", funded by BMBF. To answer this question, physicians and medical informatics have a closer look at the so-called "minimal residual disease" (MRD) after primary surgery in highly metastatic tumors where - even after successful tumor removal - a relapse can occur many years later. (*Tumor research*)
- TRENAL („Translational kidney research – from physiology to clinical application") is an interdisciplinary network project that aims at leveraging the achievements of basic kidney research and translating them into novel diagnostic and therapeutic strategies. TRENAL unites nephrologists, physiologists, nephropathologists and basic researchers from FAU, Charité-Universitätsmedizin Berlin, Yale University and University College London and the Max Planck Institute for the Physics of Light and is funded by the German Academic Exchange Service (DAAD). (*Kidney and vascular research*)
- BMBF has been funding MIRACUM (Medical Informatics for Research and Care in University Medicine) since August 2016. MIRACUM is one of four consortia that belong to BMBF's "Medical Informatics Funding Scheme" to foster IT innovations for healthcare research and medical care. It is

coordinated by the Chair of Medical Informatics and its goal is to take advantage of digitalization in medicine. All partners of MIRACUM have agreed to share data, develop common and interoperable tools and services, realize the power of such data and tools in innovative IT solutions which shall enhance patient-centered collaborative research as well as clinical care processes, and finally strengthen biomedical informatics in research, teaching and continued education. (*Medical engineering*)

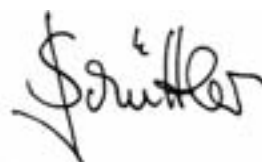
- With the funding measure "Internationalization of Leading Edge Clusters, future projects and comparable networks", the BMBF supports eleven German cluster and networks in building bridges to complementary players in the world. Medical Valley EMN is among the winners and will receive funding up to four million Euro over a period of up to five years. The projects aims at building up international innovation systems in the field of medical engineering and health economy. Already established strategic international partnerships with Boston (USA), Hongkong (China) and Porto Alegre (Brazil) will be further developed and refined. (*Medical engineering*)
- The Federal Joint Committee (G-BA), the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany, funds two projects at the Faculty of Medicine – among others in pediatrics – as part of the innovation fund with altogether 14 million Euro.

Besides these excellent new research projects, the core research area medical engineering could be reinforced by the establishment of the Chair of e-Health/m-Health (electronic and mobile applications in medicine) as part of Zentrum Digitalisierung.Bayern (ZD.B). The chair is part of the new topics platform "Digital Health/Medicine" of ZD.B and is located at the Institute of Medical Informatics, Biometry, and Epidemiology. It will focus on reusing healthcare data from hospitals for medical research and aims at further strengthening the national and international reputation in medical informatics. Its goal is to promote the collaboration between pure computer science and applied research in medicine and industrial production, thereby ensuring that basic research can be put into practice as quickly as possible.

Finally, we are very proud that Prof. Dr. A. Bozec, junior professor, leader of an Emmy Noether independent junior research group and researcher at the Department of Medicine 3, has received the Heinz Maier-Leibnitz Prize 2016, the most important award for early career researchers in Germany.

I would like to thank you all as well as the Bavarian taxpayers. I would further like to thank the numerous people who passed an expert opinion on our project proposals and publications, thus helping us to maintain the high quality of our research. Without the support of sponsors and experts, we were not able to sow the seeds for the distinctive feature of our Faculty of Medicine, i.e. the thrilling synthesis of innovative research 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 good of patients.

Erlangen, August 2017



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



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# 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
- MD: Doctor of Medicine
- M.Sc.: Master of Science
- NFZ: Nikolaus-Fiebiger-Center of Molecular Medicine
- PhD: Doctor of Philosophy
- PI: Principal investigator
- SFB: Collaborative research center
- UK Erlangen: Universitätsklinikum Erlangen

# Institute of Anatomy

## Chair of Anatomy I

### Address

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### Director

Prof. Dr. Winfried Neuhuber  
(until 31.3.2017)  
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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 Chair

Professorships: 1

Personnel: 16

- Doctors (of Medicine): 5
- Scientists: 1 (thereof funded externally: 0)
- Graduate students: 6

### Special structural feature

The Institute of Anatomy is collegially led by both chairs.

### Research

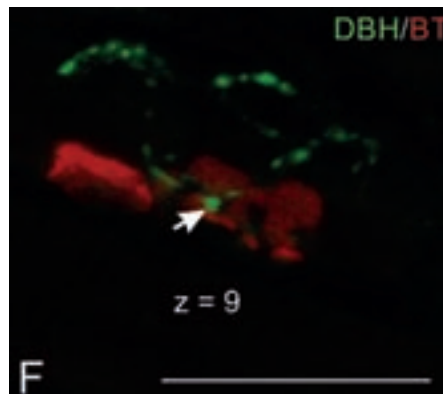
The main focus is on functional anatomy of the autonomic nervous system, in particular the vagus and the enteric nervous system. In addition, neuro-immunomodulation is studied in collaboration with other institutions.

### Innervation of the gastrointestinal tract

PI: Prof. Dr. W. Neuhuber, Prof. Dr. J. Woerl, Prof. Dr. M. Raab, Prof. Dr. A. Brehmer, PD Dr. S. Jabari

Studies on the esophagus focused on novel mediators of enteric co-innervation, in particular catecholamines. Mechanosensory vagal terminals around myenteric ganglia, so-called intraganglionic laminar endings (IGLEs), probably exert also additional purposes in the enteric

neuronal circuitry. They were further characterized with respect to pre- and postsynaptic proteins, e.g. synaptotagmin1, bassoon and homer1. This further supports the idea of their synaptic influence onto enteric neurons. Morpho-chemical phenotyping of enteric neurons in healthy human intestines as well as morphological and immunohistochemical characterization of enteric neurons in Chagas-induced megacolon was continued. This line of research is serving as a paradigm for forthcoming investigations on the enteric nervous system in other gastrointestinal disorders. As a novel paradigm, the relationship between the intestinal microcirculation and particular enteric neuron types was studied.



A motor endplate in the rat esophagus (red) is approached by a varicose nerve fiber (green) positive for dopamine- $\beta$ -hydroxylase. This nerve fiber originated most likely from noradrenergic enteric neurons in the esophagus. Bar = 25  $\mu$ m

### Studies on the vagus nerve

PI: PD Dr. M. Kressel<sup>1</sup>, Prof. Dr. W. Neuhuber<sup>2</sup>  
Understanding the widespread regulatory functions of the vagus nerve requires detailed knowledge of course and innervation territory of all vagal fibers which is still incomplete. Neuronal tracing was used to study the course of hitherto unrecognized small vagus nerve branches issued immediately above the diaphragm<sup>1</sup>.

With regard to transcutaneous vagus nerve stimulation to treat epilepsy and depression, the fiber spectrum of the auricular branch of the human vagus nerve was studied<sup>2</sup>.

### Nervous system, inflammation, and pain

PI: Prof. Dr. W. Neuhuber

In collaboration with colleagues of the Department of Medicine 4 – Nephrology and Hypertension, nerve fiber populations relevant for nephritis pathophysiology and their regenera-

tion were studied. The relationship of sympathetic neurons to specific renal tubules was investigated in collaboration with the Institute of Cellular and Molecular Physiology. In collaboration with the Institute of Physiology and Pathophysiology and Steigerwald GmbH (Darmstadt), studies on innervation of the cranial dura and neuronal modulation in experimental esophagitis and colitis were continued.

### Cell biology of the NF2 tumor suppressor protein

PI: 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 NF2 gene mutation, typically results in neurinomas of the VIIIth cranial nerve. A direct binding partner of merlin was immunohistochemically detected in varicose substance P positive nerve fibers of the central and peripheral nervous system. Cell culture experiments were used to elucidate the exact relationship of this binding molecule to substance P.

### Teaching

The Chair of Anatomy I contributes to the curriculum of medicine and dentistry with obligatory courses and electives. In particular, interdisciplinary preclinical and clinical lectures as well as seminars are provided. Special mention deserves the training of specific procedures, e.g., thorax drainages, on anatomical specimens in the context of the skills lab „Perle“.

Besides MD and PhD theses, Bachelor's and Master's theses are also supervised.

### Selected Publications

Mansley MK, Neuhuber W, Korbacher C, Bertog M. Norpinephrine stimulates the epithelial Na<sup>+</sup> channel in cortical collecting duct cells via  $\alpha$ 2-adrenoceptors. *Am J Physiol Renal Physiol* 2015, 308: F450-8

Abdel-Aziz H, Schneider M, Neuhuber W, Kassem AM, Khailah S, Müller J, Gamaleldeen H, Khairy A, Khayyal MT, Shcherbakova A, Efferth T, Ulrich-Merzenich G. GPR84 and TREM-1 signaling contribute to the pathogenesis of reflux esophagitis. *Mol Med* 2015, 21: 1011-1024

van der Keylen P, Garreis F, Steigleder R, Sommer D, Neuhuber WL, Woerl J. Involvement of catecholaminergic neurons in motor innervation of striated muscle in the mouse esophagus. *Histochem Cell Biol* 2016, 145: 573-585

Jabari S, Neuhuber W, Brehmer A. Neurovascular Interface in Porcine Small Intestine: Specific for Nitrergic rather than Nonnitrergic Neurons. *Cells Tissues Organs* 2016, 201: 203-210

Safi S, Ellrich J, Neuhuber W. Myelinated Axons in the Auricular Branch of the Human Vagus Nerve. *Anat Rec* 2016, 299: 1184-1191

Neuhuber WL, Wörl J. Enteric co-innervation of striated muscle in the esophagus: still enigmatic? Histochem Cell Biol 2016, 146: 721-735

### **International Cooperations**

Prof. H.-R. Berthoud, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge: USA

Prof. A. da Silveira, University of Uberlandia, Uberlandia: Brazil

Prof. Y. Shimizu, Gifu University, Gifu: Japan

Prof. J.-P. Timmermans, University of Antwerp, Antwerpen: Belgium



# Institute of Anatomy

## Chair of Anatomy II

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### Research Focus

- Temperature sensitive Transient Receptor Potential (TRP) channels at the ocular surface
- Pathomechanisms of the Meibom Gland Dysfunction (MGD)
- Influence of Osteopontin (OPN) to neurodegenerative changes in the eye
- New therapeutic concepts for the treatment in glaucoma using RNA interference to block tight junctional transcripts in mice
- Surfactant proteins
- Influencing factors with regard to learning related behavior of medical and dental students
- Ocular tissue interactions of a refractive UV femtosecond laser

### Structure of the Chair

Professorships: 2

Personnel: 26

- Doctors (of Medicine): 3
- Scientists: 11 (thereof funded externally: 3)
- Graduate students: 27

### Special structural features

- Lecture room for lessons in Histology with 160 microscopes
- Electron Microscopy unit

The Institute of Anatomy is collegially led by both chairs.

### Research

For many years, the Institute of Anatomy II has been working on scientific topics about the development and diseases of the eye (basic research). In addition, topics about the upper and lower respiratory tract, joints and medical education are part of the research record of our Institute.

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

PI: Dr. F. Garreis, Prof. Dr. F. Paulsen

The Transient Receptor Potential (TRP) proteins belong to the group of membrane-bound, li-

gand-gated cation channels. They serve as multiple sensors. A functional subgroup of the TRP family is 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 endogens and exogenous substances, e.g. capsaicin (chillies). Here, the expression of thermo-TRP 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 various cells of the human eye. 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.

### Pathomechanisms of the Meibom Gland Dysfunction (MGD)

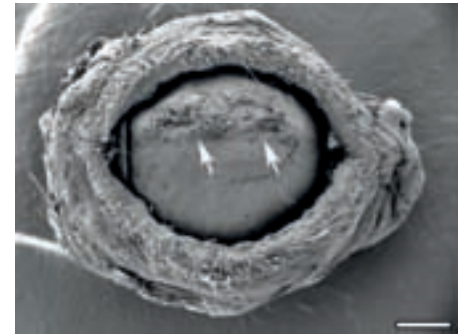
PI: Prof. Dr. F. Paulsen, Dr. F. Garreis

Meibomian gland dysfunction (MGD), a term used to describe a diffuse abnormality of the meibomian glands, which are specialized sebaceous glands in the eye lids, is considered to be the most common cause of dry eye syndrome (DES), a disease with an estimated prevalence of 12 million people alone in Germany. It is currently thought that MGD is caused primarily by terminal duct obstruction due to hyperkeratinization of the ductal epithelium and an increased viscosity of meibum. However, the molecular mechanisms that underlie this process are unclear. Many proteins being essential for epidermal differentiation and keratinization constitute the 'epidermal differentiation complex' (EDC). They function beside epidermal differentiation and keratinization also in innate immune defense belonging to the group of antimicrobial peptides (AMP).

The hypotheses are: Chronic inflammatory conditions at the ocular surface induce upregulation of AMPs which are correlated to genes of the EDC that function in epidermal differentiation and keratinization. Thus, induction of EDC associated AMPs triggers hyperkeratinization of meibomian glands and increases viscosity of meibum.

Our goal is to get deeper insights into the pathophysiology of MGD by performing in vivo experiments in an established mouse model of dry eye and in vitro experiments using cultivated human meibomian gland epithelial cells

in three-dimensional culture to determine factors that could serve as possible targets for therapeutic intervention in MGD.



Scanning electron microscope image of a mouse eye with changes of the cornea epithelium (arrows), as they can occur with the dry eye syndrome (DES); scale bar: 500µm

### Influence of Osteopontin (OPN) to neurodegenerative changes in the eye

PI: 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<sup>-/-</sup>) mouse. Retinal ganglion cells (RGCs) are the only neuronal cell type of the retina, which are able to express OPN under physiological conditions. 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 mouse 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<sup>-/-</sup> mouse was performed. The results of validated analyses will give evidence about the effects due to the absence (OPN<sup>-/-</sup>) or pathological overexpression of OPN (DBA/2J) with regard to neurodegenerative changes within the eye.

### New therapeutic concepts for the treatment in glaucoma using RNA interference to block tight junctional transcripts in mice

PI: Prof. Dr. E. Lütjen-Drecoll, Prof. Dr. C. Flügel-Koch

Resistance to outflow of aqueous humour that is increased in glaucoma is mediated by the endothelial cells of Schlemm's canal that are sealed by tight junctions, and by the directly adjacent lying juxtacanalicular trabecular meshwork. The aim of our investigations is directed to a new therapeutic approach to lower intraocular pressure by targeting the tight

junctions of inner wall endothelium with siRNA-mediated suppression of tight junctional transcripts. It could be shown that intracameral injection of siRNAs to ZO-1 and tricellulin increased outflow facility significantly. Transmission electron microscopy revealed significantly more open junctions and clefts between endothelial cells. These results form the base for a new promising therapeutic approach for glaucoma therapy.

### Surfactant proteins

PI: 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 and dental students

PI: 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 about 500 medical and dental students of the preclinical terms at the FAU. 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 tissue interactions of a refractive UV femtosecond laser

PI: Dr. C.M. Hammer, Prof. Dr. F. Paulsen

In cooperation with the local eye clinic and WaveLight GmbH first preclinical experiments regarding the tissue interactions of a novel UV femtosecond laser were conducted. The laser was developed by WaveLight GmbH for refractive surgery and represents the first refractive femtosecond laser working with ultraviolet light. Therefore, it was necessary to check, whether the system compares to common infrared laser platforms in terms of safety and precision. Experiments based on isolated rabbit and porcine eyes as well as animal tests showed that corneal UV laser cuts heal without complications. Furthermore, deeper ocular tissues like lens and retina were demonstrated to remain free of any stray light damage like cataract or retinal damage. Scanning electron microscopy revealed the UV laser cuts to be comparable to cuts administered by common infrared laser systems. A marked superiority of the UV laser was demonstrated regarding intraoperative gas production and tissue tolerance of the vulnerable corneal endothelium. The markedly reduced amount of intraoperatively produced gas may allow for a significantly enhanced surgical precision. These investigations paved the way for the onset of the clinical testing phase.

### Teaching

The Chair of Anatomy II was involved in the teaching of macroscopic anatomy at the Institute of Anatomy. Each semester a variety of elective subjects can be offered for medical and dental students in the pre-clinical semesters. Moreover, Bachelor's and Master's theses as well as medical and scientific doctorates are supervised. Virtual courses of histology, macroscopy and embryology are offered in cooperation with the virtual university of Bavaria (vub).

### Selected Publications

Hampel U, Schröder A, Mitchell T, Brown S, Snikeris P, Garreis F, Kunnen C, Willcox M, Paulsen F. Serum-induced keratinization processes in an immortalized human meibomian gland epithelial cell line. *PLoS One* 2015, 10(6):e0128096

Ackermann P, Hetz S, Dieckow J, Schicht M, Richter A, Kruse C, Schröder IS, Jung M, Paulsen F. Isolation and investigation of presumptive murine lacrimal gland stem cells. *Invest Ophthalmol Vis Sci* 2015, 56:4350-4363

Schicht M, Rausch F, Jacobi C, Garreis F, Hartjen N, Beileke S, Kruse F, Bräuer L, Paulsen F. Palate Lung Nasal Clone (PLUNC), a novel protein of the tear film: three dimensional structure, immune activation and involvement in dry eye disease (DED). *Invest Ophthalmol Vis Sci* 2015, 56:7312-7323

Hammer CM, Petsch C, Klenke J, Skerl K, Paulsen F, Kruse FE, Seiler T, Menzel-Severing J. Corneal tissue interactions of a new 345 nm ultraviolet femtosecond laser. *J Cataract Refract Surg* 2015, 41(6):1279-88

Schröder A, Abrar DB, Hampel U, Schicht M, Paulsen F, Garreis F. In vitro effects of sex hormones in human meibomian gland epithelial cells. *Exp Eye Res* 2016, 151:190-202

Scholz M, Neumann C, Ropohl A, Paulsen F, Burger PH. Risk factors for mental disorders develop early in German students of dentistry. *Ann Anat* 2016, 208:204-207

### International Cooperations

Prof. S. Weber, Medical School, State University São Paulo, UNESP, Botucatu: Brazil

Prof. Dr. E. Eppler, Zurich: Switzerland

Dr. E. Cuerda, King Juan Carlos University, Móstoles: Spain

Dr. J. Ali, Humboldt Fellow, Hyderabad: India

N. Asano, Santen Pharmaceuticals. Co. Ltd: Japan

# Institute of Biochemistry – Emil-Fischer-Center

## Chair of Biochemistry and Molecular Medicine

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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
- Molecular mechanisms of hepatic metastasis
- In vivo functions of glycine transporters
- Physiological and pathological functions of alpha synuclein
- Structure and function of synaptic signaling complexes in the central nervous system
- Pathobiology of non-alcoholic fatty liver diseases

### Structure of the Chair

Professorships: 3

Personnel: 52

- Scientists: 34 (thereof funded externally: 26)
- Graduate students: 9

### Special structural feature

The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as professorships for Bioinformatics and Molecular Imaging.

### Research

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

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

PI: Prof. Dr. A.K. Bosserhoff, PD Dr. S. Kuphal, Dr. P. Dietrich, Dr. M. Kappellmann-Frenzl  
Malignant melanoma, also called black skin cancer, shows a drastic increase in incidence and an unchanged high mortality in recent decades. Melanoma is a clinically relevant tumor, characterized by gradual progression, metastatic dissemination, rapid and pronounced resistance to therapy. As metastatic melanoma curative therapy approaches are still lacking, the 10-year survival rate is below 5%. The pathogenesis of the disease is probably due to an accumulation of specific genetic and epigenetic alterations leading to deregulation of transcriptional regulation and signaling pathways in melanocytes or their precursors. The particular malignancy of melanoma is based on a specific combination of cell cycle autonomy, differentiation defects, apoptosis resistance, deregulated interaction with stromal and immune cells as well as distinctive invasiveness and metastatic ability. 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 microRNA are investigated. Next to the analysis of the function of mature microRNA as key posttranscriptional regulatory elements, their processing in melanoma is in the center of our current research.

### Chondrocytic differentiation and pathophysiological processes in cartilage

PI: Prof. Dr. A.K. Bosserhoff, Dr. U. Rottensteiner-Brandl

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 so far not curable until 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

PI: Prof. C. Hellerbrand, Prof. Dr. A. Bosserhoff, Dr. P. Dietrich

The liver is the central organ of the metabolism. Nutrients get to the liver from the digestive tract via the portal vein for subsequent degradation and/or metabolism. Thus, the liver supplies the body with vital components such as proteins, carbohydrates, and lipids. Another important function of the liver is detoxification. Alcohol abuse, obesity, metabolic disorders (e.g. hemochromatosis), viral infections (hepatitis B and C), or intoxication with chemicals and environmental toxins are common causes of liver damage. Hepatocellular injury can result in liver inflammation (hepatitis). Hepatitis can progress with hepatic fibrosis which can lead to liver cirrhosis. Cirrhosis is causing organ dysfunction and is the most important risk factor for the development of hepatocellular carcinoma (HCC). Thus, hepatic fibrosis is the central step in the progression of chronic liver injury. Pathological fibrosis resembles impaired wound healing in which the strictly regulated repair processes are impaired after cellular injury. Since the components that are involved in wound healing or fibrosis (connective tissue cells, extracellular matrix, growth factors) are 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 growth factors of the FGF and BMP families. Furthermore, we could characterize BMP6 as an essential regulator of iron metabolism in recent years.

### In vivo functions of glycine transporters

PI: PD 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 GlyT. By complex genetic, 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 GlyT. 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 re-

search has contributed to a better understanding of how glial and neuronal expressed transporters 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.

### Physiological and pathological functions of alpha synuclein

PI: PD Dr. W. Xiang

Parkinson disease (PD) is one of the most common neurodegenerative diseases. Abnormal aggregation of the protein alpha synuclein ( $\alpha$ Syn) plays a crucial role in the pathogenesis of PD. We are interested in mechanisms underlying the unusual aggregation of  $\alpha$ Syn and the detrimental effects of aggregated  $\alpha$ Syn on neurons. Our data show that oxidative stress promotes  $\alpha$ Syn aggregation through posttranslational modifications. Oxidative stress-induced  $\alpha$ Syn alterations in turn lead to neuronal loss. In addition to its intracellular effects, extracellular aggregated  $\alpha$ Syn can be preferentially incorporated by neighboring cells. Internalized exogenous  $\alpha$ Syn triggers the aggregation of endogenous  $\alpha$ Syn and evokes further damage, e.g. disturbances in protein degradation pathways, to recipient cells. Deleterious effects of aggregated  $\alpha$ Syn can be induced by the loss of its physiological structure and function. To understand physiological structure and function of  $\alpha$ Syn, we are currently characterizing changes in structure and subcellular localization of  $\alpha$ Syn during the differentiation of neurons.

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

PI: 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 and 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 receptors for

endocannabinoids, GABA and glutamate. We compare the expression of interacting proteins in retina and cochlea, 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.

### Molecular mechanisms of hepatic metastasis

PI: Prof. Dr. C. Hellerbrand, Prof. Dr. A.K. Bosserhoff

Metastasis determines morbidity and mortality in most cancer patients. Most frequently, the majority of tumor entities metastasize into the liver. Only in part this can be explained by the blood flow or the anatomical localization of the liver, respectively. The underlying mechanism of the liver being very attractive for tumor cells is unknown. We are analyzing the reasons of this phenomenon in experimental models and human tissue samples from primary tumors and hepatic metastases. We were able to show that defined non-parenchymal liver cells (hepatic stellate cells) interact with tumor cells, thus inducing different steps of metastasis. Our current aim is to identify the mediators of this interaction and to analyze whether such factors can be therapeutic targets.

### Pathobiology of non-alcoholic fatty liver diseases

PI: Prof. Dr. C. Hellerbrand, Dr. A. Mahli

Almost all individuals with obesity develop significant lipid accumulation (steatosis) in the liver. Steatosis can progress with inflammation (steatohepatitis) and fibrosis. The pathological picture is very similar to alcoholic liver injury, and is called non-alcoholic fatty liver diseases (NAFLD). Today, NAFLD is the most common type of liver disease worldwide. We are analyzing in experimental in vitro and in vivo models the mechanisms driving the progression of NAFLD, trying to inhibit already early steps of the pathobiological cascade. We could identify defined hop constituents as promising therapeutic targets which can inhibit the uptake of fatty acids into hepatocytes as well as the development of steatohepatitis.

Also application of some chemotherapeutic drugs can cause steatohepatitis which can significantly affect morbidity and mortality of cancer patients. We were able to identify the molecular mechanisms by which irinotecan and fluorouracil (5-FU) cause hepatic steatosis and inflammation. Currently, we are investigating

strategies to interfere with this pathomechanisms to improve the tolerability of the chemotherapeutic drugs.

## Teaching

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

## Selected Publications

Werdehausen R, Mittnacht S, Bee LA, Minett MS, Armbruster A, Bauer I, Wood JN, Hermanns H, Eulenburg V. The lidocaine metabolite N-ethylglycine has antinociceptive effects in experimental inflammatory and neuropathic pain. *Pain*. 2015 Sep;156(9):1647-59

Linck L, Binder J, Haynl C, Enz R. Endocytosis of GABA(C) receptors depends on subunit composition and is regulated by protein kinase C- $\zeta$  and protein phosphatase 1. *J Neurochem*. 2015 Jul;134(2):233-46

Xiang W, Menges S, Schlachetzki JC, Meixner H, Hoffmann AC, Schlötzer-Schrehardt U, Becker CM, Winkler J, Klucken J. Posttranslational modification and mutation of histidine 50 trigger alpha synuclein aggregation and toxicity. *Mol Neurodegener*. 2015 Mar 11;10:8

Niebler S, Schubert T, Hunziker EB, Bosserhoff AK. Activating enhancer binding protein 2 epsilon (AP-2)-deficient mice exhibit increased matrix metalloproteinase 13 expression and progressive osteoarthritis development. *Arthritis Res Ther*. 2015 May 12;17:119

Ott CA, Linck L, Kremmer E, Meister G, Bosserhoff AK. Induction of exportin-5 expression during melanoma development supports the cellular behavior of human malignant melanoma cells. *Oncotarget*. 2016, Sep 20;7(38):62292-62304

Völler D, Linck L, Bruckmann A, Hauptmann J, Deutzmann R, Meister G, Bosserhoff AK. Argonaute Family Protein Expression in Normal Tissue and Cancer Entities. *PLoS One*. 2016 Aug 12;11(8):e0161165

## International Cooperations

C. Aragón, B. López-Corcuera, Departamento de Biología Molecular and Centro de Biología Molecular "Severo Ochoa", Universidad Autónoma de Madrid, Madrid: Spain

M. Herlyn, Wistar Institute, Philadelphia: USA

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

T. F. Outeiro, H. Vicente Miranda, Cell and Molecular Neuroscience Unit, Instituto de Medicina Molecular, University Lisbon: Portugal

Y. Zhang, Department of Medicinal Chemistry, Virginia Commonwealth University, Richmond: USA

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



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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
- $\beta$ -thymosins, substrates of transglutaminases during blood coagulation, angiogenesis, wound healing, and apoptosis

### Structure of the Chair

Professorships: 2  
Personnel: 27  
• Scientists: 6 (thereof funded externally: 1)  
• Graduate students: 12

### Special structural feature

The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as professorships for Bioinformatics and Molecular Imaging.

### Research

The groups belonging to the Chair of Biochemistry and Pathobiochemistry work in the field of neuroscience and attempt to unravel regulatory mechanisms of physiological and pathophysiological processes with methods of biochemistry, molecular genetics and cell biology. 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

PI: 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

PI: Prof. Dr. C. Stolt

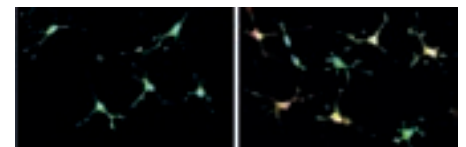
The three closely related SoxD proteins Sox5, Sox6, and Sox13 participate as regulatory proteins in the development of several neuronal subpopulations and glial cells of the nervous system. Own studies indicate that SoxD proteins function as modulators of SoxE function in glia. Both, Sox5 and Sox6, antagonize 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

PI: 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.



Cultivated mouse oligodendrocytes before (left) and after (right) Cre-dependent gene deletion.

### Impaired signal transduction in mitochondrial and neuromuscular myopathies

PI: 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  $\beta$  subunit, phosphorylates it and thus regulates the stability of acetylcholine receptor clusters. Moreover, CK2 $\beta$ -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.

### **$\beta$ -thymosins, substrates of transglutaminases during blood coagulation, angiogenesis, wound healing, and apoptosis**

PI: Prof. Dr. E. Hannappel

Thymosins were originally isolated from thymus, but do not represent thymic hormones. Thymosin  $\beta$ -4 (T $\beta$ 4) is a main intracellular G-actin sequestering peptide in most mammalian cells. Apart from this intracellular function, T $\beta$ 4 seems to be a player in wound healing and inflammation. T $\beta$ 4 is a substrate of transglutaminases. Glutaminy residues of T $\beta$ 4 can be cross-linked to amino groups of other molecules. Blood platelets contain high concentrations of T $\beta$ 4. During aggregation T $\beta$ 4 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. T $\beta$ 4 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. T $\beta$ 4 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 T $\beta$ 4 and PDGF-BB, arguing that T $\beta$ 4 could be used as an antifibrotic drug for treatment of liver fibrosis.

## **Teaching**

The Chair of Biochemistry and Pathobiochemistry participates in the curricula in medicine, molecular medicine and dentistry. Special mention deserves the interdisciplinary teaching in developmental biology and neurosciences in the master program molecular medicine. Additionally, the chair organizes teaching for the bachelor program medical engineering of the Faculty of Engineering.

The Chair supervises Bachelor's and Master's theses as well as MD and PhD theses.

### **Selected Publications**

Bischof M, Weider M, Küspert M, Nave KA, Wegner M. Brg1-dependent chromatin remodelling is not essentially required during oligodendroglial differentiation. *J. Neurosci.* 2015, 35: 21-35

Weider M, Wegener A, Schmitt C, Küspert M, Hillgärtner S, Bösl MR, Hermans-Borgmeyer I, Nait-Oumesmar B, Wegner M. Elevated in vivo levels of a single transcription factor directly convert satellite glia into oligodendrocyte-like cells. *PLoS Genet.* 2015, 11: e1005008

Baroti T, Zimmermann Y, Schillinger A, Liu L, Lommes P, Wegner M, Stolt CC. Transcription factors Sox5 and Sox6 exert direct and indirect influences on oligodendroglial migration in spinal cord and forebrain. *Glia* 2016, 64: 122–138

Ettle B, Kerman BE, Valera E, Gillmann C, Schlachetzki JC, Reiprich S, Büttner C, Ekici AB, Reis A, Wegner M, Bäuerle T, Riemenschneider MJ, Masliah E, Gage FH, Winkler J.  $\alpha$ -Synuclein-induced myelination deficit defines a novel interventional target for multiple system atrophy. *Acta Neuropathol.* 2016, 132: 59-75

Quintes S, Brinkmann BG, Ebert M, Fröb F, Kungl T, Arlt FA, Tarabykin V, Huylebroeck D, Meijer D, Suter U, Wegner M, Sereda MW, Nave KA. Zeb2 is essential for Schwann cell differentiation, myelination and nerve repair. *Nat. Neurosci.* 2016, 19: 1050-1059

Huraskin D, Eiber N, Reichel M, Zidek LM, Kravic B, Bernkopf D, von Maltzahn J, Behrens J, Hashemolhosseini S. Wnt/ $\beta$ -catenin signaling via Axin2 is required for myogenesis and, together with YAP/Taz and Tead1, active in Ila/Ilx muscle fibers. *Development* 2016, 143: 3128-3142

### **International Cooperations**

Prof. B. Nait-Oumesmar, Institut du Cerveau et de la Moelle Epinière, Paris : France

Prof. L. Sommer, Universität Zürich, Zurich: Switzerland

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

Prof. P. Casaccia, Friedman Brain Institute at Mount Sinai, New York: USA

Prof. S. Philipsen, Erasmus Medical School, Rotterdam: The Netherlands

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## Professorship of Bioinformatics

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### Research Focus

- Computational analysis of host-pathogen interactions
- Investigation of the aggregation behavior of the A $\beta$ -peptide of Alzheimer's disease
- Application of information-theoretic methods in protein-docking analysis
- Simulation of pH-effects on protein structure

### Structure of the Professorship

Professorships: 1  
Personnel: 8

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

### Special structural features

The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry as well as the Professorships for Bioinformatics and Molecular Imaging, respectively.

### Research

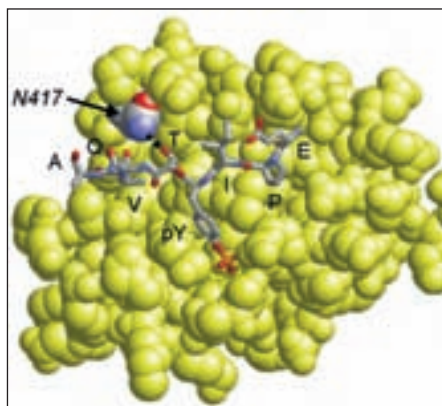
The research focus is on the computational characterization of protein-protein interactions. The identification of the underlying principles of molecular recognition is important for the understanding of regulatory mechanisms as well as for the prediction of novel, physiologically relevant protein interactions.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

### Computational analysis of host-pathogen interactions

Specific interactions with host proteins are pivotal for a successful infection by a pathogen.

This project focuses on the prediction and structural characterization of host-pathogen protein interactions using computational tools. The recognition processes either occur between short sequence motifs 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 challenge for the prediction of functional interaction motifs is the short length of the respective sequence patterns resulting in a large number of false-positive hits 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 judging the likelihood of an interaction based on a three-dimensional structure.



Host pathogen interaction between the *Helicobacter pylori* CagA protein and human PI3-kinase. The EPIYTQVA motif of CagA is shown in stick presentation and PI3K in yellow. Residue N417 of PI3K (labeled) plays an important role for the interaction (adapted from: Zhang et al., 2015).

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.

### Investigation of the aggregation behavior of the A $\beta$ -peptide of Alzheimer's disease

Protein conformational diseases are unique since they result from a drastic change in protein three-dimensional structure. Most often, the change in conformation involves a structural conversion from primarily  $\alpha$ -helical conformation with good solubility to an insoluble  $\beta$ -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 hallmarks of many neurodegenerative diseases.



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

The most prevalent neurodegenerative disease is Alzheimer's disease which is characterized by extracellular protein deposition of the peptide fragment A $\beta$  from the amyloid precursor protein, and intracellular tau-containing filaments, called neurofibrillary tangles. The 3D structure of the A $\beta$  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

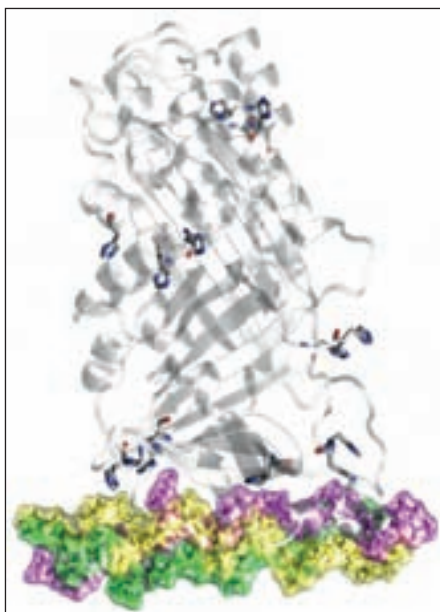
of solubilizing aggregates by targeting those residues that represent the hot spots of binding affinity in the fibrillar structure. We address this point by molecular dynamics simulations of A $\beta$  oligomers and thermodynamic analyses of the aggregation interfaces. In addition, we investigate the effect of different solvent environments on the conformational stability of such A $\beta$  oligomers.

### 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 data sets and more sophisticated structural features to obtain a robust and widely applicable approach.

### Simulation of pH-effects on proteins

Changes in pH regulate many biological processes in bacteria, viruses, vertebrates, and plants. For example, some bacteria are able to survive the acidic conditions in the stomach of their host by using acid-activated chaperones which protect substrate proteins from aggregation. In viruses, some of the fusion proteins that mediate cell entry were described to act pH-dependently. Other proteins in vertebrates undergo pH changes on their way through the endoplasmic reticulum and the Golgi apparatus. In order to mimic pH-titration experiments, we investigate pH-dependent proteins by conducting molecular dynamics (MD) simulations, in which pH is changed gradually. This method allows the calculation of titration curves and pK<sub>a</sub> values of ionizable groups. By using this strategy, we investigate on an atomic level the effects of pH changes which affect protein local conformations, macromolecular assemblies as well as structural stability.



Structure of the complex between the chaperone HSP47 (grey) and collagen (purple, green, yellow). The interaction is pH-dependent and is regulated by changes of the protonation state of HSP47 histidines (stick presentation). Mutations in HSP47 are observed in context of Osteogenesis imperfecta.

### Teaching

The Professorship of Bioinformatics organizes lectures, seminars, and tutorials in the course program of Molecular Medicine. In addition, the Professorship is involved in interdisciplinary teaching in the master programs Life Science Engineering and Integrated Life Sciences in collaboration with the Faculties of Engineering and Sciences.

The Professorship also supervises Bachelor's and Master's theses as well as PhD theses.

### Selected Publications

Zhang XS, Tegtmeyer N, Traube L, Jindal S, Perez-Perez G, Sticht H, Backert S, Blaser MJ. A specific A/T polymorphism in Western tyrosine phosphorylation B-motifs regulates Helicobacter pylori CagA epithelial cell interactions. PLoS Pathog. 2015, 11:e1004621

Übelhart R, Hug E, Bach MP, Wossning T, Dühren-von Minden M, Horn AHC, Tsiantoulas D, Kometani K, Kurosaki T, Binder CJ, Sticht H, Nitschke L, Reth M, Jumaa H. Responsiveness of B cells is regulated by the hinge region of IgD. Nat Immunol. 2015, 16:534-43

Müller-Schiffmann A, Herring A, Abdel-Hafiz L, Chepkova AN, Schäble S, Wedel D, Horn AHC, Sticht H, de Souza Silva MA, Gottmann K, Sergeeva OA, Huston JP, Keyvani K, Korth C. Amyloid- $\beta$  dimers in the absence of plaque pathology impair learning and synaptic plasticity. Brain. 2016, 139:509-25

Stump JD, Sticht H. Investigation of the dynamics of the viral immediate-early protein 1 in different conformations and oligomerization states. J Biomol Struct Dyn. 2016, 34:1029-41

Socher E, Sticht H. Mimicking titration experiments with MD simulations: A protocol for the investigation of pH-dependent effects on proteins. Sci Rep. 2016, 6:22523

Socher E, Sticht H. Probing the Structure of the Escherichia coli Periplasmic Proteins HdeA and YmgD by Molecular Dynamics Simulations. J Phys Chem B. 2016, 120:11845-11855

### International Cooperations

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

Dr. F. Halary, Université de Nantes, Nantes: France

Prof. Dr. M. Blaser, New York University School of Medicine, New York: USA

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

Dr. C. Brodski, Ben-Gurion University of the Negev, Beer Sheva: Israel

# 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 Professorship

Professorships: 1  
Personnel: 10

- Scientists: 2 (there of funded externally: 1)
- Graduate students: 8

### Special structural feature

The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry as well as the Professorships for Bioinformatics and Molecular Imaging, respectively.

### Research

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

### 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, we discovered the SoxC group transcription factors SOX4 and SOX11 as key regulators of neuronal fate determination of adult neural stem cells. Intriguingly, our new data indicate that SoxC proteins may fulfill critical functions in neuronal development and plasticity beyond fate determination. Indeed, genetic, histological and electrophysiological analyses revealed that SOX11 regulates the synaptic integration of adult-born neurons. We also found evidence that activity-dependent expression of SOX11 in mature hippocampal neurons is critical for hippocampus-dependent learning and memory. Ongoing projects are investigating to which extent impaired SOX11-dependent plasticity contributes to cognitive and emotional deficits in neuropsychiatric disorders. This project is conducted in close collaboration with the research group of Prof. Dr. J. Winkler (Division of Molecular Neurology).  
Funding: 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 a stem cell is accompanied by profound changes in cellular metabolism. We previously demonstrated 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. In a recent project we found that specific mitochondrial metabolic pathways control distinct steps in neuronal de-

velopment. Thus, we demonstrated that the generation of highly proliferative precursor cells from stem cells is critically dependent on electron transport chain function and oxidative phosphorylation. Interestingly, we found that inhibition of these metabolic pathways reproduced multiple hallmarks of ageing in hippocampal neurogenesis, whereas pharmacological enhancement of mitochondrial function ameliorates age-associated neurogenesis defects. Together with the finding of age-associated alterations in mitochondrial function and morphology in neural stem cells, our data suggest mitochondrial function as a potential target to ameliorate neurogenesis-defects in the ageing hippocampus.

### 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. In ongoing studies we are investigating how SOX11 drives CNS development in conjunction with intellectual disability-related transcription factors in order to understand the function of the SOX11-transcriptional network in the pathogenesis of intellectual disability. This project is conducted in close collaboration with Prof. Dr. A. Reis (Institute of Human Genetics).  
Funding: IZKF Erlangen

### Teaching

The Professorship of Molecular Medicine with focus on Molecular Imaging contributes to the teaching curriculum of human and dental medicine by offering obligatory and elective courses. It provides interdisciplinary training for students of the master degree program Molecular Medicine which is performed together with the Departments of Psychiatry and Psychotherapy and of Nuclear Medicine, the Institute of Radiology, and the Division of Molecular Neurology. Aim is to theoretically and practically teach the students state-of-the-art technologies of molecular imaging.

Bachelor and master students as well as medical and scientific graduate students are supervised in our group to successfully finish their thesis projects.

### **Selected Publications**

Andreu Z, Khan MA, González-Gómez P, Negueruela S, Hortigüela R, San Emeterio J, Ferrón SR, Martínez G, Vidal A, Fariñas I, Lie DC, Mira H. The cyclin-dependent kinase inhibitor p27 kip1 regulates radial stem cell quiescence and neurogenesis in the adult hippocampus. *Stem Cells*. 2015 Jan;33(1):219-29

Marschallinger J et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. *Nat Commun*. 2015 Oct 27;6:8466

Beckervordersandforth R, Zhang CL, Lie DC. Transcription-Factor-Dependent Control of Adult Hippocampal Neurogenesis. *Cold Spring Harb Perspect Biol*. 2015 Oct 1;7(10):a018879

Cernilogar FM, Di Giaimo R, Rehfeld F, Cappello S, Lie DC. RNA interference machinery-mediated gene regulation in mouse adult neural stem cells. *BMC Neurosci*. 2015 Sep 19;16:60

Gebara E, Bonaguidi MA, Beckervordersandforth R, Sultan S, Udry F, Gijls PJ, Lie DC, Ming GL, Song H, Toni N. Heterogeneity of Radial Glia-Like Cells in the Adult Hippocampus. *Stem Cells*. 2016 Apr;34(4):997-1010

### **International Cooperations**

Prof. S. Jessberger, University of Zurich, Zurich: Switzerland

Prof. H. Song, Johns Hopkins University School of Medicine, Baltimore: USA

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

Prof. N. Toni, University of Lausanne, Lausanne: Switzerland



# 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

Professorships: 2

Personnel: 22

- Scientists: 8 (thereof funded externally: 3)
- Graduate students: 2

### Research

The research focus of the Institute of Cellular and Molecular Physiology 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. A range of sophisticated electrophysiological, molecular biological and cell physiological methods is used to study the function and regulation of ion transport processes using cultured cells, native tissues and animal models (e.g. transgenic mouse lines). 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.

#### Renal epithelial ion channels

PI: Prof. Dr. C. Korbmacher

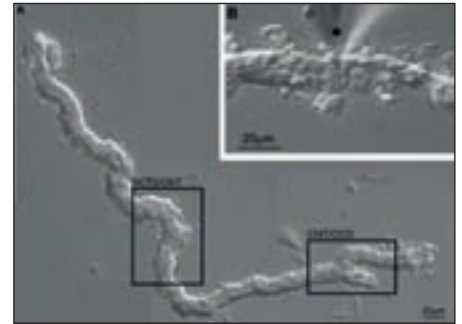
In the kidney and other epithelial tissues, ion channels are involved in the highly selective and regulated control of ion fluxes across apical and basolateral membranes of epithelial cells. These ion channels are important for intracellular ion

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 TRPV4 (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 distal mouse nephron

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

#### Cardiac ion channels

PI: Prof. Dr. T. Volk

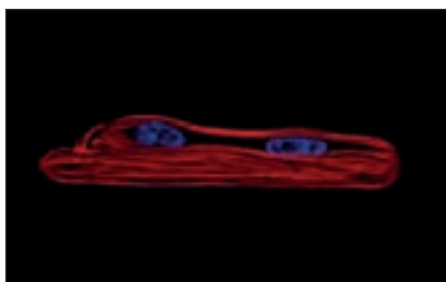
The key interest of this group is to identify cellular and molecular mechanisms that regulate the function and expression of cardiac ion channels and thereby lead to differences in action potential duration (APD) and contractility in the heart.

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.

In order to further understand the underlying mechanisms, this group investigates the regulation and pharmacology of ion channels ( $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$  channels) that are responsible for cardiac excitation and repolarization by using animal models as well as tissue or cell culture. At present, the primary focus lies in the identification of signaling cascades that participate in the regulation of those ion channels under pathophysiological conditions. A promising target is the cardiac mineralocorticoid receptor which participates in the regulation of cardiac  $\text{Ca}^{2+}$  and  $\text{K}^+$  channels.

It is hoped that a more detailed characterization of cardiac ion channels will lead to a better understanding of the mechanisms underlying cardiac repolarization and will help to develop therapeutic strategies to influence the organization of repolarization and hence prevent the development of malignant arrhythmia.



*Isolated rat cardiomyocyte  
Using fluorescent dyes, nuclei were stained blue, actin filaments red.*

## Teaching

The Institute of Cellular and Molecular Physiology is involved in the curricular teaching (lectures, seminars, and practical classes) for medical and dental students and for students following the course of Molecular Medicine (Bachelor and Master).

The Institute provides research opportunities for medical students working towards a doctoral degree and for bachelor, master and graduate students.

## Selected Publications

Mansley MK, Neuhuber W, Korbmacher C, Bertog M. Norepinephrine stimulates the epithelial  $\text{Na}^+$  channel in cortical collecting duct cells via  $\alpha_2$ -adrenoceptors. *Am J Physiol Renal Physiol* 2015, 308:F450-8

Agsten M, Hessler S, Lehnert S, Volk T, Rittger A, Hartmann S, Raab C, Kim DY, Groemer TW, Schwake M, Alzheimer C, Huth T.J. BACE1 modulates gating of KCNQ1 (Kv7.1) and cardiac delayed rectifier KCNQ1/KCNE1 (IKs). *Mol Cell Cardiol* 2015, 89:335-48

Rudakova E, Wagner M, Frank M, Volk T. Localization of Kv4.2 and KChIP2 in lipid rafts and modulation of outward  $\text{K}^+$  currents by membrane cholesterol content in rat left ventricular myocytes. *Pflugers Arch.* 2015, 467:299-309.

Ilyaskin AV, Diakov A, Korbmacher C, Haerteis S. Activation of the human epithelial sodium channel (ENaC) by bile acids involves the degenerin site. *J Biol Chem* 2016, 291:19835-47

Nesterov V, Krueger B, Bertog M, Dahlmann A, Palmisano R, Korbmacher C. In Liddle Syndrome, epithelial sodium channel is hyperactive mainly in the early part of the aldosterone-sensitive distal nephron. *Hypertension* 2016 Jun, 67:1256-62

Grahammer F, Nesterov V, Ahmed A, Steinhardt F, Sandner L, Arnold F, Cordts T, Negrea S, Bertog M, Ruegg MA, Hall MN, Walz G, Korbmacher C, Artunc F, Huber TB. mTORC2 critically regulates renal potassium handling. *J Clin Invest.* 2016, 126:1773-82

## International Cooperations

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

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

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

Prof. P. McIntyre, RMIT University, Melbourne: Australia

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

# Institute of Physiology and Pathophysiology

## Chair of Physiology

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### Research Focus

- Neurophysiologic substrates of higher brain functions
- 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

Professorships: 3  
Personnel: 70  
• Scientists: 20  
(thereof funded externally: 8)  
• Graduate students: 9

### Special structural feature

Experimental set-ups at the Departments of Anesthesiology, Medicine 1 and 4, and at a Junior Group of the IZKF, each with close methodical and thematic ties to the research groups of the Institute.

### Research

The overarching research objective at our Institute is to understand the bioelectrical and neurochemical processes that constitute the basic language of the nervous systems and enable communication between nerve cells. What factors elicit an electric impulse in a neuron, if, for instance, pain or temperature stimuli impact on the body? What mechanisms mediate signal transmission between nerve cells and how is information processed in neuronal networks? From answers to questions like these, how can we elucidate the underpinnings of cognition and emotion and of disorders thereof? We explore such issues with a broad spectrum of methods ranging from modern electrophysio-

logical, optical, cell and molecular biological techniques to microneurography and fMRI in healthy volunteers and patients.

### Neurophysiologic substrates of higher brain functions

PI: 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- $\beta$  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<sup>+</sup> and K<sup>+</sup> channels.



*Schematic model of how environmental enrichment (EE) and electroconvulsive therapy (ECT) may produce epigenetic modification through enhanced activin signaling and transcription of the activin target gene Kdm6b. KDM6B acts as a histone demethylase, thereby promoting gene expression of transcriptionally repressed genes. Background: In situ hybridization of coronal mouse brain section showing pronounced increase in *Inhba* mRNA level in dentate gyrus 2 h after ECT-like electrical stimulation. (Modified after Link AS et al. Front. Mol. Neurosci 2016. 9:32)*

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

PI: Prof. Dr. S. Sauer, Prof. Dr. P.W. Reeh

The research focuses on primary nociceptive neurons, their electrophysiological and neurochemical responses to noxious and pruritogenic stimuli and chemical mediators. Isolated preparations and cultured dorsal root ganglion cells as well as transfected cell lines are used to study action potential discharge, ionic currents, calcium transients, and release of the neuropeptides substance P and calcitonin gene-related peptide. Aim is to elucidate nociceptive transduction and integration of stimuli as well as possible pharmacological interventions. Specific topics are sensitization by tissue acidosis, inflammatory mediators, metabolites, toxins and gasotransmitters 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 propagation 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.

### Trigeminal nociception and headache generation

PI: Prof. Dr. K. Messlinger

Our group is working on nociceptive mechanisms in the cranial dura mater, the trigeminal ganglion, and the spinal trigeminal nucleus as the neurobiological basis for the generation of headaches. Extracellular recordings from single afferent fibers in the isolated rodent dura mater are performed to study the sensitivity and response of meningeal afferents and the role for receptors and ion channels 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 trigemino-vascular 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

PI: PD Dr. B. Namer

Morphological and electrical properties of peripheral unmyelinated neurons (C-fibers) are studied directly in healthy subjects, patients with painful and painless neuropathies or chronic pruritus. Especially patients with defined mutations of ion channels that change the excitability of peripheral C-fibers are of interest, which change pain and itch sensations. Neurons and mechanisms signaling pain and itch sensations are examined. The methods to examine C-fibers in awake humans include non-invasive assessment of axon reflexes and psychophysical studies as well as microneurography. Our aim is to build a bridge from patients and their symptoms of chronic itch and pain to mechanistic research on cells and ion channels.

## Functional imaging of brain activity by fMRI

PI: Prof. Dr. C. Forster

Functional magnetic resonance imaging (fMRI) is a well-established method to image the activity of the human brain during the processing of various stimuli and tasks. The method is used to identify brain regions involved in the central processing of pain and itch. By variation of the experimental paradigms, the function of various brain regions and their contribution in the perception of the corresponding stimulus should be determined. Common projects with the Department of Psychiatry and Psychotherapy analyze the central changes induced by psychogenic or emotional stress or by addiction.

## Teaching

In addition to its contribution to the preclinical curricula of students of human medicine, dentistry, and molecular medicine, the Institute gives lectures, seminars and practical courses in physiology for students of the Faculties of Engineering and Sciences, in particular courses for the degree programs medical technology and pharmacy.

The Institute supervises Bachelor's and Master's theses as well MD and PhD theses.

## Selected Publications

Hessler S, Zheng F, Hartmann S, Rittger A, Lehnert S, Völkel M, Nissen M, Edelmann E, Saftig P, Schwake M, Huth T, Alzheimer C.  $\beta$ -secretase BACE1 regulates hippocampal and reconstituted M-currents in a  $\beta$ -subunit-like fashion. *J Neurosci* 2015, 35: 3298-3311

Zheng F, Puppel A, Huber SE, Link AS, Eulenburg V, van Brederode JF, Müller CP, Alzheimer C. Activin controls ethanol potentiation of inhibitory synaptic transmission through GABAA receptors and concomitant behavioral sedation. *Neuropsychopharmacol* 2016, 41: 2023-2044

Babes A, Sauer SK, Moparthy L, Kichko TI, Neacsu C, Namer B, Filipovic M, Zygmunt PM, Reeh PW, Fischer MJ. Photosensitization in Porphyrrias and Photodynamic Therapy Involves TRPA1 and TRPV1. *J Neurosci*. 2016, 36 : 5264-5278

Bressan E, Touska F, Vetter I, Kistner K, Kichko TI, Teixeira NB, Picolo G, Cury Y, Lewis RJ, Fischer MJ, Zimmermann K, Reeh PW. Crotaiphine desensitizes TRPA1 ion channels to alleviate inflammatory hyperalgesia. *Pain* 2016, 157: 2504-2516

Dux M, Will C, Vogler B, Filipovic MR, Messlinger K. Meningeal blood flow is controlled by H2S-NO crosstalk activating a HNO-TRPA1-CGRP signaling pathway. *Br J Pharmacol*. 2016, 173: 431-45

Denner AC, Vogler B, Messlinger K, De Col R. Role of transient receptor potential ankyrin 1 (TRPA1) receptors in rodent models of meningeal nociception - experiments in vitro. *Eur J Pain* 2016, 15. doi: 10.1002/ejp.986

## International Cooperations

Prof. G. Kobal, Altria CS Inc., Richmond: USA

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

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

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

## Chair of Occupational and Social Medicine

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### Research Focus

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

### Structure of the Institute

Professorships: 2  
Personnel: 50  
• Doctors (of Medicine): 5  
• Scientists: 9 (thereof funded externally: 5)  
• Graduate students: 21

### Clinical focus areas

- Outpatient-clinic of occupational, social and environmental medicine
- Biological monitoring
- Occupational medical service for FAU and UK Erlangen
- Occupational medical service for teachers at schools in Northern Bavaria

### Special structural features

- Chair and scientific secretary of the DFG working group „Setting of Threshold Limit Values in Biological Material“ (Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area)
- Chair and scientific secretary of the DFG working group „Analyses of Hazardous Substances in Biological Material“ (Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area)

- Management and certification center of the quality assessment program for human biological monitoring (German External Quality Assessment Scheme, G-EQUAS)

### Research

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

#### Work related health research

Manifest diseases, resulting from chronic exposure at work, often cause substantial social-medical problems. Therefore, IPASUM carries out field studies at the work place 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 analyze not only the exposure, but also the data of ambient monitoring (inhalative and dermal exposure).

Funding: Gesetzliche Unfallversicherungsträger (German Social Insurance), German State Ministries, 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 public facilities, phthalates in pharmaceuticals/toys, or aluminum in deodorants.

Funding: Local authorities, Bavarian State Ministry of the Environment and Public Health, German Federal Environment Agency

### Biomarker in Occupational Medicine

PI: Prof. Dr. S. Schmitz-Spanke

This working group examines the cellular response to exposure to hazardous substances in the low dose range. In cellular models, toxicological endpoints (such as cell proliferation, production of oxygen radicals, alterations in the mitochondrial membrane potential, DNA damage) are correlated with alterations on the proteome and metabolome level. Here, the sequence of the cellular defense mechanism is analyzed and the transition from adaptive to adverse effects is characterized. The resultant data sets are comprehensively processed and modeled to simulate different conditions yielding insight into the mechanisms which are involved in this transition. An additional 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).

Funding: DFG, 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 DFG Commission of Investigation of Health Hazards of Chemical Compounds in the Work Area. Clinical research in the area of dermatotoxicology considers procedures to early diagnose subclinical skin damages and irritations. IPASUM developed and validated the Hand Eczema Score for Occupational Screenings (HEROS).

### Molecular markers of exposure to hazardous substances

This research area develops and validates procedures for the quantitative assessment of molecular markers of individual exposure to hazardous substances (exposure monitoring), for the disposition for hazardous substances in the metabolism (susceptibility monitoring), and examines the effects of hazardous substances (biological effect monitoring). A special focus is laid on the biological effect monitoring which particularly quantifies reaction products of mutagenous substances, covalently bound as adducts to macromolecules, like proteins or DNA. The valency of the biomarkers is exam-



ined 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 58<sup>th</sup> round robin test of G-EQUAS was finished within the report period. At the moment G-EQUAS comprises 182 analyses 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 de-

centralized 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 of Students. IPASUM shares in the curricular teaching of the Faculty of Medicine by compulsory and optional subjects. Particularly highlighted is the management of the cross-sectional courses Q3 and Q10 as well as the tutelage of the exploration of occupational fields by the students. Moreover, Bachelor's and Master' theses as well as MD and PhD theses are supervised by the Institute.

### **Selected Publications**

Clarner A, Graessel E, Scholz J, Niedermeier A, Uter W, Drexler H. Work-related posttraumatic stress disorder (PTSD) and other emotional diseases as consequence of traumatic events in public transportation: a systematic review. *Int Arch Occup Environ Health*. 2015;88(5): 549-64

Verma N, Pink M, Petrat F, Rettenmeier AW, Schmitz-Spanke S. Proteomic Analysis of Human Bladder Epithelial Cells by 2D Blue Native SDS-PAGE Reveals TCDD-Induced Alterations of Calcium and Iron Homeostasis Possibly Mediated by Nitric Oxide. *J Proteome Res*. 2015;14(1): 202-13

Weistenhöfer W, Wacker M, Bernet F, Uter W, Drexler H. Occlusive gloves and skin conditions: is there a problem? Results of a cross-sectional study in a semiconductor company. *Br J Dermatol*. 2015;172(4): 1058-65

Dennerlein K, Kieseewetter F, Kilo S, Jäger T, Göen T, Korinth G, Drexler H. Dermal absorption and skin damage following hydrofluoric acid exposure in an ex vivo human skin model. *Toxicol Lett*. 2016;248: 25-33

Jäger T, Drexler H, Göen T. Human metabolism and renal excretion of selenium compounds after oral ingestion of sodium selenite and selenized yeast dependent on the trimethylselenium ion (TMS<sub>e</sub>) status. *Arch Toxicol*. 2016;90(5): 1069-80

Munker S, Kilo S, Röß C, Jeitner P, Schierl R, Göen T, Drexler H. Exposure of the German general population to platinum and rhodium - Urinary levels and determining factors. *Int J Hyg Environ Health*. 2016;219(8): 801-810

### **International Cooperations**

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

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

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

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

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

# Institute for Biomedicine of Aging

## Chair of Internal Medicine (Geriatrics)

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### Research Focus

- Clinical nutrition in the elderly
- Mobility in the elderly
- Sarcopenia
- Clinical care for geriatric patients

### Structure of the Institute

Professorships: 2

Personnel: 31

- Doctors (of Medicine): 2
- Scientists: 18 (thereof funded externally: 15)
- Graduate students: 9

### Special structural feature

Prof. Dr. C. C. Sieber is head of the Department of General Internal Medicine and Geriatrics of the St. John of God Hospital, Regensburg, Germany (cooperation between the FAU and the St. John of God Hospital).

### Research

The research of the Institute for Biomedicine of Aging (IBA) is conducted in Nuremberg as well as in the St. John of God Hospital in Regensburg. Clinical, epidemiological, experimental as well as intervention studies are conducted with the help of the interdisciplinary team. The focuses are on the areas nutrition and metabolism in the elderly, age-related decline of muscle mass and function (sarcopenia), the improvement of the medical care for geriatric patients, and mobility and frailty.

### Clinical nutrition in the elderly

PI: Prof. Dr. D. Volkert

In the field of clinical nutrition, a major research focus of IBA is the investigation of the relationship between nutrition and physical function - ality, performance and frailty in older persons in various health and life situations. IBA is one of the two study centers of the Bavarian nutritional

expert cluster "enable" that has been founded by the BMBF. It is the aim of this interdisciplinary joint project to comprehensively characterize nutrition during the whole life span. Furthermore, together with food industries innovative products will be developed that will help to consume a healthy diet. Besides the recruitment and the phenotyping of an elderly cohort, IBA evaluates the effects of visually appealing, fortified and texture modified diet on energy and nutrients intake by nursing home residents who suffer from chewing and swallowing disorders. Other sub-projects aim to improve the drinking behavior of nursing home residents by using technical aids and to increase the amino acid intake of senior citizens by a protein enriched drink specifically developed for this target group.

On behalf of the German Nutrition Society (DGE) the quality of catering in institutions for older people is examined with the aim to derive new approaches for improvement. Evaluations of the international "nutritionDay" project aim to improve our understanding of the role of nutritional interventions to treat malnutrition in older persons living in nursing homes.

Furthermore, IBA, as a partner of the European research network DEDIPAC (Determinants of Diet and Physical Activity), is involved in the development of a complex framework of determinants of nutrition and eating during the whole life span (DONE framework) and has prepared two systematic reviews to identify determinants of dietary intake in older people. Together with Prof Dr. M. Visser from the University of Amsterdam, the European joint project MaNUEL (Malnutrition in the Elderly Knowledge Hub) is co-coordinated which started in 2016. Within this project, the definition, screening, prevention and treatment of malnutrition in old age are the main subjects. For example, determinants of malnutrition will be identified by systematic reviews and secondary data analysis. Overarching aims of the project are to build a sustainable international expert network and to harmonize research methodology and clinical practice.

Additionally, the preparation and publication of specific guidelines on clinical nutrition for older people suffering from dementia was headed in cooperation with the European expert association ESPEN (European Society for Clinical Nutrition and Metabolism).

### Mobility and frailty

PI: PD Dr. E. Freiburger

The demographic change poses a challenge for the public health care systems. In the future the approach of diagnose specific action in older persons will not be enough for the main goal of

preservation of independence, mobility and quality of life in the older population, or to reduce the risk of co-morbidity.

The two lifestyle factors, physical activity and nutrition, play a major role – next to medical intervention – to conquer the above-mentioned challenge. At present, there is enough evidence and international recommendations of targeted exercise intervention or increase in physical activity levels the functional performance on population level and participation in society can improve, and independence in the older persons longer maintained. The movement section under the head of PD Dr. E. Freiburger from the IBA is responsible for conducting exercise interventions.

The IBA is active on multiple levels for physical activity/exercise promotion to maintain function/independence in older persons by partaking in international and national projects. On international level the IBA is a partner in the project SPRINTT (Sarcopenia and Physical Activity IN older people: multi-component Treatment strategies; Innovative Medicine Initiative call), and was involved in the years 2015/16 in the RCT work package (WP) 7 with recruitment and intervention of participants. Related to the SPRINTT project there are currently two medical doctoral thesis and four master thesis in gerontology ongoing.

Physical activity plays an important role for older persons to be able to maintain independent status, and reduce the sedentary behavior for decreasing risk of mortality. The promotion of physical activity was the topic in the EU project DEDIPAC (Determinants of Diet and Physical Activity Choice), and the movement section of the IBA was involved in the WP of sedentary behavior in a systematic review as well as taking part at an expert workshop to define determinants of sedentary behavior.

Furthermore, specific target groups of older persons are at special risk of functional decline and new intervention methods are warranted. The IBA is targeting two very specific populations: In 2016 the FORMOSA project (Sarcopenia and Osteoporosis – consequences of reduced regeneration at old age) concluded the intervention part and the results were published in international journals. In addition, the target group of persons with intellectual disability are at an increased risk of earlier decline and present a special target group in aging research. Especially in this population, scientific expertise is missing. The PREFALLID (Prevention of falls in persons with intellectual disability) project published the results in international journal and resulted in a PhD thesis. In a collaboration with Prof. Dr. S. Wurm of the Institute for Psychogerontology

the influence of exercise instructors and location was investigated in a small project resulting in a MA thesis. A doctoral thesis is still ongoing under the supervision of Prof. Dr. S. Wurm. Next to the individual level of health promotion through physical activity, the political level also plays a central role. The aim is to build up an interdisciplinary and transactional networking of organizations in the area of health promotion e.g. movement scientists, health and social workers as well as medical professions. The movement section of the IBA is partaking on international level in the steering committee of EUNAAPA – European Network for Action on Ageing and Physical Activity). Furthermore, for EUNAAPA the IBA movement section is taking part in the dissemination WP of the EU horizon 2020 research project „PROMISS“ (Prevention of Malnutrition in Senior Subjects in the EU) which started in 2016 and will continue for three years.

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

PI: Dr. R. Kob

Obesity and high amounts of dietary fat have been assumed to be major risk factors for genesis and progression of sarcopenia. Therefore, we developed a rat model that chronically receives a high fat diet during maturity 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. Furthermore, nutrition, physical activity as well as handgrip strength were recurrently measured. 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. This project is part of the Bavarian research association “Sarcopenia and Osteoporosis – consequences of reduced regeneration at old age” (FORMOSA) and was conducted in close collaboration with the university hospital of Regensburg.

### **Clinical Research in Regensburg**

PI: Prof. Dr. C.C. Sieber

The project SCOPE (Screening for Chronic Kidney Disease (CKD) among Older People across Europe) is financed by the Horizon 2020 program of the EU and includes eight European centers. Within this study, scientists of the IBA, in cooperation with physicians at the St. John of God hospital in Regensburg, recruit patients to

improve screening and care of chronic renal diseases in older persons.

With its nursing expertise, the department supports the development of an intelligent bed, that helps to prevent and treat decubitus by automatic measurement of contact pressure and automatic repositioning of the patient.

The BMBF funded, multicentric and interdisciplinary project M-Endol (MRSA in End-of-Life Care) aims at investigating the impact of a MRSA/MRE infection on life quality of patients at the end of life and their relatives. Therefore economic investigations as well as qualitative and quantitative interviews, based on analyses according to the grounded theory, are carried out. The focus is to develop a need-oriented dealing with the affected, hospitalized patients and their relatives and the clinical staff.

### **Teaching**

The practical geriatric training (Q 7) of the Chair of Internal Medicine provides students with the requirements of medicine in old age. The compulsory elective subjects of the IBA are interdisciplinary with focuses on nutritional issues of hospital patients as well as physical activity and falls.

Several lectures and courses of the master degree course gerontology (Faculty of Humanities, Social Sciences, and Theology) are organized by the IBA.

IBA supervises Bachelor's and Master's theses as well as MD and PhD theses.

### **Selected Publications**

Chastin SF, Buck C, Freiburger E, Murphy M, Brug J, Cardon G, O'Donoghue G, Pigeot I, Oppert JM; DEDIPAC consortium. Systematic literature review of determinants of sedentary behaviour in older adults: a DEDIPAC study. *Int J Behav Nutr Phys Act.* 2015 Oct 6;12:127

Goisser S, Schrader E, Singler K, Bertsch T, Gefeller O, Biber R, Bail HJ, Sieber CC, Volkert D. Malnutrition According to Mini Nutritional Assessment Is Associated With Severe Functional Impairment in Geriatric Patients Before and up to 6 Months After Hip Fracture. *J Am Med Dir Assoc.* 2015 Aug 1;16(8):661-7

Kob R, Fellner C, Bertsch T, Wittmann A, Mishura D, Sieber CC, Fischer BE, Stroszczyński C, Bollheimer CL. Gender-specific differences in the development of sarcopenia in the rodent model of the ageing high-fat rat. *J Cachexia Sarcopenia Muscle.* 2015 Jun; 6(2):181-91.

Ritt M, Schwarz C, Kronawitter V, Delinic A, Bollheimer LC, Gassmann KG, Sieber CC. Analysis of Rockwood et al's Clinical Frailty Scale and Fried et al's Frailty Phenotype as Predictors of Mortality and Other Clinical Outcomes in Older Patients Who Were Admitted to a Geriatric Ward. *J Nutr Health Aging.* 2015 Dec;19(10):1043-8

Volkert D, Chourdakis M, Faxen-Irving G, Frühwald T, Landi F, Suominen MH, Vandewoude M, Wirth R, Schneider SM. ESPEN guidelines on nutrition in dementia. *Clin Nutr.* 2015 Dec;34(6):1052-73

Freiberger E, Kemmler W, Siegrist M, Sieber C. Frailty and exercise interventions: Evidence and barriers for exercise programs. *Z Gerontol Geriatr.* 2016 Oct;49(7):606-611

### **International Cooperations**

Prof. J. Brug, M. Visser, VU University Medical Center (multicentric), Amsterdam: The Netherlands

R. Bernabei, Università Cattolica del Sacro Cuore (multicentric), Rom: Italy

F. Lattanzio, Istituto Nazionale Di Riposo E Cura Per Anziani INRCA (multicentric), Ancona: Italy

# Institute of Clinical and Molecular Virology

## Chair of Clinical and Molecular Virology

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### Research Focus

- Retroviral infections
- Herpesviral infections

### Structure of the Chair

Professorships: 4  
Personnel: 107  
• Doctors (of Medicine): 5  
• Scientists: 15 (thereof funded externally: 12)  
• Graduate students: 22

### Clinical focus areas

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

### Research

Despite substantial progress in our understanding of viral host cell interactions and the interplay between viruses and the immune system, there still is an unmet medical need for prevention, control, and eradication of persistent viruses, particularly in an aging population with decreasing immune competence. Human herpesviruses and retroviruses continue to be major health threats internationally as well as in Germany and are therefore the focus of the Institute's research efforts.

### Retroviral infections

PI: Dr. A. Thoma-Kreß, Prof. Dr. U. Schubert, Prof. Dr. T. Gramberg, Prof. Dr. K. Überla, Dr. V. Temchura

One HTLV research group and three HIV research groups are working at the Institute. The HTLV research group studies interactions of human T-cell leukaemia virus Type 1 (HTLV-1) with the host cell to decipher molecular mechanisms of HTLV-1 cell-to-cell transmission. The

group identified an essential role of the actin-bundling protein Fascin in HTLV-1 release and cell-to-cell transmission. The second research group investigates the late processes of the HIV-1 replication cycle, particularly virus assembly and budding. It was shown that the HIV-1 p6 Gag protein regulates not only those late processes, but also membrane association, ubiquitination, and thus the entry of Gag into the MHC-I antigen presentation pathway. Moreover, it was shown that the accessory protein Vpu induces downregulation of the co-activating NK-cell receptors NTB-A and CD155, and thus subverts NK-cell responses against HIV-1 infected T cells. The third research group is characterizing the innate and intrinsic immune response during retroviral infection. The group focuses on the antiviral restriction factors SAMHD1 and the TRIM protein family. The laboratory found that SAMHD1 has broad antiretroviral activity against which most retroviruses, like HIV-1, have not found an escape mechanism. Furthermore, the group was able to analyze the function of murine SAMHD1 in vitro and in vivo using knockout mice. The fourth research group is exploring effector mechanisms of the adaptive immunity to HIV and aims at developing an HIV vaccine. In a relevant animal model, they could show for the first time that antibodies to HIV Env can block infection of the very first cell after mucosal exposure. For vaccine development the group uses gene-based vaccine approaches, liposomal vaccines, virus-like particle vaccines and nanoparticles.

### Herpesviral infections

PI: Prof. Dr. T. Stamminger, Prof. Dr. M. Marschall, Prof. Dr. M. Mach, Dr. K. Korn, Prof. Dr. A. Ensser, PD Dr. B. Biesinger, PD Dr. F. Neipel, Prof. Dr. W. Dörfler

Several aspects of human cytomegalovirus infections are investigated. A major research emphasis is on the analysis of HCMV effector proteins that exert essential functions for viral replication. During the last two years evidence was obtained that a structure of the cell nucleus, termed PML nuclear bodies, acts both as a direct restriction factor for viral infections and as a coactivator of the interferon response. Consequently, the IE1 protein of HCMV which exhibits significant structural similarity to immunoregulatory proteins of the TRIM family, was found to antagonize both, intrinsic immunity and the interferon response. The regulatory role of protein kinases in the replication of the human cytomegalovirus and related herpesviruses was also studied. In particular, the importance of protein

kinases for the nucleo-cytoplasmic egress of viral particles has been demonstrated. A functional involvement of the cytomegalovirus-encoded protein kinase pUL97 in these processes was shown, as well as their regulatory interaction with cellular cyclins. Further viral and cellular components of the nuclear egress complex were identified by the use of proteomics approaches and were functionally characterized. Particular importance had the x-ray-based resolution of the crystal structure of the nuclear egress core heterodimer as a functional platform for the nuclear release of HCMV. Moreover, an investigation of the antiviral potential of protein kinase inhibitors illustrated that these viral and cellular kinase activities can be exploited as promising targets for future antiviral strategies.



Nuclear colocalization of the two cytomegalovirus proteins pUL50 and pUL53

Using a double-staining confocal immunofluorescence imaging approach, the two proteins that mediate the nuclear egress of cytomegalovirus particles from infected host cell nuclei were detected in their fine-localization at the nuclear envelope (HeLa cells, nuclear DNA counterstaining by DAPI). Note the complete pUL50-pUL53 recruitment and colocalization, in part visible as a fine-speckled structure which is depicted in three different orientations by the use of confocal laser-scanning microscopy. (Figure: Eric Sonntag / team Marschall)

In attempts to define the protective antibody response against CMV, a number of monoclonal antibodies specific for glycoprotein B, one of the major antigens for the induction of antibodies, were isolated. In in vivo protection experiments in mice, it was shown that both neutralizing as well as non-neutralizing antibodies have the capacity to protect immunodeficient hosts from the lethal course of the infection with neutralizing antibodies being superior. During this work  $\gamma\delta$  T cells were serendipitously identified as yet another cell type that is involved in protection from CMV infection. The findings could have implications in the stem cell transplant setting, as antigen recognition by  $\gamma\delta$  T cells is not MHC-restricted and dual reactivity against CMV and tumors has been described. Together with Prof. Dr. W. Holter and PD Dr. M. Lehner (St. Anna Kinderspital and Children's Cancer Research Institute, Vienna), a translational approach for an antiviral, adoptive immunotherapy of CMV infection using chimeric antigen receptors (CAR) is also pursued. These studies revealed a new

HLA-recognition independent resistance of CMV infected cells toward T cell killing. The clinical diagnostics section established a simple screening approach for congenital CMV and currently determines in collaboration with Prof. Dr. K. Neumann (Pedaudiology, Ruhr-University Bochum) the prevalence of congenital CMV infections. This study aims to demonstrate the feasibility of a general CMV screening in neonates and to estimate benefits and costs for such a screening.

In addition to HCMV, oncogenic herpesviruses are also targeted for research. One group addresses the mechanisms of viral effectors in circumventing cellular restriction factors that are concentrated in the nuclear domain 10 (ND10). These comparative studies of rhadinoviral tegument proteins (in Kaposi's Sarcoma associated human Herpesvirus 8, Rhesus Rhadinovirus, Herpesvirus saimiri) revealed a proteasome-independent degradation of major ND10 components SP100 and PML by the KSHV model virus RRV, but also a restriction of this primate virus by DAXX. The mechanisms by which oncoproteins of T-lymphotropic rhadinoviruses are capable to transform human T cells to permanent growth in culture are also analyzed. The studies focused on the interactions with TNF receptor-associated factors (TRAF). It could be demonstrated that the viral oncoproteins utilize these cellular proteins to regulate NF- $\kappa$ B and other signaling pathways which may contribute to viral persistence. For the oncogenic Kaposi sarcoma-associated herpesvirus (KSHV) it could be shown for the first time that the Ephrin receptor tyrosinkinase A2 (EphA2) is an essential receptor for KSHV upon infection of endothelial and epithelial cells. It could be demonstrated in 2015 and 2016 that the intracellular part of EphA2 is not required for KSHV infection and that KSHV-RTA regulates EphA2 expression by post-transcriptional mechanisms. Another group investigated the impact of virus infections (Ad12, ASFV, HIV-1, HSV1, and AcMNPV) on epigenetic regulation of transcription and found global increases in cellular DNA methylation patterns upon Ad12 or ASFV infections, possibly as part of the apoptotic pathway.

## Teaching

Curricular lectures and courses on infectiology and immunology for students of human medicine, dentistry, pharmacy and molecular medicine are jointly given by the Institute of Clinical and Molecular Virology and the Institute of Clinical Microbiology, Immunology, and Hygiene.

In collaboration with further colleagues from the UK Erlangen as well as from Würzburg and Nuremberg, members of the Institute engage in the interdisciplinary course on infectiology and immunology (Q4). Furthermore, the Institute of Clinical and Molecular Virology offers a series of elective and compulsory optional courses for students of the Faculty of Medicine and the Faculty of Sciences. Thus, teaching in virology extends to B.Sc. und M.Sc. degree programs in molecular medicine, biology, integrated life sciences and molecular sciences. The course offerings are completed by the supervision of Bachelor's, Master's, MD, and PhD theses.

## Selected Publications

Herzner AM et al. Sequence-specific activation of the DNA sensor cGAS by Y-form DNA structures as found in primary HIV-1 cDNA. *Nat Immunol* 2015, 16 (10): 1025–33

Sell S, Dietz M, Schneider A, Holtappels R, Mach M, Winkler TH. Control of murine cytomegalovirus infection by  $\gamma\delta$  T cells. *PLoS Pathog* 2015, 11 (2): e1004481

Storcksdieck genannt Bonsmann M, Niezold T, Temchura V, Pissani F, Ehrhardt K, Brown EP, Osei-Owusu NY, Hannaman D, Hengel H, Ackerman ME, Streeck H, Nabi G, Tenbusch M, Überla K. Enhancing the quality of antibodies to HIV-1 envelope by GagPol-specific Th cells. *J Immunol* 2015, 195 (10): 4861–72

Walzer SA, Egerer-Sieber C, Sticht H, Sevwana M, Hohl H, Milbradt M, Muller YA, Marshall M. Crystal structure of the human cytomegalovirus pUL50-pUL53 core nuclear egress complex provides insight into a unique assembly scaffold for virus-host protein interactions. *J Biol Chem* 2015, 290 (46): 27452–27458

Gross C, Wiesmann V, Millen S, Kalmer M, Wittenberg T, Gettemans J, Thoma-Kress AK. The Tax-inducible actin-bundling protein fascin is crucial for release and cell-to-cell transmission of Human T-Cell Leukemia Virus Type 1 (HTLV-1). *PLoS Pathog* 2016, 12 (10): e1005916

Scherer M, Stamminger T. Emerging role of PML nuclear bodies in innate immune signaling. *J Virol* 2016, 90 (13): 5850–4

## International Cooperations

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

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

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

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

Prof. Dr. D. Barouch, The Ragon Institute of MGH, MIT and Harvard, Boston: USA



# Institute of Clinical and Molecular Virology

## Division of Experimental Therapy

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### Research Focus

- Mechanisms of pathogenic protein cross-seeding in neurodegenerative disorders (Cross-Seeds)
- Therapeutic modulation of the cholinergic system in a rat model of amyloidosis
- Characterization of the contribution of transglutaminase 6 to Huntington's and Alzheimer's disease
- Characterization of the role of glutaminyl-cyclase and its isoform during Huntington's disease
- Potentiation of Neuropeptide Y (NPY) mediated effects in stress-associated and neurodegenerative disorders via NPY-degradation inhibitors

### Structure of the Division

Professorships: 1

Personnel: 6

- Doctors (of Medicine): 1
- Scientists: 2 (thereof funded externally: 1)
- Graduate students: 3

### Special structural features

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

### Research

Research is focused on experimental therapeutic studies in animal models of human neurodegenerative and psychiatric disorders (Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), Spinocerebellar ataxia type 17, Schizophrenia, stress-induced disorders, attention deficit hyperactivity disorder). After comprehensive phenotyping of a certain disease model, we search for, characterize, and

target post-translational protein-modifications by transglutaminases, dipeptidyl-peptidase 4, glutaminyl-cyclase and its isoform ultimately trying to identify novel interventional approaches. A present focus is on neurodegenerative processes in the course of protein aggregation disorders.

### Mechanisms of pathogenic protein cross-seeding in neurodegenerative disorders (Cross-Seeds)

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

### Therapeutic modulation of the cholinergic system in a rat model of amyloidosis

AD is a devastating neurodegenerative disorder that impairs memory and causes progressive cognitive and psychiatric deficits. Loss of memory (episodic memory, declarative memory) is usually the most common symptom lamented by affected patients. The cholinergic system is involved in regulating a number of physiological functions, including motor control and sensory processing, additionally to cognition and sleep. Cholinergic dysfunction is particularly relevant to AD because it emerges early on during the pathology. Pharmacological treatments aimed at potentiating cholinergic neurotransmission are approved interventional strategies that produce some positive effects in the early stages of the disease, although their effects wear out as the pathology progresses. Aims of the project are

- a) to pin down the contribution of attention deficit and hyper-arousal to the behavioral symptoms associated with amyloid pathology in a transgenic rat model of AD;
- b) to analyze the impact of cholinergic-enhancing drugs on the observed phenotype(s);
- c) to demonstrate the efficacy of chronic cotinine administration as a novel pharmacological intervention in this animal model.

### Characterization of the contribution of transglutaminase 6 to Huntington's and Alzheimer's disease

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

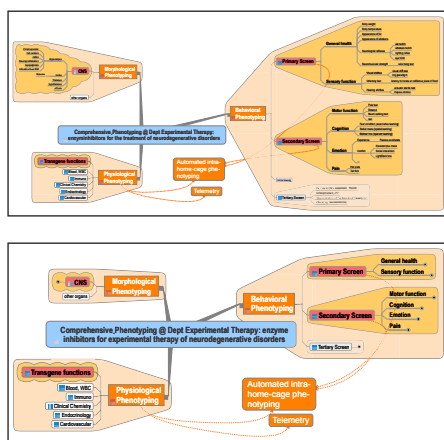
### Characterization of the role of glutaminyl-cyclase and its isoform during Huntington's disease

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

### Potentiation of Neuropeptide Y (NPY) mediated effects in stress-associated and neurodegenerative disorders via NPY-degradation inhibitors

The concept of stress protection in the CNS via potentiation of endogenous stress-protective signaling is neither fully explored nor clinically translated. Neuropeptide Y (NPY) exerts many stress- and neuroprotective actions in the brain and may well be pharmacologically modulated by inhibiting the corresponding enzymatic degradation. In addition, neurodegenerative disorders such as HD may benefit from such approaches. Surprisingly, in the degenerating striatum of HD patients, those medium spiny

neurons expressing NPY survive. We will analyse this endogenous NPY-based neuroprotection in animal models of HD. Genetic and pharmacological inhibition of the NPY-degrading enzyme dipeptidyl-peptidase IV will be used to develop a novel HD delaying approach via inhibitor-mediated potentiation of NPY-mediated neuroprotection.



*Comprehensive phenotyping on behavioral, morphological, and physiological levels is used for the evaluation of the therapeutic potential of specific enzyme inhibitors targeting dipeptidyl-peptidase IV, glutamyl cyclases, and transglutaminase 6 in transgenic animal models for human neurodegenerative disorders. Novel technologies, such as intra-home-cage-phenotyping and advanced telemetry, are applied.*

## Teaching

The Division of Experimental Therapy contributes to the international degree program Molecular Medicine as well as to electives in medicine. Our seminar on interdisciplinary preclinical studies using animal models of human disorders is much appreciated.

We supervise Bachelor's and Master's theses as well as MD and PhD theses in the fields of neurobiology and neuropathophysiology of neurodegenerative diseases.

## Selected Publications

Golub Y, Canneva F, Funke R, Frey S, Distler J, von Hörsten S, Freitag CM, Kratz O, Moll GH, Solati J. Effects of In utero environment and maternal behavior on neuroendocrine and behavioral alterations in a mouse model of prenatal trauma. *Dev Neurobiol.* 2016 Nov;76(11):1254-1265

Höfling C, Morawski M, Zeitschel U, Zanier ER, Moschke K, Serdaroglu A, Canneva F, von Hörsten S, De Simoni MG, Forloni G, Jäger C, Kremmer E, Roßner S, Lichtenthaler SF, Kuhn PH. Differential transgene expression patterns in Alzheimer mouse models revealed by novel human amyloid precursor protein-specific antibodies. *Aging Cell.* 2016 Oct;15(5):953-63

Wagner L, Björkqvist M, Lundh SH, Wolf R, Börgel A, Schlenzig D, Ludwig HH, Rahfeld JU, Leavitt B, Demuth HU,

Petersén Å, von Hörsten S. Neuropeptide Y (NPY) in cerebrospinal fluid from patients with Huntington's Disease: increased NPY levels and differential degradation of the NPY1-30 fragment. *J Neurochem.* 2016 Jun;137(5):820-37

Wagner L, Kaestner F, Wolf R, Stiller H, Heiser U, Manhart S, Hoffmann T, Rahfeld JU, Demuth HU, Rothermundt M, von Hörsten S. Identifying neuropeptide Y (NPY) as the main stress-related substrate of dipeptidyl peptidase 4 (DPP4) in blood circulation. *Neuropeptides.* 2016 Jun;57:21-34

Schulze-Krebs A, Canneva F, Schnepf R, Dobner J, Dieterich W, von Hörsten S. In situ enzymatic activity of transglutaminase isoforms on brain tissue sections of rodents: A new approach to monitor differences in post-translational protein modifications during neurodegeneration. *Brain Res.* 2016 Jan 15;1631:22-33

Becker A, Eichentopf R, Sedlmeier R, Waniek A, Cynis H, Koch B, Stephan A, Bäuscher C, Kohlmann S, Hoffmann T, Kehlen A, Berg S, Freyse EJ, Osmand A, Plank AC, Roßner S, von Hörsten S, Graubner S, Demuth HU, Schilling S. IsoQC (QPCTL) knock-out mice suggest differential substrate conversion by glutamyl cyclase isoenzymes. *Biol Chem.* 2016 Jan;397(1):45-55

## International Cooperations

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

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

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

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

# Institute of Clinical Microbiology, Immunology, and Hygiene

## Chair of Microbiology and Immunology of Infection

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### Research Focus

- Regulation of innate immunity in infection and inflammation
- Innate immunity, macrophages, arginase, and NO synthase
- Innate immunity and mast cells
- Genetic and bacterial factors in chronic inflammation
- Pathogenicity of *Coxiella burnetii*
- Microbial phosphatases
- Innate immunity, NK cells and therapy of leishmaniasis
- Malaria molecular biology
- Molecular mycology

### Structure of the Chair

Professorships: 4

Personnel: 89

- Doctors (of Medicine): 9
- Scientists: 8 (thereof funded externally: 1)
- Graduate students: 21

### Clinical focus areas

- Accredited clinical-microbiological diagnostics division
- 24/7 microbiological on-call service and emergency diagnostic testing
- Clinical infection related ward rounds for critical cases in the wards of the UK Erlangen
- Accredited hygiene laboratory
- Hospital hygiene related consultation and assistance of the UK Erlangen
- University outpatients' clinic for vaccination and travel medicine

### Research

The different research groups of the Institute of Clinical Microbiology, Immunology, and Hygiene study the innate and adaptive immune response during infectious diseases, investigate

mechanisms of microbial virulence, and analyze the regulation of basic inflammatory processes, using immunological, cell-biological, and molecular techniques. Various infectious disease models are studied which include infections with *Coxiella*, *Listeria*, *Mycobacteria*, *Leishmania*, *Plasmodia* and *Aspergillus*. The Institute is fully equipped with laboratories, 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.

### Regulation of innate immunity in infection and inflammation

PI: 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. In a second research project, we focus on the functional analysis of the "dual-specificity phosphatases" (DUSP) which inhibit signal transmissions of receptors for pathogen recognition as well as cytokines. A third project aims at identifying the immunological factors involved in the chronification during *Coxiella burnetii* infection in vivo.

### Innate immunity, macrophages, arginase, and NO synthase

PI: Prof. Dr. C. Bogdan

Nitric oxide (NO) which is synthesized from the amino acid L-arginine by the interferon (IFN)- $\gamma$  inducible NO synthase (iNOS) in macrophages and other cells is essential for the defense against intracellular pathogens and a central regulator of the immune system. The enzyme arginase can inhibit the enzymatic activity of iNOS because both enzymes use the same substrate. In tumor necrosis factor (TNF)-deficient mice, an overexpression of host cell arginase 1 can be observed correlating with a reduced ability to control the intracellular, NO-sensitive parasite *Leishmania* (L.) major. The group therefore aims to elucidate the molecular mechanisms by which TNF prevents an upregulation of host cell arginase 1. The long-term goal is to unravel whether the host or parasite arginase are critical for the lifelong survival of *Leishmania* in vivo.

Finally, the group studies the interaction between iNOS/NO and the iron metabolism.

### Innate immunity and mast cells

PI: Prof. Dr. H.U. Beuscher

The group investigates to which extent mast cells are able to bind, phagocytize and kill bacteria (i.e. *Escherichia coli*) and how they contribute to antibacterial host defense. Therefore, a main focus lays on bacterial fimbria and their relevance for the activation of mast cells.

### Genetic and bacterial factors in chronic inflammation

PI: Prof. Dr. J. Mattner

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

### Pathogenicity of *Coxiella burnetii*

PI: PD Dr. A. Lührmann

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

### Microbial phosphatases

PI: Dr. D. Soulat

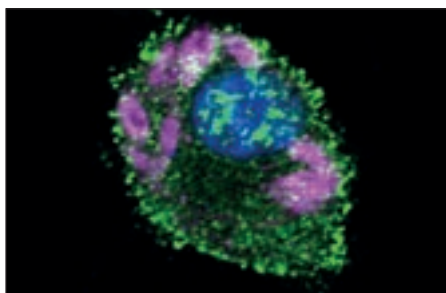
Human pathogens have developed numerous strategies to invade their host cell targets. One important virulence mechanism is the secretion of proteins that interfere with host cell signaling (e.g. microbial phosphatases). Pathogen-

secreted phosphatases are able to hijack the cellular immune response in a manner that leads to the creation of a pathogen-friendly environment inside the infected host. The research group currently 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 protozoan *Leishmania major* (i.e. LmPRL-1). For this purpose, we want to analyze mutants of the respective pathogens.

### Innate immunity, NK cells and therapy of leishmaniasis

PI: PD Dr. U. Schleicher

Both innate and adaptive lymphocytes contribute to the immune response against *Leishmania* parasites. In the mouse models of cutaneous and visceral leishmaniasis, the group investigates which of the different subpopulations of the so called innate lymphoid cells (ILC) is relevant for the defense against *Leishmania* and by which signals effector functions of ILC are activated and influenced. In the human system, we mainly focus on the activation of cytotoxic ILC1 (NK cells) by *leishmania*. In another project, the group analyzes how B cells regulate the immune response in visceral leishmaniasis.



Macrophages (blue nucleus) infected with *Leishmania major* (purple) and stimulated with Interleukin 4 produce Arginase 1 (green).

### Malaria molecular biology

PI: Dr. M. Petter

Malaria pathogenesis relies on various cellular processes in the life cycle of malaria parasites that each represent promising targets for therapeutic interventions and vaccine development. These include host cell invasion, the expression of virulence factors, and the differentiation of sexual stages which are transmitted by the vector, the *Anopheles*-mosquito. The research group is interested in understanding the molecular mechanisms governing the transcriptional control of these vital processes, focusing on the functional and mechanistic characterization of chromatin associated proteins such as the bro-

modomain protein PfBDP1 which contributes to epigenetic gene regulation in malaria parasites by binding to acetylated histones.

### Molecular mycology

PI: Prof. Dr. S. Krappmann

Omnipresent molds of the genus *Aspergillus* and predominantly *A. fumigatus* represent a prevalent threat for immunocompromised patients. Research efforts in this group aim at identification and characterization of fungal-specific virulence determinants, such as its versatile metabolism that allows for propagation inside a susceptible host. Furthermore, the sexual cycle of *A. fumigatus* and its impact on fungal secondary metabolism is investigated, while most recent research efforts in collaboration with Prof. Dr. D. Vöhringer (Division of Infection Biology) aim at the interplay of *A. fumigatus* with eosinophils, as it is relevant in the context of allergic reactions.

### Teaching

The Institute offers lectures and teaching courses for students of human medicine, dental medicine, molecular medicine, biology, and pharmaceuticals. Particularly noteworthy is the integrative teaching of the interdisciplinary subject infectious diseases and immunology. In cooperation with the Institute of Clinical and Molecular Virology, our Institute organizes a special medical education course on various infectious diseases for local physicians. We supervise Bachelor's and Master's theses as well as MD and PhD theses.

### Selected publications

Ostrop J, Jozefowski K, Zimmermann S, Hofmann K, Straszer E, Lepenies B, Lang R. Contribution of MINCLE-SYK Signaling to Activation of Primary Human APCs by Mycobacterial Cord Factor and the Novel Adjuvant TDB. *J Immunol* 2015, 195:2417-28

Bogdan C. Nitric oxide synthase in innate and adaptive immunity: an update. 2015. *Trends Immunol* 36: 161-178

Amich J, Dumig M, O'Keefe G, Binder J, Doyle S, Beilhack A, Krappmann S. Exploration of Sulfur Assimilation of *Aspergillus fumigatus* Reveals Biosynthesis of Sulfur-Containing Amino Acids as a Virulence Determinant. *Infect Immun* 2016, 84:917-29

Bisler S, Klingenbeck L, Borges V, Sobotta K, Schulze-Luehrmann J, Menge C, Heydel C, Gomes JP, Luhrmann A. The inhibition of the apoptosis pathway by the *Coxiella burnetii* effector protein CaeA requires the EK repetition motif, but is independent of survivin. *Virulence* 2016, 7:400-12

Schey R, Dornhoff H, Baier JL, Purtak M, Opoka R, Koller AK, Atreya R, Rau TT, Daniel C, Amann K, Bogdan C, Mattner J. CD101 inhibits the expansion of colitogenic T cells. *Mucosal Immunol* 2016, 9:1205-17

Schleicher U, Paduch K, Debus A, Obermeyer S, König T, Kling JC, Ribechini E, Dudziak D, Mouggiakakos D, Murray

PI, Ostuni R, Korner H, Bogdan C. TNF-Mediated Restriction of Arginase 1 Expression in Myeloid Cells Triggers Type 2 NO Synthase Activity at the Site of Infection. *Cell Rep* 2016, 15:1062-75

### International Cooperations

Prof. N. Osheroov, Human Microbiology, Tel Aviv University, Ramat Avi: Israel

Prof. R.K. Kandasamy, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim: Norway

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

Prof. P. Murray, St. Jude Children's Research Hospital, Memphis: USA

Dr. R. Ostuni, San Raffaele Telethon Institute for Gene Therapy, Milan: Italy

Prof. J.P. Gomes, Department of Infectious Diseases, National Institute of Health, Lisbon: Portugal



# Institute of Clinical Microbiology, Immunology, and Hygiene

## Division of Infection Biology

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### Contact

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### Research Focus

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

### Structure of the Division

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

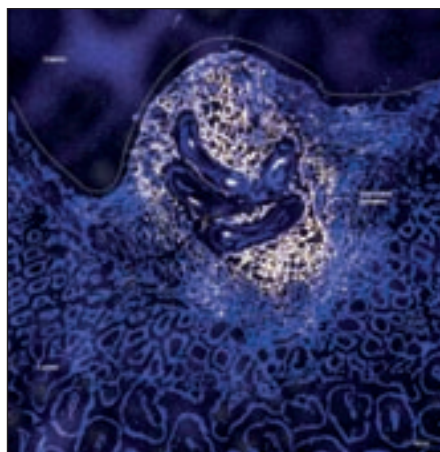
### Research

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

#### Immune response against helminths and allergens

Main focus of the research activities is the characterization of type 2 immune responses which are elicited by parasitic worms (helminths) and allergens. In both situations, the immune system reacts with an increase in Th2 cells, 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 Bio-

logy 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 helminth-specific antibodies bind. These helminth-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.



Picture shows *Heligmosomoides polygyrus* L3 larva surrounded by macrophages (white) in the submucosa of the small intestine of an infected mouse.

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

Memory-like T cells (T<sub>M</sub>L) 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 T<sub>M</sub>L 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 DC, 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 an ERC starting grant, 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 Uniklinik RWTH Aachen 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.

#### Teaching

The Division of Infection Biology offers lectures and teaching courses for students of medicine and dental medicine.



Bachelor's and Master's theses are supervised as well as PhD theses.

### **Selected Publications**

Schwartz C, Willebrand R, Huber S, Rupec RA, Wu D, Locksley R, Voehringer D. Eosinophil-specific deletion of  $\kappa B\alpha$  in mice reveals a critical role of NF- $\kappa B$ -induced Bcl-xL for inhibition of apoptosis. *Blood* 2015, 125:3896-3904

Ohnmacht C, Park JH, Cording S, Wing JB, Atarashi K, Obata Y, Gaboriau-Routhiau V, Marques R, Dulauroy S, Fedoseeva M, Busslinger M, Cerf-Bensussan N, Boneca IG, Voehringer D, Hase K, Honda K, Sakaguchi S, Eberl G. The microbiota regulates type 2 immunity through ROR $\gamma$ t+ T cells. *Science* 2015, 349:989-993

Oeser K, Maxeiner J, Symowski C, Stasse M, Voehringer D. T cells are the critical source of IL-4/IL-13 in a mouse model of allergic asthma. *Allergy* 2015, 70:1440-1449

Turqueti-Neves A, Otte M, Schwartz C, Lindner C, Pabst O, Yu P, Voehringer D. The extrafollicular domains of IgG1 and T cell-derived IL-4/IL-13 are critical for the polyclonal memory IgE response in vivo. *PLOS Biology* 2015, 13:e1002290

Otte M, Mahler V, Kerpel A, Pabst O, Voehringer D. Persistence of the IgE repertoire in birch pollen allergy. *J Allergy Clin Immunol* 2016, 137:1884-1887

Schwartz C, Eberle JU, Hoyler T, Diefenbach A, Lechmann M, Voehringer D. Opposing functions of TSLP-responsive basophils and dendritic cells in atopic dermatitis. *J Allergy Clin Immunol* 2016, 138:1443-1446

### **International Cooperations**

Dr. G. Eberl, Institute Pasteur, Paris: France

Prof. Dr. D. Finke, University of Basel, Basel: Switzerland

Prof. Dr. S. Hendricks, Hasselt University, Diepenbeek: Belgium

Prof. R. Maizels, University of Edinburgh, Edinburgh: UK

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

# Institute of Experimental and Clinical Pharmacology and Toxicology

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### Research Focus

- Signal transduction of cardiac rhythmogenesis and hypertrophy
- HCN channels in the nervous system
- Renal function and sepsis
- Physiology of chemical senses
- Pharmacological imaging by the use of fMRI

### Structure of the Chair

Professorships: 2

Personnel: 26

- Scientists: 8 (thereof funded externally: 3)
- Graduate students: 7

### Special structural feature

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

### Research

Various functions in the cardiovascular system as well as in the central and peripheral nervous system of mammals are studied. Research foci are the mechanisms underlying the generation of the cardiac rhythm in the sinoatrial node as well as the signal transduction mechanisms of cardiac hypertrophy. Another research area is the pathogenesis of septic acute kidney injury. The role of HCN channels in the nervous system and in particular in the development of pain is analyzed. Finally, the action of diverse drugs is studied by non-invasive brain imaging using functional magnetic resonance imaging (fMRI).

### Signal transduction of cardiac rhythmogenesis and hypertrophy

PI: PD Dr. J. Stieber, PD Dr. S. Herrmann, Prof. Dr. A. Ludwig

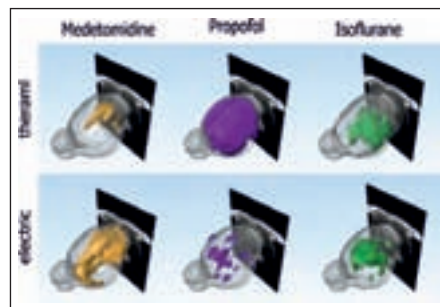
The role of RyR2 ryanodine receptors for rhythmogenesis in the sinoatrial node was analyzed

by using a sinoatrial mouse mutant of the receptor. We could show that RyR2 is essential for the generation of the cardiac rhythm, since lack of this sarcoplasmic calcium channel resulted in a pronounced slowing of the generation of action potentials in sinoatrial node cells. Unexpectedly, we found that both ventricular RyR2 - and  $\text{Ca}_v1.2$ -calcium channel mouse mutants develop a cardiac phenotype resembling human dilative cardiomyopathy (DCM). Currently, new treatment strategies are tested in these mouse models. In addition, the role of protein kinase A (PKA) in the development of cardiac hypertrophy was examined by generation and analysis of an inducible heart-specific PKA-mutant. We could show that in an early stage of cardiac remodeling PKA inhibition alleviates cardiac hypertrophy. However, the long-term inhibition of the kinase seems to be detrimental for cardiac function implicating a protective role of ventricular PKA activity in cardiac hypertrophy and failure.

### HCN channels in the nervous system

PI: PD Dr. S. Herrmann, Prof. Dr. A. Ludwig

We could show earlier that HCN channels are involved in the development of allodynia and hyperalgesia following inflammation. We now studied the interaction between PKA and HCN2 in nociceptive neurons. Facilitation of Ih via cAMP, a hallmark of the Ih current, was abolished in neurons without PKA activity. These results suggest that PKA-dependent activation of HCN2 underlies cAMP-triggered neuronal sensitization. In collaboration with Prof. Dr. T. Budde (Westfälische Wilhelms-Universität Münster), the role of HCN4 ion channels in the thalamus was analyzed. We could demonstrate that HCN4 is essential for the generation of rhythmic activity in thalamic neurons and the thalamocortical network.



Areas in the mouse brain activated by thermal and electrical stimulation in the presence of different anesthetic drugs. Dependent on the stimulus, the drugs vary in their ability to suppress the nociceptive brain response.

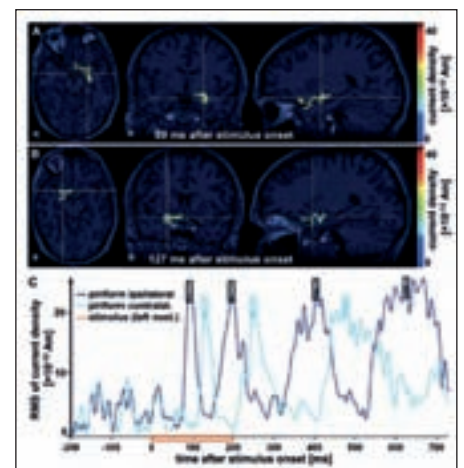
### Renal function and sepsis

PI: 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. Hyporeactivity to vasoconstrictors, such as thromboxane (Tx) A<sub>2</sub>, is commonly observed in patients and animal models of sepsis. Since the formation of TxA<sub>2</sub> depends on the activity of cyclooxygenase (COX), we investigated the impact of COX-1 and COX-2 activity on lipopolysaccharide (LPS)-induced renal TxA<sub>2</sub> formation and on endotoxemia-induced AKI in mice. Endotoxemia decreased glomerular filtration rate (GFR) and increased plasma and renocortical tissue levels of TxA<sub>2</sub>. The COX-1 inhibitor SC-560 attenuated the LPS-induced fall in GFR and inhibited the increase in plasma and renocortical tissue levels of TxA<sub>2</sub> in response to LPS. In contrast, the COX-2 inhibitor SC-236 further enhanced the LPS-induced decrease in GFR and did not alter the LPS-induced increase in TxA<sub>2</sub>. Our study indicates that the COX-1 inhibitor SC-560 has a protective effect on the decrease in renal function in response to endotoxin. Hence, our data support a role for TxA<sub>2</sub> in the development of AKI in response to LPS.

### Physiology of chemical senses

PI: PD Dr. B. Renner



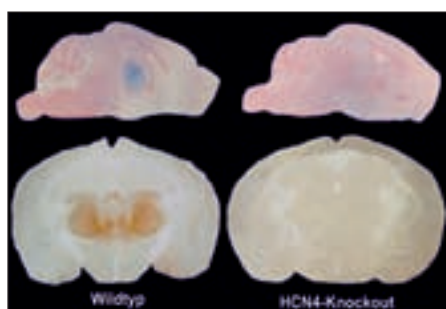
Areas in the human brain, activated by olfactory stimulation using magnetoencephalography (MEG) recordings with a high time resolution (A B). Time course of the early neuronal activity (here shown after repeated stimulation with hydrogen sulfide) depends on the activated brain structure and on the side of stimulated nostril (C).

Screening tests for children with olfactory disorders were further developed and new test strips for the examination of taste disorders

were validated. In a collaboration with the Department of Neurosurgery (Prof. Dr. A. Stadlbauer, Prof. Dr. M. Buchfelder), a localization study for deep cortical and subcortical responses following olfactory stimulation was carried out. The use of MRI and EEG and exact stimulation by using an olfactometer permitted results at high time resolution. With this technique, problems in epilepsy, olfactory disorders (e.g. parosmia) and neurodegenerative diseases will be studied.

### Pharmacological imaging by the use of fMRI

PI: Prof. Dr. A. Hess



*Deletion of HCN4 ion channels in the mouse brain*  
In the wildtype brain (left), HCN4 is highly expressed in the thalamus. In brain-specific HCN4 mutants (right), the protein is lacking completely.

The non-invasive imaging of brain function by using functional magnetic resonance imaging (fMRI) is ideally suited to determine the effect of very different drugs in various diseases in a translational setting. In collaboration with Prof. Dr. M. Neurath und Prof. Dr. R. Atreya (Department of Medicine 1), we could demonstrate that fMRI is able to indicate at very early time points a successful response to anti-TNF therapy in patients suffering from Crohn's disease. In these patients, brain activity in response to a painful stimulus was markedly diminished after application of the drug. In collaboration with Prof. Dr. G. Schett and PD Dr. J. Rech (Department of Medicine 3), we use the same approach to study another TNF-antagonist for the therapy of rheumatoid arthritis in a multicentric, randomized, placebo-controlled Phase III study. Together with Prof. Uder (Institute of Radiology), the TU Darmstadt and the GSI Darmstadt (BMBF project „NeuroRad“), we found preliminary evidence that postnatal low-dose radiation induces significant changes in the brain function of mice. In collaboration with Prof. Pischetsrieder (Chair of Food Chemistry, Faculty of Sciences), we perform the „Neurotrition“ study to analyze the interaction between food and brain function and examined the impact of

various fatty acids on food intake. In an attempt to translate the results of animal experiments to humans, we study in collaboration with Dr. S. Horndasch and PD Dr. O. Kratz (Division of Child and Adolescent Mental Health) the changes of brain function during eating in patients suffering from anorexia nervosa. Finally, we studied the effect of different anesthetic drugs on central pain processing.

### Teaching

In addition to the teaching duties in the degree programs Human Medicine and Molecular Medicine, the Chair provides the complete training in pharmacology for pharmacy students (as required to acquire the license to practice pharmacy). This includes lectures covering pharmacology and pathophysiology as well as seminars and laboratory internships.

Bachelor's and Master's theses as well as MD and PhD theses are supervised.

### Selected Publications

Ebelt H, Geißler I, Ruccius S, Otto V, Hoffmann S, Korth H, Klöckner U, Zhang Y, Li Y, Grossmann C, Rueckschloss U, Gekle M, Stieber J, Frantz S, Werdan K, Müller-Werdan U, Loppnow H. Direct inhibition, but indirect sensitization of pacemaker activity to sympathetic tone by the interaction of endotoxin with HCN-channels. *Clin Exp Pharmacol Physiol.* 2015, 42:874-880

Herrmann S, Schnorr S, Ludwig A. HCN channels—modulators of cardiac and neuronal excitability. *Int J Mol Sci.* 2015, 16:1429-1447

Hess A, Roesch J, Saake M, Sergeeva M, Hirschmann S, Neumann H, Dorfler A, Neurath MF, Atreya R. Functional Brain Imaging Reveals Rapid Blockade of Abdominal Pain Response Upon Anti-TNF Therapy in Crohn's Disease. *Gastroenterology* 2015, 149: 864-866

Hoch T, Kreitz S, Gaffling S, Pischetsrieder M, Hess A. Fat/carbohydrate ratio but not energy density determines snack food intake and activates brain reward areas. *Sci Rep* 2015, 5: 10041

Mederle K, Meurer M, Castrop H, Höcherl K. Inhibition of COX-1 attenuates the formation of thromboxane A2 and ameliorates the acute decrease in glomerular filtration rate in endotoxemic mice. *Am J Physiol Renal Physiol.* 2015, 309:F332-40

Stadlbauer A, Kaltenhäuser M, Buchfelder M, Brandner S, Neuhuber WL, Renner B. Spatio-temporal pattern of human cortical and subcortical activity during early-stage odor processing. *Chem. Senses* 2016, 41: 783-794

### International Cooperations

Prof. D. Chetkovich, Northwestern University, Chicago: USA

Prof. Lei Zhou, Virginia Commonwealth University, Richmond: USA

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

Prof. K. Chien, Karolinska Institutet, Stockholm: Sweden

Prof. D. Drucker, Samuel Lunenfeld Research Institute, Toronto: Canada

# 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 and transporter-mediated drug-drug interactions
- Molecular and clinical characterization of new cardiovascular risk factors and risk markers
- Analysis of drugs and endogenous substances
- Medication safety

### Structure of the Chair

Professorships: 2

Personnel: 25

- Doctors (of Medicine): 3
- Scientists: 7 (thereof funded externally: 2)
- Graduate students: 10

### Special structural feature

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

### Clinical focus areas

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

### Research

The groups at the Chair of Clinical Pharmacology and Clinical Toxicology investigate mechanisms underlying interindividual differences in drug effects using molecular and cellular biology as well as clinical studies. The following topics, funded e.g. by the 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, mechanisms underlying drug-drug interactions, genetic determinants of drug effects (pharmacogenomics), cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism, and medication safety.

### Molecular characterization of drug transporters and transporter-mediated drug-drug interactions

PI: 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. Simultaneously administered drugs or food constituents can modify transporter-mediated uptake or elimination of victim drugs. This leads to altered plasma concentrations and drug effects of the victim drug and possibly an increased risk of adverse drug reactions. We could identify functionally relevant amino acid residues in the hepatic uptake transporter OATP1B1. We could show that in vitro inhibition of the renal uptake transporter OCT2 depended on the used substrates. Furthermore, the molecular mechanism of renal secretion of the dopamine receptor agonist pramipexole could be identified and evidence was generated for the use of the endogenous metabolite N1-methylnicotinamide as potential biomarker for renal drug-drug interactions mediated by cation transporters.



Selective or overlapping inhibition of OCT2-mediated uptake of the oral antidiabetic drug metformin (MF) and of the prototypical OCT2 substrates ASP<sup>+</sup> (4-(4-dimethylaminostyryl)-N-methylpyridinium) and MPP<sup>+</sup> (1-methyl-4-phenylpyridinium) by frequently used drugs (reproduction with permission of PLOS ONE from Hacker et al., PLOS ONE 2015, DOI:10.1371/journal.pone.0136451)

### Molecular and clinical characterization of new cardiovascular risk factors and risk markers

PI: Prof. Dr. R. Maas

A major focus of the group is the experimental and clinical characterization of new cardiovascular risk markers and risk factors as potential targets for therapeutic intervention. Currently the group investigates transport and metabolism of homoarginine, β-aminoisobutyrate, nitrate and the methylarginines ADMA and SDMA. The investigations were conducted in long standing cooperations with the Depart-

ment of Medicine 4 – Nephrology and Hypertension, the Universities of Dresden and Kiel and the Framingham Heart Study (USA).

### Analysis of drugs and endogenous substances

PI: Dr. M. Mieth

The drug analysis unit uses samples from both, cell culture experiments and clinical trials. Analytical methods (mostly LC/MS/MS) are developed, optimized, and validated in our laboratory. The spectrum of the analytes ranges from various drugs, such as pravastatin, etoposide, metformin, clopidogrel and trimethoprim, to endogenous substances, such as derivatives of arginine, N<sup>1</sup>-methylnicotinamide and β-amino-isobutyric acid.

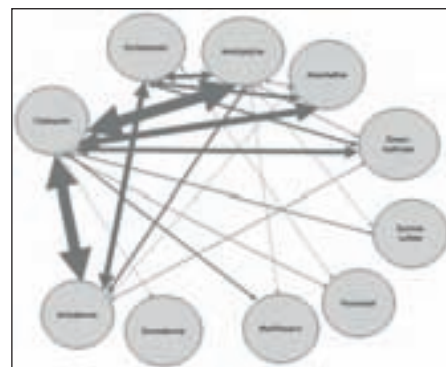
### Medication safety

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

As a partner of the therapeutic systems project that is part of the BMBF funded cluster Medical Valley EMN, we developed a new software to improve medication safety in psychiatry. In a joint project with Prof. Dr. F. Dörje (Pharmacy of UK Erlangen), we conducted a project within the Comprehensive Cancer Center Erlangen-EMN on medication safety in oncology with a particular focus on drug-drug interactions by abiraterone and enzalutamide in patients with metastatic castration-resistant prostate cancer (in cooperation with the AURONTE unit of the UK Erlangen).

Funding: German Cancer Aid

In addition, problems of medication safety in elderly patients (e.g. QT-interval prolonging drugs) are in the focus of collaborative projects with the Geriatrie in Bayern-Database (GiB-DAT). Moreover, in a BMG-funded collaborative project, we evaluate the new nationwide medication plan in clinical praxis (MMP16). The Chair also coordinates the community of practice "Medication Safety" of the Medical Valley EMN e.V.



Simultaneous prescription of QT-interval prolonging drugs in a cohort of 130,434 patients treated in geriatric units. The thickness of the arrows is proportional to the number of patients who received the respective combination (co-

operation with Prof. K.-G. Gaßmann, Geriatrie-Zentrum Erlangen and GiB-DAT; reproduction with permission of PLOS ONE from Schächtele et al., PLOS ONE 2016: DOI:10.1371/journal.pone.0155649)

## Teaching

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

## Selected Publications

Müller F, Pontones CA, Renner B, Mieth M, Hoier E, Auge D, Maas R, Zolk O, Fromm MF. N<sup>1</sup>-methylnicotinamide as an endogenous probe for drug interactions by renal cation transporters: studies on the metformin-trimethoprim interaction. *Eur J Clin Pharmacol*, 2015, 71: 85-94

Knop J, Misaka S, Singer K, Hoier E, Müller F, Gläser H, König J, Fromm MF. Inhibitory effects of green tea and (-)-epigallocatechin gallate on transport by OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K and P-glycoprotein. *PLOS ONE*, 2015, 10: e0139370

Stratz C, Bömicke T, Younas I, Kittel A, Amann M, Valina CM, Nührenberg T, Trenk D, Neumann FJ, Hochholzer W. Comparison of immature platelet count to established predictors of platelet reactivity during thienopyridine therapy. *J Am Coll Cardiol*, 2016, 68: 286-93

Schächtele S, Tümena T, Gaßmann KG, Fromm MF, Maas R. Co-prescription of QT-interval prolonging drugs: an analysis in a large cohort of geriatric patients. *PLOS ONE*, 2016, 11: e0155649

Gruetz M, Sticht H, Glaeser H, Fromm MF, König J. Analysis of amino acid residues in the predicted transmembrane pore influencing transport kinetics of the hepatic drug transporter organic anion transporting polypeptide 1B1 (OATP1B1). *BBA Biomembranes*, 2016, 1858: 2894-2902

Schlesinger S, Sonntag SR, Lieb W, Maas R. Asymmetric and symmetric dimethylarginine as risk markers for total mortality and cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *PLOS ONE*, 2016, 11: e0165811

## International Cooperations

Prof. L. Gustafsson, Karolinska Institutet, Stockholm: Sweden

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

Prof. R. Vasan, Framingham Heart Study, Framingham: USA

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

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



# Institute of Forensic Medicine

## Chair of Forensic Medicine

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### Research Focus

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

### Structure of the Institute

Professorships: 1  
Personnel: 17  
• Scientists: 6 (thereof funded externally: 0)

### Research

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

PI: 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.

### Teaching

In addition to the education of the students of the degree program Medicine according to the Statutes of the Medical Act (ÄAppO), courses are held for students of the Faculty of Business, Economics, and Law, and the Faculty of Sciences as well as for medical students from

the University of Regensburg. Students are welcome during the whole year to sit in autopsies, court trials, and practical courses in the field of forensic analytic.

### Selected Publications

Lenz B, Thiem D, Bouna-Pyrrou P, Mühle C, Stoessel C, Betz P, Kornhuber J. Low digit ratio (2D:4D) in male suicide victims. *J Neural Transm (Vienna)*. 2016 Dec;123(12):1499-1503

Wiest I, Alexiou C, Friese K, Betz P, Tübel J, Goletz S, Dian D, Jeschke U. Expression of the Tumor-associated Mucin 1 Epitope Analyzed with the Humanized PankoMab-GEX™ Antibody in Malignant and Normal Tissues of the Head and Neck. *Anticancer Res*. 2016 Jun;36(6):3179-84



# 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

Professorships: 2  
Personnel: 49  
• Doctors (of Medicine): 8  
• Scientists: 9 (thereof funded externally: 4)  
• Graduate students: 10

### Clinical focus areas

- Genetic outpatient clinic for all aspects of genetic diseases
- Interdisciplinary clinic for familial cancer in children and adults
- Wide range of pre- and postnatal genetic analyses including genome sequencing

### Research

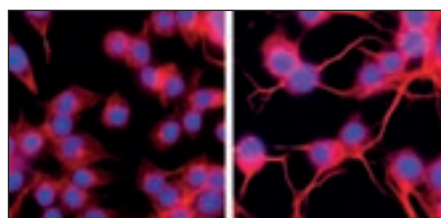
Research at the Institute of Human Genetics focuses on the elucidation of causes and pathomechanisms of genetic disease and genotype/phenotype correlation. In particular, modern genomic technologies such as microarray analysis and exome/genome sequencing are used. For various projects large groups of patients have been recruited and clinically characterized in detail. In addition, cellular models including induced pluripotent stem cells and genome editing using CRISPR-Cas9 are used. The Institute cooperates with numerous departments and institutes within the Faculty and operates the core unit „Next Generation Sequencing“.

### Genetic factors of intellectual disability

PI: PD Dr. C. Zweier, PD Dr. R. Abou Jamra, Prof. Dr. A. Reis

Genetic factors are the main cause of intellectual disability (ID) in Germany. In many cases,

ID co-occurs with additional symptoms and malformations in a syndromic presentation. Genetic causes are very heterogeneous and all modes of Mendelian inheritance occur. Over the recent years, including the reporting period, the working groups at the Institute identified numerous single gene defects. Autozygosity mapping and massively parallel sequencing was used to identify several new autosomal recessive gene defects in multiplex families with consanguineous parents. As autosomal dominant de novo mutations represent the main cause of sporadic ID, sequencing of the entire coding sequence (exome sequencing) of parent-child trios is the ideal strategy. In this group, genetic defects of members of the BAF complex, including ARID1B, are particularly frequent. In functional studies, the effect of this chromatin remodeling complex on the Wnt/ $\beta$ -catenin signaling pathway could be demonstrated. In addition, the genetic and clinical spectrum of X-linked NAA10 deficiency in girls and boys was extended and the groups made important contributions to the characterization of the clinical and genetic spectrum of FOXP2- and CNTNAP2-associated developmental disorders. Furthermore, a publicly accessible, manually curated database of all ID associated genes has been created. This integrated resource containing genetic and phenotypic data combined with information on biological functions allows novel insights into the clinical and biological landscape of ID.



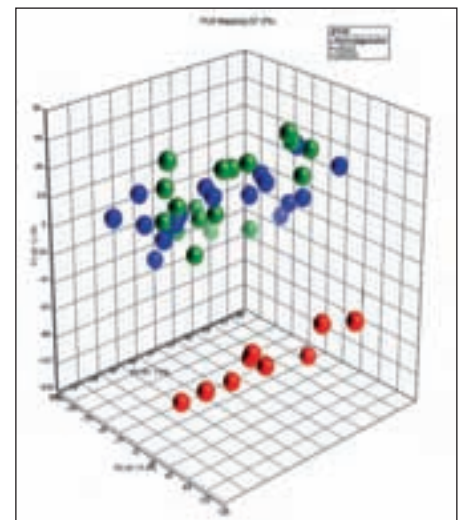
Knock-down of ARID1B in neuronal cells (N2A) induces differentiation. Right control cells

### Genetics of complex diseases

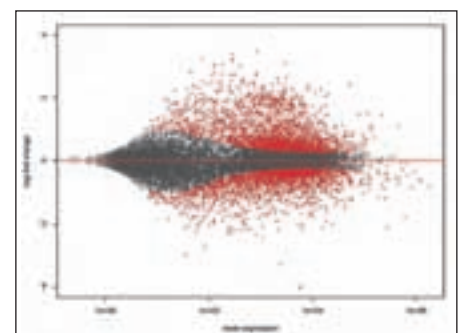
PI: PD Dr. U. Höffmeier, Prof. Dr. A. Reis

Complex or multifactorial diseases are caused by a combination of mostly unknown environmental and genetic factors. Numerous genetic variants, each with a small effect size, act as susceptibility factors. These can be detected with genetic association studies in large patient groups and promise insights into the pathomechanisms of the particular disease or trait. At the Institute, psoriasis, psoriasis arthritis and glaucoma are of particular interest. In the reporting period, a long-standing international association study on secondary glaucoma with exfoliation syndrome was

completed and a common risk-variant mapping to CACNA1A could be newly identified. Based on previous studies in patients with psoriasis and psoriatic arthritis, the previously identified susceptibility locus at the RUNX3 gene was investigated in search for the causative variant and the associated signaling pathway. In addition, the working group analyzed generalized and palmoplantar forms of pustular psoriasis for genetic variants in the IL36RN gene and CARD14.



PCA plot showing clustering of three tissue types based on genome wide expression profiles



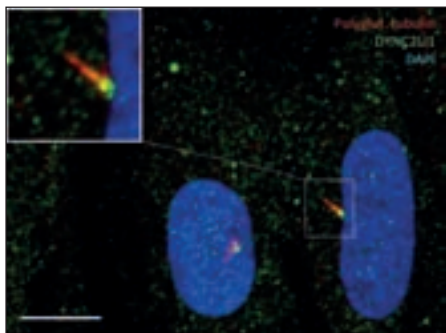
MA plot showing distribution of genome wide gene expression values

### Growth retardation

PI: PD Dr. C. Thiel

The elucidation of genetic causes of growth disturbances allows insights into the regulation of fundamental cellular processes. The working group combines genetic and genomic techniques with functional characterization of factors involved in idiopathic short stature and ciliary growth disorders. In close cooperation with the Department of Pediatric and Adolescent Medicine and external partners, large patient groups were established. With a genome-wide approach

using exome sequencing, the molecular and clinical spectrum of known entities could be extended and novel causes for idiopathic short stature identified. Moreover, exome sequencing combined with functional characterization of the ciliary protein NEK1 led to the identification of the interaction partner DYNC2LI1 as novel candidate gene for autosomal recessive short stature. Defects of DYNC2LI1 disrupt the retrograde protein transport and finally the function of the primary cilium.



*Immunofluorescence of the primary cilium in a human fibroblast cell line*

*The primary cilium is localized on nearly all vertebrate cells and plays an important role in many processes during development. It is composed of the basal body (green) and the axoneme (red). During mitosis the basal body breaks down into the centrioles involved in spindle formation.*

### Developmental genetics

PI: 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 ovarian cancer patients. The group was able to show that SPOC1 functions as an epigenetic reader and writer of histone modifications and 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. Bachelor's and Master's theses as well as MD and PhD theses were supervised.

### Selected Publications

Aung T et al. A common variant mapping to CACNA1A is associated with susceptibility to exfoliation syndrome. *Nat Genet.* 2015, 47: 387-92

Vasileiou G, Ekici AB, Uebe S, Zweier C, Hoyer J, Engels H, Behrens J, Reis A, Hadjihannas MV. Chromatin-Remodeling-Factor ARID1B Represses Wnt/ $\beta$ -Catenin Signaling. *Am J Hum Genet.* 2015, 97: 445-56

Boycott KM et al. Autosomal-Recessive Intellectual Disability with Cerebellar Atrophy Syndrome Caused by Mutation of the Manganese and Zinc Transporter Gene SLC39A8. *Am J Hum Genet.* 2015, 97: 886-93

Mössner R, Frambach Y, Wilschmann-Theis D, Löhr S, Jacobi A, Weyergraf A, Müller M, Philipp S, Renner R, Traupe H, Burkhardt H, Kingo K, Köks S, Uebe S, Sticherling M, Sticht H, Oji V, Hüffmeier U. Palmoplantar Pustular Psoriasis Is Associated with Missense Variants in CARD14, but Not with Loss-of-Function Mutations in IL36RN in European Patients. *J Invest Dermatol.* 2015, 135: 2538-41

Kessler K, Wunderlich I, Uebe S, Falk NS, Gießl A, Brandstätter JH, Popp B, Klinger P, Ekici AB, Sticht H, Dörr HG, Reis A, Roepman R, Seemanová E, Thiel CT. DYNC2LI1 mutations broaden the clinical spectrum of dynein-2 defects. *Sci Rep.* 2015, 5: 11649

Kochinke K, Zweier C, Nijhof B, Fenckova M, Cizek P, Honti F, Keerthikumar S, Oortveld MA, Kleefstra T, Kramer JM, Webber C, Huynen MA, Schenck A. Systematic Phenomics Analysis Deconvolutes Genes Mutated in Intellectual Disability into Biologically Coherent Modules. *Am J Hum Genet.* 2016, 98: 149-64

### International Cooperations

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

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

Prof. R. Roepman, University of Nijmegen, Nijmegen: The Netherlands

Prof. Tin Aung, Singapore National Eye Centre, Singapore: Singapore

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

# 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 Chair

Professorships: 2

Personnel: 17

- Scientists: 11 (thereof funded externally: 6)
- Graduate students: 2

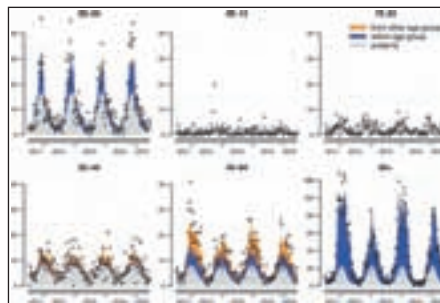
### Research

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

#### Computational Biostatistics

PI: PD Dr. W. Adler, Prof. Dr. O. Gefeller, Dr. B. Hofner, Dr. A. Mayr, Dr. E. Waldmann  
The statistical analysis of high-dimensional data containing large numbers of features has become increasingly important in biomedical practice. Consequently, statistical methods for analyzing data with complex dependency patterns and for separating informative features from non-informative ones are needed. Boosting is a promising statistical method to address these issues. The project focuses on improving and developing boosting methodology for data structures that cannot yet be analyzed with the

help of classical boosting techniques. For example, 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.



Weekly counts of norovirus gastroenteritis in Berlin, 2011-W27 to 2015-W26, stratified by age group  
The dots correspond to numbers reported to the Robert Koch Institute according to §7.1 of the German Infection Protection Act (data source: SurvStat@RKI 2.0). The stacked curves are estimates from a spatio-temporal regression model which incorporates the social contact structure between the age groups and thus decomposes the fitted counts into different transmission routes. (From: Meyer S et al. *Biostatistics*. 2017, 18(2):338-351)

#### Dermatoepidemiology

PI: Prof. Dr. A. Pfahlerberg, 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 (increase, possibly in particular subgroups) and for quality control purposes. Addi-

tionally, 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 2015/16, two surveys ("Erking Sun 2015", "Francis") addressing knowledge on prevention of UV exposure in kindergarten staff and actual protective measures (shading etc.) in the institutions were 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 cohort study in the field of occupational medicine with follow-up of 259 incident cases of psychological stress reactions after accidents in public transports drivers;
- A study in cooperation with the Chair of Psychiatry and Psychotherapy concerning non-pharmacological interventions for dementia and counselling and training of relatives of demented persons;
- 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;
- The ProPricare study with the overall aim to systematically investigate medical overuse in patients undergoing regular thyroid examination, including the identification of events or patient-specific characteristics that trigger this medical overuse.



- A European multicenter study “SCOPE” (“Screening for Chronic Kidney Disease among Older People across Europe”) in cooperation with the Institute for Biomedicine of Aging.

## Teaching

The Chair of Medical Biometry and Epidemiology contributes to curricular teaching in terms of mandatory and optional courses in medicine, molecular medicine and medical process management. Concerning interdisciplinary teaching, the cooperation in the context of “Querschnittsbereich I” with the Chair of Medical Informatics and the Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine is of note.

The Chair supervises Bachelor’s and Master’s theses as well as MD and PhD doctoral theses.

## Selected Publications

Keller AK, Uter W, Pfahlberg AB, Radespiel-Tröger M, Mayer I, Gefeller O: Replacing surrogate measures by direct quantification of ultraviolet radiation exposure in registry-based analyses of seasonality of melanoma diagnoses. *Melanoma Res.* 2015;25(6): 543-9

Uter W, Gefeller O, Giménez-Arnau A, Frosch P, Duus Johansen J, Schuttelaar ML, Rustemeyer T, Larese Filon F, Dugonik A, Bircher A, Wilkinson M. Characteristics of patients patch tested in the European Surveillance System on Contact Allergies (ESSCA) network, 2009-2012. *Contact Dermatitis.* 2015;73(2): 82-90

Mayr A, Hofner B, Schmid M. Boosting the discriminatory power of sparse survival models via optimization of the concordance index and stability selection. *BMC Bioinformatics.* 2016;17: 288

Adler W, Gefeller O, Gul A, Horn FK, Khan Z, Lausen B. Ensemble Pruning for Glaucoma Detection in an Unbalanced Data Set. *Methods Inf Med.* 2016;55(6): 557-563

Gefeller O, Uter W, Pfahlberg AB. Long-term development of parental knowledge about skin cancer risks in Germany: Has it changed for the better? *Prev Med.* 2016;89: 31-6

Hepp T, Schmid M, Gefeller O, Waldmann E, Mayr A. Approaches to Regularized Regression - A Comparison between Gradient Boosting and the Lasso. *Methods Inf Med.* 2016;55(5): 422-430

## International Cooperations

Multicentric:

Prof. C. Lidén, Prof. J.D. Johansen, Prof. C. M. Bonefeld, Dr. Ian R. White, Prof. J.-P. Lepoittevin  
Karolinska Institutet, Copenhagen University, Kings College London, Université de Strasbourg  
Stockholm, Copenhagen, London, Strasbourg  
Sweden, Denmark, UK, France

# Institute of Medical Informatics, Biometry, and Epidemiology

## Chair of Medical Informatics

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### Director

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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 Chair

Professorships: 1

Personnel: 18

- Doctors (of Medicine): 1
- Scientists: 15 (thereof funded externally: 11)
- Graduate students: 3

### Research

Various working groups are concerned with the development and the introduction of electronic medical records, the integration of clinical decision support functions into hospital information systems (HIS), the modelling and optimization of clinical workflows, both data warehouse and data mining applications, the evaluation of the effect of health technology interventions on processes and persons involved in the health system, the use of mobile technologies in medicine and the development of IT infrastructures for research and teaching. Prof. Dr. H.-U. Prokosch is as Chief Information Officer also responsible for the strategic development of information processing at the UK Erlangen.

### Process support through health information systems

One of the major challenges in the design, establishment, and management of HIS is the intersectoral interoperability which is important

to optimize the cooperation of the various health service providers across institutional boundaries in outpatient and inpatient care in order to deliver the best patient care. For an additional reduction of patient risks, we integrate clinical decision support functionalities into HIS. Clinical information flow and communication functionalities should ultimately involve and benefit patients, e.g. by the application of medication plans or by the use of a personal electronic health record. In addition to grant funded projects, the Chair also pursues and supports several innovative pilot projects embedded in the SOARIAN® HIS environment of UK Erlangen (e.g. a complete clinical cancer documentation embedded in a comprehensive clinical data reuse concept). The direct integration of the patient by means of an online-based capturing of follow-up information and the idea of a patient portal which is integrated into HIS and its IHE (Integrating the Healthcare Enterprise)-based integration with a patient's personal electronic health record complete the range of research on this focus.

### 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 were included in the knowledge model. Based on this, a data- and model-driven software prototype for individualized, optimized psychiatric pharmacotherapy was designed, developed, and evaluated. Within the patient data management system of an ICU, a clinical decision support system has been integrated to monitor the exceedance of threshold values or to monitor critical trends of various laboratory values and, as a consequence, to have a direct feedback sent as a text message to the DECT telephone of the clinician on duty. Further use cases comprise the automated patient-individual monitoring of the expiratory tidal volume to avoid lung injury in patients under mechanical ventilation as well as the implementation of cross-patient dashboards and their integration into the existing computer system with a parallel evaluation and optimization of their usability. Against this background, we are concerned with all aspects of the use of software as a medicinal product.

### Evaluation of health information systems

When introducing new information technologies, it is essential to evaluate their effect on user satisfaction, work processes, and process costs to avoid adverse effects of these technologies on medical care. Successful use of IT in medicine may be hindered by negative user attitudes, user-unfriendly interfaces, and insufficient usability in general. In numerous evaluation studies, we have applied methods, such as usability questionnaires, observations, thinking aloud, and cognitive walkthrough, to both optimize and evaluate the acceptance of different kinds of IT artefacts. In the context of the European project "Electronic Health Records for Clinical Research (EHR4CR)", the acceptance and the interface design of a platform for cohort identification have been evaluated internationally and measures for the further development have been derived from this step. Moreover, in the context of different master theses a tool for calculating percentiles and an Arden dashboard have been evaluated for the Department of Pediatric and Adolescent Medicine and the interdisciplinary operative ICU of UK Erlangen, respectively, in terms of their efficacy and efficiency in clinical routine.

### Analysis, assessment, and visualization of medical data

An increasing amount of data is documented electronically in clinical IT systems during routine patient care. To avoid information overload or overlooking of essential facts, appropriate and flexible visualization methods are required. We have been creating a learning health system by reusing such data for research projects. In cooperation with Harvard University Medical Center, the i2b2 (informatics for integrating biology and the bedside) platform has been integrated with UK Erlangen Clinical Data Warehouse and enhanced with semantic ontology annotations as well as timeline-based visualization methods. It has been established as a research integration platform for several projects at UK Erlangen, but also within national collaborations. The project "Klinische Datenintelligenz" (clinical data intelligence) aims at integrating both structured and free-text data as well as images and genomic data for research. Complex algorithms are processed on the basis of Big Data technologies (e.g. Hadoop) and can be analyzed in interactive applications (e.g. tranSMART). Furthermore, we have provided the tranSMART platform for different research groups at our Faculty for the purpose of integrating genomic data

into clinical data. In this context the chair is evaluating both the use and the usability of the platform for its application in the fields of cohort identification and data exploration. In 2016, J. Christoph was awarded the prize for the best master thesis in the field of German medical informatics (“Prototypic integration of high-throughput data with clinical data at the UK Erlangen”).

### 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 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. Moreover, current activities comprise IT infrastructures to support biobanking - especially the national (German Biobank Node) and international (BBMRI Common Service IT / ADOPT) linkage of biobanking. A further focus was layed on the single-source reuse of patient data for clinical and translational research. The Chair is member and active partner in many projects and working groups of the TMF (German technology and methods platform for networked medical research) and leads the GMDS working group “Reusing electronic patient records for clinical research”. We were partner in the EHR4CR project developing adaptable, reusable, and scalable solutions for reusing data from electronic health record systems for clinical research. The solutions were 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. Subsequently, we became involved in projects linked to the European Institute for Innovation through Health Data which had arisen from the afore-said EU project, and evaluated different IT platforms that had originated from this project and aimed at linking pharmaceutical companies and research institutes.

### 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 (CCC) 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. A further aspect of research in this field was the draft and the establishment of a study registry for CCC which provides the basis for all study-related analyses and reports, for the official listing of studies on the CCC homepage and, at the same time, for the study assignment within HIS ‘Soarian Clinicals’ for the patients of UK Erlangen.

### Teaching

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

### Selected Publications

Christoph J, Griebel L, Leb I, Engel I, Köpcke F, Toddenroth D, Prokosch HU, Laufer J, Marquardt K, Sedlmayr M. Secure secondary use of clinical data with cloud-based NLP services: Towards a highly scalable research infrastructure. *Methods Inf Med.* 2015, 54(3): 276-282

Griebel L, Prokosch H, Köpcke F, Toddenroth D, Christoph J, Leb I, Engel I, Sedlmayr M. A scoping review of cloud computing in healthcare. *BMC Med Inform Decis Mak.* 2015, 15: 17

Mate S, Köpcke F, Toddenroth D, Martin M, Prokosch HU, Bürkle T, Ganslandt T. Ontology-based data integration between clinical and research systems. *PLoS One.* 2015, 10(1): e0116656

Kraus S, Drescher C, Sedlmayr M, Castellanos I, Prokosch HU, Toddenroth D. Using Arden syntax for the creation of a multi-patient surveillance dashboard. *Artif Intell Med.* 2015 Oct 9. pii: S0933-3657(15)00126-8

Toddenroth D, Sivagnanasundaram J, Prokosch HU, Ganslandt T. Concept and implementation of a study dashboard module for a continuous monitoring of trial recruitment and documentation. *J Biomed Inform.* 2016, 64: 221-231

Sedlmayr M, Würfl T, Maier C, Häberle L, Fasching P, Prokosch HU, Christoph K. Optimizing R with SparkR on a commodity cluster for biomedical research. *Comput Methods Programs Biomed.* 2016, 137: 321-328

### International Cooperations

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

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

Prof. Dr. K.-P. Adlassnig, Medizinische Universität Wien, Vienna: Austria

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

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

# Institute of Medical Physics

## Chair of Medical Physics

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### Research Focus

- Effects of whole-body electromyostimulation (WB-EMS) and administration of protein on the sarcopenic obesity of the older man
- 3D imaging and image processing for musculoskeletal applications
- High-resolution computed tomography of the breast

### Structure of the Institute

Professorships: 3

Personnel: 29

- Scientists: 9 (there of funded externally: 5)
- Graduate students: 9

### Research

The focus of the research projects and cooperations is the development and the application of imaging procedures in medical diagnosis and image-guided therapy. In the field of computed tomography (CT) where the Institute of Medical Physics (IMP) has gained a worldwide leading position, the foci being on dose reduction and the development of a special CT scanner for early detection of breast cancer. The main topic of the medical imaging processing group are musculoskeletal problems in the area of osteoporosis, inflammatory diseases, osteoarthritis, and sarcopenia. The focus of the osteoporosis research group lies on the prevention and therapy of osteoporosis by non-pharmacological intervention. The achievements and experiences of IMP in the area of imaging procedures and their development for the determination of bone density, bone erosion, muscle tissue and imaging processing emphasizing on quantitative CT ensure the scientific evaluation of the extensive and high frequented studies and substantiate the impressive results.

### Effects of whole-body electromyostimulation (WB-EMS) and administration of protein on the sarcopenic obesity of the older man

PI: Prof. Dr. W. Kemmler

In this clinical study, 100 men aged 70+ and living on their own were included and, by computer generated block randomization, assigned to three different groups: (a) WB-EMS and supplementation of protein (WB-EMS&P), (b) supplementation of protein (P) and (c) inactive control group (CG). All three groups received a vitamin-D-supplementation of 800 IE/d. The supplementation of protein contained of 1.7-1.8 g/kg/d based on a nutrition analysis. The WB-EMS application was carried out 1.5x20 min/week (85 Hz, 350 µs, intermittent 4s – 4s). After 14 weeks at the end of the study, the results showed a significant improvement of morphological and functional parameters of sarcopenia in the WB&EMS group as well as a significant improvement of morphological parameters in the P group. Both verum groups showed a significant reduction of the body fat percentage that, in accordance to the other morphometric parameters of sarcopenia, differed significantly from the results of the CG. This follow-up project of the FORMoSA study, carried out in cooperation with miha-bodytec (Gersthofen), INKO-Sport (Roth) and Physiomed (Laipertsdorf), shows clearly the potential of WB-EMS and/or protein as a treatment option for sarcopenic obesity.



Video-guided Whole-Body EMS training

### 3D imaging and image processing for musculoskeletal applications

PI: Prof. Dr. K. Engelke

Main topic is the development of innovative 3D imaging and analysis techniques to improve the diagnosis and monitoring of osteoporosis, osteoarthritis, rheumatoid arthritis and sarcopenia. The research is based on the analysis toolkit MIAF (Medical Image Analysis Framework) which has been developed at IMP. MIAF has

been used in many international clinical trials for osteoporosis prevention to determine bone mineral density and structure in the spine and hip. In cooperation with the University of Bern, these examinations are extended to also include strength, using "Finite Element Analysis".

In collaboration with the Institute of Radiology, the new approach of prognostic screening of osteoporosis is investigated. This technique is based on the reuse of clinical CT scans primarily intended for other purposes, e.g. for tumor diagnosis. The implementation of prognostic screening in the clinical routine would allow implementing preventive measures at an early stage for patients with existing, but unknown high risk of osteoporotic fracture.

Another project is in vivo imaging of muscle by using both, CT and MRT, to diagnose sarcopenia. This work is associated with the recently established Muscle Research Center Erlangen (MURCE). So far new sequences for the quantification of the fat percentage of muscle tissue were developed within the research collaboration FORMoSA (Research Consortium Muscle Wasting (Sarcopenia) and Osteoporosis – Consequences of impaired tissue regeneration in the elderly) and in cooperation with Siemens Healthcare and the Institute of Radiology. This project was supported by the Bavarian Research Foundation (BFS). The innovative imaging procedures are now also applied in the BMBF supported research collaboration METARTHROS (Metabolic Impact on Joint and Bone Diseases; compare own report) to determine the muscle fat content of the hand in patients with rheumatoid arthritis in order to prove a possible associations between fat tissue and inflammation parameters.

The importance of the subchondral bone for the diagnosis and progression of osteoarthritis of the knee is investigated within the European research collaboration Approach (Applied Public-Private Research enabling OsteoArthritis Clinical Headway) and in a close collaboration with the Radiology Ostéo-Articulaire, Paris. Basis is a multimodal image processing of high-resolution CT and MR patient scans and micro-CT scans of single bones.

### High-resolution computed tomography of the breast

PI: Prof. Dr. W.A. Kalender

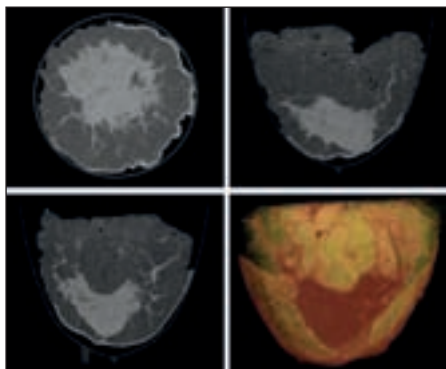
Since 2008, the early detection of breast cancer using CT has been a main topic, based on funding by the European Union (FP 7), the BMBF and the DFG. Very good results have been achieved in different respects. Especially the fea-

sibility of the proposed concepts and the target performance parameters were verified.

On the occasion of the worldwide biggest radiology congress (the RSNA in Chicago), the project was presented at the booth of the BMBF “Germany – Land of Ideas” in 2014 and found great positive feedback. In the following two year, the performance of a breast CT demonstrator was successfully validated by measuring 30 surgical specimens. In addition, novel concepts for image quality assurance and patient-specific dose control were implemented. These results were presented at the annual meeting of the RSNA in 2016. In 2017, clinical testing of two breast CT systems is planned at the university hospitals in Erlangen and Aachen.



Photon-counting breast-CT scanner



3D soft tissue views (breast resectates without compression)

## Teaching

Besides the teaching, Bachelor's and Master's theses as well as doctoral (PhD) theses are supervised.

## Selected Publications

Töpfer D, Gerner B, Finzel S, Kraus S, Museyko O, Schett G, Engelke K. Automated three-dimensional registration of high-resolution peripheral quantitative computed tomography data to quantify size and shape changes of arthritic bone erosions. *Rheumatology (Oxford)*. 2015 Dec;54(12): 2171-80

Rößler AC, Wenkel E, Althoff F, Kalender W. The influence of patient positioning in breast CT on breast tissue coverage and patient comfort. *RöFo* 2015; 187(2): 115-122

Kalender WA, Kolditz D, Steiding C, Ruth V, Lück F, Rößler AC, Wenkel E. Technical feasibility proof for high-resolution low-dose photon-counting CT of the breast. *Eur Radiol* 2016; 27(3), 1081-1086

Museyko O, Bousson V, Adams J, Laredo JD, Engelke K. QCT of the proximal femur—which parameters should be measured to discriminate hip fracture? *Osteoporos Int*. 2016, 27(3):1137-1147

Kemmler W, Teschler M, Weissenfels A, Bebenek M, von Stengel S, Kohl M, Freiburger E, Goisser S, Jakob F, Bollheimer C, Sieber C, Engelke K. Ganzkörper-Elektromyostimulation und Sarcopenic Obesity. Ergebnisse der randomisierten kontrollierten FORMOsA-Sarcopenic Obesity Study. *Osteologie* 2016; 25(3): 204-211

Kemmler W, Engelke K, von Stengel S. Long-Term Exercise and Bone Mineral Density Changes in Postmenopausal Women—Are There Periods of Reduced Effectiveness? *J Bone Miner Res*. 2016, 31(1):215-22

## International Cooperations

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

Prof. S. Napel, Department of Radiology, University Stanford - Medicine, Stanford: USA

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

Prof. V. Bousson, Radiology Ostéo-Articulaire, Hôpital Lariboisière, Université Paris VII Denis Diderot, Paris: France

Prof. P. Zysset, Institute for Surgical Technology and Biomechanics, University of Bern, Bern: Switzerland

Prof. J. Mayhew, Trueman State University Kirksville Missouri, Kirksville: USA



# Institute of Neuropathology

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### Research Focus

- Focal human epilepsies
- Molecular myopathology
- Neuro-oncology

### Structure of the Institute

Professorships: 2

Personnel: 18

- Doctors (of Medicine): 2
- Scientists: 6 (thereof funded externally: 5)
- Graduate students: 2

### Clinical focus areas

- Since 2006 neuropathological reference center for epilepsy surgery and host of the European Epilepsy Brain Bank
- Management of the German registry for pituitary adenoma (from the German Society of Endocrinology)
- Member of the panel of the German reference center for brain tumors

### Research

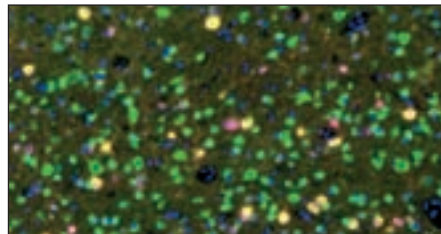
As a comprehensive and visible bridge between clinical research and neurosciences, the Institute of Neuropathology carries out research on diseases of the central nervous system and of skeletal muscles. We cover the complete field of clinical diagnosis including molecular-diagnostic procedures and offer an international expertise in the fields of epilepsy, tumors of the sella region, and myopathologies. The DFG research group FOR 1228 (compare own report) is an interdisciplinary research team addressing basic disease mechanisms in protein aggregation myopathies using various transgenic animal models.

### Focal human epilepsies

PI: Prof. Dr. I. Blümcke

This research project is focused on drug-resistant focal epilepsies in humans to decipher mo-

lecular pathomechanisms and clinically define 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 with 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). Extensive collaboration with our clinical and neuropathology colleagues from Germany and many other European countries were helpful to establish the European Epilepsy Brain Bank, a reference and consultation center for neurosurgical epilepsy tissue specimen. We support the EU-funded prospective and randomized clinical trial EDIBLE to evaluate the effect of a ketogenic diet as disease modifying therapy in children with difficult-to-treat focal epilepsies. We study the epigenetic machinery in relation to epileptic neuronal activity using human surgical specimens and an experimental cell culture model, i.e. histone code modifications, DNA methylation, or miRNA.  
Funding: EU



Whole slide imaging of 4-triple immunofluorescence from cerebral cortex of an epileptic baboon (NIH-funded project with Dr. C. Szabo, University San Antonio, Texas, USA)

### Molecular myopathology

PI: Prof. Dr. R. Schröder

The central research topic of this group is the pathogenesis of myofibrillar myopathies which are morphologically characterized by the presence of pathological protein aggregation in cross-striated muscle cells. 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 and cell 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 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.  
Funding: DFG (FOR 1228, compare own report), German Society for Muscular Dystrophy

### Neuro-oncology

PI: Prof. Dr. R. Buslei

The field of neuro-oncology plays an important role within the clinical-neuropathological diagnostics. Due to the longstanding focus of the Department of Neurosurgery on the treatment of tumors of the sellar region (e.g. pituitary adenomas, craniopharyngiomas and Rathke's cleft cysts), 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.

In its research of craniopharyngiomas, our group identified that the adamantinomatous (ACP) and papillary (PCP) subtype could be clearly distinguished by their mutational, transcriptional and epigenetic profiles. This may also be reflected in a potential tumor cell population which is considered to be the driving force behind the infiltrating growth of ACP tumor cells into the brain. They simultaneously show a diminished expression of the cell adhesion molecule EpCAM and an activation of the EGFR. The latter can be targeted by inhibitors displaying a promising therapeutic approach to overcome radioresistance in ACP identified in vitro. To clarify the underlying mechanisms in its detail, an in vivo setting is indispensable. Therefore, the intracranial xenotransplant animal model for human craniopharyngioma was used to establish an irradiation protocol closely resembling the clinical situation. Not only does this allow for further validation of combined radiochemotherapy, the xenotransplant model also enables the investigation of the underlying cause leading to tumor recurrence in humans even after radiotherapy.

Funding: DFG, Dr. Robert-Pfleger Foundation, International Foundation Neurobionik

### Teaching

The Institute of Neuropathology offers lectures and teaching courses in histopathology for students in medicine, dental medicine and molecular medicine. Comprehensive lectures (clinico-

pathology conferences) are organized together with the Departments of Neurology and Neurosurgery. Our medical students awarded Dr. R. Coras as best teacher in clinical medicine in winter term 2015/2016.

We supervise Bachelor's and Master's theses as well as doctoral theses of the Faculties of Medicine and Sciences, respectively.

### **Selected Publications**

Chevessier F, Schuld J, Orfanos Z, Plank AC, Wolf L, Maerkens A, Unger A, Schlötzer-Schrehardt U, Kley RA, Von Hörsten S, Marcus K, Linke WA, Vorgerd M, van der Ven PF, Fürst DO, Schröder R. Myofibrillar instability exacerbated by acute exercise in filaminopathy. *Hum Mol Genet* 2015; 24:7207-20

Clemen CS et al. The toxic effect of R350P mutant desmin in striated muscle of man and mouse. *Acta Neuropathol* 2015; 129:297-315

Coras R, Korn K, Bien CG, Kalbhenn T, Rössler K, Kobow K, Giedl J, Fleckenstein B, Blumcke I. No evidence for human papillomavirus infection in focal cortical dysplasia IIb. *Ann Neurol*. 2015 Feb;77(2):312-9

Marschallinger J, Schäffner I, Klein B, Gelfert R, Rivera FJ, Illes S, Grassner L, Janssen M, Rotheneichner P, Schmuckermair C et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. *Nat Commun*. 2015 Oct 27;6:8466

Winter L, Wittig I, Peeva V, Eggers B, Heidler J, Chevessier F, Kley RA, Barkovits K, Strecker V, Berwanger C, Herrmann H, Marcus K, Kornblum C, Kunz WS, Schröder R, Clemen CS. Mutant desmin substantially perturbs mitochondrial morphology, function and maintenance in skeletal muscle tissue. *Acta Neuropathol* 2016; 132:453-73

Blümcke I, Aronica E, Becker A, Capper D, Coras R, Honavar M, Jacques TS, Kobow K, Miyata H, Mühlebner A, Pimentel J, Söylemezoğlu F, Thom M. Low-grade epilepsy-associated neuroepithelial tumours - the 2016 WHO classification. *Nat Rev Neurol*. 2016 Dec;12(12):732-740

### **International Cooperations**

Prof. D. Zhou, Department of Neurology, West China Medical School, Chengdu: China

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

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

Dr. R. Spreafico, Neurological Institute „C. Besta“, Milano: Italy

Dr. C. Szabo, Department of Neurology, University of San Antonio, San Antonio: USA

# Institute of Pathology

## Chair of General Pathology and Pathological Anatomy

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### Director

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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 Chair

Professorships: 3

Personnel: 45

- Doctors (of Medicine): 14
- Scientists: 4 (thereof funded externally: 1)

### Clinical focus areas

Histopathology with specific expertise in

- Breast pathology
- Gynecological pathology
- Urogenital pathology
- Head and neck pathology
- Soft tissue pathology
- Molecular pathology

### Research

The main research focus of the Institute of Pathology is the identification of molecular alterations in different malignant tumors. In different research groups gastrointestinal tumors, breast cancer, gynecological tumors, tumors of the head and neck region, urological tumors and sarcomas are investigated for both, diagnostic markers and new therapeutic targets. The aim is the integration of the identified molecular alterations into diagnostic molecular pathology. An additional focus is the characterization of im-

mune and inflammatory cell infiltration in tumors and the importance of this immune response for tumor development and response prediction to immunotherapy.

### Diagnostic molecular pathology

PI: Prof. Dr. F. Haller, 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 five years and 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 is the massive parallel sequencing of multi-gene panels in lung cancer and cancer of the urogenital tract and head and neck cancer to correlate the presence of mutations among distinct genetic pathways with specific histomorphological subtypes, clinical behavior, and therapy response. The functional characterization of novel genetic or epigenetic aberrations in cell culture systems is another aim to develop the basis for future therapeutical options. In the last year, the interdisciplinary molecular tumor board has been successfully installed which aims to detect genetic aberrations in patients with advanced cancer that can be used as therapeutic targets.

### Experimental tumor pathology – gastrointestinal tumors

PI: Prof. Dr. R. Schneider-Stock, Dr. K. Erlenbach-Wünsch, Dr. M. Eckstein, Dr. C. Geppert, Prof. Dr. A. Hartmann, Prof. Dr. A. Agaimy

The main focus of our group is the molecular and biochemical characterization of genetic and epigenetic alterations in tumors and preneoplasias of the gastrointestinal tract. Research projects on initiation and progression of colorectal tumors and their molecular subtypes are in focus. We aim at identifying new valid biomarkers for tumor transformation in colorectal carcinogenesis that could be of potential therapeutic interest. We are interested in tumor invasion front and thus in regulation of EMT and stemness to drive invasion and metastasis. A broad spectrum of 2D and 3D models, co-culture mod-

els, and CRISPR-ko cell lines is established. We are especially interested in three proteins: DAP-kinase, ATF2, and EZH2, that have dual function in tumors and can act as tumor suppressor or oncogene. To investigate these genes, novel experimental conditional ko mice were designed. Since many years we have been studying successfully the anti-cancer effects of plant-derived drugs for colorectal tumor cells.



*Tumor development in the experimental AOM-DSS-model of colorectal carcinogenesis*  
*Mini-endoscopy of DAPK1 IEC mouse where DAPK is deleted only in the intestinal epithelium (representative endoscopic image of the colon taken at day 51).*

### Breast and gynecological tumors

PI: Prof. Dr. A. Hartmann, Prof. Dr. A. Agaimy, PD Dr. D. Wachter, Dr. J. Strehl, Dr. K. Brunner, Dr. R. Erber

This group focuses in cooperation with the Department of Obstetrics and Gynecology 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

PI: Prof. Dr. A. Agaimy, Prof. Dr. A. Hartmann, Prof. Dr. F. Haller, Dr. K. Brunner, Prof. Dr. R. Rieker

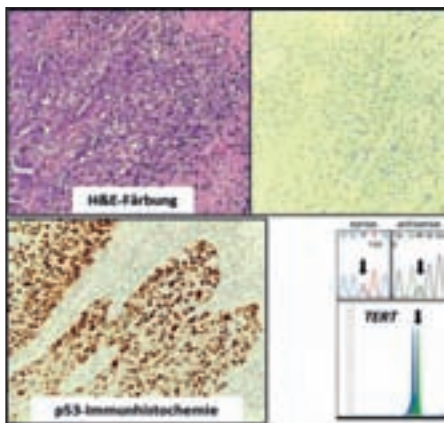
We investigate the molecular changes in tumors of the head and neck region in cooperation with the Departments of Otorhinolaryngology – Head and Neck Surgery and of Oral and Cranio-Maxillofacial Surgery. This research project has two objectives: One is to compile a molecular-pathological and histopathological 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.

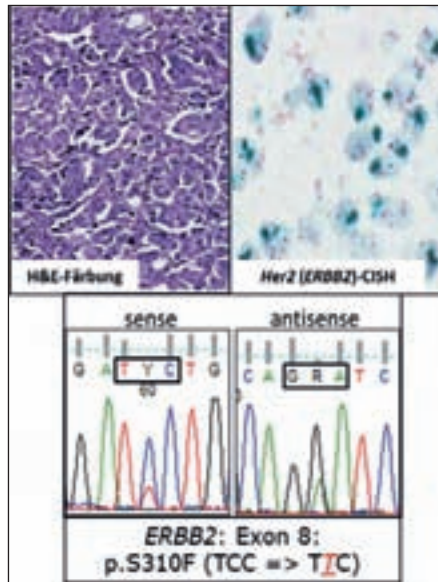
### Clinical and predictive molecular pathology of urogenital carcinomas

PI: Prof. Dr. A. Hartmann, PD Dr. R. Stöhr, Dr. C. Stöhr, Dr. J. Giedl, Dr. S. Bertz, Dr. M. Eckstein, I. Polifka

The group investigates the basic molecular principles of the development, progression and subtyping of urothelial carcinoma of the urinary bladder, prostate cancer, squamous cell carcinoma of the penis and renal cell carcinoma. There is a close cooperation with the Department of Urology, the Institute of Clinical and Molecular Virology and with numerous national and international cooperation partners. The objective is the identification of genomic and epigenetic changes in urothelial carcinomas of the urinary bladder and kidney tumors to identify new markers for early diagnosis and new therapeutic target molecules. In addition, gene expression analyses are used to establish a risk stratification of the tumors that should support the finding of the ideal treatment option for a patient in daily clinical routine. Another focus of the groups' work is the molecular investigation of patients with early-onset disease. These analyses should clarify if tumors in young patients have distinct molecular developmental pathways as compared with tumors from aged patients. Moreover, molecular investigation of tumors from patients with early-onset disease could allow the identification of predisposing factors and disease-initiating events helping to define individuals with high disease risk.



*Squamous cell carcinoma of the penis (usual type)  
TERT promoter mutations are significantly associated with HPV negativity and no expression of p16. Therefore, TERT promoter mutations might act as a new molecular marker for biologically aggressive penis carcinomas.*



*Micropapillary bladder cancer is an aggressive subtype of urothelial carcinoma associated with a bad clinical course  
Alterations in the Her2/ERBB2 gene (amplification, mutation) were found in >35% of the analyzed cases and could act as a new therapeutic target in these tumors.*

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

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

### Selected Publications

Benderska N, Dittrich AL, Knaup S, Rau TT, Neufert C, Wach S, Fahlbusch FB, Rauh M, Wirtz RM, Agaimy A, Srinivasan S, Mahadevan V, Rümmele P, Rapti E, Gazouli M, Hartmann A, Schneider-Stock R. miRNA-26b overexpression in ulcerative colitis-associated carcinogenesis. *Inflamm Bowel Dis*. 2015 Sep;21(9):2039-51

Ivanovska J, Zlobec I, Forster S, Karamitopoulou E, Dawson H, Koelzer VH, Agaimy A, Garreis F, Söder S, Laqua W, Lugli A, Hartmann A, Rau TT, Schneider-Stock R. DAPK loss in colon cancer tumour buds: implications for migration capacity of disseminating tumour cells. *Oncotarget*. 2015 Nov 3;6(34):36774-88

Ivanovska J, Zehnder T, Lennert P, Sarker B, Boccaccini AR, Hartmann A, Schneider-Stock R, Detsch R. Biofabrication of 3D alginate-based hydrogel for cancer research: Comparison of cell spreading, viability, and adhesion characteristics of colorectal HCT116 tumor cells. *Tissue Eng Part C Methods*. 2016 Jul;22(7):708-15

Hedegaard J et al. Comprehensive transcriptional analysis of early stage urothelial carcinoma. *Cancer Cell*. 2016 Jul 11;30(1):27-42

Giedl J, Rogler A, Wild A, Riener MO, Filbeck T, Burger M, Rümmele P, Hurst C, Knowles M, Hartmann A, Zinnall U, Stoehr R. TERT core promoter mutations in early-onset bladder cancer. *J Cancer*. 2016 May 7;7(8):915-20

Haller F, Knopf J, Ackermann A, Bieg M, Kleinheinz K, Schlesner M, Moskalev EA, Will R, Satir AA, Abdelmagid IE, Giedl J, Carbon R, Rompel O, Hartmann A, Wiemann S, Metzler M, Agaimy A. Paediatric and adult soft tissue sarcomas with NTRK1 gene fusions: a subset of spindle cell sarcomas unified by a prominent myopericytic/haemangiopericytic pattern. *J Pathol*. 2016 Apr;238(5):700-10

### International Cooperations

Prof. H. Gali-Muhtasib, Department of Biology, American University of Beirut, Beirut: Lebanon

Prof. P. Aman, Department of Pathology and Genetics, University of Gothenburg, Gothenburg: Sweden

Prof. M. Galvonas Jasiulionis, Ontogeny and Epigenetic Laboratory, Universidade Federal de São Paulo (UNIFESP), Sao Paulo: Brazil

Prof. T. Dale, Cardiff Cancer Stem Cell Research Institute, Cardiff University, Cardiff: UK

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



# Institute of Pathology

## Division of Nephropathology

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### Head of Division

Prof. Dr. med. Kerstin Amann

### Contact

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### Research Focus

- Afferent renal innervation
- Cell cycle control in podocytes as a therapeutic target in renal disease
- Pathomechanisms and modulation of impaired angiogenesis and angioadaptation in chronic renal failure
- The role of DPP4 in renal diseases and cardiovascular damage
- The role of PAR-2 in cardiovascular injury
- Mechanisms of cardiac injury and regeneration
- Role of the receptor GPR126 in heart development
- Cardiac tissue engineering
- Terminal differentiation of heart muscle cells

### Structure of the Division

Professorships: 2  
Personnel: 30

- Doctors (of Medicine): 6
- Scientists: 9 (thereof funded externally: 6)
- Graduate students: 17

### Clinical focus areas

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

### Research

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

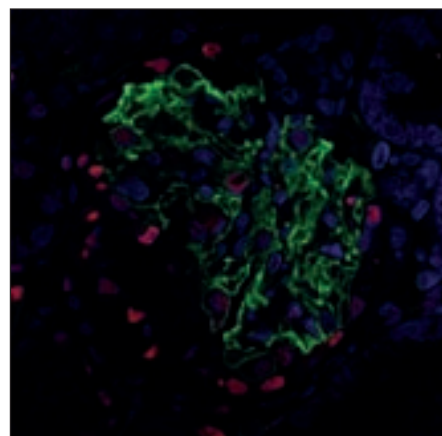
### Afferent renal innervation

PI: Prof. Dr. K. Amann  
In cooperation with Prof. Dr. K. Veelken (Depart-

ment of Medicine 4) we investigate the role of afferent renal nerves and its control of the sympathetic nerve system. Here we look for the effects of afferent renal innervation on pathological changes in the heart using animal models for chronic kidney disease and hypertension. The plasticity of afferent renal innervation will be analyzed by its potential to regenerate. Furthermore, the relevance of afferent renal nerve tracts for heart pathophysiology and cardiac afferent innervation for pathophysiologic renal changes will be analyzed to get a comprehensive understanding of neurogenic aspects of the cardiorenal syndrome.  
Funding: DFG

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

PI: PD Dr. C. Daniel, Prof. Dr. K. Amann  
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 (EFI): CYDER



*Diseased glomerulus showing some proliferating (red fluorescence) podocytes (green fluorescence)*

### Pathomechanisms and modulation of impaired angiogenesis and angio-adaption in chronic renal failure

PI: Prof. Dr. K. Amann  
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 characteristic 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: DFG

### The role of DPP4 in renal diseases and cardiovascular damage

PI: PD Dr. C. Daniel  
In cooperation with Prof. Dr. S. von Hörsten (Division of Experimental Therapeutics), we examine whether the lack or inhibition of dipeptidyl-peptidase IV (DPP4) reduces development of CKD and subsequent cardiovascular damage. In a rat model for CKD and anti-GBM-nephritis, we investigate consequences of DPP4 deficiency on disease progression and vascular as well as cardiac damage.  
Funding: ELAN-Fonds; Boehringer Ingelheim GmbH

### The role of PAR-2 in cardiovascular injury

PI: PD Dr. C. Daniel  
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: Johannes and Frieda Marohn-Foundation

### Mechanism of cardiac injury and regeneration

PI: Prof. Dr. F.B. Engel  
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 tries to identify the mechanisms that regulate cardiomyocyte proliferation 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**

PI: Prof. Dr. F.B. Engel

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**

PI: Prof. Dr. F.B. Engel

Materials for the generation of artificial heart tissue are tested for tissue replacement therapy. In close collaboration with Prof. Dr. A.R. Boccaccini (Department of Biomaterials, Faculty of Engineering), 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. In addition, we began to study recombinantly produced silk as a material for cardiac tissue engineering in close collaboration with Prof. T. Scheibel (Bayreuth Materialzentrum (BayMAT), University of Bayreuth).

Funding: ELAN-Fonds, DFG

### **Terminal differentiation of heart muscle cells**

PI: Prof. Dr. F.B. Engel

Heart muscle cells of mammals differentiate and become post-mitotic. Therefore, they cannot regenerate their heart by heart muscle cell prolif-

eration as observed in zebrafish. The 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: EFI: CYDER

### **Teaching**

The Division of Nephropathology participates in the teaching of the Institute of Pathology and acts as "Advanced Training Center for Nephropathology" of the European Society of Pathology.

Bachelor's and Master's theses as well as MD and PhD theses are supervised. A seminar for doctoral candidates will train the students in skills essential for their preparation.

### **Selected Publications**

Zebrowski DC, Vergarajaregui S, Wu CC, Piatkowski T, Becker R, Leone M, Hirth S, Ricciardi F, Falk N, Giessl A, Just S, Braun T, Weidinger G, Engel FB. Developmental alterations in centrosome integrity contribute to the post-mitotic state of mammalian cardiomyocytes. *Elife*. 2015 Aug 6;4

Soonpaa MH, Zebrowski DC, Platt C, Rosenzweig A, Engel FB, Field LJ. Cardiomyocyte cell cycle activity during preadolescence. *Cell* 2015, 163(4):781-2

Floege J, Amann K. Primary glomerulonephritides. *Lancet* 2016, 387: 2036-2048

Hagen M, Pfister E, Kosel A, Shankland S, Pippin J, Amann K, Daniel C. Cell cycle re-entry sensitizes podocytes to injury induced death. *Cell cycle* 2016, 15: 1929-1937

Olmes G, Buttner-Herold M, Ferrazzi F, Distel L, Amann K, Daniel C. CD163+ M2c-like macrophages predominate in renal biopsies from patients with lupus nephritis. *Arthritis Res Ther*. 2016, 18: 90

Roeder SS, Stefanska A, Eng DG, Kaverina N, Sunseri MW, McNicholas BA, Rabinovitch P, Engel FB, Daniel C, Amann K, Lichtnekert J, Pippin JW, Shankland SJ. Changes in glomerular parietal epithelial cells in mouse kidneys with advanced age. *Am J Physiol Renal Physiol*. 2015, 309: F164-178

### **International Cooperations**

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

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

Prof. L. Field, Herman B Wells Center for Pediatric Research, Indiana University, Indianapolis: USA

Prof. D. Andersen, Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense C: Denmark

# Institute of the History of Medicine and Medical Ethics

## Chair of the History of Medicine

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### Director

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### Contact

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### Research Focus

- 200 Years of UK Erlangen, 1815–2015
- 275 Years Faculty of Medicine at FAU
- Galen – Compendium and catalogue of Galenic writings
- Receptions of ancient psychopathology
- „Health as a behavioral code“. Systematic aspects of public health in pre-modern Europe
- 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 nazism
- Polish-German cooperation in the history of medicine
- History of hospitals
- Medical history in objects – Collecting and displaying medical past

### Structure of the Chair

Professorships: 1

Personnel: 7

- Doctors (of Medicine): 1
- Scientists: 6 (thereof funded externally: 3)
- Graduate students: 2

### Special structural feature

The Chair of the History of Medicine and the Professorship for Medical Ethics constitute the Institute of the History of Medicine and Medical Ethics.

### Research

Concerning modern medical history, research focuses on the history of medicine at FAU and the surrounding area. This includes medicine in National Socialism which is studied both from a prosopographical and thematic perspective.

Other research is concerned with ancient medicine, medicine in pre-modern times and medical historian museology.

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

PI: Prof. Dr. K.-H. Leven, A. Plöger

Duration: 2013–2015

Funding: UK Erlangen

A historiographical monograph dedicated to the 200 years of its history will be published in autumn 2015 to mark the bicentenary of UK Erlangen. From its modest beginnings to the modern internationally noted institution the book chronologizes the development of the branches, important individuals and innovations, and the edifying sprawl of UK Erlangen. It focuses on the 20<sup>th</sup> century, including UK Erlangen during the NS regime.



### 275 Years Faculty of Medicine at FAU

PI: Prof. Dr. K.-H. Leven, Dr. S. Ude-Koeller, P. Rauh, A. Thum, Prof. Dr. R. Wittern-Sterzel

Duration: 2016–2018

Funding: Faculty of Medicine

To mark the upcoming 275<sup>th</sup> birthday of FAU, a historiographical monograph will outline the chronological and structural development of the Faculty of Medicine outlining its protagonists and prevalent interests before their scientific, cultural, social and politic backgrounds. A special focus rests on the 20<sup>th</sup> and beginning 21<sup>st</sup> centuries.

### Galen – Compendium and catalogue of Galenic writings

PI: Prof. Dr. K.-H. Leven

The Greek physician Galenus of Pergamum (129 – approx. 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 contexts. Furthermore an annotated catalogue of all remaining Galenic writings is devised.

### Receptions of ancient psychopathology

PI: 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 19<sup>th</sup> 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 Paulus Nikaios (approximately 7<sup>th</sup>/9<sup>th</sup> 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 19<sup>th</sup> century medicine.

### „Health as a behavioral Code“.

### Systematic aspects of public health in pre-modern Europe

PI: PD Dr. F. Dross

At the beginning of modern Europe, the critical junctures are studied which connect individual and public health care. Back then, health was first configured as both public asset and trans-individual value, arbitrated between medical expertise, professional practice by diverse health care professions, municipal administration and personal plight.

### Medical crime and the social practice of terror – SS-physicians in concentration camps, 1934–1945

PI: Prof. Dr. K.-H. Leven, P. Rauh

Funding: Johannes and Frieda Marohn-Foundation, DFG

This project surveys the biographical development of SS-physicians active in German concentration camps 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 concentration camps 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, a 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”**

PI: Prof. Dr. K.-H. Leven, Dr. S. Ude-Koeller

Funding: Research Foundation of Medicine at UK Erlangen, Staedtler-Stiftung

The so-called “T 4-Aktion” (forced euthanasia) and systematic starvation to death were implemented in Erlangen Heil- und Pflegeanstalt (Erlangen mental hospital) during the Nazi 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 Nazism**

PI: PD Dr. F. Dross, PD Dr. W. Frobenius, Dr. U. Thoms

Under nazism, 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.

### **Polish-German cooperation in the history of medicine**

PI: 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**

PI: PD Dr. F. 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 framework 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 past**

PI: PD Dr. F. Dross

Funding: 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 accessible this important source for medical historiography.

### **Teaching**

Curricular teaching by the Chair for History of Medicine includes both compulsory and elective courses for students of human, dental and molecular medicine. Each semester and in collaboration with the Chair of Anatomy I, the interprofessional seminar „Death and Dying in Cultural Perspective“ is held. Furthermore, the wide range of teaching includes excursion seminars preparing field trips to the Flossenbürg KZ memorial site or the Deutsches Medizinhistorisches Museum Ingolstadt. Regularly, seminars are held in conjunction with colleagues from the Faculty of Humanities, Social Sciences, and Theology. We supervise medical doctorate theses.

### **Selected Publications**

Metzger N. Kynanthropy. Canine Madness in Byzantine Late Antiquity. In: History of Psychiatry 2015, 26: 318–331

Rauh P. Der Krieg gegen die „nutzlosen Esser“. Psychiatriepatienten als Opfer der NS-„Euthanasie“. In: Dieckmann C, Quinkert B (Hg.). Kriegführung und Hunger. Zum Verhältnis von militärischen, wirtschaftlichen und politischen Interessen, Wallstein: Göttingen 2015 (= Beiträge zur Geschichte des Nationalsozialismus, Band 30): 33–58

Dross F, Frobenius W, Thum A, Bastian A. Ausführer und Vollstrecker des Gesetzeswillens – die Deutsche Gesellschaft für Gynäkologie im Nationalsozialismus. Stuttgart: Thieme, 2016

Brinkschulte E, Dross F, Magowska A, Moskalewicz M, Teichfischer P (Hg.). Medizin und Sprache – die Sprache der Medizin = Medycyna i język – język medycyny, Frankfurt am Main 2016

Leven KH, Plöger A (Hg.). 200 Jahre Universitätsklinikum Erlangen, 1815–2015. Böhlau: Köln, Weimar, Wien 2016

Ude-Koeller S. Ein Krankenhaus braucht Pflege - zur Geschichte der Krankenpflege in Erlangen. In: Leven KH, Plöger A (Hg.). 200 Jahre Universitätsklinikum Erlangen, 1815–2015. Köln, Weimar, Wien 2016: 409–437

### **International Cooperations**

Dr. M. Moskalewicz, Poznan University of Medical Sciences, Poznań: Poland

Prof. Dr. V. Nutton, Centre for the History of Medicine, The University College, London: UK

Prof. Dr. P. E. Porman, Classics and Graeco-Arabic-Studies, The University of Manchester, Manchester: UK

Prof. Dr. E. Samama, Institut d'études culturelles et internationales (IECI), Université de Versailles, St-Quentin-en-Yvelines, Versailles: France

Dr. P. Singer, Department of History, Classics and Archaeology, University of London, London: UK

# Institute of the History of Medicine and Medical Ethics

## Professorship for Medical Ethics

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### Head of Division

Prof. Dr. med. Andreas Frewer, M.A.

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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 Division

Professorships: 1

Personnel: 14

- Doctors (of Medicine): 3
- Scientists: 7 (thereof funded externally: 4)
- Graduate students: 18

### Special structural feature

The Professorship for Medical Ethics is responsible for moderation and management of the Clinical Ethics Committee at UK Erlangen.

The Chair of the History of Medicine and the Professorship for Medical Ethics constitute the Institute of the History of Medicine and Medical Ethics.

### Research

The main areas of research are clinical ethics and ethics consultation, medicine and human rights, and global health ethics and philosophy of medicine. The field of clinical ethics deals with foundational ethical questions concerning the adequate care for patients, motivation of the acts of physicians during the daily routine, and conflict situations in hospital and other medical facilities. Central questions 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, dementia, terminal care, euthanasia etc.). Some important means of clinical ethics are the analysis of arguments of applied medical ethics and bioethics, advice via ethics

committees, and empirical research. The Professorship is partner for the GK "OptiDem" (on Dementia Care), runs the "Forum Medicine and Human Rights" and edits ten book series.

### Clinical Ethics and Ethics Consultation

PI: Prof. Dr. A. Frewer, PD Dr. L. Bergemann, Dr. C. Hack, Dr. M. Kaschube, Dr. Dr. D. Preuß  
A main field of expertise of the Professorship for Medical Ethics is research concerning clinical ethics consultation whereby a close cooperation with the Clinical Ethics Committee is given. Theoretical groundwork and documentation of ethics consultation and the evaluation of ethical consultation belong to this field of inquiry. Files of patient's advocates are being dealt with in the project "Clinical Ethics from the Patient's Perspective". Further fields of research, particularly using methods of empirical ethics, are end of life conflicts, e.g. projects on ethical consultation, cultures of dying, and advance directives. As part of this field of research, an annual "Ethics Day" and an intensive course "Clinical Ethics" (BMBF) were organized, the "Yearbook Ethics in Clinics" and the book series "Clinical Ethics" are being edited.

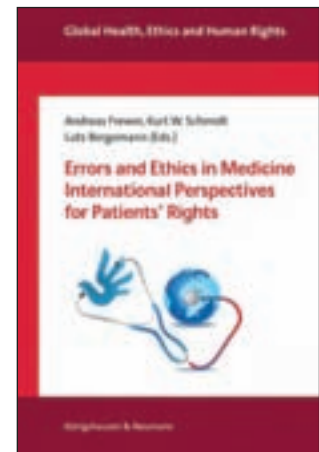


### Medicine and Human Rights

PI: Prof. Dr. A. Frewer, Dr. M. Mylius, W. Bornschlegel, Dr. M. Schmidhuber

This field of research bears on problems of determining the place of human dignity and human rights in the area of medical and bioethical controversy. The possibilities and limits of a rights-based medical ethics and bioethics are considered from a theoretical perspective and several dimensions of the concepts of human dignity and human rights are studied in this context. In a practical vein, this area of research involves questions of medical investigation and the documentation of human rights violations, application of the Istanbul Protocol of the United Nations to document torture, but also the participation of physicians in human rights violations.

Not least of all, it inquires into the therapy and "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 three academic book series are being edited.



### Human Rights in Healthcare (EFI Project)

PI: Prof. Dr. A. Frewer, PD Dr. L. Bergemann, Dr. M. Schmidhuber



The Emerging Fields Project "Human Rights in Healthcare" (compare own report) 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 deci-



sions 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

PI: Prof. Dr. A. Frewer, Dr. A. Reis, Dr. M. Schmidhuber

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, two academic book series are being edited.



### Teaching

The Professorship for Medical Ethics contributes with obligatory and facultative subjects to the education of the students. Special units are offered within the GK "OptiDem" (on Dementia Care) and the interdisciplinary seminars "Q2" and "Q13" together with the Institute for Biomedicine of Aging. Particularly mentioned should be seminars on "Ethical Communicative Competencies" (with role plays for students and simulated patients, some inter-professional). This broad offer on the complex ethical ques-

tions (modules: Breaking Bad News (BBN), Speaking about Death and Dying (SST), Intercultural Kommunikation (IKK), Acting at Borders – Coping with dementia (ÄHG), Communicative Competencies for Errors in Medicine (KKF)) is unique at medical faculties in Germany. Bachelor's and Master's theses and medical or philosophical dissertations are supervised.

### Selected Publications

Mylius M, Frewer A. Access to healthcare for undocumented migrants with communicable diseases in Germany. A quantitative study. *European Journal of Public Health* 2015, 25 (4): 582-586

Schmidhuber M, Bergemann L, Frewer A. Public Health and Clinical Ethics for Patients with Dementia. Synopsis of International Perspectives. In: *Jahrbuch Ethik in der Klinik (JEK)*, 2015, 8: 269-278

Frewer A, Bergemann L, Schmidhuber M (Hrsg.). Demenz und Ethik in der Medizin. *Jahrbuch Ethik in der Klinik*, 2015, 8 Würzburg

Bergemann L, Reis A, Frewer A (Hrsg.). Global Ethics and Universal Health Coverage. *Human Rights in Practice. Global Health, Ethics and Human Rights (GEH)* 2. Würzburg, 2016

Frewer A, Bielefeldt H (Hrsg.). Das Menschenrecht auf Gesundheit. Normative Grundlagen und aktuelle Diskurse. Bielefeld, 2016

Frewer A, Schmidt KW, Bergemann L (Hrsg.). Errors and Ethics in Medicine. *International Perspectives for Patients' Rights. Global Health, Ethics and Human Rights (GEH)* 1. Würzburg, 2016

### International Cooperations

Prof. Dr. J. D. Moreno, Department of Medical Ethics and Health Policy, University of Pennsylvania: USA

Dr. A. Reis, M.Sc., Department of Ethics, World Health Organization, Genf: Switzerland

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





# Nikolaus-Fiebiger-Center of Molecular Medicine

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

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### Director

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### Research Focus

- Cellular plasticity as driving force of metastasis
- EMT-activators in cancer-associated fibroblasts (CAF) and macrophages (CAM)
- Nuclear co-factors of the tumorigenic EMT-activator ZEB1
- Role of the EMT-activator ZEB1 in pancreas development und homeostasis
- Role of the EMT-activator ZEB1 in skeletal development and osteosarcoma
- Dual pathways to endochondral osteoblasts: A novel chondrocyte derived osteoprogenitor cell identified in hypertrophic cartilage

### Structure of the Chair

Professorships: 1

Personnel: 14

- Doctors (of Medicine): 1
- Scientists: 5 (thereof funded externally: 2)
- Graduate students: 5

### Special structural features

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

### Research

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

### Cellular plasticity as driving force of metastasis

PI: Dr. M. Stemmler, Dr. S. Brabletz, Prof. Dr. T. Brabletz

We have shown that the ability of cancer cells to adapt to changing conditions und demands

is a major determinant of malignant progression towards a therapy-resistant, metastatic disease. This ability is termed aberrant cellular plasticity. The molecular basis in many cases is a molecular motor which we identified, i.e. the ZEB1/miR-200 feedback loop. Thereby the transient expression of ZEB1 in cancer cells activates stemness properties and a partial epithelial-mesenchymal transition (EMT) which stimulates invasion, therapy resistance dissemination and finally metastasis in solid cancer types. The central role of ZEB1 in tumorigenicity, plasticity and metastasis was proven by us by a conditional knockout of ZEB1 in a genetic mouse model of pancreatic cancer.

### EMT-activators in cancer-associated fibroblasts (CAF) and macrophages (CAM)

PI: Dr. M. Stemmler, Dr. S. Brabletz, Prof. Dr. T. Brabletz

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

### Nuclear co-factors of the tumorigenic EMT-activator ZEB1

PI: Dr. S. Brabletz, Dr. M. Stemmler, Prof. Dr. T. Brabletz

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

### Role of the EMT-activator ZEB1 in pancreas development und homeostasis

PI: Dr. M. Stemmler

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

### Role of the EMT-activator ZEB1 in skeletal development and osteosarcoma

PI: Dr. S. Brabletz, Prof. Dr. T. Brabletz

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

### Dual pathways to endochondral osteoblasts: A novel chondrocyte derived osteoprogenitor cell identified in hypertrophic cartilage

PI: Prof. Dr. K. von der Mark

This research has been focusing on the molecular and cellular events in the cartilaginous growth plate of long bones and vertebrae involved in the control of growth and development of the skeleton. A number of transgenic mouse lines were developed which allowed deciphering the specific role of growth factors, hormones and transcription factors of hypertrophic chondrocytes in the regulation of cartilage-bone turnover. According to the general understanding, the chondrocyte lineage terminates with the elimination of late hypertrophic cells by apoptosis in the growth plate. However, in recent genetic lineage tracing experiments using mouse lines which express reporter genes under the collagen 10 promotor, the group challenged this concept and demonstrated that murine hypertrophic chondrocytes can survive beyond

“terminal” differentiation and gives rise to a progeny of osteoblasts participating in endochondral bone formation.

## 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, human medicine, and biology.

Bachelor’s and Master’s theses are supervised.

## Selected Publications

Meidhof M, Brabletz S, Lehmann W, Preca BT, Mock K, Ruh M, Schüler J, Bertold M, Weber A, Burk U, Lübbert M, Puhr M, Culig Z, Wellner U, Bronsert P, Küsters S, Hopt UT, Stemmler MP, Brabletz T. ZEB1-associated drug resistance in cancer cells is reversed by the class I HDAC-inhibitor mocetinostat. *EMBO Mol Med* 2015, 7: 831-47

Mock K, Preca BT, Brummer T, Brabletz S, Stemmler MP, Brabletz T. The EMT-inducer ZEB1 induces bone metastasis associated genes including BMP-inhibitors. *Oncotarget* 2015, 6:14399-412

Preca BT, Bajdak K, Mock K, Sundararajan V, Pfannstiel J, Maurer J, Wellner U, Hopt UT, Brummer T, Brabletz S, Brabletz T, Stemmler MP. A self-enforcing CD44s/ZEB1 feedback loop maintains EMT and stemness properties in cancer cells. *Int J Cancer* 2015, 137: 2566-77

Sundararajan V, Gengenbacher N, Stemmler MP, Brabletz T, Brabletz S. The ZEB1/mir-200c feedback loop regulates invasion via actin interacting proteins MYLK and TK55. *Oncotarget* 2015, 6: 27083-96

Sasaki T, Stoop R, Sakai T, Hess A, Deutzmann R, Schlötzer-Schrehardt U, Chu ML, von der Mark K. Loss of fibulin-4 results in abnormal collagen fibril assembly in bone, caused by impaired lysyl oxidase processing and collagen cross-linking. *Matrix Biol* 2016, 50:53-66

Lehmann W, Mossmann D, Kleemann J, Mock K, Meisinger C, Brummer T, Herr, R, Brabletz S, Stemmler MP, Brabletz T. ZEB1 turns into a transcriptional activator by interacting with YAP1 in aggressive cancer types. *Nat Comm* 2016, Feb 15;7:10498

## International Cooperations

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

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

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

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

Dr. B. deCrombrughe, MD, Anderson Cancer Center, Houston: USA

# Nikolaus-Fiebiger-Center of Molecular Medicine

## Chair of Experimental Medicine II (Molecular Oncology)

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### Research Focus

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

### Structure of the Chair

Professorships: 1

Personnel: 12

- Scientists: 2 (thereof funded externally: 0)
- Graduate students: 6

### Special structural features

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

### Research

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

### Molecular oncology of Wnt signaling

The Wnt signaling pathway controls the stability of  $\beta$ -catenin and thereby regulates various processes during embryonic development and can lead to cancer. Wnt are secreted glycoproteins which induce the accumulation of  $\beta$ -catenin in cytoplasm and nucleus by binding to frizzled and LRP receptors.  $\beta$ -Catenin interacts with TCF transcription factors and activates target genes. The destruction of  $\beta$ -catenin is induced by phosphorylation in a multi-protein complex which consists of the scaffold components axin or con-

ductin, the serine/threonine kinase GSK3 $\beta$ , and the tumor suppressor APC (Adenomatous Polyposis Coli). The Wnt signal inhibits phosphorylation of  $\beta$ -catenin and thereby leads to its stabilization. In colorectal tumors, mutations of APC or of the serine/threonine phosphorylation sites of  $\beta$ -catenin lead to stabilization of  $\beta$ -catenin and trigger constitutive signaling to the nucleus. Such  $\beta$ -catenin mutations are also found in a multitude of other tumor types suggesting that aberrant activation of Wnt signaling is a key mechanism of oncogenic transformation. We are analyzing the molecular roles of central components of the pathway which are mainly involved in  $\beta$ -catenin degradation. Among these are Amer1, Axin, Conductin as well as the phosphatase PGAM5 which all modulate  $\beta$ -catenin phosphorylation.

### Amer proteins

PI: Dr. S. Ntourmas

The Amer protein family consists of Amer1, Amer2, and Amer3. Amer stands for APC membrane recruitment indicating the fact that Amer1 and Amer2 interact with APC and can recruit it to the plasma membrane thereby acting as negative regulators of Wnt signaling. Amer3 also binds to APC, but acts as an activator of the pathway. Amer1 is the best characterized member of the Amer family. The Amer1 gene is mutated in Wilms tumors and colorectal carcinomas in a frequency of about 7 - 12% of the cases. Moreover, Amer1 mutations are underlying the inherited disease OSCS which is characterized by bone malformations and defects in other organs. We could identify four independent APC binding regions in Amer1 and could narrow these down to stretches of 10 - 13 amino acids by deletion and mutational analyses. We could also specify individual amino acids in these sites which are essential for the interaction with APC. In collaboration with Dr. G. Wu (University Shanghai) we were able to generate crystal structures of three of the four binding sites in complexes with APC which verified these results. Based on these results it was possible to generate an Amer1 mutant completely lacking binding to APC. We have furthermore identified the only  $\beta$ -catenin binding site in Amer1 as the GAME sequence which binds to  $\beta$ -catenin via acidic amino acids. From these results it will be possible to define the functional relevance of individual Amer interactions.

### Role of Axin/Conductin as negative Wnt regulators

PI: Dr. D. Bernkopf

Axin and conductin (also known as axin2) are structurally related inhibitors of Wnt/ $\beta$ -catenin

signaling that promote degradation of  $\beta$ -catenin. Whereas axin is constitutively expressed, conductin is a Wnt target gene implicated in Wnt negative-feedback regulation. Despite the similarities in their amino acid sequence we could identify functional differences between these two proteins. We found that axin and conductin differ in their functional interaction with the upstream Wnt pathway component Dvl (dishevelled), leading to lesser inhibition of conductin function by Dvl as compared to axin. This increases the effectivity of conductin's action as a negative feedback regulator. Axin and conductin also differ in their intracellular localization. Whereas axin accumulates in cytoplasmic puncta, conductin is diffusely distributed. We found that these differences are based on differences in the RGS domains present in both proteins and could describe a molecular mechanism leading to differential distribution. Our results are of potential therapeutic value: Conductin is massively upregulated in colorectal tumors, its activity in inhibiting Wnt signaling and thereby blocking cancer growth might be increased by stimulating its redistribution from diffuse to axin-like puncta. Recently, we could demonstrate an interaction of axin with the mitochondrial phosphatase PGAM5. PGAM5 inhibits the Wnt pathway, however, after damage of the mitochondrial membrane potential, PGAM5 gets cleaved and released to the cytoplasm where it stabilizes  $\beta$ -catenin by dephosphorylation. Given that Wnt stimulation increases the number of mitochondria, we speculate that the PGAM5-Axin- $\beta$ -catenin axis is involved in maintaining mitochondrial homeostasis.

### 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, human medicine, and biology.

Bachelor's and Master's theses are supervised.

### Selected Publications

Zhang Z, Akyildiz S, Xiao Y, Gai Z, An Y, Behrens J, Wu G. Structures of the APC-ARM domain in complexes with discrete Amer1/WTX fragments reveal that it uses a consensus mode to recognize its binding partners. *Cell Discovery* 2015, 1:15016

Vasileiou G, Ekliz AB, Urebe S., Zweier C, Hoyer J, Engels H, Behrens J, Reis A, Hadjihannas MV. Chromatin-Remodeling-Factor ARID1 B Represses Wnt/ $\beta$ -Catenin Signaling. *Am. J. Hum. Genet.* 2015, 97:445-456

Bernkopf DB, Hadjihannas MV, Behrens J. Negative-feedback regulation of the Wnt pathway by conductin/axin2 involves insensitivity to upstream signalling. *Cell Sci* 2015, 128:33-39

Mishra HK, Prots I, Havlicek S, Kohl Z, Perez-Branguli F, Boerstler T, Anneser L, Minakaki G, Wend H, Hampl M, Leone M, Bruckner M, Klucken J, Reis A, Boyer L, Schuierer G, Behrens J, Lampert A, Engel FB, Gage FH, Winkler J, Winner B. GSK3ss-Dependent Dysregulation of Neurodevelopment in SPG11-Patient Induced Pluripotent Stem Cell Model. *Ann. Neurol.* 2016, 79:826-840

Huraskin D, Eiber N, Reichel M, Zidek LM, Kravic B, Bernkopf D, von Maltzahn J, Behrens J, Hashemolhosseini S. Wnt/beta-catenin signaling via Axin2 is required for myogenesis and, together with YAP/Taz and Tead1, active in Ila/Ilx muscle fibers. *Development* 2016, 143:3128-3142

### **International Cooperations**

Prof. V. Katanaev, University Lausanne, Lausanne: Switzerland

Prof. G. Wu, Shanghai University, Shanghai: China

# 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

Professorships: 1  
Personnel: 8  
• Doctors (of Medicine): 4  
• Graduate students: 47

### Clinical focus areas

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

### Research

The clinical and experimental investigations of total hip and knee arthroplasty form the main focus of the research at the Department of Orthopedics. Another main focus is research for neuromuscular disorders. Information and experiences about seldom neuromuscular disorders are collected and analyzed in clinical studies. Another important area is the development of diagnostic procedures like e. g. of mobile gait and posture analysis.

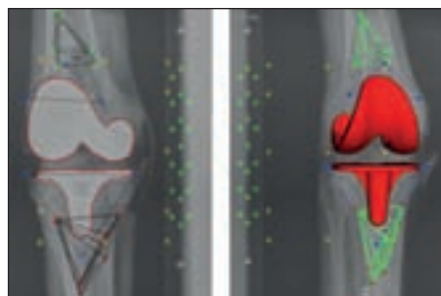
### Radiostereometric analysis (RSA) for quality control in total hip and knee arthroplasty

PI: Prof. Dr. R. Forst, Dr. S. Sesselmann

Radiostereometric measurements of migrations of hip and knee arthroplasty components allow precise predictions about the long-term outcome of these artificial joints within the first two years after surgery. The quality control is achieved with thorough documentation and precise analysis of fixation. Measurements on conventional radiographs can have an accuracy of 1-5 mm 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. It 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 25-250 µm and 0.15°-1.15°. 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.



Typical RSA radiography of an artificial knee joint  
On the left picture the contour of the implant is marked red for model-based RSA purpose, on the right picture the 3D model of the implant coincides the contour. The various colored circles focus on small tantal markers that serve calibration on the one hand and function as bone and implant markers for marker-based RSA on the other hand.

### Neuromuscular disorders

PI: Prof. Dr. J. Forst, Dr. A. Fujak, Prof. Dr. R. Forst  
The research group for neuromuscular disorders is engaged in an evaluation of orthopedic symptoms, conservative and operative treatment in children and adult patients with neuromuscular disorders. The aim of research is the optimization of orthopedic treatment, improvement of the medical care and quality of life of these patients. The studies are particularly focused on anterior horn cell diseases, spinal muscular atrophies, post-polio syndrome, and muscular dystrophies. Although knowledge of the gene defect and the coded protein – the dystrophin – is given, there is no causal therapy of Duchenne muscular dystrophy (DMD) – the most common neuromuscular disease. The natural history of this disease includes beside the obligatory restrictive respiratory insufficiency the cardiomyopathy contractures of the extremities and progressive scoliosis in almost all patients.

The results of operative treatment of contractures of lower extremities particularly in early course of the disease are investigated in a prospective study in a collective of more 500 patients with genetically confirmed diagnosis of DMD. Positive effect of this treatment could be proven, and a stage-oriented therapy concept could be developed.

In close cooperation with the Department of Anesthesiology, the special features in anesthesia and pain therapy in patients with the neuromuscular disorders are investigated. In common projects with the Division of Pediatric Cardiology and the Institute of Radiology, the participation of the heart musculature in DMD is examined.

### Mobile gait and posture analysis

PI: Prof. Dr. R. Forst, Dr. S. Sesselmann  
Video-based gait and posture analysis gains importance in diagnostics and therapeutic monitoring of gait and posture disturbances. Well-established systems for gait and posture analysis in general are expensive and installed stationary in special laboratories. Therefore such laboratories mostly are built up in special research centers. Hence, applying gait and posture analysis in routine is currently hardly realizable.

The main goal of this study is to establish a cost-efficient (less than 10,000 Euro) system for gait and posture analysis that can be set up easily in diverse surroundings.

The mobile gait and posture measurement system allows accuracy values of 0.46° for angles, 0.21 cm for lengths and 0.24 cm for heights. Changes of gait and posture caused by orthopedic devices are quantified and standards for therapeutic monitoring are set up to realize a routine use for gait and posture analysis in future.





Scene of a gate analysis video sequence with the mobile equipment installed in the patients' yard of the hospital. The flexion angle between the elongated femur axis and the shank axis was determined.

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

PI: Prof. Dr. R. Forst, Dr. S. Sesselmann

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

The Department of Orthopedics organizes compulsory and elective subjects for medical students. Supported by the Deutsche Arthrose-Hilfe, „Orthopädie Summer/Winter Schools“ are organized each semester. In cooperation with the Central Institute of Medical Engineering (ZiMT) and supported by the Innovationsfonds

für Lehre of FAU, a „Scientific Speed Dating“ is arranged to bring students in contact to researchers and companies of the health care sector. Interdisciplinary lectures and seminars are held for medical students and students of medical engineering.

Bachelor's and Master's theses of the Faculty of Engineering and doctoral theses are supervised.

### Selected Publications

Dittrich S, Tuerk M, Haaker G, Greim V, Buchholz A, Burkhardt B, Fujak A, Trollmann R, Schmid A, Schroeder R. Cardiomyopathy in Duchenne Muscular Dystrophy: Current Value of Clinical, Electrophysiological and Imaging Findings in Children and Teenagers. *Klin Padiatr* 2015; 227 (4): 225-231

Tschunko F, Wagner B, Hong Y, Söder S, Wölfel R, Müller LA, Forst R, Sesselmann S. Radiostereometric migration analysis of the Cerafit femoral stem: 28 patients followed for 2 years. *Biomed Tech (Berl)*. 2016 Jun 1;61(3):291-8

Sesselmann S, Hong Y, Schlemmer F, Wiendieck K, Söder S, Hussnaetter I, Müller LA, Forst R, Wierer T. Migration measurement of the cemented Lubinus SP II hip stem - a 10-year follow-up using radiostereometric analysis. *Biomed Tech (Berl)*. 2016 Jul 14. pii: /j/bmte.ahead-of-print/bmt-2015-0172/bmt-2015-0172.xml

Sesselmann S, Xiang Y, Wehmöller M, Forst R, Keilholz D, Scharrer T. Methods for assessing the effectiveness of custom-made foot orthoses – a systematic review of literature. *Foot & Shoe* 2016; 2: 37-39

Keilholz D, Scharrer T, Xiang Y, Wehmöller M, Forst R, Sesselmann S. The current state of evidence on treatment with foot orthoses – a systematic review of literature. *Foot & Shoe* 2016; 2: 28-36

Burow M, Forst R, Forst J, Hofner B, Fujak A. Perioperative complications of scoliosis surgery in patients with Duchenne muscular dystrophy and spinal muscular atrophy, focussing on wound healing disorders. *Int J Neurosci* 2016 Jun 21:1-7

# Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

## Division of Orthopedic Rheumatology

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### Head of Division

Prof. Dr. med. Bernd Swoboda

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### Research Focus

- Arthroscopic synovectomy
- Endoprostheses for degenerative and inflammatory joint diseases
- Dynamic pedobarography
- Conventional B-mode ultrasound, Acoustic Radiation Force Impulse (ARFI) elastography and contrast-enhanced ultrasound (CEUS)

### Structure of the Division

Professorships: 1  
Personnel: 4  
• Doctors (of Medicine): 2  
• Graduate students: 3

### Clinical focus areas

- Arthritis surgery of patients with degenerative and inflammatory joint diseases
- Joint preserving operations
- Joint arthroplasties of the lower extremities (hip and knee)
- Treatment of patients with rare diseases of the synovia (synovial joint chondromatosis, pigmented villonodular synovitis, etc.)
- Audited center for arthritis surgery
- Active collaboration within the rheumatology center Erlangen

### Research

Clinical research still focusses on the outcome of arthroscopic synovectomies as well as joint replacements of hip and knee. Basic osteoarthritis research (in cooperation with Prof. Dr. K. Gelse, Division of Trauma Surgery) works on chondrocyte differentiation in human osteoarthritis. Dynamic pedographic measurements, started on rheumatoid patients, are in the meanwhile also pathologies in soccer players. A new field of research is the contrast-enhanced ultrasound of soft tissues.

### Arthroscopic synovectomy

PI: Prof. Dr. B. Swoboda

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

### Endoprostheses for degenerative and inflammatory joint diseases

PI: 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 pre-operative findings, surgical requirements, post-operative outcome, and patient satisfaction are compared.

### Dynamic pedobarography

PI: Dr. T. Hotfiel

Dynamic pedobarography has been considered as an important measurement device and has been used in various orthopedic and biomechanic investigations. Dynamic pedobarography enables to assess various kinetic parameters such as pressure, force or contact-time in the interface between the plantar skin and the measurement surface. It can be used in different conditions such as walking, running or specific movements. Increased and asymmetric plantar pressure conditions can be seen as risk factors for the development of metatarsal stress fractures or plantar ulcers and is associated with prolonged and complicated recurrence of existing tissue damages. Moreover the assessment of foot loads can be helpful for the evaluation of orthotic devices or given weight bearing conditions in the field of rehabilitation.

- Systematic comparison of foot pressure conditions between insole and platform based pedobarography systems
- Plantar pressure distributions in adolescent and professional adult soccer players
- Assessing foot load distribution during rehabilitation and strengthening exercises.

### Conventional B-mode ultrasound, Acoustic Radiation Force Impulse (ARFI) elastography and contrast-enhanced ultrasound (CEUS)

PI: Dr. T. Hotfiel

Ultrasound has been utilized for imaging and diagnostic of muscle tissue for a long time and

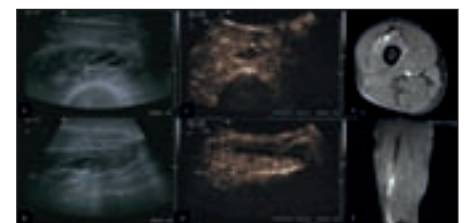
has been widely described in literature. Its advantages include the rapid availability, cost effectiveness and the possibility to perform a real-time dynamic examination with high spatial resolution. The tissue perfusion can be determined by means of Spectral Doppler and power Doppler by assessing blood flow parameters. ARFI is a modality that enables to calculate the speed of the transverse mechanical waves (shear waves) which are generated in the tissue as a consequence of a high-energy focused acoustic radiation force impulse. It is commonly observed that shear wave velocities (SWV) are directly correlated with the stiffness of a tissue and accordingly a stiffer tissue leads to increasing SWV. Changes in dynamic microperfusion can be visualized in a contrast agent preset (contrast-enhanced ultrasound, CEUS) through signals from the gas-filled microbubble contrast agent which will be eliminated as gas (sulphur hexafluoride) via the lungs. CEUS quantification parameters can be obtained in order to distinguish between physiological conditions and pathologies, such as tumors or an inflammatory process. The diagnostic modalities are used under various experimental conditions:

- CEUS in imaging of Delayed Onset Muscle Soreness (DOMS): a quantitative analysis of intramuscular perfusion
- Influence of compression therapy on clinical and imaging findings in ultrastructural muscle injuries by the example of DOMS – a randomized trial clinical assessment, CEUS, elastography and 3T MRT T2 mapping
- Application of ARFI elastography in imaging of ankle joint ligament structures

Cooperation partners:

Dr. R. Heiß, Institute of Radiology, Prof. M. Raitchel, Department of Medicine 2, Gastroenterology and Interventional Endoscopy, Waldkrankenhaus St. Marien, PD Dr. D. Wildner, Department of Medicine 1

Funding: GOTS Research Grant 2016



Transverse and longitudinal scan of the anterior upper thigh of a soccer player sustained by a grade II injury of the vastus intermedius

Conventional ultrasound (A, B), CEUS modality (C, D) and the sagittal proton-density-weighted fat-suppressed (PD-w fat sat) MR images (E, F) demonstrate a muscle tear grade II.

## Teaching

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

We supervise MD and PhD theses.

## Selected Publications

Schaefer A, Hotfiel T, Pauser J, Swoboda B, Carl HD. Incompliance of total hip arthroplasty (THA) patients to limited weight bearing. Arch Orthop Trauma Surg. 2015;135(2):265-9

Zingler C, Carl HD, Swoboda B, Krinner S, Hennig F, Gelse K. Limited evidence of chondrocyte outgrowth from adult human articular cartilage. Osteoarthritis Cartilage. 2016;24(1): 124-8

Hotfiel T, Carl HD, Wendler F, Jendrissek A, Heiß R, Swoboda B. Plantar pressures increase with raising body weight: A standardized approach with paired sample using neutral shoes. J Back Musculoskelet Rehabil. 2016 Dec 23. doi: 10.3233/BMR-150442

Wild L, Carl HD, Golditz T, Swoboda B, Hotfiel T. How do leg press exercises comply with limited weight bearing? Phys Ther Sport. 2016;22: 1-5

Hotfiel T, Carl HD, Swoboda B, Heinrich M, Heiß R, Grim C, Engelhardt M. [Current Conservative Treatment and Management Strategies of Skeletal Muscle Injuries]. Z Orthop Unfall. 2016;154(3): 245-53

Jendrissek A, Hotfiel T, Swoboda B, Söder S, Janka R. [Pigmented villonodular synovitis. A rare differential diagnosis of synovial joint swelling]. Z Rheumatol. 2016;75(2): 157-65

## International Cooperations

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

# Department of Anesthesiology

## Chair of Anesthesiology

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### Research Focus

- Clinical and experimental pharmacology of anesthesia
- Experimental pain research: Pathomechanisms of cold hyperalgesia and cold allodynia, pain models for rare pain syndromes
- Clinical research in perioperative medicine
- Medical technology of diagnostic and therapeutic procedures
- Research projects furthering the medical education

### Structure of the Department

Professorships: 3

Personnel: 433

- Doctors (of Medicine): 133
- Scientists: 5 (thereof funded externally: 2)
- Graduate students: 13

### Clinical focus areas

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

### Special structural features

- 50 anesthesia workplaces
- Anesthesia outpatient department
- Pain outpatient department, pain ward (4 hospital beds)
- Two intensive care units (36 critical care beds)
- Pain management unit (in cooperation with the Department of Neurology)
- Medical management of the emergency service (Erlangen, Landkreis Erlangen-Höchstädt, Herzogenaurach)
- Medical care in air rescue services and in transport within UK Erlangen

### Research

Research at the Department of Anesthesiology is focused on the clinical and experimental

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

### Clinical and experimental pharmacology of anesthesia

This research is focused on the quantitative mathematical modeling of the pharmacokinetics and pharmacodynamics of anesthetic drugs with respect to model identification, computer simulation to improve study design and for educational purposes, and model based dosing strategies for therapeutic optimization.

In the reporting period, the pharmacokinetics and pharmacodynamics of the opioid hydromorphone were investigated during postoperative pain therapy in cardiac surgery patients. Focus of these investigations was the validation of a pharmacokinetic model of hydromorphone that has been developed in previous studies, and the development of a pharmacodynamic model for the analgesic effect of hydromorphone. Further, we investigated the propofol effect on arterial blood pressure in volunteers and developed a new pharmacodynamic model.

### Experimental pain research: Pathomechanisms of cold hyperalgesia and cold allodynia, pain models for rare pain syndromes

In the field of experimental pain research, a Heisenberg Professorship has been funded by the DFG since May 2014. The research topic of this program is the pathomechanisms of cold hyperalgesia and cold allodynia, which are examined in the somatic and the trigeminal system. In detail, the mechanisms of altered temperature processing in the brain were investigated for a special form of cold allodynia, which can be locally induced in the skin by ciguatoxins known as fish poisons. A new device has been developed and validated for improved quantification of cold avoidance and temperature preference in mice. It is based on an automated analysis without experimenter bias. Another translational subproject investigates hereditary differences in the development of cold allodynia by screening inbred mouse strains and comparing differences across strains with differences in the haplotype pattern.

A further research area focuses on the investigation of rare pain syndromes using human stem cells. In cooperation with the Division of

Stem Cell Biology (Institute of Human Genetics, IZKF advanced project), skin biopsies are obtained from healthy individuals and pain patients, and are further cultured and reprogrammed to stem cells. Similar to steps in early development, these so-called human induced pluripotent stem cells are differentiated into nociceptors to overcome the lack of human tissue which is otherwise not available for functional analysis. We recently characterized the expression and function of voltage-gated sodium channels (Navs) in this model system using molecular and electrophysiological methods in order to model rare hereditary pain syndromes caused by mutations in Navs and to influence their pharmacology in vitro.

### Clinical research in perioperative pain

One major project in clinical pain research investigates the molecular background of increased analgesic consumption in patients with Crohn's disease. Differences in gene expression rather than an increased level of sensoric perception may be a possible explanation of these observations, as revealed by quantitative sensory testing and genomic DNA analyses. Further scientific projects in perioperative medicine focus on the analysis of huge data amounts recorded during anesthesia procedures. This work is performed in cooperation with the chair of medical informatics and deals with the identification and selection of mathematical derivatives that allow an accurate description of the time course of monitoring parameters like blood pressure, heart rate and oxygen saturation in more than 400.000 anesthesia protocols. In addition, machine learning methods will be applied in order to automatically identify risk profiles for clinical outcome parameters like mortality and cardiac morbidity.

### Medical technology of diagnostic and therapeutic procedures

Within the scope of the National Leading Edge Cluster Medical Valley EMN, our research focused on the development of innovative monitoring techniques and new technologies for continuous and variable intravenous application of fluid drugs. A further research goal was the development and implementation of new methods for a more precise measurement of total and unbound concentration of anesthetics in blood plasma.

During the reporting period, we developed a new method for individual and effect related intravenous dosing of opioids and validated it using the opioid hydromorphone in two clinical

trials in patients after cardiac surgery. The comparison with gold standard pain therapy as well as the contribution of respiratory and cardiovascular variables to the identification of opioid adverse effects is still under investigation. On the basis of the gathered experiences, the next step will be the implementation of new dosing algorithms that consider selected physiological variables for dosing adjustment to minimize the adverse effects of opioids.

### Research projects furthering the medical education

An emphasis of the scientific work during the reporting period is the development of curricula. Using a six step approach for curriculum development, several curricula for the management of emergencies and a sample curriculum for the specialization in anesthesiology have been implemented on behalf of the German association for anesthesiology and intensive care (DGAI). Furthermore, several human factors have been researched in virtual reality scenarios in acute medicine. In this context the influence of hierarchies and checklists on strategies of decision making and actions in an operative setting have been analyzed. In cooperation with industrial partners, the usability and practicability of medical products are regularly tested in the simulation- and training center.

## Teaching

The Department of Anesthesiology is committed in mandatory and elective courses in the field of medicine and dentistry. It has to be pointed out, that the Department takes responsibility for a number of interdisciplinary course formats including pain medicine, emergency care medicine and rehabilitation / physical medicine / naturopathic treatment as well as emergency medicine for dentists in cooperation with the department of oral-maxillofacial surgery. The elective course "rescue medicine" bridges into multiprofessional teaching. Furthermore the Department of Anesthesiology is one of the hosts for the oral examination for the European diploma of anesthesiology and intensive care medicine (EDA).

For the training in education new teaching concepts could be implemented, including virtual situative learning in the simulation and training center.

Master's theses as well as MD and PhD theses are supervised.

### Selected Publications

Münster T, Eckl S, Leis S, Göhring-Waldeck G, Ihmsen H, Maihöfner C. Characterization of somatosensory profiles in

patients with Crohn's disease *Pain Practice* 2015; 15(3): 265-71

Jelezacov C, Lavielle M, Schüttler J, Ihmsen H. Pharmacodynamic response modelling of arterial blood pressure in adult volunteers during propofol anaesthesia. *Br J Anaesth* 2015; 115(2):213-26

Eberhardt E, Havlicek S, Schmidt D, Link AS, Neacsu C, Kohl Z, Hampl M, Kist AM, Klinger A, Nau C, Schüttler J, Alzheimer C, Winkler J, Namer B, Winner B, Lampert A. Pattern of functional TTX-resistant sodium channels reveals developmental stage of human iPS- and ES cell-derived nociceptors. *Stem Cell Reports* 2015; 5(3): 305-13

Touska F, Winter Z, Mueller A, Vlachova V, Larsen J, Zimmermann K. Comprehensive thermal preference phenotyping in mice using a novel automated circular gradient assay. *Temperature (Austin)* 2016; 3(1): 77-91

Jelezacov C, Ihmsen H, Saari TI, Rohde D, Mell J, Fröhlich K, Kraljicovic L, Fechner J, Schwilden H, Schüttler J. Patient-controlled Analgesia with Target-controlled Infusion of Hydromorphone in Postoperative Pain Therapy. *Anesthesiology* 2016; 124(1): 56-68

Breuer G, Knipfer C, Huber T, Huettl S, Shams N, Knipfer K, Neukam FW, Schuettler J, Stelzle F. Competency in managing cardiac arrest: A scenario-based evaluation of dental students. *Acta Odontol Scand* 2016; 74(4): 241-249

### International Cooperations

Prof. E. Jørum, University Oslo: Norway

Prof. M. Lavielle, Inria Saclay-Île-de-France, Ecole Polytechnique, Palaiseau Cedex: France

Prof. J. Mogil, McGill University, Montreal: Canada

Prof. G. Peltz, Stanford Medical School, Stanford: USA

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



# Department of Anesthesiology

## Division of Molecular Pneumology

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### Research Focus

- Immunopathogenesis of lung tumor
- Immunopathogenesis of allergic asthma

### Structure of the Division

Professorships: 1

Personnel: 13

- Scientists: 6 (thereof funded externally: 2)
- Graduate students: 3

### Research

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

#### Immunopathogenesis of lung tumor

Lung cancer has the highest death-rate of all cancers in the world. Besides cigarette smoking, different other risk factors comprising gender and specific genetic traits are thought to contribute to lung cancer. Our group has been focusing in the last ten years in the analysis of T cells present in the tumor microenvironment, including tumor infiltrating lymphocytes (TIL), and focuses on a number of genes which play a role in the exhaustion of these cells. In most of the established tumors, effector functions of TIL are restricted by several environmental factors including the accumulation of immuno-suppressive cells and the increased expression of inhibitory receptors, e.g. PD1 or CTLA4. These inhibitory receptors contribute to the functional impairment of T cell activation and promote T cell exhaustion. Cancer immunotherapies have been developed that reawaken exhausted TIL by blocking inhibitory checkpoint receptors or other immunoregulatory cells.

During the last five years we analyzed in collaboration with the Division of Thoracic Surgery lung samples of at least 90 patients who were

suffering from non-small cell lung cancer (NSCLC), underwent surgery and gave their approval to being enrolled in this study. The diagnosis of lung cancer was based on pathological confirmation at the Institute of Pathology. The histological types of lung cancer were classified according to the classification of the World Health Organization (WHO), formulated in 2004. The staging of lung cancer was based on the Cancer TNM Staging Manual, formulated by the International Association for the Study of Lung Cancer (IASLC) in 2010.

Tissue samples were taken from the tumor area (TU: solid tumor tissue) as well as from the tumor free control area (CTR: at least 5cm away from the solid tumor) of the surgically removed lung material. From these tissues histological tissue arrays were generated, RNA and proteins were extracted and we are able to isolate TIL by fluorescence activated cell sorting (FACS). This whole procedure is substantial to understand the precise biomarkers trait present in each patient which is a very important task to set up new therapeutical approaches. In fact, although surgery is the elected therapy for this kind of tumor, in the last period immunotherapy against immunosuppressive genes has been successfully used to cure at least partially lung cancer. By using single gene deficient mice in a murine model of lung carcinoma, we identified several proteins that play a protective role in the immuno-regulation of lung cancer development. Some examples for those proteins are described below:

- The role of NFATc1 in T cell specific immune responses during the development of NSCLC NFATc1 is a member of the family of Nuclear Factor of Activated T cells (NFAT) controlled by Ca<sup>2+</sup> signaling. In peripheral T cells, NFATc1 contributes to effector functions by regulating the expression of e.g. IL-2 and IFN $\gamma$  and controls cell cycle regulation and apoptosis. As NFATc1 is important for T cell signaling and effector functions, we asked whether this transcription factor could be important for the activation of TIL to turn against established NSCLC tumors. This will be analyzed in samples from patients with NSCLC as well as in NFATc1 $\Delta$ CD4 mice in a murine model of lung carcinoma.
- The role of Tbet+Foxp3+CD4+ T cells in NSCLC anti-tumoral immune responses require the function of T helper 1 (Th1) and cytotoxic T cells (Tc1) which are both characterized by the expression of the hallmark transcription factor T-box expressed in T cells (Tbet, Tbx21). Tbet controls the differentiation of Th1 cells and

promotes the production of cytolytic effector molecules by Tc1 cells. By contrast, regulatory T cells (Treg) are known to suppress pro-inflammatory immune responses, including Tbet-mediated effects. Therefore, Treg are regarded as one of the major obstacles for efficient anti-tumor immunity. A characteristic feature of Treg cells is the expression of the transcription factor forkhead box protein 3 (Foxp3) that controls the development and function of these cells. Despite the opposite roles of Tbet and Foxp3 in the immune system as well as in tumor biology, there is evidence for the existence of CD4+ T cells, expressing both transcription factors. The biological function of these Tbet+Foxp3+CD4+ T cells, especially in the context of tumor diseases, is unknown. Our aim is therefore to investigate if Tbet and Foxp3 co-expressing CD4+ T cells could be involved in the immune-pathogenesis of lung cancer. For this purpose, we analyze Tbet<sup>fl/fl</sup>Foxp3<sup>Cre</sup> mice which lack Tbet-expression in Foxp3+ Treg cells in a murine model of lung carcinoma. Moreover, we are able to test the appearance as well as the possible function of Tbet+Foxp3+CD4+ T cells in human lung samples from patients with NSCLC.

- The role of Interleukin (IL)-9 in NSCLC

The type of immune reaction that is being induced at the tumor site can be influenced by a variety of factors. For instance, anti-tumoral responses can be increased or suppressed depending on the composition of the cytokine milieu. In this context, we investigate the influence of interleukin 9 (IL-9) on lung tumor growth. It has been shown before that IL-9 can be secreted by CD4+ Th9 cells. This T cell subtype develops in the presence of interleukin 4 (IL-4) as well as the immunosuppressive cytokine transforming growth factor  $\beta$  (TGF $\beta$ ). Previous studies have shown that adoptive transfer of Th9 cells can enhance the anti-tumoral immune response in a murine model of melanoma. In order to investigate the role of IL-9 in lung tumor as well as the effects of IL-9 on anti-tumoral immune responses, we analyze IL-9 deficient mice in an experimental model of lung carcinoma. Also in this project we have the possibility to reinforce our data from the murine model by the analysis of human lung carcinoma samples.

- The role of Interleukin (IL)-10 in NSCLC IL-10 is one of the major cytokines which is significantly involved in immunosuppressive and pro-tumoral processes in the immune system. IL-10 is mainly produced by tumor asso-

ciated macrophages (M2), T regulatory cells (Treg) and Th2 cells, but also by bronchial epithelial cells which are the initial source of NSCLC. Moreover, IL-10 is able to inhibit Th1 cells, antigen presenting cells (APC) and classical-activated macrophages (M1) which play an important role in tumor defense.

In our working group we analyze the role of IL-10 and its impact on the immune system during lung tumor development. A better understanding of the cytokine IL-10 is of crucial importance to develop improved immunotherapy methods.

### **Immunopathogenesis of allergic asthma**

Allergic asthma is an increasing chronic-inflammatory disease of the airways that affects millions of people worldwide. It is characterized by increased airway inflammation, hyperresponsiveness and remodeling after allergen and rhinovirus challenge.

While the classical model of allergy-induced airway inflammation focuses on a Th2 driven immune-reaction, Th1 and T regulatory cells play instead a protective role in this disease. Th2 cytokines can also influence B cells which then develop into plasma cells producing IgE which activates mast cells via binding to the high affinity IgE receptor, resulting in the release of bronchoconstrictors like histamine.

In the course of the European asthma study PreDicta (since 2011) with healthy and asthmatic pre-school children aged between 4 to 6 years, we have gained insight into important immunological processes during asthma development in general and in context to viral infections in particular. Since 2016, a local follow-up study (AGENDAS) has been recruiting healthy and asthmatic school children (6 to 10 years) with the aim to substantiate and extend the results obtained in PreDicta. Especially the connection between rhinovirus infections and interferon type I and type III responses are a major research focus in our Division, but also T and B cell responses as well as innate lymphoid cells (ILC) are of interest to our group. Here we concentrate on cytokine patterns released by the different cell populations, e. g. IL-4 release from Th2 cells, and the expression of key transcription factors, such as T-bet in Th1 cells. To support our findings from the human studies, also mouse models of allergic asthma are used. Here, mouse models lacking e. g. single transcription factors, cytokines or cytokine receptors, e. g. BATF- or IL-17-deficient mice, contribute to determine the role of these factors/mediators in al-

lergic asthma. As a model antigen we use ovalbumin (OVA), but we are currently also establishing a model with the human relevant allergen house dust mite (HDM). These studies should contribute to the development of new therapeutic approaches and prevention strategies for asthma.

At the moment our studies focus on those research topics:

- Role of the transcription factor NFATc1 in allergic asthma
- Determining the role of acid sphingomyelinase (ASM) in allergic asthma
- Interferon type I and type III immune responses to rhinovirus infections in asthma
- Role of TGF- $\beta$  in anti-rhinovirus immune responses in asthmatic patients
- IL-33/ST2 immune responses to respiratory bacteria and viruses in pediatric asthma
- The Role of Innate lymphoid cells type 2 (ILC2) in experimental allergic asthma.

### **Teaching**

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

### **Selected Publications**

Reppert S, Zinser E, Holzinger C, Sandrock L, Koch S, Finotto S. NFATc1 deficiency in T cells protects mice from experimental autoimmune encephalomyelitis. *Eur J Immunol.* 2015 May;45(5):1426-40

Koch S, Reppert S, Finotto S. NFATc1 deletion in T lymphocytes inhibits the allergic trait in a murine model of asthma. *Clin Exp Allergy.* 2015 Aug;45(8):1356-66

Andreev K, Trufa ID, Siegemund R, Rieker R, Hartmann A, Schmidt J, Sirbu H, Finotto S. Impaired T-bet-pSTAT1 $\alpha$  and perforin-mediated immune responses in the tumoral region of lung adenocarcinoma. *Br J Cancer.* 2015 Sep 15;113(6):902-13

Koch S, Graser A, Mirzakhani H, Zimmermann T, Melichar VO, Wölfel M, Croteau-Chonka DC, Raby BA, Weiss ST, Finotto S. Increased expression of nuclear factor of activated T cells 1 drives IL-9-mediated allergic asthma. *J Allergy Clin Immunol.* 2016 Jun;137(6):1898-1902.e7

Graser A, Ekici AB, Söpel N, Melichar VO, Zimmermann T, Papadopoulos NG, Taka S, Ferrazzi F, Vuorinen T, Finotto S. Rhinovirus inhibits IL-17A and the downstream immune responses in allergic asthma. *Mucosal Immunol.* 2016 Sep;9(5):1183-92

Bergauer A, Söpel N, Kroß B, Vuorinen T, Xepapadaki P, Weiss S, Blau A, Sharma H, Kraus C, Springel R, Rauh M, Mittler S, Graser A, Zimmermann T, Melichar VO, Kiefer A, Kowalski ML, Sobanska A, Jartti T, Lukkarinen H, Papadopoulos NG, Finotto S. IFN- $\alpha$ /IFN- $\lambda$  responses to respiratory viruses in paediatric asthma. *Eur Respir J.* 2016 Nov 11. pii: ERJ-00969-2016

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### Research Focus

- Ethical aspects in palliative care
- Health services research
- Informal caregiver research
- Research projects furthering the curriculum and medical education

### Structure of the Division

Professorships: 1  
Personnel: 40  
• Doctors (of Medicine): 7  
• Scientists: 5  
(thereof funded externally: 4)  
• Graduate students: 17

### Clinical focus areas

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

### Research

The Division of Palliative Medicine followed four different research focus areas in 2015-2016. Besides concentrating on ethical aspects at the end of life (especially the investigation of 'palliative sedation' in the German palliative care and hospice setting), informal caregiver and family members of deceased patients were included in palliative care research to gain insights into the estimated quality of care and quality of dying and death. Moreover, several projects from health care research were run and additionally, the student teaching of the Division was studied for scientific purposes.

### Ethical aspects in palliative care

PI: PD Dr. S. Stiel, 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.

a) Following an ELAN-funded online survey study in 2012 on the practice of PS in German palliative care units, community palliative care teams and inpatient hospices, a document analysis was conducted in 2015 and published by the work group in 2016. In sum 57 scores for the evaluation of depth of sedation or symptom severity, protocols and internal guidelines of participating services were grouped according to their contents, frequent and infrequent contents described, and all contents compared to the framework of the European Association for Palliative Care (EAPC).

b) Data collected in the online survey were investigated with a focus on correlations between demographic factors of participating physicians, treatment measures from PS practice, and the rating of case scenarios each with the prevalence rates of palliative sedation in the institution.

c) Based on the document analysis, a practical documentation recommendation for PS was developed for German palliative care and hospice services by the work group. The results from a Delphi consensus procedure are expected in 2017.

Funding: Staedtler Stiftung

### Health services research

PI: 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" 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.

Project partners: Prof. Dr. C. Sieber (Institute for Biomedicine of Aging), Prof. Dr. C. Bogdan (Institute of Clinical Microbiology, Immunology, and Hygiene), Prof Dr. F. Lang (Institute of Psychogerontology, Faculty of Humanities, Social Sciences, and Theology), Prof. Dr. O. Schöffski (Chair for Health Management, Faculty of Business, Economics, and Law)

Funding: BMBF

- "Coordination Office Palliative Care in the network of German Comprehensive Cancer Centers"

During the reference period, a "best practice strategy" for a systematic integration of palliative care in clinical care, education, and research was developed.

Funding: German Cancer Aid

- "Hospice and Palliative Care- in Bavaria: well connected – optimally cared for!" (PallBay-Net)

Several inpatient and community palliative care providers established regional hospice and palliative care networks in Bavaria aiming at connecting different services. Following the hypothesis that the best possible care for terminally ill and dying people not only requires individual and numerous general and specialized resources, but also a well-connected care provision, these networks have to be investigated in detail. The project gains insights into the general patterns of work and collaboration, the organization and communication within networks and between partners. A best practice recommendation on the collaboration in networks is developed by the work group.

Funding: Bavarian State Ministry of Public Health and Care Services

### Informal caregiver research

PI: Prof. Dr. C. Ostgathe, PD Dr. S. Stiel

- Validation of the "Quality of Dying and Death" (QoDD) questionnaire

During the past years, first international instruments for the evaluation of contents of the comprehensive approach of palliative care have been developed. The American version of the QoDD assesses family caregivers' and professionals' experiences from the dying phase and circumstances of death. In collaboration with the University Hospital Mainz, the QoDD questionnaire was translated into German and validated in terms of its psychometric properties. The questionnaire is now ready for standard use in clinical practice and end-of-life care research.

Funding: German Cancer Aid

- Validation of the "Care of the Dying Evaluation (CODE)" for deceased patients' informal caregivers in German"

In collaboration with the University Hospital Mainz, the CODE questionnaire consisting of 30 items has undergone a validation study since 2016. The questionnaire assesses central aspects of quality of care. The provision of this questionnaire requires a comprehensive em-

pirical testing with regard to psychometric properties such as the reliability and validity. In the future, CODE can be used as a practical tool for the measurement of quality of care and allows comparisons between institution or countries.

Funding: DFG

Stiel S, Heckel M, Christensen B, Ostgathe C, Klein C. In-service documentation tools and statements on Palliative Sedation in Germany - Do they meet the EAPC framework recommendations? A qualitative document analysis. *Support Care Cancer* January 2016, 24(1): 459-467

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

PI: Dr. T. Steigleder

Studies encompass a wide spectrum from assessing the best teaching formats, attitudes towards death and dying, ethical and spiritual aspects of medical students unto psychological effects as the endowment effect and loss aversion or prenatal testosterone exposition on medical decision making and behavior in medical students.

### **Teaching**

The Division of Palliative Medicine is an integral part of the teaching force for human medicine, psychogerontology, and medical process management. In addition to the comprehensive curricular teaching it offers workshops for medical students as part of the clinical team on treating palliative care patients with simulated patients under constant supervision and with structured feedback. Furthermore we established a multi-professional seminar in 2013 which takes place once each term. Tutors and participants both comprise many different health professions.

The Division of Palliative Medicine offers the chance to accomplish a medical doctoral thesis or a dissertation in human biology as well as Bachelor's and Master's theses of many degree programs.

### **Selected Publications**

Stiel S, Heckel M, Bussmann S, Weber M, Ostgathe C. End-of-life research with bereaved informal caregivers - Analysis of recruitment strategy and participation rate from a multi-centre validation study. *BMC Palliat Care* 2015, 2(14):21

Heckel M, Bussmann S, Stiel S, Weber M, Ostgathe C. Validation of the German Version of the Quality of Dying and Death Questionnaire for Informal Caregivers (QoDD-D-Ang). *Pain Symptom Manage* 2015, 50(3):402-13

Berendt J, Stiel S, Simon ST, Schmitz A, van Oorschot B, Stachura P, Ostgathe C. Integrating Palliative Care into Comprehensive Cancer Centers: Consensus-based development of Best Practice Recommendations. *Oncologist*, Oct 2016; 21(10):1241-49

Berendt J, Oechsle K, Thomas M, van Oorschot B, Schmitz A, Radbruch L, Simon S, Gärtner J, Thuss-Patience P, Schuler U, Hensem J, Gog C, Viehrig M, Mayer-Steinacker R, Stachura P, Stiel S, Ostgathe C. Stand der Integration der Palliativmedizin in die von der Deutschen Krebshilfe e.V. geförderten Onkologischen Spitzenzentren. *Dtsch Med Wochenschr*, Jan 2016;141(2):e16-23

# 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
- 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

Professorships: 1

Personnel: 100

- Doctors (of Medicine): 15
- Scientists: 3 (thereof funded externally: 0)

### Clinical focus areas

- Adult cardiac surgery
- Heart transplantation in adults and children
- Mechanical circulatory support
- Wound management
- Heart insufficiency therapy
- Rhythm surgery
- Surgery in grown-up with congenital heart disease
- Interventionell heart valve surgery
- Interventionell aortic surgery

### Research

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

### Chronic rejection of allografts

PI: 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<sup>-/-</sup> 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

PI: Dr. R. Tandler

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

### Neuropeptide release of the heart

PI: PD Dr. T. Strecker

Calcitonin-Gen 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 sensory A-d- 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 infarction. 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

PI: 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.

### Tissue engineering of cardiovascular implants

PI: 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**

PI: Prof. Dr. M. Weyand

The support of the insufficient heart muscle function by artificial support systems is worldwide an intensive field of research and an aim sought 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 research project pursues from the interpretation over the production up to the clinical validity of the system function more new, actoric, and patient-individual heart muscle support systems for the purposes of an external compression of the heart. Therefore the main focuses are the investigation of a biomechanically efficient, mechanical system as well as the development of di- or piezo-electric based actor material patterns.

#### **High speed camera investigations on heart valves in a pulse duplicator**

PI: Dr. M. Kondruweit

High-speed camera investigations on heart valves in an animal model are an already established model. In this project these proceedings are applied into a pulse duplicator to be able to compare several heart valve types in a stan-

dardized procedure. Special situations, as for example the Ventricle Assist Devices support and the effect on the hemodynamic on the heart valves, are examined. The results should show possible reasons for heart valve attrition by measuring power vectors. If possible, these reasons shall be corrected by changing the valve design.

### **Teaching**

The Department of Cardiac Surgery takes part in compulsory and elective subjects for the curricular teaching of the human medicine and dentistry.

Bachelor's and Master's theses especially from the Faculty of Engineering are supervised as well as MD and PhD theses.

#### **Selected Publications**

Motsch B, Heim C, Koch N, Ramsperger-Gleixner M, Weyand M, Ensminger SM. Microvascular integrity plays an important role for graft survival after experimental skin transplantation. *Transpl Immunol*. 2015 Nov;33(3):204-9

Strecker T, Bertz S, Wachter DL, Weyand M, Agaimy A. Mesothelial/monocytic incidental cardiac excrescences (cardiac MICE) associated with acute aortic dissection: a study of two cases. *Int J Clin Exp Pathol*. 2015 Apr 1;8(4):3850-6

Heim C, Gebhardt J, Ramsperger-Gleixner M, Jacobi J, Weyand M, Ensminger SM. Clopidogrel significantly lowers the development of atherosclerosis in ApoE-deficient mice in vivo. *Heart Vessels*. 2016 May;31(5):783-94

Beier JP, Arkudas A, Lang W, Weyand M, Horch RE. Sternal osteomyelitis - Surgical treatment concepts. *Chirurg*. 2016 Jun;87(6):537-50

Heim C, Bernhardt W, Jalilova S, Wang Z, Motsch B, Ramsperger-Gleixner M, Burzlaff N, Weyand M, Eckardt KU, Ensminger SM. Prolyl-hydroxylase inhibitor activating hypoxia-inducible transcription factors reduce levels of transplant arteriosclerosis in a murine aortic allograft model. *Interact Cardiovasc Thorac Surg*. 2016 May;22(5):561-70

Heim C, Motsch B, Jalilova S, Bernhardt WM, Ramsperger-Gleixner M, Burzlaff N, Weyand M, Eckardt KU, Ensminger SM. Reduction of obliterative bronchiolitis (OB) by prolyl-hydroxylase-inhibitors activating hypoxia-inducible transcription factors in an experimental mouse model. *Transpl Immunol*. 2016 Nov;39:66-73

# Department of Cardiac Surgery

## Division of Pediatric Cardiac Surgery

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### Head of Division

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### Research focus area

- Organ protection: Cerebral perfusion/beating-heart-surgery
- Heart valve surgery
- Extracorporeal circulatory support
- Transmural endocardial pacing
- Thymus immunology
- Migration of plasticizers into patient's blood

### Structure of the Division

- Professorships: 1
- Personnel: 10
- Doctors (of Medicine): 5
- Graduate students: 15

### Clinical focus areas

- Surgery for children and adult patients with congenital heart disease
- Extracorporeal support for children with severe heart and/or lung failure
- Arrhythmia surgery

### Research

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

#### Organ protection: Cerebral perfusion/beating-heart-surgery

Organ protective management during aortic arch surgery has become a major focus of the Division of Pediatric Cardiac Surgery. After experimental validation of selective brain perfusion as an intraoperative measure for cerebral protection, the cerebral perfusion could now be

determined and compared in both hemispheres with the use of intraoperative transfontanellar ultrasound.

An additional focus of previous animal experiments was about the overall cardioprotective management. After validation of the „beating heart“ method, in which the heart is constantly perfused and beating during the entire aortic arch operation, a modified form of blood cardioplegia has been adapted to pediatric physiology and was shown to preserve cardiac contractility better than conventional cardioplegic solutions. It was then successfully implemented into everyday clinical practice.

#### Heart valve surgery

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 (pulmonary valve replacement). Pulmonary homografts are still supposed to be the „gold standard“, but are only limited available. Existing xenogenous pulmonary valve prostheses offer an alternative, but are only available in limited sizes due to their diameter. Particularly for patients after Fallot correction, markedly dilated pulmonary arteries and an aneurysmatic enlarged right ventricular outflow tract due to long-term pulmonary valve regurgitation are present. In this case, existing large-sized manufactured xenogenic prostheses are proposed which are actually intended for aortic valve replacement, but can also be used as a pulmonary conduit after sewing into a Dacron prosthesis. The advantage of this method are low transvalvular gradients and an ideal „landing zone“ for later transfemoral pulmonary valve interventions or replacement.

#### Extracorporeal circulatory support

Extracorporeal circulatory support systems are used for patients with acute or chronic terminal cardiac and/or pulmonary failure. Novel diagonal pumping systems have been introduced into clinical practice since 2013. These systems provided an improved management and regulation of the applied device for patients on support by a more intensive monitoring of pump-specific characteristics. It was demonstrated that overall improvement in the management results in more safety and improved outcomes for patients on support.

#### Transmural endocardial pacing

Pacemaker surgery seems to be of rather marginal relevance in pediatric heart surgery be-

cause of the low incidence of patients with rare congenital heart defects or with acquired heart block. Transvenous pacemaker leads, usually used in adults, cannot be applied in small children because of small vessel sizes and later somatic patient growth. Epicardial pacemaker systems offer a temporary alternative, but are frequently difficult to apply because of epicardial scarring on the hearts surface after numerous reoperations.

Endocardial „screwing-in-leads“ commonly used for adults can be implanted transmural into the intraventricular septum or the atrial appendage „from the outside“. This method provided excellent long term results in our hands for small often reoperated patients.

#### Thymus immunology

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

#### Migration of plasticizers into patient's blood

A recent research focus is the investigation of phthalate plasticizers (DEHP) migration from the tubes of the heart-lung machine into blood. These plasticizers have toxic potential in the blood of patients, especially in children. In a joint project with the Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine (Prof. Dr. T. Göen), the Division of Pediatric Cardiac Surgery investigates alternative emollients with regard to their washout and alternative materials which do not use those toxic plasticizers. The topic has a health-political relevance. In recent years, for example, toxic plastic particles contamination has been found in children's plastic toys, baby bottles and pacifiers. It has been shown that plasticizers as „endocrine disruptors“, especially in children, cause a change in the development of reproductive organs and fertility.

#### 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 can be followed on additional screens in the operating room.

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

### **Selected Publications**

Janssen C, Kellermann S, Munch F, Purbojo A, Cesnjevar RA, Rüffer A. Myocardial Protection During Aortic Arch Repair in a Piglet Model: Beating Heart Technique Compared With Crystalloid Cardioplegia. *Ann Thorac Surg.* 2015 Nov;100(5):1758-66

Buchholz C, Mayr A, Purbojo A, Glockler M, Toka O, Cesnjevar RA, Rüffer A. Performance of stented biological valves for right ventricular outflow tract reconstruction. *Interact Cardiovasc Thorac Surg.* 2016 Dec;23(6):933-939

Sandrio S, Purbojo A, Toka O, Dittrich S, Cesnjevar R, Rüffer A. Transmural Placement of Endocardial Pacing Leads in Patients With Congenital Heart Disease. *Ann Thorac Surg.* 2016 Jun;101(6):2335-40

Eckert E, Munch F, Goen T, Purbojo A, Müller J, Cesnjevar R. Comparative study on the migration of di-2-ethylhexyl phthalate (DEHP) and tri-2-ethylhexyl trimellitate (TOTM) into blood from PVC tubing material of a heart-lung machine. *Chemosphere.* 2016 Feb;145:10-6

Gerstner S, Köhler W, Heidkamp G, Purbojo A, Uchida S, Ekici AB, Heger L, Luetke-Eversloh M, Schubert R, Bader P, Klingebiel T, Koehl U, Mackensen A, Romagnani C, Cesnjevar R, Dudziak D, Ullrich E. Specific phenotype and function of CD56-expressing innate immune cell subsets in human thymus. *J Leukoc Biol.* 2016 Dec;100(6):1297-1310

Speth M, Munch F, Purbojo A, Glockler M, Toka O, Cesnjevar RA, Rüffer A. Pediatric Extracorporeal Life Support Using a Third Generation Diagonal Pump. *ASAIO J.* 2016 Jul-Aug;62(4):482-90

### **International Cooperations**

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# 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
- Role of miRNA in cancer and immune-related diseases
- Composition, function, and clinical relevance of plasma extracellular vesicles (pEV)
- Characterization of the topography 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

Professorships: 6

Personnel: 167

- Doctors (of Medicine): 33
- Scientists: 15 (thereof funded externally: 12)
- Graduate students: 10

### Clinical focus areas

- Immunotherapy of melanoma (checkpoint blockade, dendritic cell vaccination)
- Treatment of psoriasis and autoimmune diseases
- Experimental treatment with regulatory T cells
- Recombinant allergens for diagnosis and therapy

### Research

The research activities of the Department of Dermatology focus primarily on malignant mel-

anoma. Under this overall topic several directions developed, including studies to understand the pathogenesis of melanoma, the immunological response, the immune therapy and the identification of melanoma biomarkers. Under these main directions projects were initiated analyzing the biology and function of dendritic cells, optimizing antigen specific tumor vaccines using dendritic cells, analyzing the function of extracellular vesicles from plasma and analyzing tissue sections with an improved automated immunofluorescence technology called the MELC technology. Additional projects analyzing the pathogenesis of HIV infection and autoimmune diseases were continued. The Department established a broad interaction between basic molecular and immunological research and clinical application.

### Cellular immune intervention

PI: PD Dr. B. Schuler-Thurner

The production and clinical testing of innovative cellular therapies is the task of this working group (experimental immunotherapy) consisting of the GMP laboratory and a clinical trial unit. After seven phase I and II trials using Dendritic Cell (DC) vaccines, we started in July 2014 a multicenter phase III trial using tumor mRNA as vaccine antigen. The goal of this trial is the prevention of tumor relapse in uveal melanoma by induction of tumor-specific T cells (200 patients planned, cooperation with the Department of Ophthalmology and seven university hospitals in Germany). Production of the tumor mRNA and the DC vaccine is performed by our GMP laboratory. Since the start of the trial, 82 patients have been screened and 40 have been included. In 2017 a clinical trial using Tregs produced by our GMP lab will start in cooperation with the Department of Medicine I. Current improvements are the use of Next Generation Exon and RNA sequencing in conjunction with HLA-epitope prediction in order to improve the vaccination strategy. Based on preclinical work, the adoptive transfer of T cells reprogrammed by RNA transfection is planned. The GMP-quality team has successfully developed the implementation of all cellular therapies. Immunomonitoring is performed by the Core Unit FACS.

### RNA electroporation to improve DC vaccines and to generate antigen-specific T cells

PI: 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  $\gamma/\delta$  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 CAR for treatment of malignant melanoma, and a trial is planned for 2017.

### Functional role of DC subpopulations and antigen presentation

PI: 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 multi-color confocal immunofluorescence analysis and 17-color flow cytometry and human antigen targeting antibodies are generated.

### Role of miRNA in cancer and immune-related diseases

PI: Prof. Dr. J. Vera-González

MicroRNA are non-coding RNA 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 miRNA 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)

PI: Prof. 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. In 2016 biomarker profiles were established that could be used for the early detection of melanoma and cancer in general.

### **Characterization of the toponome of tissue and cells by multi-epitope-ligand cartography (MELC)**

PI: Prof. 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. The results from this study are currently used to discriminate early melanomas from dysplastic naevi.

### **Pathomechanisms of chronic inflammatory skin diseases**

PI: Prof. Dr. M. Sticherling

Chronic-inflammatory diseases make up a major part of skin diseases. Apart from e.g. psoriasis, atopic eczema, and granulomatous diseases, autoimmune mediated diseases restricted to the skin, like bullous autoimmune skin disorders, as well as specific skin involvement among multiorgan 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**

PI: Prof. Dr. L. Heinzerling

This research group focuses on predictive and therapeutic biomarkers in melanoma to opti-

mize 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**

PI: Dr. C. Bosch-Voskens

The focus of this project funded by KFO 257 (compare 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**

PI: 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 Skin and Venereal Diseases teaches students of human medicine, dental medicine, 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 laboratories, lectures as well as Bachelor's, Master's, and MD theses. The Department is responsible for the organization of dermatological advanced training courses for physicians.

## **Selected Publications**

Hecht M et al. Radiosensitization by BRAF inhibitor therapy - mechanism and frequency of toxicity in melanoma patients. *Ann Oncol*, 2015, 26(6):1238-44

Ostalecki C, Wittki S, Lee JH, Geist MM, Tibroni N, Harrer T, Schuler G, Fackler OT, Baur AS. HIV Nef- and Notch1-dependent Endocytosis of ADAM17 Induces Vesicular TNF Secretion in Chronic HIV Infection. *EBioMedicine*. 2016;13:294-304

Lee JH, Schierer S, Blume K, Dindorf J, Wittki S, Xiang W, Ostalecki C, Koliha N, Wild S, Schuler G, Fackler OT, Saksela K, Harrer T, Baur AS. HIV-Nef and ADAM17-Containing Plasma Extracellular Vesicles Induce and Correlate with Immune Pathogenesis in Chronic HIV Infection. *EBioMedicine*. 2016, 6:103-13.

Santos G, Nikolov S, Lai X, Eberhardt M, Dreyer FS, Paul S, Schuler G, Vera J. Model-based genotype-phenotype mapping used to investigate gene signatures of immune sensitivity and resistance in melanoma micrometastasis. *Scientific Reports* 2016, 6:24967

Heidkamp GF et al. Human lymphoid organ dendritic cell identity is predominantly dictated by ontogeny, not tissue microenvironment. *Science Immunology* 2016, 1, eaai7677; 1-17

Kirchberger MC, Hauschild A, Schuler G, Heinzerling L. Combined low-dose ipilimumab and pembrolizumab after sequential ipilimumab and pembrolizumab failure in advanced melanoma. *Eur J Cancer* 2016, 65:182-4

## **International Cooperations**

Prof. K. Saksela, Department of Virology, University of Helsinki, Helsinki: Finland

Prof. Dr. P. Coulie, de Duve Institut and the Université catholique de Louvain, Brussels: Belgium

Prof. Dr. H.-G. Rammensee, Interfaculty Institute for Cell Biology, Department of Immunology, Tübingen: Germany

Prof. Dr. J. Ravetch, Rockefeller University, New York: USA

Prof. Dr. H. Schmidt, Department of Pharmacology and Personalised Medicine, Maastricht University, Maastricht: The Netherlands



# Department of Dermatology

## Division of Immune Modulation

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### Head of Division

Prof. Dr. Alexander Steinkasserer, PhD

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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 of DC and viruses

### Structure of the Division

Professorships: 1

Personnel: 20

- Scientists: 12 (thereof funded externally: 10)
- Graduate students: 7

### Research

The translation research, i.e. the translation of basic research findings into new and applicable therapeutic strategies for patients, is within the prime focus of our research Division. Immune modulation, in the context of autoimmune disorders and transplantation as well as tumor- and infectious diseases, are in the center of our research projects.

#### Immune-modulation in autoimmunity and transplantation by soluble CD83

PI: 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 paralyzes 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, also 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 (Treg) 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, whereby high concentrations of sCD83 correlated with a reduced treatment free survival in CLL patients, indicating its relevance also in tumor patients. The therapeutic potential as well as the mode of action of sCD83 is currently under investigation using murine arthritis models as well as conditional KO animals whereby CD83 is specifically deleted only in DC, Treg or in B cells. This allows the elucidation of the biological function of CD83 expression in specific cell populations.

#### Transcriptional in vivo targeting of dendritic cells (DC) using the human CD83 promoter

PI: Dr. I. Knippertz

Focus of the research group is the transcriptional targeting of DC and Treg for the treatment of cancer, chronic viral infections, and autoimmune diseases. Regarding this transcriptional targeting strategy, the human DC- and maturation specific CD83 promoter has been successfully characterized in the past. The membrane-bound CD83 molecule is a 45 kDa glycoprotein expressed on the surface of mature, immunogenic DC. Since CD83 is not expressed on immature, tolerogenic DC, its regulatory DNA region, the CD83 promoter, is of high interest in the context of DC-mediated in vivo vaccination strategies directly in patients. For this purpose, therapeutic adenoviruses and nanoparticles are currently generated encoding different immune-modulatory and therapeutic transgenes under the control of the cell type- and stadium specific CD83 promoter. The potency of these therapeutic vectors will then be determined in vivo in humanized tumor mouse models. Recent data from our Division demonstrated CD83 not only to be expressed by mature DC, but also by activated Treg. Interestingly, transcriptional regulation is different in DC and Treg. Therefore, another aim of our group is the characterization of the CD83 promoter in activated Treg, e.g. by ChIP-Seq for the development of new transcriptional targeting strategies for the treatment of autoimmune diseases. The third emphasis of our group is to study the mechanisms by which different Aryl hydrocarbon receptor (AhR)-agonists modulate DC-specific CD83 expression on transcriptional level, thereby modulating the immune response in physiology and pathophysiology. Bioinformatic analyses revealed two transcription factor binding

sites for AhR within the human CD83 promoter region which have been proven experimentally afterwards. The incubation of DC with different AhR-agonists in vitro led to a specific downregulation of CD83, accompanied with an altered cytokine secretion profile and T cell stimulatory capacity. The underlying molecular mechanisms are currently under investigation.

#### Intracellular signal transduction of CD83 in DC

PI: 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-modulation by TSLP and CD83

PI: 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 protein. 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 was addressed in different inflammatory and infectious diseases models as well as in models for autoimmunity. It was demonstrated that TSLP has an important protective function in the development of chronic inflammatory bowel diseases, is capable to directly stimulate intestinal epithelial cells and promotes the regeneration of the epithelial barrier. 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. We reported that CD83-positive T cells had mainly the phenotype of

regulatory T cells as well as Treg-like suppressor functions in vitro and in vivo. Based on these findings the group now investigates, using a Treg-specific conditional CD83 KO-mouse, the influence of CD83 on differentiation and function of regulatory T cells. Third, with regard to the therapeutic application of sCD83, a 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. Essential for this immunomodulatory function of sCD83 was the induction of the IDO. The immunomodulatory sCD83 is also endogenously expressed in inflamed colonic tissue. The questions which cells express CD83 in the intestine and which immune cell types and intestinal epithelial cells are direct targets of CD83 as well as how CD83 modulates intestinal homeostasis and pathogenesis are currently under investigation.

### Interaction of DC and viruses

PI: Dr. C. Heilingloh

This project group analyzes the impact of viral infections on dendritic cells (DC). Particular attention has been given to HSV-1 and HCMV infections. In this respect, the group identified 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. Our group demonstrated that the viral immediate early protein ICP0 induces a proteasomal CD83 degradation which interestingly is independent of its E3 ubiquitin ligase function and the ubiquitin machinery. Furthermore, infection of mature DC with HCMV also induces a proteasomal degradation of the CD83 molecule with immediate-early kinetics. The exact mechanism of these degradation mechanisms is subject of current research. 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. In this regard, we were able to show that HSV-1 infected mature DC release so-called L particles which contain several viral proteins, but lack capsid and DNA. These non-infectious L particles were shown to be able to transfer functional viral proteins to uninfected bystander DC inducing e.g. CD83 degradation, revealing important biological functions of these particles during lytic replication. Therefore, the transfer of viral proteins by L particles to modulate

uninfected bystander cells may represent an additional strategy for viral immune escape. An additional project deals with the HSV-1 mediated modulation of DC migration. In this respect we showed that HSV-1 induces the adhesion of mDC which in turn reduces chemokine mediated DC-migration which is an absolutely essential step in order to induce potent antiviral immune responses.

### Teaching

The co-workers of the Division teach 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's, Master's, and PhD theses. In addition, the SFB 643 (compare own report) was coordinated together with the Department of Dermatology.

### Selected Publications

Eckhardt J, Döbbeler M, König C, Kuczera K, Kuhnt C, Ostalecki C, Zinser E, Mak TW, Steinkasserer A, Lechmann M. Thymic stromal lymphopoietin deficiency attenuates experimental autoimmune encephalomyelitis. *Clin Exp Immunol* 2015. 181(1):51-64

Heilingloh CS, Kummer M, Muhl-Zurbes P, Drassner C, Daniel C, Klewer M, Steinkasserer A. L Particles Transmit Viral Proteins from Herpes Simplex Virus 1-Infected Mature Dendritic Cells to Uninfected Bystander Cells, Inducing CD83 Downmodulation. *J Virol* 2015, 89, 11046-11055

Kreiser S, Eckhardt J, Kuhnt C, Stein M, Krzyzak L, Seitz C, Tucher C, Knippertz I, Becker C, Günther C, Steinkasserer A, Lechmann M. Murine CD83-positive T cells mediate suppressor functions in vitro and in vivo. *Immunobiology* 2015. 220(2):270-9

Rothe T, Gruber F, Uderhardt S, Ipseiz N, Rössner S, Oskolkova O, Blüml S, Leitinger N, Bicker W, Bochkov VN, Yamamoto M, Steinkasserer A, Schett G, Zinser E, Krönke G. 12/15-lipoxygenase-mediated enzymatic lipid oxidation regulates DC maturation and function. *J. Clin. Invest.*; 2015, 125 (5): 1944-1954

Rohrscheidt J, Petroziello E, Nedjic J, Federle C, Krzyzak L, Ploegh H, Ishido S, Steinkasserer A, Klein L. Thymic CD4 T cell selection requires attenuation of March8-mediated MHCII turnover in cortical epithelial cells through CD83. *J. Exp. Med.* 2016, 213(9):1685-1694

Krzyzak L, Seitz C, Ubat A, Hutzler S, Ostalecki C, Gläsner J, Hiergeist A, Gessner A, Winkler TH, Steinkasserer A, Nitschke L. CD83 modulates B cell activation and germinal center responses. *J. Immunol.* 2016, 196:3581-3594

### International Cooperations

Prof. Dr. H. Wang, Lawson Health Research Institute, University of Western Ontario, London: Canada

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

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

Prof. Dr. N. Romani, Department of Dermatology, 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
- Therapeutic targets for treatment of inflammatory bowel diseases
- Division of clinical and experimental pulmonology
- Molecular endoscopy
- Molecular gastroenterology
- Patient-oriented research and innovative therapeutic strategies in IBD
- Ultrasound
- Cytokines and transcription factors in IBD and carcinoma

### Structure of the Department

Professorships: 9  
Personnel: 196  
• Doctors (of Medicine): 66  
• Scientists: 18 (thereof funded externally: 14)  
• Graduate students: 11

### Clinical focus areas

- Gastroenterology
- Pneumology
- Endocrinology and Diabetology
- Hepatology
- Nutritional Medicine
- Intensive Care
- Emergency Reception

### Research

Researchers at the Department of Medicine 1 study the functions and interactions of genes and proteins that are relevant to disease by means of immunological, molecular biological and cell biologic methods. A methodological focus of our research activities is the development of procedures for diagnosis and prognosis of diseases in humans. For this purpose, we run a laboratory for Experimental Diagnostic Imag-

ing which contains a series of state-of-the-art devices for the representation of biological molecules and processes in the living organism (in vivo imaging).

### Intestinal diseases

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

### Endocrinology

PI: 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

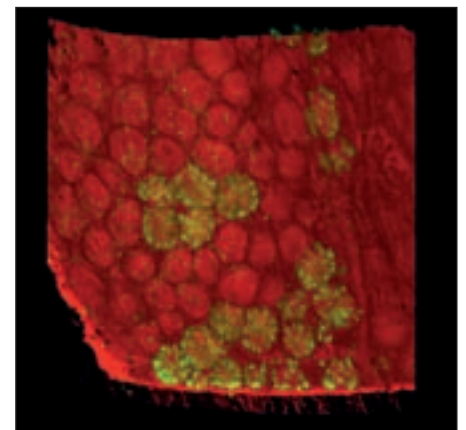
PI: PD Dr. S. Wirtz  
In this research area, we work on pathophysiological processes that drive the initiation and progression of acute and chronic liver disorders. We are particularly interested in novel signal transduction pathways that trigger the occurrence of massive hepatocyte death which is a common feature of acute hepatic inflammation and toxin-dependent liver injury. In this context, we could demonstrate that besides apoptotic cell death other forms of regulated cell death, such as programmed necrosis (necroptosis), substantially contribute to hepatocellular death during liver inflammation. Here, the production of type I, type II and type III interferons by various immune cell subsets proved to be of seminal importance. Therefore, we currently evaluate in preclinical studies and patient cohorts how the interferon-dependent induction of hepatocellular necrosis contributes to gradual accumulation of extracellular matrix compo-

nents and hepatic tissue remodeling. In the long run, we want to identify in these translational research projects new molecular mechanisms of liver pathophysiology and potential prognostic markers or therapeutic targets in liver disease.

### Therapeutic targets for treatment of inflammatory bowel diseases

PI: Dr. I. Atreya

We try to achieve improved insights into the immunopathogenesis of chronic inflammatory diseases and inflammation-associated tumorigenesis. In this context, we in particular focus on the process of post-translational prenylation and the activation of Rho proteins in intestinal epithelial cells and lamina propria immune cells. For instance, our data were able to demonstrate that intestinal epithelial cells in the inflamed gut of patients suffering from inflammatory bowel diseases (IBD) are characterized by diminished levels of prenylation and an altered RhoA signaling. In another project, we are analyzing those mechanisms which are able to regulate the accumulation and activation of innate lymphoid cells within inflamed tissue. Overall, our investigations intend to identify new therapeutic target structures for an improved treatment of inflammatory diseases.



*Small intestinal epithelial stem cells*

### Division of clinical and experimental pulmonology

PI: PD Dr. F. Fuchs, Prof. Dr. K. Hildner

Our clinical research unit attempts to test innovative imaging technologies during clinical routine. Current data demonstrate that malignant cells within pleural effusions can be reliably distinguished from benign cells using in vivo confocal laser-endomicroscopy. In addition, further clinically meaningful areas are investigated employing the surplus of novel bronchoscopic imaging. The assessment of samples collected

in our biobank allows us to perform preclinical studies on the immunological microenvironment of non-small cell lung cancers.

### **Molecular endoscopy**

PI: Prof. Dr. H. Neumann

Through the combination of highly specific fluorescence-labeled molecular probes together with high-resolution imaging, molecular endoscopy enables the ultrastructural visualization of single molecules or receptors during ongoing endoscopy. Molecular endoscopy therefore allows visualizing and quantifying the therapeutic targets of antibody-based biological therapy. Based on this approach, we aim to develop more effective and personalized therapeutic strategies and individualized algorithms for the prediction of therapeutic responses and success. We utilize molecular endoscopy for more specific and personalized diagnostics and therapy in patients with IBD, Barrett's esophagus and colorectal polyps.

### **Molecular gastroenterology**

PI: 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. During the reporting period, the working group carried out various studies on the role of cell death in the development of inflammation. The researchers were able to show that necroptosis in the intestine can be regulated via microbial stimulation. Important objectives in the research of necroptosis were not only the elucidation of the cellular signaling pathways and the investigation of the importance of necroptosis in various diseases, but also the development of specific and simple detection methods for necroptosis and for the delineation of necroptosis from other forms of cell death.

### **Patient-oriented research and innovative therapeutic strategies in IBD**

PI: 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**

PI: 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, DEGUM)
- CEUS for the characterization of hepatic tumors and monitoring of antiangiogenic 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 DEGUM).

### **Cytokines and transcription factors in IBD and carcinoma**

PI: PD Dr. B. Weigmann

Crohn's disease and ulcerative colitis are distinct disease entities of IBD which are characterized by a specific cytokine pattern. Patients with Crohn's disease have increased levels of Th1 cytokines like IL-12 and IFN- $\gamma$  in contrast to ulcerative colitis which are characterized by higher levels of Th2 cytokines like IL-5 and IL-9. The research focuses of the working group are specific proteins so-called transcription factors and immunologically relevant cytokines. A special role is played by the transcription factor family NFAT. These transcription factors are important for the activation of T cells and have been brought in connection with ulcerative colitis in earlier studies. For example NFATc2 controls the development of pro-inflammatory cytokine IL-6, that is important for carcinoma induction, especially in patients suffering of chronic inflammatory diseases. Another focus is interleukin-9 which was identified in relation with IBD and which is expressed from a so-called T-cell population, Th9 cells. A regulation of IL-9 by the use of specific blocking antibodies and antisense-oligonucleotides against the responsible transcription factor PU.1 could be found as a basis for a new effective therapeutic approach. Furthermore, the influence of IL-9 on the induction of colorectal carcinoma is currently under investigation. Finally, the influence of the immunosuppressive drug ciclosporin A which is used as a therapeutic approach during

ulcerative colitis is actually in analysis. Main topic is to clarify the underlying mechanism, because CsA is not effective in patients with Crohn's disease and acute colitis.

### **Teaching**

The Department of Medicine 1 is involved in the curricular teaching of human and dental medicine with compulsory and elective courses. Particularly noteworthy is the interdisciplinary teaching within the cross section lectures together with the Departments of Medicine 2 - 5 as well as the Institutes of Clinical Microbiology, Immunology, and Hygiene and of Clinical and Molecular Virology, respectively.

The Department of Medicine 1 offers a student ultrasound training with exclusive devices for this purpose.

MD and PhD doctorates are supervised.

### **Selected Publications**

Foersch S, Sperka T, Lindner C, Taut A, Rudolph KL, Breier G, Boxberger F, Rau TT, Hartmann A, Stürzl M, Wittkopf N, Haep L, Wirtz S, Neurath MF, Waldner MJ. VEGFR2 Signaling Prevents Colorectal Cancer Cell Senescence to Promote Tumorigenesis in Mice With Colitis. *Gastroenterology*. 2015 Jul;149(1):177-189

Günther C, Buchen B, He GW, Hornef M, Torow N, Neumann H, Wittkopf N, Martini E, Basic M, Bleich A, Watson AJ, Neurath MF, Becker C. Caspase-8 controls the gut response to microbial challenges by Tnf-alpha-dependent and independent pathways. *Gut*. 2015 Apr;64(4):601-10

Monteleone G. et al. Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn's disease. *N Engl J Med*. 2015 Mar 19;372(12):1104-13

Fischer A, Zundler S, Atreya R, Rath T, Voskens C, Hirschmann S, López-Posadas R, Watson A, Becker C, Schuler G, Neufert C, Atreya I, Neurath MF. Differential effects of alpha 4 beta 7 and GPR15 on homing of effector and regulatory T cells from patients with UC to the inflamed gut in vivo. *Gut*. 2016 Oct;65(10):1642-64

López-Posadas R, Becker C, Günther C, Tenzer S, Amann K, Billmeier U, Atreya R, Fiorino G, Vetrano S, Danese S, Ekici AB, Wirtz S, Thonn V, Watson AJ, Brakebusch C, Bergö M, Neurath MF, Atreya I. Rho-A prenylation and signaling link epithelial homeostasis to intestinal inflammation. *J Clin Invest*. 2016 Feb;126(2):611-26

Leppkes M. et al. Externalized decondensed neutrophil chromatin occludes pancreatic ducts and drives pancreatitis. *Nat Commun*. 2016 Mar 11;7:10973

### **International Cooperations**

M. Lacucci, MD, PhD, Institute of Translational Medicine, University of Birmingham, Birmingham: UK

R. S. Blumberg, MD, Brigham Research Institute Division of Gastroenterology, Brigham and Women's Hospital, Boston: USA

Prof. A. Kaser, Department of Medicine, University of Cambridge, Cambridge: UK



# Department of Medicine 2 – Cardiology and Angiology

## Chair of Internal Medicine II

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### Research Focus

- Molecular and experimental cardiology
- Interventional cardiology
- Interventional valve therapy
- Electrophysiology
- Cardiac magnetic resonance tomography (MRT)
- Cardiac computed tomography
- Sports cardiology

### Structure of the Department

Professorships: 1

Personnel: 210

- Doctors (of Medicine): 52
- Scientists: 4 (thereof funded externally: 1)
- Graduate students: 14

### Clinical focus areas

- Interventional cardiology
- Electrophysiology
- Intensive care medicine
- Cardiac imaging

### Research

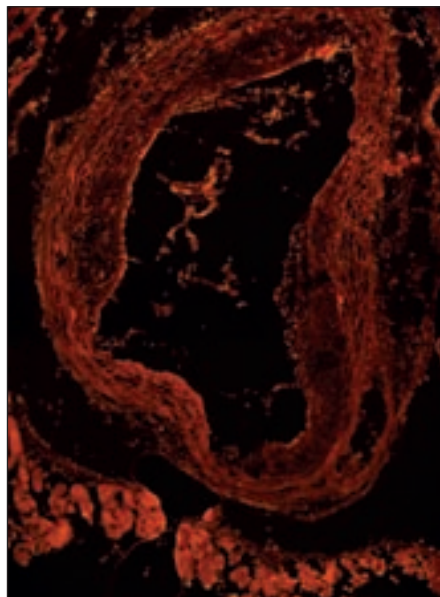
The Department of Medicine 2 focuses on clinically oriented research. Several working groups pursue research projects particularly in the field of cardiac intervention as well as coronary heart disease and atherosclerosis. A special focus lies traditionally in the field of cardiac imaging, especially the link between cardiac imaging and its implementation for planning and guiding several cardiac interventions which has developed into a growing field of research in the recent years. Most of the research projects performed in the Department are patient-related projects with a close relationship to patient care.

### Molecular and Experimental Cardiology

PI: Dr. B. Dietel, Dr. M. Tauchi-Brück

The laboratory for molecular and experimental cardiology is concerned with the fundamentals

of the development of atherosclerotic vascular changes. A special focus is the influence of blood flow profiles on atherogenesis. It is of note that particularly in vascular bifurcations, atherosclerotic lesions arise due to turbulent shear forces. These shear forces activate endothelial cells and induce inflammatory processes that affect the progression of atherosclerosis. Using cell culture models, surface molecules of endothelial cells and their activation are analyzed. In addition to shear forces-induced activation of endothelial cells, various immunomodulatory therapeutic approaches in the atherosclerotic model of the ApoE (apolipoprotein E) knockout mice are investigated. The working group further analyzes mechanisms that contribute to plaque destabilization through histological analyses of human atherosclerotic plaques, supplemented by analysis of gene expression and naturally occurring genetic polymorphisms.



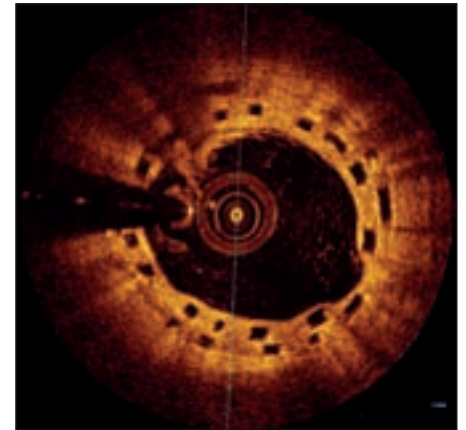
TUNEL stain of a murine aortic root

### Interventional cardiology

PI: Dr. C. Schlundt

This working group is dedicated to the further development of the interventional therapy of coronary heart disease (CHD) as well as structural heart disease. In addition to the systematic evaluation of coronary physiology by means of pressure wire measurement (FFR) and intracoronary imaging (OCT) to support complex interventions, the link between non-invasive imaging and interventional therapy in the catheter laboratory constitutes the target of several research projects. This includes several structural heart disease interventions as well as recanaliza-

tion of chronic total coronary occlusion. Moreover, the systematic evaluation of innovative stent technologies is performed in cooperation with several other university clinics in Germany.



Optical Coherence Tomography: Overlap of two bioresorbable coronary scaffolds

### Interventional valve therapy

PI: Dr. M. Arnold

The scientific evaluation and further development of transcatheter heart valves, in particular for aortic valve replacement (TAVI), is a main focus of the Department of Medicine 2. Several research projects are performed together with colleagues of the Department of Cardiac Surgery, focusing on the value of cardiac computer tomography for planning and follow-up of patients referred for transcatheter aortic valve replacement as well as the advantages of a modified surgical approach for the transfemoral aortic valve replacement. In addition, the Department is involved in several national and international studies and long-term registries for interventional aortic valve replacement.

### Electrophysiology

PI: Dr. M. Arnold

The working group is engaged in the development and evaluation of continuous remote monitoring algorithms for patients with advanced heart failure. In cooperation with other working groups and industry partners, monitoring facilities are further developed and their clinical use as well as the influence of various external interfering factors are analyzed. The automated analysis of cardiac arrhythmias is a joint area of research field with the „Digital Sports Group“ of FAU and Fraunhofer Institute for Integrated Circuits. The working group is further engaged in the evaluation of new ICD (Implantable Cardioverter Defibrillator) and pacemaker leads as well as new technologies for tachycardia detection. Furthermore, the clinical assessment of various



ablation procedures for supraventricular arrhythmias is an area of evaluation.

### Cardiac magnetic resonance tomography (MRT)

PI: Dr. G. Gitsioudis

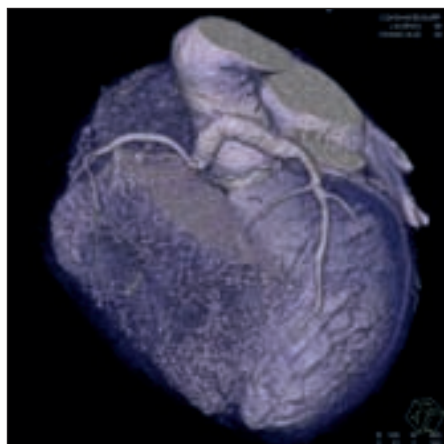
The research focus of the working group - in collaboration with the Institute of Radiology and Siemens Healthineers Erlangen - is the assessment of morphological and functional cardiac function parameters for the improvement of individual patient-specific risk assessment for various cardiovascular diseases.

In the context of clinical trials, this working group investigates the importance of assessment of segmental myocardial function and late gadolinium enhancement (LGE) for the prediction of successful therapy after revascularization of chronically occluded coronary arteries. Moreover, the role of the T1 mapping for performing contrast-free imaging of areas of myocardial scarring and fibrosis in patients with myocardial infarctions or cardiomyopathies (such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), peri-/myocarditis, cardiac amyloidosis) is an important research area. Technically oriented projects concern the development of high-resolution sequences for optimizing assessment of myocardial ischemia by perfusion imaging under adenosine stimulation.

### Cardiac computed tomography

PI: PD Dr. M. Marwan

The working group conducts numerous projects around CT imaging of the heart and coronary arteries. One of the main research areas is the characterization of coronary atherosclerosis. This includes the analysis and quantification of coronary atherosclerotic plaques and evaluation of their prognostic significance as well as the evaluation of the hemodynamic relevance of coronary lesions, for example by means of „virtual FFR“. Further projects - in cooperation with several national and international partners - concern the development and validation of strategies for the reduction of radiation exposure. Furthermore, the use of cardiac computed tomography to guide cardiac interventions in the sense of „therapeutic imaging“ is a field of particular importance. Members of the working group comprehensively evaluate the use of CT for coronary interventions (especially for chronic coronary artery occlusions) and non-coronary cardiac interventions (transcatheter aortic valve replacement, left atrial appendage occlusion and other structural heart disease interventions).



3D-reconstructed coronary CT angiography: Cabrol shunt for coronary anastomosis following implantation of an ascending aortic conduit

### Sports cardiology

PI: PD Dr. C. Stumpf

The working group investigates the effects of physical activity on the cardiovascular system for various age-groups and functional capabilities. A special focus of the working group is on the evaluation of the training therapy for chronic heart failure patients and its influence on remodeling as well as on the inflammatory mechanisms and their pathogenesis through endurance training (EndoHEART). A further focus of the working group is in the field of cardiovascular prevention, in particular in the assessment of the pathophysiological mechanisms of endothelial dysfunction and the influence on physical training on it.

### Teaching

The Chair of Internal Medicine II participates in the curricular in medicine.  
The Chair supervises MD theses.

### Selected Publications

Dietel B, Budinsky L, Kuehn C, Uder M, Achenbach S, Hess A. Quantification of plaque lipids in the aortic root of ApoE-deficient mice by 3D DIXON magnetic resonance imaging in an ex vivo model. *Eur Radiol.* 2015 Mar;25(3):736-44

Nørgaard BL, Gaur S, Leipsic J, Ito H, Miyoshi T, Park SJ, Zvaigzne L, Tzemos N, Jensen JM, Hansson N, Ko B, Bezerra H, Christiansen EH, Kaltoft A, Lassen JF, Bøtker HE, Achenbach S. Influence of Coronary Calcification on the Diagnostic Performance of CT Angiography Derived FFR in Coronary Artery Disease: A Substudy of the NXT Trial. *JACC Cardiovasc Imaging.* 2015 Sep;8(9):1045-55

Rittger H, Waliszewski M, Brachmann J, Hohenforst-Schmidt W, Ohlow M, Brugger A, Thiele H, Birkemeyer R, Kurowski V, Schlundt C, Zimmermann S, Lonke S, von Cramon M, Markovic S, Daniel WG, Achenbach S, Wöhrle J. Long-Term Outcomes After Treatment With a Paclitaxel-Coated Balloon Versus Balloon Angioplasty: Insights From the PEPCAD-DES Study (Treatment of Drug-eluting Stent [DES] In-Stent Restenosis With SeQuent Please Paclitaxel-Coated Percutaneous Transluminal Coronary Angioplasty

[PTCA] Catheter). *JACC Cardiovasc Interv.* 2015 Nov;8(13):1695-700

Schlundt C, Bietau C, Klinghammer L, Wiedemann R, Rittger H, Ludwig J, Achenbach S. Comparison of intracoronary versus intravenous administration of adenosine for measurement of coronary fractional flow reserve. *Circ Cardiovasc Interv.* 2015 May;8(5). pii: e001781

Kuehn C, Tauchi M, Stumpf C, Daniel C, Bäuerle T, Schwarz M, Kerek F, Steinkasserer A, Zinser E, Achenbach S, Dietel B. Suppression of proatherogenic leukocyte interactions by MCS-18—Impact on advanced atherosclerosis in ApoE-deficient mice. *Atherosclerosis.* 2016 Feb;245:101-10

Tröbs M, Achenbach S, Röther J, Redel T, Scheuering M, Winneberger D, Klingenberg K, Itu L, Passerini T, Kamen A, Sharma P, Comaniciu D, Schlundt C. Comparison of Fractional Flow Reserve Based on Computational Fluid Dynamics Modeling Using Coronary Angiographic Vessel Morphology Versus Invasively Measured Fractional Flow Reserve. *Am J Cardiol.* 2016 Jan 1;117(1):29-35

### International Cooperations

Dr. U. Hoffmann, Massachusetts General Hospital, Boston: USA

Dr. D. Berman, Damini Dey, Cedars Sinai Medical Center, Los Angeles: USA

Prof. Dr. S. Neubauer, University of Oxford, Oxford: UK

Dr. P. Maurovich-Horvat, Semmelweis University, Budapest: Hungary

Dr. M. Ferencik, Knight Cardiovascular Institute, Oregon Health and Science University, Portland: USA

# Department of Medicine 3 – Rheumatology and Immunology

## Chair of Internal Medicine III

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### Director

Prof. Dr. med. Georg Schett

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### Research Focus

- Activation of synovial fibroblasts by microparticles in rheumatoid arthritis (RA)
- Apoptosis, necrosis, and NETosis as immune modulators
- Activation of neutrophil granulocytes
- National and international clinical trials
- Immunogenetics and transplantimmunology
- Immunodeficiencies and infectious diseases
- Mechanisms for the activation of fibroblasts in systemic sclerosis (SSc)
- Molecular signaling pathways in RA
- Metabolic impact on inflammation
- Pathomechanisms of bone destruction in RA
- Analysis of risk factors and long-term outcome in patients with systemic lupus erythematosus (SLE)
- The role of 12/15-lipoxygenase (12/15-LO) in the regulation of innate and adaptive immunity
- Analysis of inflammatory mechanisms in adult onset Still's disease
- Molecular and cellular immunology in metabolism

### Structure of the Department

Professorships: 6

Personnel: 163

- Doctors (of Medicine): 18
- Scientists: 28 (thereof funded externally: 24)
- Graduate students: 47

### Clinical focus areas

- Rheumatology (In- and outpatient department)
- Immunology (In- and outpatient department)

### Research

The Department of Internal Medicine 3 focuses on translational and clinical inflammation research to decipher the mechanisms which are

responsible for pathogenesis and perpetuation of rheumatic inflammatory and autoimmune diseases. The emphasis of the experimental research is on the interaction between immune cells and cells of affected organs. The main focus of the clinical research is besides drug trial studies on interdisciplinary cooperations to optimize imaging methods.

### Activation of synovial fibroblasts by microparticles in rheumatoid arthritis (RA)

PI: Prof. Dr. J. Distler

Microparticles are realized 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.

### Apoptosis, necrosis, and NETosis as immune modulators

PI: Prof. Dr. Dr. M. Herrmann

We utilize 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.

### Activation of neutrophil granulocytes

PI: 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.

### National and international clinical trials

PI: PD Dr. J. Rech, Dr. A. Kleyer, PD 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 pro-inflammatory cytokine  $\text{TNF}\alpha$ , IL-6, IL-17, IL-12/23, JAK3-kinase. We initiated and conducted a multicenter phase II trial in patients with erosive finger osteoarthritis.

### Immunogenetics and transplantimmunology

PI: Prof. 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.

### Immunodeficiencies and infectious diseases

PI: Prof. Dr. T. Harrer

The major research interests of this 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.

### Mechanisms for the activation of fibroblasts in systemic sclerosis (SSc)

PI: Prof. Dr. J. Distler

SSc is characterized by organ fibrosis, mediated by an uncontrolled production of ECM by fibroblasts. 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

PI: Prof. Dr. G. Schett, PD 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.

### Metabolic impact on inflammation

PI: Prof. Dr. G. Schett, Prof. Dr. A. Bozec

Arthritis, adipose and diabetes appear to form an alliance which has an pro-inflammatory and

destructive effect on joints and bones. We investigate central transcription factors and signaling pathways relevant as checkpoints for differentiation and activation in osteoclast, osteoblasts and adipocytes.

### **Pathomechanisms of bone destruction in RA**

PI: 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.

### **Analysis of risk factors and long-term outcome in patients with systemic lupus erythematosus (SLE)**

PI: 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.

### **The role of 12/15-lipoxygenase (12/15-LO) in the regulation of innate and adaptive immunity**

PI: Prof. 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 (dendritic 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).

### **Analysis of inflammatory mechanisms in adult onset Still's disease**

PI: PD 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.

### **Molecular and cellular immunology in metabolism**

PI: Dr. M. Zaiss

Different types of immune responses require alterations in metabolism – vice versa, are immunomodulators (e.g. cytokines) dictating direct alterations in metabolism which highlight the interaction between these two aspects? Our aim is the investigation of the interplay of immunology, metabolism and nutrition in order to prevent or resolve autoimmune diseases.

### **Teaching**

The Department of Medicine 3 is embedded into the curriculum-based teaching of the human and dental medicine. In the course of interdisciplinary teaching, the lecture "Dr. House in Erlangen – surgical and internal differential diagnosis for first-year students" is to highlight particularly.

Furthermore Master's as well as MD and PhD theses are supervised.

### **Selected Publications**

Rothe T, Gruber F, Uderhardt S, Ipseiz N, Rössner S, Oskolkova O, Blüml S, Leitinger N, Bicker W, Bochkov VN, Yamamoto M, Steinkasserer A, Schett G, Zinser E, Krönke G. 12/15-Lipoxygenase-mediated enzymatic lipid oxidation regulates DC maturation and function. *J Clin Invest.* 2015 May;125(5):1944-54

Luo Y, Chen GL, Hannemann N, Ipseiz N, Krönke G, Bäuerle T, Munos L, Wirtz S, Schett G, Bozec A. Microbiota from Obese Mice Regulate Hematopoietic Stem Cell Differentiation by Altering the Bone Niche. *Cell Metab.* 2015 Nov 3;22(5):886-94

Harre U, Lang SC, Pfeifle R, Rombouts Y, Frühbeißer S, Amara K, Bang H, Lux A, Koeleman CA, Baum W, Dietel K, Gröhn F, Malmström V, Klareskog L, Krönke G, Kocijian R, Nimmerjahn F, Toes RE, Herrmann M, Scherer HU, Schett G. Glycosylation of immunoglobulin G determines osteoclast differentiation and bone loss. *Nat Commun.* 2015 Mar 31;6:6651

Palumbo-Zerr K, Zerr P, Distler A, Fliehr J, Mancuso R, Huang J, Mielenz D, Tomcik M, Füllrohr BG, Scholtyssek C, Dees C, Beyer C, Krönke G, Metzger D, Distler O, Schett G, Distler JH. Orphan nuclear receptor NR4A1 regulates transforming growth factor- $\beta$  signaling and fibrosis. *Nat Med.* 2015 Feb;21(2):150-8

Muñoz LE, Bilyy R, Biermann MH, Kienhöfer D, Maueröder C, Hahn J, Brauner JM, Weidner D, Chen J, Scharin-Mehmann M, Janko C, Friedrich RP, Mielenz D, Dumych T, Lootsik MD, Schauer C, Schett G, Hoffmann M, Zhao Y, Herrmann M. Nanoparticles size-dependently initiate self-limiting NETosis-driven inflammation. *Proc Natl Acad Sci U S A.* 2016 Oct 4;113(40):E5856-E5865

Chen Z, Andreev D, Oeser K, Krljanac B, Hueber A, Kleyer A, Voehringer D, Schett G, Bozec A. Th2 and eosinophil responses suppress inflammatory arthritis. *Nat Commun.* 2016 Jun 7;7:11596

### **International Cooperations**

Prof. L. Klareskog, Karolinska Institute, Stockholm: Sweden

Prof. Dr. S. Kiechl, Medizinische Universität Innsbruck, Innsbruck: Austria

Prof. M. Hansson, Uppsala University, Uppsala: Sweden

Prof. Dr. E. Wagner, Spanish National Cancer Research Centre (CNIO), Madrid: Spain

Prof. I. McInnes/Dr. C. Goodyear, University of Glasgow, Glasgow: United Kingdom

# Department of Medicine 3 – Rheumatology and Immunology

## Division of Molecular Immunology

### Address

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### Head of Division

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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

Professorships: 1

Personnel: 21

- Scientists: 6 (thereof funded externally: 3)
- Graduate students: 8

### Research

The Division of Molecular Immunology concentrates on the development of mature B cells and their differentiation in effector cells. In addition, we develop human monoclonal antibodies against tumors of the B cell lineage.

#### The role of miRNA in B cell maturation and pathogenesis of multiple myeloma

PI: Prof. Dr. H.-M. Jäck, Dr. J. Wittmann

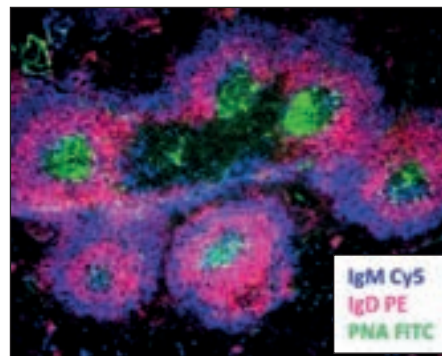
One research focus is on the role of microRNA (miRNA) during central and peripheral development of B cells, the antigen-induced differentiation of mature B cells, as well as the pathogenesis of diseases, such as multiple myeloma or Epstein-Barr virus infection. MiRNA are small, 22-nt long, non-coding RNA (ribonucleic acid) that control the expression of specific target genes at the post-transcriptional level. MiRNA bind to the 3'-untranslated region of mRNA (messenger RNA) which results either in a block of translation or an acceleration of the degradation of the target mRNA. MiRNA play a significant role in the regulation of cell fate and cell differentiation processes

in animals and plants. Dysregulation of miRNA expression was detected in various tumors. Therefore, we are investigating the function of miRNA during development of normal B cells as well as the pathogenesis of multiple myeloma and B cell autoimmune diseases. Currently, we are analyzing miRNA expression profiles in different B cell stages and myeloma as well as lymphoma cells by high-throughput-sequencing of miRNA libraries which will serve as a platform for further functional analysis of specific miRNA involved in the B cell maturation and the generation of multiple myeloma or B cell lymphoma.

#### Nonsense-codon mediated decay of non-functional mRNA

PI: Prof. Dr. H.-M. Jäck, Dr. J. Wittmann

Another research focus is the molecular control of recognition and decay of non-functional immunoglobulin (Ig)-mRNA, a pathway that is termed nonsense-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 because of a defective VDJ recombination. As faulty mRNA can be translated into potentially toxic proteins, the elucidation of control mechanisms and factors involved in mRNA decay is of interest for B and T cell maturation. The role of NMD in central B cell maturation is analyzed in a mouse line in which a specific NMD factor which was discovered in our laboratory can be conditionally deleted in developing B cell progenitors. In parallel, immunoprecipitation analyses followed by mass spectrometry analyses are carried out to identify novel interaction partners and their role in the degradation of faulty mRNAs and early B cell maturation.



Flow cytometric detection of plasma cell subpopulations

#### Molecular control of early B cell differentiation

PI: Prof. Dr. H.-M. Jäck, Dr. W. Schuh

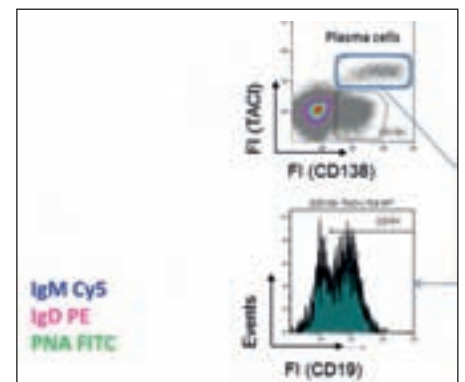
One major focus is the analysis of mechanisms that control early B cell development and signaling of the pre-B cell receptor. For example,

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 several small noncoding 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 activation and plasma cell differentiation

PI: 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. In addition, we want to analyze the role of KLF2 in B cell activation and plasma cell homeostasis in Gut-associated lymphoid tissues (GALT) and in the context of IgA immune responses.



Immunohistochemical detection of activated B cells (green)



## Selection of B cells

PI: PD Dr. D. Mielenz

The unique passport of each single B cell is BCR (B cell receptor). 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 degree programs in biology, life science engineering, and molecular medicine. Students can work on their Bachelor's and Master's theses embedded in the research focus of the Division of Molecular Immunology. Furthermore, the Division of Molecular Immunology engages in educating and training doctoral students from GK 1660 (compare own report) by offering numerous workshops and seminars, like journal clubs or scientific writing and presentation workshops.

## Selected Publications

Beck-Engeser GB, Winkelmann R, Wheeler ML, Shansab M, Yu P, Wünsche S, Walchhütter A, Metzner M, Vettermann C, Eilat D, DeFranco A, Jäck HM, Wabl M. APOBEC3 enzymes restrict marginal zone B cells. *Eur J Immunol.* 2015;45(3): 695-704

Porstner M, Winkelmann R, Daum P, Schmid J, Pracht K, Côté-Real J, Schreiber S, Haftmann C, Brandl A, Mashregi MF, Gelse K, Hauke M, Wirries I, Zwick M, Roth E, Radbruch A, Wittmann J, Jäck HM. miR-148a promotes plasma cell differentiation and targets the germinal center transcription factors *Mitf* and *Bach2*. *Eur J Immunol.* 2015;45(4): 1206-15

Fürnrohr BG, Stein M, Rhodes B, Chana PS, Schett G, Vyse TJ, Herrmann M, Mielenz D. Reduced Fluorescence versus Forward Scatter Time-of-Flight and Increased Peak versus Integral Fluorescence Ratios Indicate Receptor Clustering in Flow Cytometry. *J Immunol.* 2015;195(1): 377-85

Brandl A, Daum P, Brenner S, Schulz SR, Yap DY, Bosl MR, Wittmann J, Schuh W, Jäck HM. The microprocessor component, DGCR8, is essential for early B-cell development in mice. *Eur J Immunol.* 2016 Dec;46(12):2710-2718

Herglotz J, Unrau L, Hauschildt F, Fischer M, Kriebitzsch N, Alawi M, Indenbirken D, Spohn M, Müller U, Ziegler M, Schuh W, Jäck HM, Stocking C. Essential control of early B-cell development by *Mef2* transcription factors. *Blood.* 2016;127(5): 572-81

Liu P, Baumgart M, Groth M, Wittmann J, Jäck HM, Platzer M, Tuckermann JP, Baschant U. Dicer ablation in osteoblasts by *Runx2* driven *cre-loxP* recombination affects bone integrity, but not glucocorticoid-induced suppression of bone formation. *Sci Rep.* 2016;6: 32112

## International Cooperations

Prof. K. Knight, Loyola University of Chicago, Maywood: USA

Prof. M. Wabl, University of California, San Francisco: USA



# Department of Medicine 4 – Nephrology and Hypertension

## Chair of Internal Medicine IV

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### Director

Prof. Dr. med. Kai-Uwe Eckardt  
(until 31.3.2017)

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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

Professorships: 6

Personnel: 146

- Doctors (of Medicine): 87
- Scientists: 8 (thereof funded externally: 5)
- Graduate students: 18

### Clinical focus areas

- Diagnosis and treatment of all acute and chronic kidney diseases
- Kidney transplantation including living donor transplantation
- Sepsis and multiorgan failure
- Extracorporeal blood purification
- Refractory arterial hypertension

### Special structural features

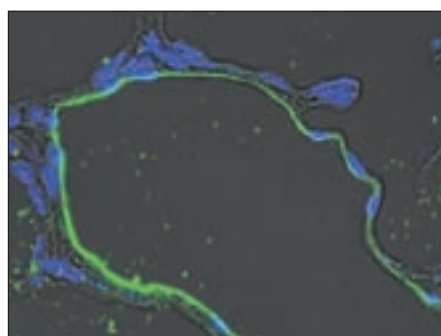
Association with the Department of Nephrology at the Klinikum Nürnberg

### Research

Research at the Department of Nephrology and Hypertension has a strong translational focus. Accordingly projects encompass experimental and patient-orientated research. Our research aims at a better understanding of the initiation and course of acute and chronic kidney diseases and of the development and complications of arterial hypertension.

### 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 (compare own report), has been initiated. Nine regional centers and several institutes at other universities collaborate with the coordinating center in Erlangen (CCC; compare own report) to study 5,000 patients with chronic kidney disease and to follow them for up to ten years. Funding: BMBF, Foundation for Preventive Medicine of the Kuratorium für Heimdialyse. Studies of the genetic causes of kidney disease play an important role within this large 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.

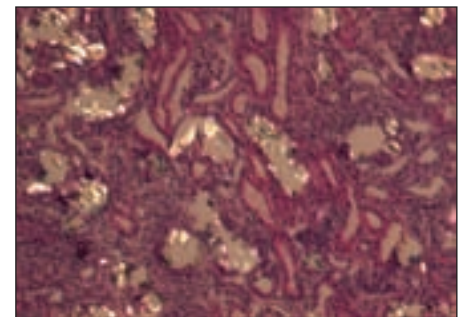


*Mechanisms of renal cyst growth*

### 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.



*Immunology of crystal-induced kidney diseases*

### 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 micro-neurography – in humans, too. In addition, sympathetic 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 dimethylarginine (ADMA), of oxalate crystal deposition, 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. 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 contributes in various ways to the teaching schedule, including interdisciplinary teaching in intensive care medicine together with the Department of Anesthesiology.

The chair supervises Bachelor's and Master's theses as well as MD and PhD theses.

### **Selected Publications**

Forschbach V, Goppelt-Strube M, Kunzelmann K, Schreiber R, Piedagnel R, Kraus A, Eckardt KU, Buchholz B. Anoctamin 6 is localized in the primary cilium of renal tubular cells and is involved in apoptosis-dependent cyst lumen formation. *Cell Death Dis.* 2015;6: e1899

Eckardt KU et al. High cardiovascular event rates occur within the first weeks of starting hemodialysis. *Kidney Int.* 2015;88(5): 1117-25

Schley G, Scholz H, Kraus A, Hackenbeck T, Klanke B, Willems C, Wiesener MS, Heinze E, Burzlaff N, Eckardt KU, Buchholz B. Hypoxia inhibits nephrogenesis through paracrine Vegfa despite the ability to enhance tubulogenesis. *Kidney Int.* 2015;88(6): 1283-1292

Lobo MD et al. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial. *Lancet.* 2015;385(9978): 1634-41

Rodionova K, Fiedler C, Guenther F, Grouzmann E, Neuhauser W, Fischer MJ, Ott C, Linz P, Freisinger W, Heinlein S, Schmidt ST, Schmieder RE, Amann K, Scroggin KE, Veelken R, Ditting T. Complex reinnervation pattern after unilateral renal denervation in rats. *Am J Physiol Regul Integr Comp Physiol.* 2016;310(9): R806-18

Grampp S, Platt JL, Lauer V, Salama R, Kranz F, Neumann VK, Wach S, Stöhr C, Hartmann A, Eckardt KU, Ratcliffe PJ, Mole DR, Schödel J. Genetic variation at the 8q24.21 renal cancer susceptibility locus affects HIF binding to a MYC enhancer. *Nat Commun.* 2016;7: 13183

### **International Cooperations**

Prof. R. Kleta, University College, London: UK

Prof. P. Aronson, University of Yale, New Haven: USA

Prof. P.J. Ratcliffe, University of Oxford, Oxford: UK

Prof. M.D. Feldman, University of Philadelphia, Philadelphia: USA

Prof. J. Coresh, Johns Hopkins University, Baltimore: USA

# Department of Medicine 5 – Hematology and Oncology

## Chair of Hematology and Oncology

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### Research Focus

- Immune regulation by DN T cells
- Adoptive cell therapy with memory B-lymphocytes for patients after allogeneic stem cell transplantation (alloSCT)
- T cells between immunotherapy and autoimmunity
- Immunometabolism
- Tumor associated macrophages and post-transcriptional regulation by Hoxa9
- Communication of tumor cells and microenvironment
- Molecular immunotherapy
- T cell-based immunotherapy of ocular melanoma
- Tumor microenvironment
- Tumor immune escape
- Cellular immunotherapy
- HLA-laboratory

### Structure of the Department

Professorships: 2

Personnel: 120

- Doctors (of Medicine): 34
- Scientists: 8 (thereof funded externally: 7)
- Graduate students: 15

### Clinical focus areas

- In-patient and out-patient care of patients with leukemia, lymphoma, and non-malignant hematologic diseases
- Allogeneic and autologous stem cell transplantation
- Out-patient stem cell transplant unit
- In-patient and out-patient care of patients with urological tumors, bone and soft tissue sarcoma, head and neck tumors, lung tumors and other solid tumors
- Out-patient unit for urological tumors (AURONTE)
- Hematological diagnostics

### Research

The main research focus of the Department of Medicine 5 concentrates on tumor immunology. Several research groups examine basic immunological mechanisms of tumor formation, tumor defense and tumors escape. We have a special research focus on the characterization and blockade of graft-versus-host reactions after allogeneic stem cell transplantation and the improvement of graft-versus-leukemia responses. The long-term goal is to translate these concepts into innovative cell-based therapies.

#### Immune regulation by DN T cells

PI: Prof. Dr. A. Mackensen, Dr. S. Völkl

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.

Funding: SFB 1181 (project B04), IZKF

#### Adoptive cell therapy with memory B-lymphocytes for patients after allogeneic stem cell transplantation (alloSCT)

PI: Dr. J. Winkler, Prof. Dr. T. Winkler, Prof. Dr. M. Mach

The aim of our project is the preclinical development of a new, first-in-man cell based therapy for the improvement of humoral immune responses in patients after alloSCT. We developed a study protocol for a phase I/IIa clinical trial for the adoptive transfer of allogeneic donor B-lymphocytes for patients four months after alloSCT according to GCP. The application of allogeneic B lymphocytes is intended for 15 patients in escalating cell dosages. So far, 13 patients received the B-cell product and no severe adverse events were observed.

Funding: SFB 643 (project C09)

#### T cells between immunotherapy and autoimmunity

PI: PD Dr. Dr. A.N. Kremer

The main focus of this group is the separation of beneficial graft versus leukemia (GvL) effect after allogeneic stem cell transplantation from detrimental GvHD. By characterization of the intracel-

lular processing pathways of HLA class II restricted antigens, we could identify a group of antigens that potentially mediate a selective GvL effect.

Further we analyze the role of these antigens in the pathogenesis of autoimmune diseases and the CD4 $^+$  T cell mediated eradication of HLA class II negative tumors via indirect antigen presentation.

Funding: DFG, Else Kröner Fresenius Foundation, Ernst Jung-Foundation, IZKF

#### Immunometabolism

PI: Prof. Dr. D. Mougiakakos

We focus on alterations of the metabolism and the immune system in cancer and after stem cell transplantation. An understanding regarding tumor-associated (metabolic) strategies contributing to an immunosuppression will support development of therapeutic strategies. Furthermore, we aim at "learning" how tumors weaken immune responses in order to translate these findings into potential experimental approaches for the treatment of rejection reactions (GvHD) following SCT.

Funding: Deutsche Krebshilfe (Max-Eder Junior Research Group), José Carreras Leukemia Foundation, Else Kröner Fresenius Foundation, European Hematology Association, Elitenetzwerk Bavaria, ELAN, IZKF, Marohn Foundation, industry

#### Tumor associated macrophages and post-transcriptional regulation by Hoxa9

PI: Dr. H. Bruns, Dr. C. Bach

Macrophages are the main component of the tumor microenvironment in the most malignancies. Although macrophages can, in principle, target neoplastic cells and mediate antibody-dependent cytotoxicity, tumor-associated macrophages (TAM) regularly fail to exert direct cytotoxic functions. However, TAM are thought to be pro-tumorigenic because they promote angiogenesis and metastasis. The underlying mechanisms responsible for this observation remain unclear. Our research is focused on the functional and molecular analysis of the tumor microenvironment and aims at identifying and modulating potential therapeutic target structures. A further project is the post-transcriptional regulation by Hoxa9. The oncogene Hoxa9 contributes to post-transcriptional regulation by interaction with the RNA export and protein synthesis regulator eIF4e. To date, target genes of this interaction have not been identified. Therefore, we aim to identify post-transcriptional targets of Hoxa9 and eIF4e by RNA immunoprecipitation. Moreover, analyses of

altered RNA-export will be performed as functional validation. In summary, this study will help to clarify the contribution of Hoxa9 to leukemogenesis and provide a solid basis to uncover novel therapeutically relevant targets.

Funding: Wilhelm Sander Foundation, IZKF, Johannes and Frieda Marohn Foundation

### **Communication of tumor cells and microenvironment**

PI: Dr. G. Lutzny-Geier

Our group is interested in the communication of tumor cells with their microenvironment. Understanding how different signaling pathways get activated through intrinsic signals of the tumor cell itself and extrinsic signals of the microenvironment is one aim of our studies. Therefore, we investigate how the microenvironment is modulated by tumor cells and if interference with this modulation can be used as new therapeutic approaches for lymphoma patients.

Funding: ELAN, Trunk Foundation, industry

### **Molecular immunotherapy**

PI: Dr. F. Müller

The young research group exploits antibody-targeted recombinant immunotoxins to kill cancer cells specifically. The immunotoxins induce a highly immunogenic cell death which changes the immunosuppressive milieu within a tumor thereby inducing anti-cancer immunity. Central to the group's research are (i) the development of innovative immunotoxins and of (ii) understanding and augmenting the immunotoxin-induced anti-cancer immune response. The mechanism of immune modulation by immunotoxins in combination with checkpoint inhibitors and toll-like receptor agonists is studied in animal models.

Funding: IZKF

### **T cell-based immunotherapy of ocular melanoma**

PI: Dr. J. Bosch

The main focus of our research group is to develop a T cell-based immunotherapy specifically designed for treatment of ocular melanoma. We focus on analysis of immune cell infiltration in the primary tumor originating in the immune-privileged eye. In addition, we determine if uveal melanoma vaccines or bi-specific antibodies activate different subpopulations of CD4<sup>+</sup> T cells and which cytokines activated T cells secrete. Furthermore, we test if chimeric antigen receptor modified (CAR) T cells are reactive and cytotoxic against uveal melanoma cells.

Funding: DFG

### **Tumor microenvironment**

PI: Dr. Y. Resheq

Recently, we were able to show that H<sub>2</sub>O<sub>2</sub> is important for differentiation and function of human monocytic cells hence undermining the complex nature of H<sub>2</sub>O<sub>2</sub>: Using hepatic stellate cells we were able to demonstrate that contact-dependent depletion of H<sub>2</sub>O<sub>2</sub> paradoxically leads to a differentiation of human monocytes to myeloid-derived suppressor cells (MDSC) which are renowned for their immunosuppressive activity in various malignant diseases. Currently, we are analyzing to what extent tumors may use such mechanisms in order to achieve a favorable microenvironment, e.g. by inducing tolerogenic dendritic cells.

### **Tumor immune escape**

PI: Prof. Dr. A. Mackensen, Dr. M. Aigner

By modulation of their metabolism, tumors are able to generate advantages for growth and proliferation for themselves. Our group focuses on the functions of 5'-Deoxy-5'-methylthioadenosine (MTA) and its degrading enzyme MTAP as it is known that these molecules play a role in many malignancies. The influence of MTA produced by tumors on the activation, proliferation, and various effector functions of cytotoxic T cells are studied in cooperation with the University of Regensburg.

Funding: KFO 262 (project 3)

### **Cellular immunotherapy**

PI: Prof. Dr. A. Mackensen, Dr. R. Gary, Dr. M. Aigner

The cellular immunotherapy 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 SFB 643 (compare own report), the immunomonitoring was extended in collaboration with the Institute of Pathology (Charité Berlin) by single cell TCR analysis using Next Generation Sequencing.

Funding: SFB 643 (project C09), BayImmuNet

### **HLA-laboratory**

PI: Prof. Dr. B. Spriewald

In recent years, the laboratory has been interested in new methods for the detection of various subclasses of anti-HLA antibodies in solid organ transplantation. Our immunogenetic studies look into polymorphisms of several cytokines

and T cell regulatory genes and their association with rheumatic and malignant disorders. Another focus is on experimental studies for the induction of transplantation tolerance and reduction of chronic rejection. These studies are performed in close collaboration with the working group of experimental heart surgery.

### **Teaching**

The Department of Internal Medicine 5 takes part in the curricular teaching for Medicine and Dental Medicine.

Bachelor's and Master's theses as well as MD and PhD theses are offered and supervised regularly.

### **Selected Publications**

Bruns H, Büttner M, Fabri M, Mougiakakos D, Bittenbring JT, Hoffmann MH, Beier F, Pasemann S, Jitschin R, Hofmann AD, Neumann F, Daniel C, Maurberger A, Kempkes B, Amann K, Mackensen A, Gerbitz A. Vitamin D-dependent induction of cathelicidin in human macrophages results in cytotoxicity against high-grade B cell lymphoma. *Sci. Transl. Med.* 2015, 7:282ra47

Röllig C et al. Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): a multicentre, phase 2, randomised controlled trial. *Lancet Oncol.* 2015, 16: 1691-1699

Braun M, Qorraj M, Büttner M, Klein FA, Saul D, Aigner M, Huber W, Mackensen A, Jitschin R, Mougiakakos D. CXCL12 promotes glycolytic reprogramming in acute myeloid leukemia cells via the CXCR4/mTOR axis. *Leukemia* 2016, 30:1788-1792

Goebeler ME et al. Bispecific T-cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-hodgkin lymphoma: final results from a phase I study. *J. Clin. Oncol.* 2016, 34: 1104-1111

Völkl S et al. Hyperactive mTOR pathway promotes lymphoproliferation and abnormal differentiation in autoimmune lymphoproliferative syndrome. *Blood* 2016, 128: 227-38

Brand A et al. LDHA-Associated Lactic Acid Production Blunts Tumor Immunosurveillance by T and NK Cells. *Cell Metab.* 2016, 24: 657-671

### **International Cooperations**

M. Miano, MD, Department of Pediatric Haematology-Oncology, IRCCS Istituto Giannina Gaslini, Genoa: Italy

Prof. F. Falkenburg, Leiden University: The Netherlands

Dr. T. Graf, Centre for Genomic Regulation, University of Barcelona: Spain

Dr. I. Pastan, NCI, NIH, Bethesda: USA

Prof. R. Kiessling, Karolinska Institutet, Stockholm: Sweden



# Department of Neurology

## Chair of Neurology

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### Research Focus

- Stroke research – clinical and experimental
- Neurocritical care
- Telemedicine
- Epilepsy
- Neuroimmunology
- Pain and functional imaging
- Autonomic nervous system
- Neuromuscular diseases
- Dystonia and botulinum toxin therapy
- Neuro-oncology

### Structure of the Department

Professorships: 5

Personnel: 200

- Doctors (of Medicine): 59
- Scientists: 6 (thereof funded externally: 3)
- Graduate students: 35

### Clinical focus areas

- Emergency care
- Stroke
- Neurocritical care
- Epilepsy – center of epilepsy (EZE)
- Neuroimmunology
- Neuromuscular diseases
- Pain medicine
- Neuro-oncology
- Autonomic nervous system disorders
- Neurophysiology
- Ultrasound
- Dystonia und botulinum toxin therapy
- Neurocognitive disorders
- Telemedicine

### Research

The Department of Neurology is one of the largest neurological centers in Germany treating 4,000 in-patients and more than 19,000 outpa-

tients each year. During the reporting period more than 200, some of them high-ranking publications, could be published.

### Stroke research – clinical and experimental

PI: Prof. Dr. H. Huttner, PD Dr. B. Kallmünzer  
Each year about 7,000 patients are admitted to our specialized neurological emergency room. After an immediate clinical examination, adequate diagnostic procedures and prompt specific emergency treatment are initiated, if necessary. For many neurovascular clinical studies, the screening and inclusion is managed directly in the emergency room. Additionally, all stroke patients – also those transferred from the North-Bavarian telestroke network STENO – are entered into prospective registries to allow scientific analyses (e.g. „Drip-and-ship“ in cases of planned thrombectomy).

We treat more than 1,000 inpatients on our 14-bed monitored stroke unit. An extremely high level of medical care (iv-thrombolysis rate > 25 %) is combined with state-of-the-art research, including clinical studies on thrombolysis, recanalization therapy und secondary prevention of cardioembolism.

### Neurocritical care

PI: Prof. Dr. H. Huttner

In clinical routine – also addressed in clinical and translational research studies – we mainly focus on severe strokes, intracranial hemorrhage, meningitis and status epilepticus. Examples of current research projects refer to stroke treatment approaches that still are considered experimental, e.g. intraventricular fibrinolysis, brain edema management using multimodal neuromonitoring, and hypothermia.

### Telemedicine

PI: Dr. B. Breuer

Since 2007, the Department of Neurology has been coordinating the Stroke Network using Telemedicine in Northern Bavaria (STENO) which includes three stroke centers and 18 regional hospitals. As the only telestroke-network of its kind it has been certified in 2011 according to DIN EN ISO 9001:2008 for its network-wide quality management system. STENO is part of the medical standard care and ensures comprehensive stroke care in North Bavaria and southern Thuringia at the highest level. The impact and effects of STENO are investigated in scientific studies.

### Epilepsy

PI: Prof. Dr. H.M. Hamer

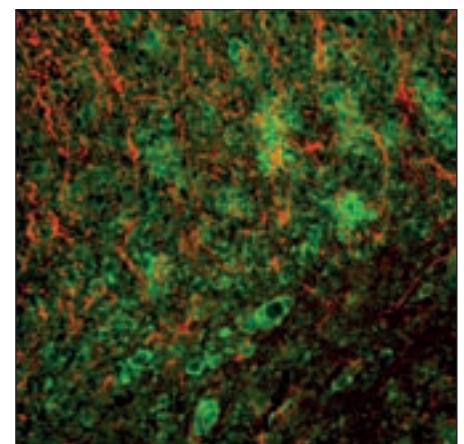
The Erlangen Epilepsy Center ranks among the top five university epilepsy centers in Germany. Scientific hot spots include: 1) Changes of the innate immune-system in epilepsy; 2) Epilepsy in CNS-malformations; 3) Automatic seizure detection; 4) Magnetoencephalography; 5) Neuropsychology/Cognition and invasive EEG; 6) Quantitative EEG in epilepsy and encephalopathy; 7) Drug monitoring; 8) Historical aspects of epilepsy; 9) Socio-economic aspects of epilepsy. Funding: EU, DFG, Bavarian State Ministry of Public Health and Care Services

### Neuroimmunology

PI: Prof. Dr. R. Linker

Three research groups successfully focus on (1) immunregulation and biomarkers in MS patients, (2) neuroprotection and neurodegeneration in experimental models with a focus on glial cells, and (3) the influence of environmental factors on the pathogenesis of MS. Further research comprises studies on new imaging modalities and studies on new treatment in a bench-to bedside approach.

Funding: IZKF, GRK 2162, industry



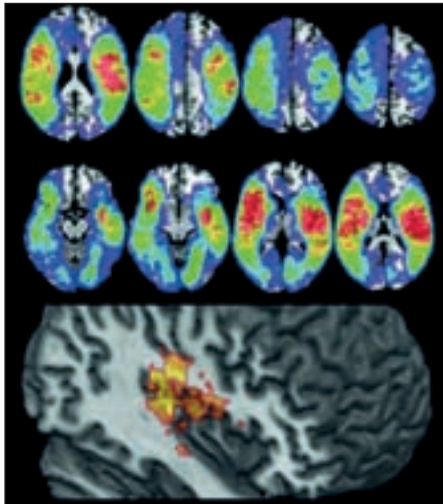
*Glutamate transporters localized on astrocytes*

### Pain and functional imaging

PI: PD Dr. F. Seifert

This group investigates neural mechanisms of sensory, autonomic and cognitive processing in pain disorders (neuropathic pain, headache), stroke and multiple sclerosis. We use psychophysical and autonomic testing combined with functional and structural brain imaging methods (voxel-based lesion symptom mapping (VLSM), functional magnetic resonance imaging (fMRI), repetitive transcranial magnetic stimulation (rTMS).





Brain areas involved in autonomic regulation detected by voxel-based lesion-symptom mapping

### Autonomic nervous system

PI: 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 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 persons who are exposed to repetitive mild head and brain injuries.

### Neuromuscular diseases

PI: Prof. Dr. R. Linker, 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 several task forces with the following key aspects:

- 1) immunopathogenesis of autoimmune myositis, myasthenia gravis, and immune neuropathies;
- 2) studies on the pathogenesis of myofibrillar myopathy and other protein aggregation myopathies.

### Dystonia and botulinum toxin therapy

PI: Dr. C. Möbius

Our main aim is to improve the diagnostic and therapeutic process for patients with dystonic movement disorders and spasticity. Other than

participating in several multicenter clinical trials, our research focus lies in the early detection and treatment of post stroke spasticity and the identification of specific muscle patterns in cervical dystonia using ultrasound and ultrasound-guided electromyography.

### Neuro-oncology

PI: Dr. M. Uhl

The goal of interdisciplinary neuro-oncology group is the treatment of patients with brain tumors. Beside the daily routine patients we have the ambition to provide attractive clinical trials for all patients. A focus here are currently translational immune therapy studies of the phases II and III.

### Teaching

Between everyday clinical practice and the teachings segment of our Department, the interdisciplinary clinical courses „Querschnittsfächer“ for immunology/ infectiology, emergency medicine and pain medicine gained widespread recognition by the students. We supervise MD and PhD theses.

### Selected publications

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*. 2015 Feb;77(2):262-8

Kuramatsu JB et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA*. 2015 Feb 24;313(8):824-36

Haghikia A et al. Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine. *Immunity*. 2015; 43(4):817-29

Herrlinger U et al. Bevacizumab Plus Irinotecan Versus Temozolomide in Newly Diagnosed O6-Methylguanine-DNA Methyltransferase Nonmethylated Glioblastoma: The Randomized GLARIUS Trial. *J Clin Oncol*. 2016 May 10;34(14):1611-9

Winder K, Linker RA, Seifert F, Deutsch M, Engelhorn T, Dörfler A, Lee DH, Hoesl KM, Hilz MJ. Neuroanatomic Correlates of Female Sexual Dysfunction in Multiple Sclerosis. *Ann Neurol*. 2016 Oct; 80(4):490-8

Gollwitzer S, Kostev K, Hagge M, Lang J, Graf W, Hamer HM. Nonadherence to antiepileptic drugs in Germany: A retrospective, population-based study. *Neurology* 2016;87:466-472

### International Cooperations

Prof. J. Frisen, Department of Cell and Molecular Biology, Karolinska Institute, Stockholm: Sweden

Prof. D. Henshall, Royal College Dublin, Dublin: Ireland (multicentric)

Dr. S. Hanslmayr, School of Psychology, University of Birmingham, Birmingham: UK (multicentric)

Prof. Dr. M.-J. Hilz, Department of Autonomic Neurology, University College London, London: UK

Prof. Dr. M.-J. Hilz, Icahn School of Medicine at Mount Sinai, New York: USA

# Department of Neurology

## Division of Molecular Neurology

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### Research Focus

- Neurodegenerative diseases
- Translational neurosciences
- Clinical research and development

### Structure of the Division

Professorships: 2

Personnel: 20

- Doctors (of Medicine): 7
- Scientists: 3 (thereof funded externally: 2)
- Graduate students: 7

### Clinical focus areas

- Outpatient clinical and research center for neurodegenerative movement disorders
- Center of the national network for Parkinson's disease and European Huntington's disease center
- Rare genetic movement disorders
- Atypical Parkinson diseases

### Research

The Division of Molecular Neurology focusses on the cellular, functional and pathological alterations in neurodegenerative diseases. By applying modern stem cell technologies, important insights are achieved by patient based translational approaches. The academic outpatient service provides state-of-the-art care for patients with neurodegenerative movement disorders with particular focus on diagnostic work-up, treatment and participation in national and international clinical studies. These activities are embedded in numerous international disease specific clinical trial activities. Furthermore, by applying medical engineering methods, an objective and optimized monitoring of patients with movement disorders is developed in the

framework of the interdisciplinary research network of the FAU (EFI-Moves; compare own report).

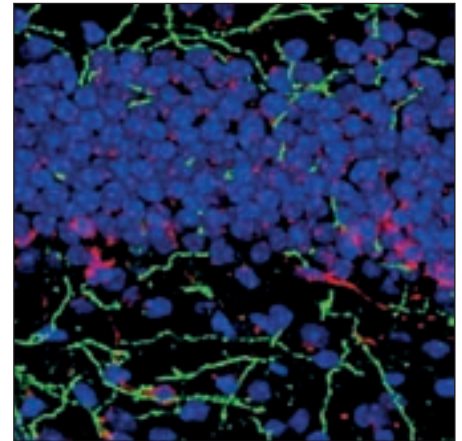
### Neurodegenerative diseases

The scientific focus of the Division of Molecular Neurology emphasizes on stem cell biology and neurodegenerative mechanisms in the context of the sporadic Parkinson-Syndrom, multiple systems atrophy, Huntington's disease, and the hereditary spastic paraplegia. Neuroregenerative mechanisms with particular interest in the generation of new neurons and glial cells in the adult brain (adult neuro- and gliogenesis) are analyzed by using cell culture approaches, such as induced pluripotent stem cells and transgenic models of the corresponding disease. In a complementary approach, neurodegenerative mechanisms underlying the interplay of intracellular and extracellular  $\alpha$ -synuclein 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 and inflammatory pathomechanisms within the CNS has become an additional major focus.

### Translational neuroscience

The Division is interested in the molecular biology of adult neural precursor and stem cells which are resident within the adult forebrain, however moving more and more towards methods to generate induced pluripotent stem cells (iPSC), derived from human fibroblasts of the skin. Adult neurogenesis is severely altered in the context of numerous neurodegenerative diseases. Amounting evidence indicates that impaired adult neurogenesis may be one of the most important cell biological events linked to non-motor-symptoms like depression, cognitive impairment and olfactory dysfunction in Parkinson's disease. Furthermore, we extended our program to characterize myelin producing oligodendrocytes, particularly affected in multiple systems atrophy, showing a severe dysfunction of these cells. Moreover, cell and molecular techniques have been established to delineate and modify pathological mechanisms associated with protein aggregation of  $\alpha$ -synuclein in synucleinopathies. Finally, a biobank for patient specific iPSC and its progeny is being established in the framework of the Bavarian Network ForIPS (compare own report). These translational research projects are embedded in multiple interdisciplinary networks.

Funding: DFG, BMBF, Bavarian State Ministry of Economic Affairs and Media, Energy and Technology, Bavarian State Ministry of Education, Science and the Arts, IZKF



Serotonergic fibers (green) in the dentate gyrus of the hippocampus get in close contact to developing young neurons (red), cell nuclei in blue

### Clinical research and development

The outpatient clinic for movement disorders (in particular Parkinson's disease, multiple systems atrophy, 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 implemented. Automated motion and gait analysis systems for stationary and mobile diagnostics have been developed in close collaboration with the Pattern Recognition Lab (Faculty of Engineering) and a local industry partner (ASTRUM IT GmbH). This joint effort was awarded the Erlanger Prize for Medicine, Technology, and Health and the Bavarian Innovation Award for Health-Telematics. In this context, a novel rehabilitation sports group for Parkinson's disease has been implemented for the long-term improvement of mobility of patients with movement disorders and in order to test novel interventional approaches. Furthermore, an interdisciplinary network comprising the Faculty of Engineering (Pattern Recognition Lab) and the Institute of Sport Science and Sport (Faculty of Humanities, Social Sciences, and Theology) has been awarded an emerging field's award. This interdisciplinary research examines the role of physical activity associated with sensory interference for postural stability in Parkinson's disease. Furthermore, a spin off company, Portables Healthcare Technology, has been founded in December 2016 in order to develop these technologies further for clinical application.



*Rehabilitation sports group UK Erlangen*

## Teaching

The Division of Molecular Neurology participates within the academic teaching activities of clinical neurology, molecular medicine and medical technology.

We supervise Bachelor's, Master's, MD and PhD theses. The neuroscience GK (GRK2162 "Neurodevelopment and vulnerability of the central nervous system"; compare own report) has successfully started.

## Selected Publications

Klucken J, Friedl KE, Eskofier BM, Hausdorff JM. Guest Editorial: Enabling Technologies for Parkinson's Disease Management. *IEEE J Biomed Health Inform.* 2015 Nov;19(6):1775-6

Mrochen A, Marxreiter F, Kohl Z, Schlachetzki J, Renner B, Schenk T, Winkler J, Klucken J. From sweet to sweat: hedonic olfactory range is impaired in Parkinson's Disease. *Parkinsonism & Rel Dis* 2015, 22:9-14

Xiang W, Menges S, Schlachetzki JC, Meixner H, Hoffmann AC, Schlötzer-Schrehardt U, Becker CM, Winkler J, Klucken J. Posttranslational modification and mutation of histidine 50 trigger alpha synuclein aggregation and toxicity *Mol Neurodegener.* 2015 Mar 11;10:8

Deußner J, Schmidt S, Ettl B, Plötz S, Huber S, Müller CP, Masliah E, Winkler J, Kohl Z. Serotonergic dysfunction in the A53T alpha-synuclein mouse model of Parkinson's disease, *J Neurochemistry*, 2015, Nov 135(3): 589–597

Kohl Z, Ben Abdallah N, Vogelgsang J, Tischer L, Deußner J, Amato D, Anderson S, Müller CP, Riess O, Masliah E, Nuber S, Winkler J. Severely impaired hippocampal neurogenesis associates with an early serotonergic deficit in a BAC  $\alpha$ -synuclein transgenic rat model of Parkinson's disease. *Neurobiol Dis*, 2016, 85: 206–21

Ettl B, Kerman BE, Valera E, Gillmann C, Schlachetzki JCM, Reiprich S, Büttner C, Ekici AB, Reis A, Wegner M, Bäuerle T, Riemenschneider MJ, Masliah E, Gage FH, Winkler J.  $\alpha$ -Synuclein-induced myelination deficit defines a novel interventional target for multiple system atrophy. *Acta Neuropathol*, 2016, 132:59–75

## International Cooperations

Prof. Dr. F. H. Gage, Laboratory of Genetics-Gage, The Salk Institute for Biological Studies, La Jolla: USA

Prof. Dr. B. Bloem, Radboud University Medical Center, Nijmegen: The Netherlands

Prof. Dr. E. M. Masliah, Department of Neurosciences, University of California, San Diego, La Jolla: USA

Prof. Dr. G. Wenning, University Hospital of Innsbruck, Innsbruck: Austria

Prof. Dr. R. Krüger, University of Luxemburg, Luxemburg: Luxemburg

# Department of Neurosurgery

## Chair of Neurosurgery

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### Research Focus

- Functional neuronavigation and intraoperative imaging
- Neuroendocrinology
- Neurooncology

### Structure of the Department

Professorships: 2

Personnel: 182

- Doctors (of Medicine): 21
- Scientists: 10 (thereof funded externally: 3)
- Graduate students: 34

### Clinical focus areas

- Endocrine neurosurgery
- Neurooncology
- Skull base surgery
- Epilepsy surgery
- Vascular neurosurgery
- Spine surgery
- Neurotraumatology
- Pediatric neurosurgery

### Research

The scope of research of the Department of Neurosurgery is primarily clinical, with special focus on the field of intraoperative imaging, neuroendocrinology and neuro-oncology.

#### 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 glioma 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 analogs 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-opera-

tive 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 Ca<sup>2+</sup>-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.

Funding: DFG

## Teaching

The Department of Neurosurgery is involved in the curricular teaching of human and dental medicine with compulsory and elective subjects. In addition, the students are exposed to the practical aspects of neurosurgery within the framework of the block practical course system through guided tours in operating rooms during live surgery. A special aspect is the interdisciplinary nature of teaching within the framework of the Neurosurgery/Neurology block.

The Department of Neurosurgery supervises Bachelor's and Master's theses as well as MD and PhD theses.

## Selected Publications

Friedlein K, Bozhkov Y, Hore N, Merkel A, Sommer B, Brandner S, Buchfelder M, Savaskan NE, Eyüpoglu IY. A new functional classification system (FGA/B) with prognostic value for glioma patients. *Sci Rep*. 2015 Jul 21;5:12373

Riebold M, Kozany C, Freiburger L, Sattler M, Buchfelder M, Hausch F, Stalla GK, Paez-Pereda M. A C-terminal HSP90 inhibitor restores glucocorticoid sensitivity and relieves a mouse allograft model of Cushing disease. *Nat Med*. 2015 Mar;21(3):276-80

Brandner S, Buchfelder M, Eyüpoglu IY, Luecking H, Doerfler A, Stadlbauer A. Visualization of CSF Flow with Time-resolved 3D MR Velocity Mapping in Aqueuductal Stenosis Before and After Endoscopic Third Ventriculostomy : A Feasibility Study. *Clin Neuroradiol*. 2016 Aug 8

Sommer B, Roessler K, Rampp S, Hamer HM, Blumcke I, Stefan H, Buchfelder M. Magnetoencephalography-guided surgery in frontal lobe epilepsy using neuronavigation and intraoperative MR imaging. *Epilepsy Res*. 2016 Oct;126:26-36

Ghoochani A, Schwarz MA, Yakubov E, Engelhorn T, Doerfler A, Buchfelder M, Bucala R, Savaskan NE, Eyüpoglu IY. MIF-CD74 signaling impedes microglial M1 polarization and facilitates brain tumorigenesis. *Oncogene*. 2016 Dec 1;35(48):6246-6261

Kreitschmann-Andermahr I, Siegel S, Kleist B, Kohlmann J, Starz D, Buslei R, Koltowska-Häggström M, Strasburger CJ, Buchfelder M. Diagnosis and management of acromegaly: the patient's perspective. *Pituitary*. 2016 Jun;19(3):268-76



# Department of Nuclear Medicine

## Chair of Clinical Nuclear Medicine

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### Research Focus

- Imaging and physics research group
- Molecular imaging and radiochemistry

### Structure of the Department

Professorships: 2

Personnel: 45

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

### Clinical focus areas

All currently available diagnostic and therapeutic procedures of this specialty

### Research

The research of the Chair of Clinical Nuclear Medicine is methodologically oriented. This involves the development of innovative hard- and software of imaging systems together with industrial partners as well as that of new radiopharmaceuticals in cooperation with the institutes of chemistry at FAU.

### Imaging and physics research group

PI: Dr.-Ing. P. Ritt

Advances in medical imaging have led to a numerous modalities for observing the functions and structures of the human body. In the field of nuclear medicine, imaging aims to depict specific metabolic processes, as well as expression and biological activity of proteins. To accomplish this goal, the distribution of radioactive tracers in the human body is measured. Images are formed by detecting the emissions of these substances as they decay (e.g. gamma photons or positrons) using SPECT (Single-Photon Emission Computed Tomography) and PET (Positron Emission Tomography) systems. The

diagnostic confidence of PET and SPECT for certain radiotracers may be increased if they are combined with modalities which image anatomical features, such as CT and MRI. These so-called multimodal devices (SPECT/CT, PET/CT, PET/MRI) represent the cutting edge in medical imaging.

In addition to imaging, the field of nuclear medicine is also responsible for therapies using liquid radioactive substances. These treatments are often applied in oncological cases and involve radiopharmaceuticals which lead to local irradiation of specific tissues in the body. The type and quantity of the radioactive substance employed are individually chosen for each patient. For the assessment of risk and benefits of a treatment, it is of great importance to determine the dose of ionizing radiation to tumor and organs as accurately as possible (dosimetry).

The focus of the imaging and physics group is the development of imaging in nuclear medicine and the improvement of image-based dosimetry.

The group has worked on the following topics during the period covered in this report:

- Absolute quantification in Tc-99m- and Lu-177-SPECT/CT

In SPECT, image quality is dependent on several factors including photon attenuation, photon scatter, the partial volume effect, and motion artefacts. These variables confound the capacity of SPECT to quantify the concentration of radioactivity within given volumes of interest in absolute units, e.g. as kilobecquerels per cubic centimetre. In the last decade, considerable technical progress has been achieved in SPECT/CT imaging which has led to a broader availability of absolute quantification capabilities. For this, absolute quantification is one of the hot topics in nuclear medicine and there is hope that it will lead to more inter-reader standardization and more accurate diagnoses. The group aims at evaluating the possibilities and limitations of this new technique, especially for application in dosimetry.

- Data-driven tracking of respiratory motion in SPECT/CT

SPECT imaging is vulnerable to blur and artifacts caused by respiratory motion occurring during respiratory cycles shorter than typical projection dwell times. In order to overcome artifacts due to respiratory motion, a number of methods have been proposed that seek to subdivide the acquisition into time bins, or gates, during which motion is small. Individual gates may then be reconstructed and

evaluated separately or used to produce a single motion-corrected reconstruction. Critical to each approach is a surrogate signal describing the respiratory state over time that can be used to drive the gating process. The imaging and physics group developed a data-driven method for extracting a respiratory surrogate signal from SPECT list-mode data without the need for costly external sensors. The approach is based on dimensionality reduction with Laplacian Eigenmaps. Using this technique, the bias resulting from respiratory motion and methods for correcting the motion are evaluated.

- Multi-modal reconstruction of SPECT data  
Multimodal devices, such as SPECT/CT, PET/CT, and PET/MRI, routinely use data from an anatomical imaging modality (CT, MRI) for correcting for scattered and attenuated photons in the reconstruction of the emission data. Lately, approaches that feature deeper integration of anatomical information into reconstruction have been developed. For example, anatomical images can be used to constrain the reconstruction of the spatial position of radioactive sources to the tissue types that are common for the specific radio-tracer. The research group helps in refining this method further and expanding its use to a wider range of radiopharmaceuticals.
- Voxel-wise dosimetry for therapies in Nuclear Medicine

Conventionally, image-based dosimetry for nuclear medicine therapies is carried out for individual volumes of interest (VOI), such as organs or target structures like tumors. This results in a value of ionizing radiation dose (measured in units of Gray) which effectively is averaged over the entire VOI. Consequently, more refined information about the spatial distribution of the dose is not available, and techniques offering more detailed information, such as dose-volume-histograms known from external beam radiation, are not available. The research group develops methods for calculating dose values on a voxel level, e.g. by application of dose-voxel-kernels or by patient-individual Monte-Carlo simulations of radiation transport.

The imaging and physics group has cooperations with multiple companies and institutes, including the Pattern Recognition Lab (Faculty of Engineering), Siemens Healthineers (Molecular Imaging), and Progenics Radiopharmaceuticals. During the period covered in this report, selected research projects were supported by Siemens Healthineers and Progenics Radiopharmaceuticals.

## Molecular imaging and radiochemistry

Pl: Prof. Dr. O. Prante

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 foci of the Professorship of Molecular Imaging and Radiochemistry are the development of new radiochemical labeling methods for the production of radiopharmaceuticals, the preclinical evaluation of novel radiopharmaceuticals in vitro and in vivo, and the translation of new radiotracers into the clinic for patient application. Important recent examples for these projects are the development of F-18-labeled glycoconjugates and Ga-68-labeled ligands for the neurotensin receptor (NTS1) and for the neuropeptide-Y receptor (Y1R). We were successful to evaluate the first F-18-labeled peptide radioligand for the in vivo detection of mammary carcinoma and a NTS2-subtype selective radioligand for the detection of NTS2-positive tumors, using preclinical animal models. These projects were supported by the DFG and were performed in close cooperation with the Chair of Pharmaceutical Chemistry (Prof. Dr. P. Gmeiner, Faculty of Sciences). The development of new radiotracers for neuropeptide receptors (NTS1 and Y1R) as tumor markers for pancreatic, mammary and prostate carcinoma has been intensively supported by small animal PET imaging studies. In the field of new developments of radioligands in the field of neurology, including studies on the interactions between neurofunction and nutrition, new aspects for the tracer development for D3 radioligands were studied in vitro and in vivo, F-18-fluoroethyl-harmol was established as a PET ligand for MAO-A and the development of F-18-FP-CMT as a highly attractive dopamine transporter ligand for PET studies in rats was successfully finished.

The GMP radiopharmacy of the clinic has received its approval for the production of radiopharmaceuticals, for example targeted against prostate cancer, by the local authorities according to §13, AMG (Medicinal Products Act).

Therefore, based on successful translational research, new radiopharmaceuticals will be available for clinical use within the Department of Nuclear Medicine.

## Teaching

The head of the Department teaches nuclear medicine to students of medicine. Furthermore, the head of the Department organizes the course on radiation safety for students of the degree program Molecular Medicine. He also participates in teaching physiology, pharmacology, and Medical Process Optimizing. 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 degree program Molecular Sciences of the Faculty of Sciences.

The Department supervises Bachelor's and Master's theses as well as MD and PhD theses.

## Selected Publications

Hofmann S, Maschauer S, Kuwert T, Beck-Sickinger A, Prante O. Synthesis and in vitro and in vivo evaluation of an <sup>18</sup>F-labeled neuropeptide Y analogue for imaging of breast cancer by PET. *Mol Pharm*. 2015, 12(4): 1121-1130

Mayer G, Bitterlich M, Kuwert T, Ritt P, Stefan H. Ictal SPECT in patients with rapid eye movement sleep behaviour disorder. *Brain* 2015 May;138(Pt 5):1263-70

Sanders JC, Kuwert T, Hornegger J, Ritt P. Quantitative SPECT/CT imaging of <sup>177</sup>Lu with in vivo validation in patients undergoing peptide receptor radionuclide therapy. *Mol Imaging Biol*. 2015, 17(4): 585-593

Maschauer S, Heilmann M, Wängler C, Schirrmacher R, Prante O. Radiosynthesis and Preclinical Evaluation of <sup>18</sup>F-Fluoroglycosylated Octreotate for Somatostatin Receptor Imaging. *Bioconjug Chem*. 2016, 27(11): 2707-2714

Maschauer S, Einsiedel J, Hübner H, Gmeiner P, Prante O. <sup>18</sup>F- and <sup>68</sup>Ga-labeled Neurotensin Peptides for PET Imaging of Neurotensin Receptor 1. *J Med Chem*. 2016, 59: 6480-6492

Sanders JC, Ritt P, Kuwert T, Vija AH, Maier AK. Fully Automated Data-Driven Respiratory Signal Extraction From SPECT Images Using Laplacian Eigenmaps. *IEEE Trans Med Imaging*. 2016, 35(11): 2425-2435

## International Cooperations

Dr A.H. Vija, Molecular Imaging, Siemens Medical Solutions, Hoffman Estates, Chicago: USA

Dr. R. Haubner, Department of Nuclear Medicine, Innsbruck Medical University, Innsbruck: Austria

Prof. P. Cumming, Institute of Health Biomedical Innovation, Queensland University of Technology, Brisbane: Australia

# Department of Obstetrics and Gynecology

## Chair of Obstetrics and Gynecology

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### Research Focus

- Laboratory for Molecular Medicine with University Breast Center Franconia and University Gynecological Cancer Center Franconia
- Molecular research in obstetrics and perinatal medicine
- Clinical trials (Clinical Research Unit and Institut für Frauengesundheit, IFG®)
- Biobanking
- Specialized obstetrics and perinatal medicine
- Laboratory for reproductive biology with gynecological endocrinology and reproductive medicine

### Structure of the Department

Professorships: 3

Personnel: 341

- Doctors (of Medicine): 54
- Scientists: 11 (funded externally: 8)
- Graduate students: 11

### Research

The focus of research in the Department of Obstetrics and Gynecology is according to the direction of the six clinical certified centers. Complementary central infrastructural units are the Laboratory for Molecular Medicine, the Laboratory for reproductive biology, the Study Center and the Biobank.

#### Laboratory for Molecular Medicine with University Breast Center Franconia and University Gynecological Cancer Center Franconia

PI: Prof. Dr. R. Strick, PD Dr. A. Hein, PD Dr. M. Schrauder, Prof. Dr. P. Fasching, Dr. M. Rübner, PD Dr. P. Strissel

- In collaboration with the Johns Hopkins University and the Sloan Kettering Cancer Center (USA) we demonstrated that DNA-demeth-

ylation of ovarian cancer cells led to an activation of the innate interferon type 1 signaling. This activation stemmed from the induction of endogenous retroviral genes, which occurred via double-stranded (ds) RNA and not via proteins. A correlation of induced genes of the interferon signaling pathway with dsRNA was also detected in primary human ovarian tumors and could therefore lead to novel treatments.

- The establishment of primary human breast cells and breast cancer cells from tissues and tumors has advantages compared to breast cancer cell lines mainly derived from metastatic tumors. Numerous primary epithelial, mesenchymal and adipose stem cell lines were established and analyzed in collaboration with the Department of Plastic and Hand Surgery. Especially the different plasticity of adipose stem cells from breast tumors compared to normal breast demonstrated the importance for tumorigenesis.

#### Molecular research in obstetrics and perinatal medicine

PI: Prof. Dr. P.A. Fasching, Prof. Dr. R. Strick, PD Dr. M.G. Schrauder, PD Dr. S. Kehl, PD Dr. F. Faschingbauer, Dr. M. Rübner, H. Hübner, F. Würfel, Dr. M. Schneider, Dr. E. Raabe, Dr. F. Stumpfe

- Functional role of tumor suppressor genes like retinoic acid regulated gene (RARRES1) and the group of gastrophilins (mainly GKN2) during human placental development and the formation of associated dysfunctions
- Importance of human endogenous retroviruses for trophoblast differentiation.
- In cooperation with the Department of Pediatric and Adolescent Medicine, mass spectrometric measurements for steroid metabolomics of placental tissues were performed. With the Institute for Clinical Chemistry and Pathochemistry of the University of Magdeburg causes of inflammasome activation in the pathology of preeclampsia were analyzed.

#### Clinical trials (Clinical Research Unit and Institut für Frauengesundheit, IFG®)

PI: Prof. Dr. P.A. Fasching, PD Dr. C.R. Löhberg, Dr. L. Häberle, Dr. B. Volz, Prof. Dr. M.P. Lux, PD Dr. A. Hein, Dr. C.M. Bayer, S. Kellner, N. Nabieva

Up to 2016, over 201 projects with clinical phase I-IV studies have been carried out. The clinical studies target the etiology, diagnosis and therapy of breast, ovarian, endometrial, cervical and primary peritoneal cancer as well as benign

gynecological diseases (e.g. endometriosis). In addition to genetic analyses and chemotherapy protocols for breast cancer, "target therapies" are examined as well as therapy approaches using PI3K-, CDK4/6 inhibitors or PD-1/PD-L1 antibodies. Trials include curative as well as palliative treatments. In 2014, the PRAEGNANT study (Prospective Academic Translational Research Network for the Optimization of Oncological Health Care Quality in the Advanced Therapeutic Setting) for metastatic breast cancer patients was in part initiated in Erlangen. This multicenter, prospective and translational research project included more than 300 patients from Erlangen of a total of 1,800 patients until the end of 2016. Molecular analyses are organized in Erlangen. The goal is the discovery of new biomarkers for the survival of patients with metastatic breast cancer. Whole genome sequencing including analysis of tumor DNA and RNA as well as the corresponding germline DNA was performed in more than 200 patients. Central biobanking for this study is managed by the Labor for Molecular Medicine at our Department. In addition, therapies for hereditary breast and ovarian cancer patients, like so-called PARP-inhibitors (Poly-ADP-Ribose-Polymerase-inhibitors) can be offered. PARP-inhibitors are a group of new drugs especially for the treatment of triple-negative or inherited breast and ovarian cancer. A study with genetically modified natural killer cells (CAR-NK-cells) for the treatment of HER2 positive breast cancer is being planned.

#### Biobanking

PI: Prof. Dr. P.A. Fasching, Dr. M. Rübner, Dr. P. Gaß, H. Hübner

The translational biobank of the Department of Obstetrics and Gynecology is one of the biggest biobanks within the field of the gynecological research in the world. Currently biomaterials from around 50,000 participants (100,000 blood, 13,500 tissue, 25,000 urine, and 100,000 serum and plasma samples) are stored. For the BCAC (Breast Cancer Association Consortium), the germline DNA from another 3,500 patients (8,500 total) from randomized multicenter breast cancer studies for 660,000 gene variants were analyzed. Within the SAPE project, the tumor samples from these studies were collected. Data from the germline can be correlated with tumor data (expression and mutation analysis). Moreover, the PRAEGNANT study network has been established. This network will build an infrastructure for metastatic breast cancer patients (~1,900 patients at 47 study sites

in Germany) which should make precision medicine available. Findings from this kind of research will present new possibilities in therapy (GPS Cancer™ test). Comparing the whole genome sequencing data from germline and tumor DNA as well as the expression profile of the tumor should identify new and directed therapies for patients.

### Specialized obstetrics and perinatal medicine

Pl: Prof. Dr. P.A. Fasching, PD Dr. F. Faschingbauer, PD Dr. S. Kehl, Prof. Dr. R. Strick, Dr. M. Rübner

Sonographic weight estimation is one of the most common examinations in routine clinical care. Fetal weight is a predictive parameter for neonatal morbidity and mortality and influences the obstetric management. In the Perinatal Center Franconia, a database of more than 10.000 patients with complete fetal biometric parameters has been established. Among others, a new weight estimation formula for „Small for gestational Age“ fetuses was developed. In a randomized multicenter trial, different method to assess amniotic fluid volume and their influence on clinical outcome were investigated. Induction of labor with pharmaceutical or mechanical methods is one of the main topics in clinical obstetrics. Tailored induction of labor resulted in reduction of caesarean section rates. In the area of mechanical labor induction with double-balloon catheter, the obstetrical research is nationally and internationally leading.

### Laboratory for reproductive biology with gynecological endocrinology and reproductive medicine

Pl: Prof. Dr. R. Dittrich, Dr. T. Hildebrandt, PD Dr. K. Heusinger, Prof. Dr. S. Cupisti, Dr. L. Lotz, PD Dr. P.G. Oppelt, Dr. S. Burghaus, Prof. Dr. S. Renner

Research focuses encompass cryopreservation of germ cells, physiology of contractions of non-pregnant uteruses, pathology of genital malformations and transsexuality. The Department of Obstetrics and Gynecology is the largest transplantation center for ovarian tissue in Germany regarding the area of fertility preservation from patients with cancer. Besides xenotransplantation of ovarian tissue in vivo, in vitro cultures of ovarian tissue were established. mTOR inhibitors are being used to influence the premature recruitment of primordial follicles in order to restore ovarian reserve. In the laboratory a uterus perfusion model has been established and for the first time a sheep uterus was

transplanted. These experiments were performed as a prior goal in order to transplant human uteri and are in cooperation with the Department of Plastic and Hand Surgery and the Division of Vascular Surgery.

At the University Endometriosis Center, the correlation between pain and the severity of the endometriosis is analyzed. Anamnestic and clinical data as well as biomaterials of patients with endometriosis are collected. The goal of an International Endometriosis Evaluation Program (IEEP-Study) is to identify risk factors and predictive markers in regards to diagnosis and recurrence of the disease as a function of the main complaint of the patient - pain, sterility or other reasons. Endometriosis was identified as a risk factor for ovarian or endometrial carcinoma. The single nucleotide polymorphism (SNP) rs11651755 in HNF1B has been shown to be associated with endometriosis. This SNP has already been described in relation with clear cell ovarian carcinoma.

### Teaching

The Department of Obstetrics and Gynecology is among the first departments at German university hospitals which has its own certified quality management (DIN EN ISO 9001:2008; since 2010) for medical education. It is regularly recertified. The Department of Obstetrics and Gynecology participates in curricular education of human medicine, including interdisciplinary teaching of medical subjects general prevention, sexual medicine and emergency medicine. The Department has a special Skills-Lab which is equipped for education in obstetrics and gynecology and is used for internships, practical years and elective periods.

The Department supervises MD theses.

### Selected Publications

Van der Ven H et al. Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates. *Hum Reprod.* 2016 Sep;31(9):2031-41

Kehl S, Schelkle A, Thomas A, Puhl A, Meqdad K, Tuschy B, Berlit S, Weiss C, Bayer C, Heimrich J, Dammer U, Raabe E, Winkler M, Faschingbauer F, Beckmann MW, Sutterlin M. Single deepest vertical pocket or amniotic fluid index as evaluation test for predicting adverse pregnancy outcome (SAFE trial): a multicentre, open-label randomised controlled trial. *Ultrasound Obstet Gynecol* 2016, 47: 674–679

Chiappinelli KB et al. Inhibiting DNA Methylation Causes an Interferon Response in Cancer via dsRNA Including Endogenous Retroviruses. *Cell* 2015, 162(5):974-86

Weigand A, Boos AM, Tasbihi K, Beier JP, Dalton PD, Schrauder M, Horch RE, Beckmann MW, Strissel PL, Strick R. Selective isolation and characterization of primary cells

from normal breast and tumors reveal plasticity of adipose derived stem cells. *Breast Cancer Res.* 2016, 18(1):32

Couch FJ et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol* 2015, 33, 304-311

Burghaus S, Häberle L, Schrauder MG, Heusinger K, Thiel FC, Hein A, Wachter D, Strehl J, Hartmann A, Ekici AB, Renner SP, Beckmann MW, Fasching PA. Endometriosis as a Risk Factor for Ovarian or Endometrial Cancer - Results of a Hospital-Based Case-Control Study. *BMC Cancer.* 2015 Oct 21;15:751

### International Cooperations

Prof. Dr. D. Easton, Breast Cancer Consortium, Cambridge: UK

Prof. Dr. D. Lambrechts, Katholieke Universiteit, Leuven: Belgium

Prof. Dr. D. Slamon, MD, PhD, UCLA, Los Angeles: USA

Prof. Dr. R. Weinshilboum, MD, Mayo Clinic, Rochester: USA

Prof. Dr. S. Baylin, John Hopkins Medical Center, Baltimore: USA



# 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 and virtual education

### Structure of the Department

Professorships: 9

Personnel: 172

- Doctors (of Medicine): 43
- Scientists: 13 (thereof funded externally: 7)
- Graduate students: 57

### Clinical focus areas

- Surgery of the frontal eye
- Cornea surgery
- Reconstructive surgery of the frontal eye
- Glaucoma seamless transconjunctival retinal-vitreous surgery (23-gauge-vitreotomy)
- Minimal invasive glaucoma surgery employing implants
- Refractive surgery with the femtosecond laser
- Cataract surgery with innovative intraocular lenses
- Intraocular injections of compounds to treat age related macular degeneration (AMD)
- Special consultation
- Departments of optometry, fluorescence angiography and laser
- Outpatients' department
- Cornea bank
- Laboratories

### Research

The Department of Ophthalmology belongs to the leading centers in the areas of lamellar corneal transplantation including structural biology of the cornea as well as diagnostics and pathophysiology of glaucomas at a national and international level. An interdisciplinary team of clinician and basic scientists conducts patient-oriented experimental and clinical research into corneal disorders, neurodegenerative diseases, such as glaucoma, and ocular tumors. The broad spectrum of methodologies applied includes molecular and cell biologic experiments, histology and electron microscopy, electrophysiology and visual psychophysics, and state-of-the-art imaging modalities, such as OCT angiography and magnetic resonance imaging. New medical devices for treatment of ocular diseases are being tested as part of multicenter studies. The major goal of the research efforts is to elucidate the pathophysiological causes underlying degenerative and vascular diseases of the eye and visual pathway on a molecular, cellular and systemic level, to advance the microsurgical techniques, to secure the quality of treatments, and to promote the development of novel therapeutic concepts and treatment strategies.

### Biomorphometry of the optic nerve

PI: 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

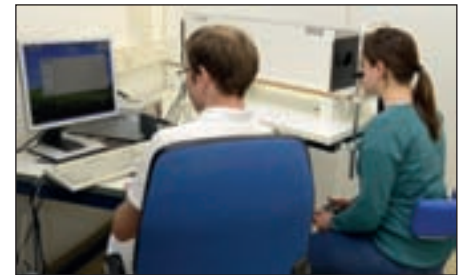
PI: Prof. Dr. J. Kremers, Dr.-Ing. F. Horn, Dr. C. Huchzermeyer

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

PI: Prof. Dr. J. Kremers

The goal of this working group is to study the function of the normal and diseased retina. To reach that goal, we record electrophysiological responses of the retina of rodent models of human diseases. In addition, we perform electrophysiological and psychophysical experiments with normal human test persons and patients to identify different signal pathways in the retina and the changes caused by a disease. The results of the animal and human experiments are related with each other so that the pathophysiological processes can be better understood.



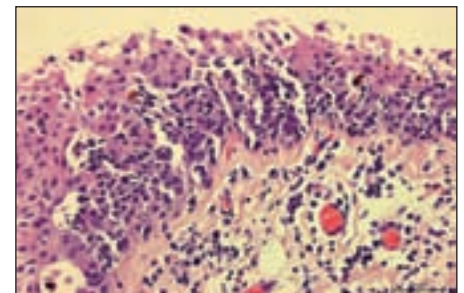
Selective measurement of temporal contrast sensitivity of different photoreceptor classes using a dedicated LED stimulator (left side: measurement of a normal subject, right side: view into the apparatus)

### Clinicopathologic concepts in diagnosis and management of ocular diseases

PI: 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.
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.



Primary acquired melanosis with marked cell atypia. Atypical melanocytic cells replace more than 75% of the epithelial thickness or melanoma in situ (pTis).



### Corneal stem cells

PI: Prof. Dr. U. Schlötzer-Schrehardt, Prof. Dr. F.E. Kruse

Transplantation of cultivated limbal epithelial progenitor cell grafts has been used to restore epithelial defects of the human cornea in patients with limbal stem cell deficiency. This research project explores the molecular characteristics of corneal stem and progenitor cells together with their specific niche microenvironment and their utilization for improved stem cell based therapies on tunable biosynthetic matrices. The applicability of alternative autologous stem cell sources for corneal epithelial tissue engineering strategies is also investigated.

### Pseudoexfoliation syndrome/glaucoma

PI: 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- $\beta$ 1, oxidative stress, and mechanical stress.

### Development of new methods for lamellar corneal transplantation

PI: 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 invasive techniques of lamellar corneal transplantation, such as DMEK (Descemet Membrane Endothelial Keratoplasty), using grafts consisting of a single cell layer to replace the diseased corneal endothelium. The clinical research group focuses on the further development of pre-, intra- and postoperative strategies and the analysis of clinical outcomes to continuously improve quality and reproducibility of the new surgical techniques.

### Circulation of the eye and the visual pathway, computer-aided diagnosis and virtual education

PI: 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 and virtual education

Ophthalmology needs new methods for medical information processing to optimize diagnosis and therapy. Automated analysis of ophthalmic images combined with automated classification leads to a fast and bias-free evaluation which is an important prerequisite for screening.

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.

### Teaching

Results of research are directly implemented in medical student and postgraduate teaching. Owing to the extensive contacts with colleagues abroad, many foreign students come to the Department of Ophthalmology for at least a part of their study (graduate or post-graduate) and for further education.

### Selected Publications

Menzel-Severing J, Petsch C, Tourtas T, Poliseti N, Klenke J, Skerl K, Wüllner C, Donitzky C, Kruse FE, Kremers J, Hammer CM. Evaluation of a 345 nm Femtosecond Laser for Corneal Surgery with Respect to Intraocular Radiation Hazard. PLoS One. 2015 Sep 11;10(9):e0137638

Berta A, Agaimy A, Braun J, Manger B, Kruse FE, Holbach L. Bilateral orbital IgG4-related disease with systemic and corneal involvement showing an excellent response to steroid and rituximab therapy. Orbit 2015;34:299-301

Tsai TI, Atorf J, Neitz M, Neitz J, Kremers J. Rod- and cone-driven responses in mice expressing human L-cone pigment. J Neurophysiol. 2015 Oct;114(4):2230-41

Weller JM, Schlötzer-Schrehardt U, Kruse FE, Tourtas T. Splitting of the Recipient's Descemet Membrane in Descemet Membrane Endothelial Keratoplasty-Ultrastructure and Clinical Relevance. Am J Ophthalmol. 2016 Dec;172:1-6

Poliseti N, Zenkel M, Menzel-Severing J, Kruse FE, Schlötzer-Schrehardt U. Cell adhesion molecules and stem cell-niche interactions in the limbal stem cell niche. Stem Cells 2016; 34: 203-219

Huchzermeyer C, Kremers J. Perifoveal L- and M-cone-driven temporal contrast sensitivities at different retinal illuminances. J Opt Soc Am A Opt Image Sci Vis. 2016 Oct 1;33(10):1989-1998

### International Cooperations

Prof. Dr. R. Ritch, New York Eye and Ear Infirmary, New York: USA

Prof. Dr. M. Greiner, Department of Ophthalmology and Visual Sciences, University of Iowa Carver College of Medicine, Iowa: USA

Prof. Dr. S. Kinoshita, Department of Frontier Medical Science and Technology for Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto: Japan

Dr. R. Kolar, Associate Professor, Department of Biomedical Engineering, Faculty of Electrical Engineering and Communication, Brno University of Technology: Czech Republic

P.T. Finger MD, FACS, The New York Eye Center, New York: USA

R.M. Conway, MD, PhD, NSW, Sydney: Australia

# Department of Otorhinolaryngology – Head and Neck Surgery

## Chair of Otorhinolaryngology

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### Research Focus

- Ultrasound, endoscopy, and salivary glands
- Division of Phoniatics and Pediatric Audiology
- Experimental Oncology/Nanomedicine (SEON)
- Cochlear implantation in the elderly
- Allergology/clinical immunology and rhinology
- Experimental otolaryngology
- Laboratory for sleep disorders/somnology

### Structure of the Department

Professorships: 6

Personnel: 167

- Doctors (of Medicine): 42
- Scientists: 29  
(thereof funded externally: 13)
- Graduate students: 28

### Clinical focus areas

- Minimal invasive surgery of salivary glands
- Lancer surgery
- Cochlear implantat surgery
- Nose/Paranasal surgery
- Clinical and surgical treatment of voice disorders
- Pediatric hearing disorders
- Diagnosis and treatment of sleep disorders

### Research

The Department of Otorhinolaryngology – Head and Neck Surgery is one of the largest hospitals in Germany and has a comprehensive research repertoire. In the clinical area, the focus is on ultrasound, the diagnosis/treatment of salivary gland diseases, tumor and voice disorders, vestibular and hearing impairments as well as somnology and allergology. These are reflected in

the basic research area. Nanomedicine, which carries out translational projects as well as extensive basic research, is another highly interdisciplinary focus.

### Ultrasound, endoscopy, and salivary glands

In modern ultrasound systems and endoscopy units, studies 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 cystadenolymphoma of the parotid gland.

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. The device that is already applied for the therapy of kidney stones has been used in the world-wide first treatment of salivary stones. The preliminary results of the first 44 treated patients were published in 2016. In 100% of the cases the patients were free of complaints, in 98% free of stones and in all cases the glands could be preserved.

### Division of Phoniatics and Pediatric Audiology

Our clinical research focuses on the development of new methods allowing for quantitative voice diagnostics. The major part is the objective analysis of endoscopic high speed recordings during voice production. Within our basic research we concentrate on physical interactions during voice production. We develop and analyze numerical models (Lumped-mass models, Finite-Volume-Models) and experimental models (synthetic silicon vocal folds and ex-vivo animal cadaver larynx models). We expect to gain more insight into the interaction between airflow, vocal fold dynamics and resulting acoustics for physiologic and pathologic voice production. Since 2016 we analyze the vocal fold tissue from the molecular-biological point of view. All these topics have the goal to enhance diagnostics and the treatment of our patients.

### Experimental Oncology/Nanomedicine (SEON)

PI: Prof. Dr. C. Alexiou

Iron oxide nanoparticles offer several possibilities for application in medicine. For instance, they can serve as drug carriers delivering therapeutics to the desired area guided by a magnetic field. Furthermore, they can be used as contrast agents in MRI or magnetize cells for magnetic tissue engineering. The Section for Experimental Oncology and Nanomedicine (SEON) works in several interdisciplinary projects to promote the translation of iron oxide nanoparticles from bench to bedside. To guarantee biocompatibility guidelines for the immune toxicological investigation of nanoparticles for medical applications have been established (bilateral BMBF funding). Concerning environmentally relevant nanoparticles, the Bavarian State Ministry of the Environment and Consumer Protection supports the development of complex standardized assay systems (e.g. HET-CAM and zebra fish model) for nanotoxicology. For the Cluster of Excellence Engineering of Advanced Materials (EAM), SEON performs toxicological investigations of technical nanoparticles designed for particular applications. All in all, new equipment and the establishment of innovative methods enabled us to achieve substantial progresses in the nanotoxicology sector in the last years. In this context, SEON organized the symposium "Nanotoxicology – research for safe application of nanoparticles in biomedicine and assessment of environmental effects with several international participants. To understand the interplay of magnetic nanoparticles with biological matrices, SEON has been engaging for several years in the Priority Program SPP1681. Concerning tissue reconstruction, in cooperation with the Division of Phoniatics and Pediatric Audiology we aim to develop a vocal fold implant by means of magnetic tissue engineering (funded by the German Cancer Aid) and we are also working on endothelialized scaffolds for heart and vascular surgery (DFG). A requirement for future clinical application is the translation of the nanoparticle synthesis from lab-scale to synthesis according to GMP guidelines which we want to address in cooperation with the pharmacy of UK Erlangen within the European FP-7 project "Nanoathero". To finally apply magnetic nanoparticles for imaging and diagnosis of tumors, their suitability is also evaluated in Magnetic Particle Imaging (supported by the DFG). Furthermore, end of 2016 the new round of the Emerging Fields Initiative (EFI) of FAU was launched.

ched in which SEON is involved in two innovative interdisciplinary projects.



*Flow cytometry enables the parallel investigation of several cellular parameters for the assessment of the biocompatibility of nanoparticles*

### Cochlear implantation in the elderly

Cochlear Implants (CI) provide an efficient treatment of profound hearing loss and deafness. Due to the ageing of the population in developed countries, an increasing number of seniors with hearing problems will be asking for cochlear implantation. One important question is whether central auditory degeneration processes may hinder the restauration of the speech perception.

We developed a battery of electrophysiology as auditory event potentials (AEP) and outcome measurements as speech perception in noisy situations and bottom-up speech training to identify differences between elderly CI subjects above 75 years and regular CI listeners. In summary, CI provision in older subjects is still efficient for hearing restauration.

### Allergology/clinical immunology and rhinology

Endonasal endoscopic sinus surgery and following desensitization with ASS come into question as a treatment for NSAID-intolerant patients. A functional blood test to determine Eicosanoid-imbalance (FET-AIT®) is under investigation. In a retrospective study, the validity of FET-AIT® as a test for identification of patients with NSAID-intolerance is going to be evaluated compared to nasal and oral provocation as a standard procedure.

### Experimental otolaryngology

Damage to the auditory system, e.g. due to noise trauma, does 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. In addition we propose a new model which relates

the development of tinnitus to the attempt of the auditory system to compensate for hearing loss. According to the model, the auditory system generates internal noise which on the one hand is perceived as tinnitus, but on the other hand improves information transmission within the cochlear nucleus via stochastic resonance. The model is supported by clinical audiometric data demonstrating that patients with tinnitus show better hearing thresholds in the speech-relevant, low frequency range up to 3 kHz than those patients without tinnitus.

### Laboratory for sleep disorders/somnology

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. These symptoms were investigated within a prospective, double-blind trial for their sensitivity, specificity, positive predictive and negative predictive value. Moreover we analyzed in a clinical trial the validity of different biomarkers from saliva and serum as a parameter for primary diagnosis or for monitoring the success of the treatment of OSA patients. In a further study the influence of total sleep time, sleep architecture, chronic intermittent hypoxia and apnea hypopnea index on subjective and objective daytime sleepiness of OSA patients was assessed.

### Teaching

The Department of Otorhinolaryngology, Head and Neck Surgery is involved in the curricular teaching of human and dental medicine with compulsory and elective subjects. Particularly the interdisciplinary teaching concerning medical technology, nanotechnology, toxicology and integrated life sciences has to be pronounced.

Bachelor's and Master's theses as well as MD and PhD theses are supervised.

### Selected Publications

Mantsopoulos K, Koch M, Klintworth N, Zenk J, Iro H: Evolution and changing trends in surgery for benign parotid tumors. *Laryngoscope*. 2015 Jan;125(1):122-7

Friedrich RP, Janko C, Poettler M, Tripal P, Zaloga J, Cicha I, Dürr S, Nowak J, Odenbach S, Slabu I, Liebl M, Trahms L, Stapf M, Hilger I, Lyer S, Alexiou C: Flow cytometry for intracellular SPION quantification: specificity and sensitivity in comparison with spectroscopic methods. *Nanomedicine (Lond)*. 2015 Jul;10(14):2133-7

Krauss P, Tziridis K, Metzner C, Schilling A, Hoppe U, Schulze H: Stochastic Resonance Controlled Upregulation of Internal Noise after Hearing Loss as a Putative Cause of

Tinnitus-Related Neuronal Hyperactivity. *Front Neurosci*. 2016 Dec 27;10:597

Schumann A, Liebscher T, Hoppe U: Phoneme discrimination training with experienced cochlear implant listeners. *HNO*. 2016 Oct;64(10):751-8

A. Schützenberger, M. Kunduk, M. Döllinger, C. Alexiou, D. Dubrovskiy, A. Seger, M. Semmler, C. Bohr. Laryngeal high-speed videoendoscopy: Sensitivity of objective parameters towards recording frame rate. *Biomed Res Int*. 2016;2016:4575437

Zaloga J, Pöttler M, Leitinger G, Friedrich RP, Almer G, Lyer S, Baum E, Tietze R, Heimke-Brinck R, Mangge H, Dörje F, Lee G, Alexiou C: Pharmaceutical formulation of HSA hybrid coated iron oxide nanoparticles for magnetic drug targeting. *Eur J Pharm Biopharm*. 2016 Apr;101:152-62

### International Cooperations

Prof. R.R. Patel, University of Indiana, Bloomington: USA

S. E. McNeil, PhD, Nanotechnology Characterization Laboratory (NCL), Frederick: USA

D. Letourneur, PhD, INSERM Laboratory, LVTS, Paris: France

Prof. Dr. Dr. Y. Temel, School for Mental Health and Neuroscience, Maastricht University, Maastricht: The Netherlands

Prof. Dr. N. Dillier, ORL, Universitätsspital Zürich, Zurich: Switzerland

# 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

Professorships: 5

Personnel: 427

- Doctors (of Medicine): 74
- Scientists: 13 (thereof funded externally: 8)
- Graduate students: 6

### Clinical focus areas

- Medical care of preterm and term newborn infants
- Pediatric gastroenterology
- Pediatric nephrology
- Neuropediatrics
- Pediatric endocrinology
- Pediatric oncology and hematology

### Research

Research at the Department of Pediatrics and Adolescent Medicine is focused on the area of perinatal medicine. This involves disease-oriented experimental, pre-clinical and clinical studies. Further main research interests lie in the fields of pediatric oncology, nephrology and neuropediatrics. The Department has its own clinical trial center which also serves as an accredited institution for professional training in the field of drug information.

### Medication safety

PI: 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. Both, the use of an electronic prescription system and evidence-based, structured dosing information increased medication safety. Our contribution to the "AMTS-Aktionsplan 2013 - 2015" (item 16: Development of recommendations for the use of drugs in children particularly in the inpatient care) has led to current BMG-funded activities of our Department to establish an evidence-based dosing information database for children in Germany. We actively participate in several EU-funded multicenter pharmacovigilance studies (e. g. long-term safety of the iron-chelating agent deferiprone). Moreover, the Department of Pediatrics and Adolescent Medicine is coordinating an EU-funded multicenter phase III study to investigate the use of clonidine as sedative agent in pediatric intensive care units (CloSed; compare own report). 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 for the studied drugs.

### Perinatal programming and early determination of renal and cardiovascular disorders

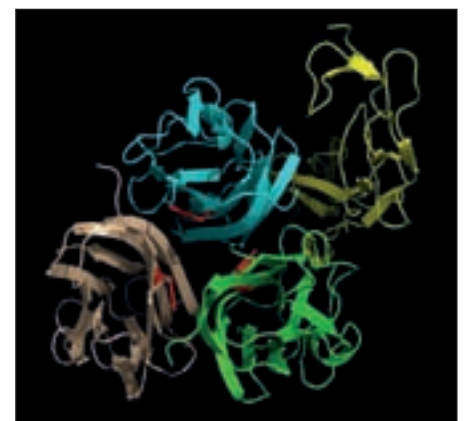
PI: Prof. Dr. A. Hartner

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

PI: 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 in DFG-funded projects the feasibility of perinatal protein replacement therapy or gene therapy in utero. From 2013 to 2016 we were leading the first clinical trial in neonates with hypohidrotic ectodermal dysplasia, a multicenter phase 2 interventional study to evaluate the safety and efficacy of a recombinant ectodysplasin A1 replacement protein, based on the promising preclinical data collected over the last years.



Model of the ectodysplasin A1 heterotrimer (monomers in cyan, green and brown) interacting with its cellular receptor (yellow).

### Genomic aberrations in childhood malignancies

PI: Prof. Dr. M. Metzler

Cancer cells are characterized by genetic alterations which are important not only for tumor development and progression, but also as specific molecular markers of the tumor. We have been establishing methods to use such markers for monitoring the response to therapy or for early detection of disease relapse, placing em-



phases on sarcomas, lymphomas and both, acute and chronic leukemias. In addition, we have been analyzing germ-line mutations predisposing to certain pediatric malignancies. Rare tumor entities have been recorded in the German Pediatric Rare Tumor Registry (STEP) and were further characterized in scientific projects.

### **Differentiation pathways during skeletal development**

PI: 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.

### **Neonatal neurology and neuroprotection**

PI: Prof. Dr. R. Trollmann

The aims of this research group are the early detection of perinatally acquired brain lesions and neuroprotection. In an established mouse model of perinatal hypoxia, we have been investigating molecular effector mechanisms of the immature brain after perinatal damage due to hypoxia and excitotoxicity as well as neuroprotective strategies, e.g. erythropoietin and prolyl hydroxylase inhibitors. We are studying the impact of acute hypoxia on early neuronal migration, angiogenesis, astrocytic and blood-brain barrier function and have been evaluating approaches to stabilize hypoxia-inducible transcription factors (HIF) by pharmacological means. Translational therapeutic strategies have been focused on the use of erythropoietin. In addition, the neuroprotective potential of activin A in the developing brain could be demonstrated in a mouse model of neonatal seizures. The investigation of hypoxia-induced neuroinflammatory mechanisms in vitro and in animal models also stimulates the progress of projects on neuroprotective strategies beyond the neonatal period. The research group is part of the Interdisciplinary Center of Neuroscience (IZN).

## **Teaching**

The Department of Pediatrics and Adolescent Medicine participates with compulsory and elective courses in the degree programs in human medicine and dentistry. Alongside traditional teaching special research seminars and interdisciplinary courses are offered. An „emergency care simulator“ adapted to the needs of neonatology and pediatric intensive care enables the training of emergency medical procedures and team-work analysis of the management strategies applied. This includes regular reviews of real emergency situations experienced in our clinic.

Individual researchers supervise Bachelor's, Master's theses as well as MD and PhD theses.



*Treatment of a virtual patient in the media center of the Department*

## **Selected Publications**

Frey D, Jung S, Brackmann F, Richter-Kraus M, Trollmann R. Hypoxia potentiates LPS-mediated cytotoxicity of BV2 microglial cells in vitro by synergistic effects on glial cytokine and nitric oxide system. *Neuropediatrics* 2015, 46:321-328

Fahlbusch FB, Heussner K, Schmid M, Schild R, Rübner M, Hübner H, Rascher W, Dörr HG, Rauh M. Measurement of amniotic fluid steroids of midgestation via LC-MS/MS. *J Steroid Biochem Mol Biol* 2015, 152, 155-160

Hammersen J, Hou J, Wünsche S, Brenner S, Winkler T, Schneider H. A new mouse model of junctional epidermolysis bullosa: the LAMB3 628G>A knockin mouse. *J Invest Dermatol* 2015, 135:921-924

Botzenhardt S, Sing CW, Wong IC, Chan GC, Wong LY, Felisi M, Rascher W, Ceci A, Neubert A. Safety profile of oral iron chelator deferiprone in Chinese children with transfusion-dependent thalassaemia. *Curr Drug Saf*. 2016, 11: 137-144

Krumbholz M, Hellberg J, Steif B, Bäuerle T, Gillmann C, Fritscher T, Agaimy A, Frey B, Juengert J, Wardelmann E, Hartmann W, Juergens H, Dirksen U, Metzler M. Genomic EWSR1 fusion sequence as highly sensitive and dynamic plasma tumor marker in Ewing sarcoma. *Clin Cancer Res* 2016, 22:4356-4365

Park J, Mazare A, Schneider H, von der Mark K, Fischer M, Schmukli P. Electric field-induced osteogenic differentiation on TiO<sub>2</sub> nanotubular layer. *Tissue Eng* 2016, 22:809-821

## **International Cooperations**

Prof. D. K. Grange, Department of Pediatrics, Washington University School of Medicine, St. Louis: USA

Dr. P. Schneider, Department of Biochemistry, University of Lausanne, Epalinges: Switzerland

Dr. O. Delattre, INSERM U830, Institut Curie, Paris: France

Prof. Dr. D. Reinhardt, Department of Anatomy & Cell Biology, McGill University, Montreal: Canada



# Department of Pediatrics and Adolescent Medicine

## Division of Pediatric Cardiology

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### Head of Division

Prof. Dr. med. Sven Dittrich

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### Research Focus

- Integrated multimodality imaging in pediatric cardiology
- Basic research on the physiology of congenital heart defects in the rat
- Genetic factors of congenital heart disease
- Pathophysiology of the Failing-Fontan circulation
- Psychosocial care research

### Structure of the Division

Professorships: 1

Personnel: 91

- Doctors (of Medicine): 21
- Scientists: 2 (thereof funded externally: 2)
- Graduate students: 18

### Clinical focus areas

- Interventional therapy of congenital heart defects in the catheter laboratory
- Surgical therapy of congenital heart defects in close cooperation with the Division of Pediatric Cardiac Surgery
- Intensive care after cardiac surgery

### Research

In the Division of Pediatric Cardiology, patient research on treatment techniques and care structures is performed. A particular focus is on different modalities of cardiovascular imaging and pathophysiology in univentricular hearts after Fontan operations. In basic research there are two working groups on the pathophysiology of congenital heart defects in the small animal model and a material biobank on the molecular genetic causes of congenital heart defects.

### Integrative multimodal imaging in pediatric cardiology

PI: PD Dr. M. Glöckler

- Use in heart catheter laboratory  
In approximately 25% of all heart catheter interventions a high-resolution 3D data set from previous examinations (MRT or CT) is available. These image data can be used for 3D navigation in the heart catheter laboratory. Various visualization techniques are used for this purpose in volume-based technology (VRT) or in stereolithographic (STL) format. The possibilities and benefits for the individual investigation are evaluated. In particular, the focus is on the reduction of the radiation exposure, the optimal angulation of both tubes, the reduction of the complete intervention time and the reduction of the contrast medium consumption. For the visualization and fusion of the data sets a prototypical software and hardware are used.
- Use for operation planning  
Pediatric heart surgery is often performed on distinctly morphologically altered hearts. About 20 described structural abnormalities in the cardiovascular system are present in complex cases. These defects of different severity are combined in different combinations so that the number of heart defects is almost unlimited. Thus, there are mostly no clear standard operations, but many individual operation decisions. Highly resolved data sets from MRI, CT, and 3D sonography are also processed to plan and facilitate surgical procedures. The possible reduction of the operating time, especially at the time of the heart-lung machine, is evaluated. In addition, these 3D data sets are increasingly being used in teaching, in order to bring early students to today's almost unlimited visualization techniques for cross sectional image data sets.



*Interrupted aortic arch, imaging with cinematic rendering for surgery planning*

### Basic research on the physiology of congenital heart defects in the rat

PI: Dr. M. Alkassar

Last year, a new rat model for the study of the hemodynamic effects of increased system venous pressure and a decreased cardiac output on parenchymatous organs such as liver, kidney, brain and intestines could be established. These changes reflect a commonly encountered hemodynamic situation in pediatric cardiology which is associated with several still very poorly understood diseases. Some diseases, such as for example a protein losing enteropathy, set in some years after surgery and can be understood due to the complex interplay of modified hemodynamics with immunological reactions in the animal model.

In collaboration with the experimental radiology, we could establish new techniques of dynamic function parameter determination using real-time 3D echocardiography in rats. 4D-MRT imaging was used for validation.

To describe the effects of an altered hemodynamics on the various parenchymatous organs, micro-CT 3D-angiography was established in order to represent the arterial and venous supply of the body.

A better understanding of the pathophysiology of altered hemodynamics on parenchymatous organ systems offers the opportunity to develop targeted therapeutic strategies for treating a variety of still poorly understood pathologies in pediatric cardiology.

### Genetic factors of congenital heart disease

PI: PD Dr. O. Toka

The investigations of our team focus 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 3,000 DNA samples and about 2,500 cardiac tissue samples of all four chambers of the heart. Since 2009, a close cooperation and funding through the National Competence-Network for congenital heart disease 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 cooperation.

Our collaborators are the Institute of Human Genetics, the Experimental and Clinical Research Center (Charité and MDC Berlin), the Department of Cardiovascular Genetics (Harvard University, Boston, USA), the Wellcome

Trust Sanger Institute (Cambridge, UK) and the Department for Medical Genetic and Human Genetic (Charité Berlin).

### **Pathophysiology of the Failing-Fontan circulation**

PI: PD Dr. O. Toka, Dr. J. Moosmann

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 losing enteropathy which leads to a so called failing of the Fontan circulation. Our investigations were funded by the Gerd-Killian award of the German heart foundation (2013-2016).

Our collaborators are the Institute of Human Genetics, the Department of Medicine 5 – Hematology and Oncology and the Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology.

Current projects are:

- Near-infrared spectroscopy for peripheral muscle oxygenation of Fontan and Failing-Fontan patients during ergometric exercise;
- Micro-RNA analysis for identifying inflammatory pathways in Failing-Fontan patients;
- Identification of immunologic alterations of lymphocytes in Failing-Fontan patients;
- Microbiome analyses of stool in Failing-Fontan patients.

### **Psychosocial care research**

PI: Dr. W. Wälisch

More than 6,000 children undergo inpatient cardiac surgery or intervention in the cardiac catheterization laboratory in Germany each year, however little is known about the impact of cardiac surgery/intervention and postprocedural pain on children's health-related quality of life during the months after the procedure. The aim of our L.I.S.A. –study (Life in Children and Families with Congenital Heart Disease – Interventions and effect of an Integration of Stationary and Ambulant Sectors) is to determine this impact on children and families and furthermore, offer and examine the potential benefits of interventional strategies such as physiotherapy, psychotherapy, nutritional counseling or family orientated rehabilitation with regard to the recovery process.

This randomized, placebo-controlled trial includes children from 3-18 years of age who had cardiac surgery or underwent an intervention in

the cardiac catheterization laboratory. Patient specific tailored recommendations for the interventional strategies are given when defined values of the questionnaires were not reached and the patient was randomized to the interventional arm of the study. By using this study design we aim to determine interventional strategies and predictors of clinically significant change in health-related quality of life in these children over the first months after surgery or intervention.

### **Teaching**

The Division of Pediatric Cardiology takes part in the general teaching program of the Department of Pediatrics and Adolescent Medicine. Additionally, medical students are taught pediatric cardiology within an elective course on pediatrics. Furthermore, we offer the possibility to perform clinical electives in our Division. MD doctorates are supervised.

### **Selected Publications**

Dittrich S, Tuerk M, Haaker G, Greim V, Buchholz A, Burkhardt B, Fujak A, Trollmann R, Schmid A, Schroeder R. Cardiomyopathy in Duchenne Muscular Dystrophy: Current Value of Clinical, Electrophysiological and Imaging Findings in Children and Teenagers. *Klin Padiatr.* 2015 Jul;227(4): 225-31

Moosmann J, Uebe S, Dittrich S, Rüffer A, Ekici AB, Toka O. Novel loci for non-syndromic coarctation of the aorta in sporadic and familial cases. *PLoS One.* 2015 May 18;10(5): e0126873

Sifrim A et al. Distinct genetic architectures for syndromic and nonsyndromic congenital heart defects identified by exome sequencing. *Nat Genet.* 2016 Sep;48(9):1060-5

Hausmann P, Stenger A, Dittrich S, Cesnjevar R, Rüffer A, Hammon M, Uder M, Rempel O, Glöckler M. Application of Dual-Source-Computed Tomography in Pediatric Cardiology in Children Within the First Year of Life. *Rofo.* 2016 Feb;188(2):179-187

Stenger A, Dittrich S, Glöckler M. Three-Dimensional Rotational Angiography in the Pediatric Cath Lab: Optimizing Aortic Interventions. *Pediatr Cardiol.* 2016 Mar;37(3):528-36

Dittrich S, Sigler M, Priessmann H. Late complete atrioventricular block after closure of an atrial septal defect with a Gore septal occluder (GSO™). *Catheter Cardiovasc Interv.* 2016 Apr;87(5):945-50

# Department of Plastic and Hand Surgery

## Chair of Plastic and Hand Surgery

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### Research Focus

- Tissue engineering
- Interaction of regenerative strategies and tumor progression
- Clinical experimental research
- Clinical retrospective studies

### Structure of the Department

Professorships: 1

Personnel: 27

- Doctors (of Medicine): 16
- Scientists: 5 (thereof funded externally: 5)
- Graduate students: 32

### Clinical focus areas

- Reconstructive microsurgery
- Esthetic surgery
- Burn surgery
- Breast surgery
- Hand surgery
- Body contouring
- Lymphedema/lipedema
- Laser
- Hyperhidrosis

### Research

Research interests of the Department of Plastic and Hand Surgery are the engineering of bioartificial tissue, tumor biology as well as clinical experimental research and clinical retrospective studies.

### Tissue engineering

PI: Prof. Dr. Dr. R.E. Horch<sup>1-5</sup>, Prof. Dr. J. Beier<sup>1,3</sup>, PD Dr. A. Arkudas<sup>2</sup>, Dr. A.M. Boos<sup>3,4</sup>, Dr. A. Weigand<sup>3,4</sup>, Dr. D. Steiner<sup>2</sup>, Dr. A. Cai<sup>1</sup>, M. Hesenauer

1) Tissue engineering of skeletal muscle

In this study 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 model including motor nerve branches will be used for inducing muscle differentiation in vivo. The final aim of this project is the generation of axially vascularized, innervated skeletal muscle tissue.

Funding: DFG

2) Tissue engineering of axially vascularized bone in a small animal model

The aim of this study is to generate axially vascularized bioartificial bone tissue in the AV loop model in the rat. In this context bone regeneration and angiogenesis are investigated using innovative bioactive matrices in combination with endothelial progenitor cells (EPC) as well as adiposal derived stem cells (ADSC).

3) Generation of axially vascularized tissue in the large animal

The transplantation of engineered bone will be evaluated in combination with angiogenic and osteogenic cells in clinically relevant dimension in the sheep tibia defect model.

4) Skin tissue engineering by the use of adipose-derived stem cells

Current treatment options for chronic wounds should be optimized using growth factors and adipose derived stem cells.

5) Intravital microscopy in the AV loop model

To understand the mechanisms concerning the de novo tissue formation in the AV loop model, we developed a suitable chamber model which allows intravital microscopic evaluation the newly forming vessel network.

### Interaction of regenerative strategies and tumor progression

PI: Prof. Dr. Dr. R.E. Horch<sup>1-8</sup>, Dr. A.M. Boos<sup>1-8</sup>, Dr. A. Weigand<sup>1-8</sup>, Dr. R. Götzl<sup>6,7</sup>, Dr. J. Suckau<sup>8</sup>

1) Effects of tumors on a developing blood vessel network

The goal of the project is the characterization of the influence of tumor cells on the development of a blood vessel network and the role of EPC in tumor associated angiogenesis.

2) Therapeutic approaches on the lymphatic vessel system in the context of regenerative medicine and tumor progression

The goal of the project is the characterization of the interaction of lymphatic endothelial cells and stem cells from the bone marrow and adipose tissue as well as the establishment of a lymphatic vessel network in the rat AV loop model.

3) Tumor angiogenesis and vasculogenesis in breast cancer

This study investigates the effect of mammary carcinoma cells on the angiogenic properties of endothelial progenitor cells (EPC).

4) Paracrine and cell-cell interaction of adipose derived stem cells and mammary epithelial cells in the focus of development of breast cancer In this study, the influence of adipose derived stem cells on the behavior of cells in the breast and breast cancer tissue will be evaluated.

5) Significance of tumor-associated fat stem cells in breast cancer progression

The surrounding adipose tissue of mammary carcinomas is probably changed by the influence of the tumor and may play a role in tumor progression. This will be investigated more closely by analyzing stem cells from tumor-associated adipose tissue compared to stem cells from healthy adipose tissue.

6) Characterization of adipose derived stem cells from different harvesting methods

Goal of that project is to clarify if different surgical procedures during the harvesting of the stem cells have a significant effect on their behavior and functionalities.

7) Interaction of adipose derived stem cells and liposarcoma cells

With a better knowledge about development of liposarcoma, possible new therapeutic targets could be identified.

8) Interaction of melanoma cells, stem cells and endothelial cells in tumor progression

To date the interaction of adipose derived stem cells and melanoma tumor cells on tumor progression is not fully understood. This knowledge is essential for a detailed understanding of melanoma progression and for the evaluation of the safety of lipotransfer in tumor beds.

### Clinical experimental research

PI: Prof. Dr. Dr. R.E. Horch<sup>1-7</sup>, Prof. Dr. J. Beier<sup>1,2</sup>, PD Dr. A. Arkudas<sup>3,7</sup>, Dr. M. Schmitz<sup>4,6</sup>, Dr. Boos<sup>5</sup>, Dr. I. Ludolph<sup>1,4-6</sup>, Dr. A. Cai<sup>2</sup>, Dr. G. Bühner<sup>7</sup>, F. Fried<sup>3</sup>

1) 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, intraoperative fluorescence imaging of tissue perfusion using a laser camera was performed. Based on these observations, a further increase of free tissue transplantation survival and a decrease of flap complications could be achieved.

2) Prospective analysis of grip force in common hand conditions

Hand conditions (such as Carpal Tunnel Syndrome) may be accompanied by a loss of hand

function or grip force. While gripping a cylindric measuring device, the total grip force and the load distribution patterns of the hand and fingers can be assessed with the Manugraphy System®. This prospective study evaluates the effect of a surgical procedure on grip force of the hand.

#### 3) Evaluation of carpal instability regarding scapholunate ligament injuries

The aim of this study is to evaluate wrist mobility between carpal bones using CT analysis in order to invent new strategies to treat ligament injuries.

#### 4) Biomaterials for coverage of silicone implants to prevent capsular fibrosis

Capsular fibrosis represents a significant complication following implantation of silicone breast implants, necessitating further surgical intervention. Experimental animal studies will be conducted to investigate if diverse biomaterials can be used as an envelope for submuscular silicone implants to reduce foreign body reaction.

#### 5) Evaluation of an innovative negative pressure dressing in postbariatric patients

To improve postoperative wound healing and achieve better scar quality, this study compares an innovative negative pressure dressing to a standard wound dressing.

6) Intraoperative assessment of tissue perfusion of the abdominal wall in postbariatric patients  
Patients receiving abdominoplasty after massive weight loss show high rates of wound healing disorders. In this study tissue perfusion and perfusion dynamic are analyzed during abdominoplasty to gain profound knowledge of perfusion dynamics of the abdominal wall and to improve wound healing.

#### 7) Comparison of shoulder function of patients after muscle-sparing and complete latissimus dorsi harvest

The aim of this study is the evaluation of the relevance of muscle-sparing latissimus dorsi flap harvesting regarding shoulder functionality and strength.

### Clinical retrospective studies

PI: Prof. Dr. Dr. R.E. Horch<sup>1-5</sup>, Prof. Dr. J.P. Beier<sup>3</sup>, Dr. M. Schmitz<sup>4</sup>, Dr. R. Götzl<sup>3</sup>, Dr. W. Müller-Seubert<sup>1,2</sup>, Dr. M. Hillenbrand<sup>5</sup>

#### 1) Analysis of soft-tissue reconstruction using the axial frontonasal flap (Marchac) between 2003-2016

Patients who underwent soft-tissue reconstruction using the axial frontonasal flap are examined afterwards to analyze the functional outcome, esthetic result and patient satisfaction.

#### 2) Analysis of defect reconstruction using temporalis fascia grafts between 2003–2016

In this study, operative means and outcomes of defect reconstruction using free or pedicled temporalis fascia graft are analyzed to record postoperative complications and the functional and aesthetic result.

#### 3) 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.

#### 4) Retrospective ten year analysis of postbariatric surgery for body contouring after massive weight loss

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.

#### 5) Vacuum Instillation Therapy in chronic-infected wounds

The aim of this retrospective study is to investigate an effect of vacuum instillation therapy with regard to a reduction of the bacterial load as well as the bacterial count in chronically infected wounds.

## Teaching

With compulsory and elective subjects, the Department of Plastic and Hand Surgery is involved in the curriculum-based teaching in medicine. In this context, a microsurgical suture course is offered besides theoretical courses.

Furthermore, MD and PhD theses are supervised.

### Selected Publications

Weigand A, Beier JP, Hess A, Gerber T, Arkudas A, Horch RE, Boos AM. Acceleration of vascularized bone tissue-engineered constructs in a large animal model combining intrinsic and extrinsic vascularization. *Tissue Eng Part A* 2015, 21(9-10): 1680-1694

Buehrer G, Balzer A, Arnold I, Beier JP, Koerner C, Bleiziffer O, Brandl A, Weis C, Horch RE, Kneser U, Arkudas A. Combination of BMP2 and MSCs significantly increases bone formation in the rat arterio-venous loop model. *Tissue Eng Part A* 2015, 21(1-2): 96-105

Weigand A, Boos AM, Tasbihi K, Beier JP, Dalton PD, Schrauder M, Horch RE, Beckmann MW, Strissel PL, Strick R. Selective isolation and characterization of primary cells from normal breast and tumors reveal plasticity of adipose derived stem cells. *Breast Cancer Res* 2016, 18(1): 32

Boos AM, Weigand A, Brodbeck R, Beier JP, Arkudas A, Horch RE. The potential role of telocytes in Tissue Engineering and Regenerative Medicine. *Semin Cell Dev Biol* 2016, 55: 70-78

Horch RE, Hohenberger W, Weber K, Arkudas A, Beier JP. Myocutaneous transpelvic flaps do improve quality of life

and help to reduce wound healing complications in patients receiving abdominoperineal resection in the real world. *Int J Colorectal Dis* 2016, 31(8): 1525-1527

Rath SN, Noeaid P, Arkudas A, Beier JP, Strobel LA, Brandl A, Roether JA, Horch RE, Boccaccini AR, Kneser U. Adipose- and bone marrow-derived mesenchymal stem cells display different osteogenic differentiation patterns in 3D bioactive glass-based scaffolds. *J Tissue Eng Regen Med* 2016, 10(10): E497-E509

### International Cooperations

Prof. S. Jiaming, Tongji Medical College, Huazhong University of Science and Technology, Wuhan: China

Prof. T. Nishimura, Faculty of Pharmacy, Keio University, Tokyo: Japan



# Department of Psychiatry and Psychotherapy

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### Research Focus

- Depression
- Dementias
- Addictive behavior
- Clinical neurochemistry and neurochemical dementia diagnosis
- Neurophotonics
- Medical care research
- Olfactometry
- Molecular psychiatry

### Structure of the Department

Professorships: 3  
Personnel: 221  
• Doctors (of Medicine): 32  
• Scientists: 18  
(thereof funded externally: 7)  
• Graduate students: 126

### Clinical focus areas

- Depression
- Memory disorders
- Dementia
- Schizophrenia
- Addiction
- Anxiety disorders

### Research

Our research is based on a broad spectrum of methods, ranging from basic clinical research to clinical research and care research. The aim of all projects is to improve the early diagnosis, main diagnosis, and treatment of important psychiatric disorders, such as depression, dementia or addiction.

### Depressions

Sphingolipids are essential components of the membrane of nerve cells and regulate the signal flow between neurons. We have shown that

these lipids are involved in a very specific manner even in mild depression-like states, such as the extinction of successful behavior. This regulation is based on the control of the activity of sphingolipid-synthesizing and -degrading enzymes which can now also be targets for improved pharmacotherapy of depression.

Funding: DFG, IZKF and Johannes und Frieda Marohn Foundation

In a further study, the role of the nicotinic-cholinergic system for the expression of anxiety and negative emotionality could be further confirmed. Homozygous carriers of the rs1044396 C-allele showed significantly higher manifestations of anxious thoughts. In a study using a multi-sensor bracelet (SenseWear® Pro3 bracelet) in patients with major depression, a significant association between depression and physical activity could be shown. An improvement in clinical symptoms was associated with an increase in physical activity. Results from a controlled, randomized study of efficacy of boulder therapeutic intervention in people with depression showed an improvement in depressive symptoms compared to a waiting group.

### Dementia

Two newly developed ELISA test systems have been validated. Based on two Alzheimer's patient cohorts, we evaluated our interpretation algorithm „Erlangen Score“. In both cohorts, the Erlangen score correlated strongly with the progression of the patients into the dementia phase. In another study, a new potential Alzheimer dementia biomarker, the non-phosphorylated tau protein, was analysed analytically and clinically. In the clinical part of the study, the non-P-tau concentration in the dementia group was significantly increased as compared to controls. In a biomarker study, the postsynaptic protein neurogranin could be confirmed as a cerebrospinal biomarker of Alzheimer's disease. In another study investigating the immunological effects of Aβ peptides, it was shown that the amyloidogenic Aβ variants have pronounced antimicrobial properties. In the area of psychometry, the test for the compilation of everyday competences in people with mild dementia or slight cognitive impairment (ETAM) has been re-validated and published internationally within the framework of a DFG project.

The DeTaMAKS study is the first controlled, randomized study of the effectiveness of non-drug therapy in day care in combination with a short-term telephone intercom. First results for the six months intervention period showed that both,

the cognitive and everyday practice abilities of people with cognitive impairments, could be stabilized at least at the initial level while they lessened in the control group.

At the start of the national graduate school „Optimization strategies for dementia“, the first Erlanger expert conference on dementia took place. Subsequently, graduate students took up their research at the participating locations.

### Addiction disorders

In international multicentric studies, new genetic mechanisms involved in the development of alcohol addiction have been identified. In animal models, the physiological mechanisms in the brain could be characterized by which spontaneous genetic changes lead to a reduced function of the reward system.

Funding: DFG, IZKF

The NOAH study investigated the role of intra-uterine and adult androgen exposure in adult alcohol addiction. Male patients had higher prenatal and adult androgen activities. The prenatal androgen exposure and the adult levels were also associated with liver, muscle and blood damage as well as relapses within twelve months. In the FRAMES and FRANCES study, those maternal factors were investigated during pregnancy that determine the child's intrauterine androgen exposure. The study showed an association of maternal stress, smoking and alcohol drinking with higher intrauterine androgen exposure. The research group was awarded the Wilhelm-Fuerlein-Research Prize 2016 for this project. An online study was conducted to characterize the new phenomenon of internet dependency. It could be shown that besides social games also social networks have a clear addiction potential. In a study within the framework of the 'nicotine' focal program, an association of known DNA polymorphisms of the nicotinic acetylcholine receptor subunit Alpha4 with the N100 amplitude of auditory event-related potentials could be shown within an oddball paradigm. In the context of evidence-based medicine, a contribution at the highest quality level in the area of pharmacotherapy was made to the preparation of the S3 guideline „Screening, Diagnostics and Treatment of Harmful and Dependent Tobacco Consumption“. A representative study with more than 9,000 young people examined the extent to which drug consumption among adolescents with an immigration background is different from those without migration background. It was shown that young people with a background of migration show more favorable pat-



terms in terms of alcohol, but less favorable patterns of cannabis and tobacco consumption.

### **Clinical neurochemistry and neurochemical dementia diagnostics**

The ISO 15189 accredited laboratory is an internationally recognized center for neurochemical dementia diagnostics. The analysis of cerebrospinal fluid (CSF) offers excellent diagnostic possibilities in a variety of neurological and psychiatric disorders. Recently, the customer base of the laboratory has also expanded to foreign senders.

### **Neurophotronics**

In 2015, the group investigated the intracellular transport of Alzheimer's disease-related proteins to the cell surface, developing new genetic tools. Programs have been developed for computer-assisted diagnosis of stroke in MRI data and for the automated diagnosis of stroke from EEG data. A project funded by the DFG investigated the properties of antipsychotic drugs that are relevant for synapse efficacy. With funding from the Else-Kröner-Fresenius Foundation, it was possible to develop a new method for the optical measurement of connectivity in nerve cell networks.

### **Medical care research**

In cooperation with the interdisciplinary pain center, an instrument for the operationalization of successful partial hospital treatment which is based on Patient Reported Outcomes (PRO) was developed in order to evaluate routines of the care. This instrument has been validated and published internationally.

### **Olfactometry**

Together with researchers of other groups, an odor test for food-associated odors was developed. With this validated test, the known gap in the food-associated odor testing could be closed.

### **Molecular psychiatry**

The research group, newly established in June 2016, is engaged with fundamental research on molecular mechanisms that control the release of neurotransmitters at the neuronal synapses. In cooperation with the UK Tübingen, the brain activity after a fast-acting antidepressant ketamine was tested by means of magnetic resonance spectroscopy. The study indicated a ketamine-induced neuroplasticity of glutamatergic neurotransmission.

Funding: DFG, BMBF

## **Teaching**

The Department of Psychiatry and Psychotherapy participates with compulsory and elective courses in the curricular teaching of human medicine and logopedics. Particularly noteworthy is the interdisciplinary teaching within the framework of the cross-sectional subjects Q9 (clinical pharmacology/ pharmacotherapy) and Q10 (prevention and health promotion) as well as within the framework of the elective course of sexual medicine. Within the scope of the curricular teaching, the Department has created a simulation-patient program in recent years highly appreciated by students. In reality, students can practice acting in difficult situations with agitated, affective, rejecting and uncooperative patients.

Bachelor's and Master's theses as well as MD and PhD theses are supervised.

### **Selected Publications**

Heilmann S et al. PLD3 in non-familial Alzheimer's disease. *Nature* 2015; 520(7545):E3-E5

Jansen WJ et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA* 2015; 313(19):1924-1938

Bauereiss A, Welzel O, Jung J, Grosse-Holz S, Lelental N, Lewczuk P, Wenzel EM, Kornhuber J, Groemer TW. Surface Trafficking of APP and BACE in Live Cells. *Traffic* 2015; 16(6):655-675

Luttenberger K, Stelzer EM, Först S, Schopper M, Kornhuber J, Book S. Indoor rock climbing (bouldering) as a new treatment for depression: study design of a waitlist-controlled randomized group pilot study and the first results. *BMC Psychiatry* 2015; 15:201

Jia T et al. Neural basis of reward anticipation and its genetic determinants. *Proc Natl Acad Sci U S A* 2016; 113(14):3879-3884

Lenz B, Thiem D, Bouna-Pyrrou P, Mühle C, Stoessel C, Betz P, Kornhuber J. Low digit ratio (2D:4D) in male suicide victims. *J Neural Transm (Vienna)* 2016; 123(12):1499-1503

### **International Cooperations**

Prof. G. Schumann, Institute of Psychiatry Psychology and Neurology, King's College London, London: UK

Prof. M. Filip, Institute of Pharmacology, Polish Academy of Sciences, Krakow: Poland

Dr. Z. Hassan, Centre for Drug Research, Universiti Sains Malaysia, Penang: Malaysia

Prof. H. Zetterberg, Sahlgrenska Academy, Mölndal: Sweden

# Department of Psychiatry and Psychotherapy

## Division of Child and Adolescent Mental Health

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### Head of Division

Prof. Dr. med. Gunther H. Moll

### Contact

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### Research Focus

- Prenatal and early risk factors for child development: FRANCES – Franconian Cognition and Emotion Studies
- Stress regulation in healthy children and in children and adolescents with generalized anxiety disorder
- Neural processing of emotional and disorder specific stimuli in girls with eating disorders
- Genes to behavior: Unlocking the code for early detection of reading disorder
- Parenting stress in the context of mental health treatments for children and adolescents
- Therapeutic interventions - Clinical effects and underlying mechanisms
- Molecular and epigenetic consequences of pre- and postnatal trauma in a mouse model

### Structure of the Division

Professorships: 1

Personnel: 144

- Doctors (of Medicine): 24
- Scientists: 5 (thereof funded externally: 2)
- Graduate students: 12

### Clinical focus areas

- Attention deficit/hyperactivity disorder (ADHD)
- Tic and obsessive-compulsive disorders
- Anxiety and depressive disorders
- Posttraumatic stress disorders
- Eating disorders
- Autism spectrum disorders
- Reduced intelligence with psychiatric comorbidity
- Regulation, feeding and behavior disorders in early childhood

### Research

The aims of the scientific projects of our Division are to contribute to a better understanding of the developmental processes and the neurobiol-

ogical basis of emotional and behavioral disorders in children and adolescents and to learn more about the neuronal mechanisms of therapeutic interventions.

The main topics addressed by the research unit (headed by PD Dr. H. Heinrich and PD Dr. O. Kratz) are described below.

### Prenatal and early risk factors for child development: FRANCES – Franconian Cognition and Emotion Studies

PI: Dr. A. Eichler

The longitudinal study with 250 families which is conducted in cooperation with the Departments of Obstetrics and Gynecology and of Psychiatry and Psychotherapy examines the long-term effects of prenatal risks (including alcohol consumption, depression, stress) on child adaptation aged between 6-8 years. Child developmental status was operationalized in a multi-level design (cognitive, emotional, social factors): In addition to neuropsychological and neurophysiological measures, neurobiological markers are of interest (e.g. alcohol metabolites in the meconium of the newborn; child and mother saliva/hair cortisol concentrations; epigenetic data from child buccal cells). Results indicate that even 'subliminal' alcohol consumption has negative effects on child brain development and that prenatal depressive symptoms affect a child's stress system which seems to be partly mediated by epigenetic changes in the DNA.

In cooperation with the Division of Pediatric Cardiology, we have added a sample of children with a risk factor of early life stress, i.e. children with a congenital simple ventricular septal defect which was surgically corrected in infancy, to compare their developmental status with the FRANCES cohort. Deficits in language development were observed which were moderated by positive parenting behavior.

Funding: Robert Enke Foundation

### Stress regulation in healthy children and in children and adolescents with generalized anxiety disorder

PI: Dr. Y. Golub

To study the regulation of the HPA-axis in healthy children and in children suffering from generalized anxiety, several methods of cortisol measurements were applied. We investigated and compared basal and stress-induced saliva/plasma cortisol and the long-term hair cortisol levels. We report age dependency of several basal and reactive cortisol parameters. Furthermore, children with internalizing symptoms showed significantly lower one-month hair cortisol levels. In children and adolescents with generalized anxiety, an up-regulation of the basal cortisol values and a

blunted HPA-axis response to stress was observed. In addition, we found an upregulation of the peripheral NPY values in the children with generalized anxiety. The remission of clinical symptoms correlated with a normalization of function of both, HPA- and NPY systems, respectively. Altogether, integrating reactive, basal and cumulative cortisol measurements can lead to our understanding of the age dependent complex changes in the regulation of the stress system that take place in the course of mental disorders.

### Neural processing of emotional and disorder specific stimuli in girls with eating disorders

PI: Dr. S. Horndasch

In adolescent girls with eating disorders (anorexia nervosa, bulimia nervosa) and typically developing girls, gaze behavior and central nervous and peripheral physiological responses were studied when viewing body scheme pictures of underweight, normal weight, and overweight women. Patients with eating disorders showed longer fixation times for unclothed body regions (visual attentional bias towards body shape-related information) and patients with anorexia nervosa were found to have the highest amplitude in an EEG event-related component (reflecting motivated attention) following pictures of strongly underweight women. By including adult patients suffering from anorexia nervosa and matching healthy controls, we were able to look at developmental aspects of the disorder and found age-specific effects e.g. for ratings of female body stimuli and for fMRI data reflecting neural processing of food stimuli.

### Genes to behavior: Unlocking the code for early detection of reading disorder

PI: Prof. L. A. Gabel

We seek to examine the connection among genetic, cognitive and behavioral aspects of reading disorder with the goal of early identification and intervention. Several cognitive and perceptual changes appear to associate with reading disorder, however it is unclear how cognitive, behavioral, and genetic measures correlate with reading disorder. The goal of this ongoing project is to examine the link between specific genetic variants, maze learning ability, and measures of reading performance in pre-readers (aged 5-6 years) and children of reading age (8-13 years old). We will determine if native German-speaking (transparent language) children with reading disorder exhibit a similar impairment on a virtual maze learning task as compared to English-speaking (non-transparent language) children with reading disorder.

Funding: Alexander von Humboldt Foundation

## Parenting stress in the context of mental health treatments for children and adolescents

PI: Dr. V. Irlbauer-Müller

The parents of children and adolescents utilizing mental health treatments face special challenges: Their stress levels can be assessed with an appropriate questionnaire which was presented to the parents of 166 children and adolescents (age: 11-18 years) who initially presented at our Division. The results illustrate high levels of parenting stress which increased when the parents described the symptoms of their child or adolescent to be high. Regarding the bidirectionality of the parent-child-interaction, these results show how important it is to assess parenting stress and to create mental health treatments for children and adolescents which are context- or parent-centered.

## Therapeutic interventions – Clinical effects and underlying mechanisms

PI: Dr. P. Studer

Neurofeedback involves a brain-computer interface which enables to learn self-control over specific aspects of neural (EEG) activity. In our earlier studies, conducted with colleagues from Göttingen, we could demonstrate the clinical effectiveness of neurofeedback (theta/beta and slow cortical potential training) as a therapeutic module in the treatment of children with ADHD. Our recent studies („short-term studies“) aimed at how to optimize neurofeedback training and learn more about the mechanisms underlying a successful training („neuroplasticity“).

Special light concepts are used to stabilize circadian rhythms in patients with psychiatric disorders (affective disorders, ADHD subtypes). We installed a light laboratory to test the clinical success of light therapy in future trials. In a pilot study, funded by the ELAN funds, the effects of different light conditions on sleep and attention/arousal were investigated in healthy adolescents. Preliminary results indicate at least a positive effect of blue (i.e. stimulating) light on attentional measures (reaction time variability).

## Molecular and epigenetic consequences of pre- and postnatal trauma in a mouse model

PI: Dr. Y. Golub

We applied our mouse model of prenatal trauma to investigate trauma-induced regulation changes of several stress-related genes at the molecular-epigenetic level. mRNA expression levels were quantified and DNA methylation were measured for these stress-related

genes in the dorsal hippocampus of traumatized dams and their offspring. We could show decreased expression of the *Crhr1* and *Nr3c2* genes in traumatized mothers which were reflected by increased methylation levels of several CpG islands of these genes. In pups an opposite regulation of the *Crhr1* expression was observed. We could furthermore show a decrease in the expression of the *Fkbp5* in the embryonic hypothalamus of traumatized pups which persisted into the adulthood. Our findings support the hypothesis that trauma-induced neuroendocrine and behavioral alterations are associated with stable changes of the methylation and expression of stress-related genes from in utero time point on.

## Teaching

The Division of Child and Adolescent Mental Health is involved in compulsory and elective courses in the curriculum of the degree program human medicine.

MD theses as well as Bachelor's and Master's theses (mainly in psychology) are supervised.

## Publications

Solati J, Kleeheaupt E, Kratz O, Moll GH, Golub Y. Inverse effects of lipopolysaccharides on anxiety in pregnant mice and their offspring. *Physiol Behav* 2015, 139:369-74

Horndasch S, Heinrich H, Kratz O, Mai S, Graap H, Moll GH. Perception and evaluation of women's bodies in adolescents and adults with anorexia nervosa. *Eur Arch Psychiatry Clin Neurosci* 2015, 265(8): 677-87

Eichler A, Grunitz J, Grimm J, Walz L, Raabe E, Goecke TW, Beckmann MW, Kratz O, Heinrich H, Moll GH, Fasching PA, Kornhuber J. Did you drink alcohol during pregnancy? Inaccuracy and discontinuity of women's self-reports: On the way to establish meconium ethyl glucuronide (EtG) as a biomarker for alcohol consumption during pregnancy. *Alcohol* 2016, 54: 39-44

Funke R, Eichler A, Distler J, Golub Y, Kratz O, Moll GH. Stress system dysregulation in pediatric generalized anxiety disorder associated with comorbid depression. *Stress Health* 2016. doi: 10.1002/smi.2736

Golub Y, Canneva F, Funke R, Frey S, Distler J, von Hörsten S, Freitag CM, Kratz O, Moll GH, Solati J. Effects of In utero environment and maternal behavior on neuroendocrine and behavioral alterations in a mouse model of prenatal trauma. *Dev Neurobiol* 2016, 76(11): 1254-65

Irlbauer-Müller V, Eichler A, Stemmler M, Moll GH, Kratz O. Elterliche Belastung und die Zuverlässigkeit von Elternangaben in der Diagnostik psychisch und verhaltensauffälliger Kinder und Jugendlicher. *Z Kinder Jugendpsychiatr Psychother* 2016, 18: 1-7

## International Cooperations

Dr. M. Arns, Brainclinics, Nijmegen: The Netherlands

Dr. T. Ros, University of Geneva, Geneva: Switzerland

Dr. C. McCabe, School of Psychology and Clinical Language Sciences, Reading: UK

# Department of Psychiatry and Psychotherapy

## Division of Psychosomatic Medicine and Psychotherapy

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### Research focus

- Psycho-oncology
- Migration and mental health
- Transplantation medicine
- Somatoform disorders and the persistent somatoform pain disorder
- Eating disorders, obesity

### Structure of the Division

Professorship: 1  
Personnel: 63  
• Doctors (of Medicine): 12  
• Scientists: 5 (thereof funded externally:0)  
• Graduate students: 16

### Clinical focus areas

- Eating disorders
- Obesity
- Somatoform disorders including persistent pain disorder
- Posttraumatic stress disorders
- Psycho-oncology

### Research

The research of the Division of Psychosomatic Medicine and Psychotherapy focuses on psycho-oncology, migration and mental health, transplantation medicine, somatoform disorders (persistent somatoform pain disorders), eating disorders and obesity.

### Psycho-oncology

PI: 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

Funding: German Cancer Aid

- Risk-adapted follow-up care in uveal melanoma cooperation project with the West German Cancer Center Essen

Funding: German Cancer Aid

- Disease management and not recognized supportive needs in oncologic patients with special consideration to a migrant background

Funding: ELAN Fund

In addition, the following topics are being investigated in doctoral theses of medical students:

- Posttraumatic growth after critical life-events during childhood: a comparison between survivors of childhood cancer, diabetes, and a normal population
- Validation of a questionnaire on dealing with cancer patients
- Disease concepts in oncologic patients with a migrant background
- Resilience and fear of prognosis in female patients seeking a second opinion (in cooperation with the Department of Obstetrics and Gynecology, Prof. Dr. M. Lux)
- Implementation of a regular paper-screening and a taxonomy of psychooncological interventions in the psychooncology services.

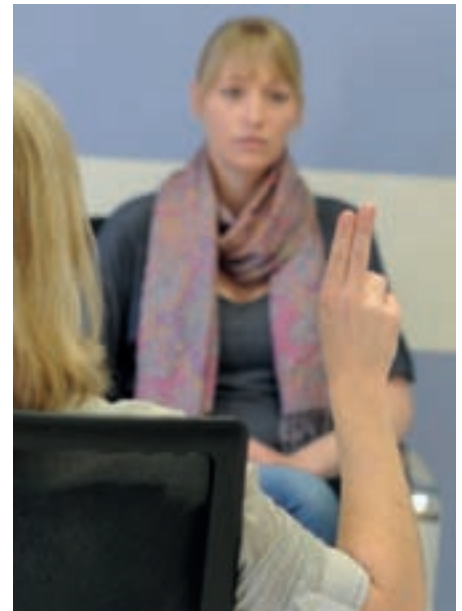
### Migration and mental health

PI: Prof. Dr. Y. Erim, Dr. E. Morawa, E. Georgiadou

Considering the demographic development in Germany showing a continuous increase of persons with a migrant background (in 2016 20% of the total population), research is indicated not only on specific burdens, but also on resources of this group. Since November 2015, the same research questions have been applied to refugees additionally.

In the period under review, a cooperation study with the Institute of Epidemiology, University Hospital of Essen, and two doctoral theses on the psychological distress of persons of Turkish and Persian descent were finished and published.

Current research projects deal with health services research. A survey investigates the intercultural opening of the psychosomatic clinics in Bavaria, an ELAN-sponsored study examines the psychological health and trauma consequence disorders of Arabic-speaking asylum seekers. The Division also examines the contextual and psychological distress, motivational factors, resources and needs of vocational and volunteer supporters of refugees.



*EMDR (eye movement desensitization and reprocessing) is an important intervention in the treatment of post-traumatic stress disorder. The effectivity of the interventions is examined in the context of flight and migration*

### Transplantation medicine

PI: Prof. Dr. Y. Erim, K. Schieber, J. Scheel

In cooperation with the Department of Medicine 4, the predictors of adherence after renal transplantation were examined. Based on the results of this study which analyzed patient reported outcomes as well as cognitive tests, a training to optimize the adherence and health behavior was developed and manualized. Within the framework of the research group Emerging Fields Initiative (EFI), a follow-up study of living kidney donors was conducted with particular emphasis on the perceived autonomy as well as fatigue complaints.

### Somatoform disorders and the persistent somatoform pain disorder

PI: Prof. Dr. Y. Erim

In the etiology of persistent somatoform pain disorder, early childhood adversities, an uncertain binding style, and altered cerebral activations (dysfunctional processing of pain and distress) are postulated as important factors and investigated in this study in cooperation with the Division of Neuroradiology (Prof. Dr. A. Dörfler). In addition to psychometric measurements, neuroimaging techniques are used.

### Eating disorders, obesity

PI: PD Dr. G. Paslakis

Currently, four studies on eating disorders are carried out using a basic research approach. In a prospective, randomized, double-blind, pla-

cebo-controlled clinical trial, the effect of substitution with an estrogen-progestin combination in adult women with anorexia nervosa is investigated. In a second study, a Go/NoGo paradigm for the detection of impulsivity is used to record the response times as a marker of impulsivity in patients with an eating disorder. Another study investigates jogging as a virtual reality in patients with eating disorder and movement urge. The results can also be used in the psychotherapy of the patients. Finally, the Approach-Avoidance Task (AAT) paradigm is used to investigate the eating habits in patients with eating disorders. Images of high-calorie and low-calorie foods are pulled or pushed away. This study also aims to create an innovative implicit therapy module.



*In the Approach-Avoidance Task (AAT) patients are presented standardized images to investigate their implicit behavior towards food*

## 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. It also offers courses for psychology students. 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". The use of simulation patients with standardized exercise cases was included into the teaching program.

The Division of Psychosomatic Medicine and Psychotherapy supervises Bachelor's and Master's theses as well as MD theses.

## Selected Publications

Morawa E, Erim Y. Health-related quality of life and sense of coherence among Polish immigrants in Germany and indigenous Poles. *Transcult Psychiatry*. 2015 Jun;52(3):376-95

Erim Y, Kahraman Y, Vitinius F, Beckmann M, Kröncke S, Witzke O. Resilience and quality of life in 161 living kidney donors before nephrectomy and in the aftermath of donation: a naturalistic single center study. *BMC Nephrol*. 2015 Oct 16;16:164.

Erim Y, Scheel J, Breidenstein A, Metz CH, Lohmann D, Friederich HC, Tagay S Psychosocial impact of prognostic genetic testing in the care of uveal melanoma patients: protocol of a controlled prospective clinical observational study. *BMC Cancer*. 2016 Jul 7;16:408

Paslakis G, Kühn S, Schaubschläger A, Schieber K, Röder K, Rauh E, Erim Y. Explicit and implicit approach vs. avoidance tendencies towards high vs. low calorie food cues in patients with anorexia nervosa and healthy controls. *Appetite*. 2016 Dec 1;107:171-179

Reber S, Morawa E, Stössel L, Jank S, Vitinius F, Eckardt KU, Erim Y. Prevalence and Modifiable Determinants of Non-Adherence in Adult Kidney Transplant Recipients in a German Sample. *Z Psychosom Med Psychother*. 2016 Sep;62(3):270-83

Erim Y, Böttcher M, Schieber K, Lindner M, Klein C, Paul A, Beckebaum S, Mayr A, Helander A. Feasibility and Acceptability of an Alcohol Addiction Therapy Integrated in a Transplant Center for Patients Awaiting Liver Transplantation. *Alcohol Alcohol*. 2016 Jan;51(1):40-6



# Department of Radiation Oncology

## Chair of Radiotherapy

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### Research Focus

- Clinical trials
- Clinical trials office
- Radiation biology
- Physical aspects of radiation oncology
- Radiation immunobiology

### Structure of the Department

Professorships: 2

Personnel: 151

- Doctors (of Medicine): 23
- Scientists: 20 (thereof funded externally: 7)
- Graduate students: 61

### Clinical focus areas

- Percutaneous radiotherapy
- Treatment planning
- Image guided radiotherapy (IGRT)
- 3D conformal radiotherapy
- Intensity modulated radiotherapy (IMRT)
- Intensity modulated arc therapy (VMAT)
- Stereotactic body radiation therapy (SBRT)
- Whole-skin- and whole-body-irradiation
- Brachytherapy
- Intensity modulated brachytherapy (IMBT)
- Image guided brachytherapy (IGBT)
- Deep regional hyperthermia
- Radio-chemo-therapy
- Radio-immuno-therapy
- Low dose radiation therapy (LDRT)

### Research

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 out-patient department, the therapeutics department as well as the treatment planning department and hyperthermia unit. Coordination of the clinical trials is carried out by the in-house

clinical trials office. Translational and basic radio(immune)-biological research is carried out by two groups, the classical radiation biology group and the radiation immune biology group. The "Medical Radiation Physics" group has the main scientific focus in respiratory and general organ motion during radiation therapy. In addition, the group is responsible for all medical physics duties of clinical radiation therapy.

### Clinical trials

PI: Prof. Dr. R. Fietkau, Prof. Dr. V. Strnad, PD Dr. O. Ott, PD Dr. S. Semrau, Dr. M. Haderlein, Dr. G. Lahmer, Dr. M. Hecht, Dr. N. Goerig  
Phase-III multicenter trials:

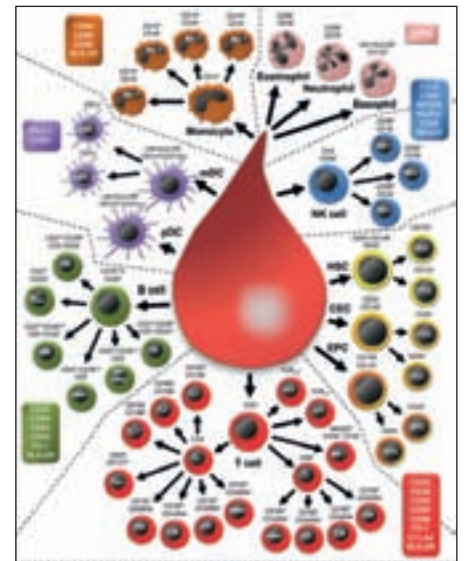
1. Preoperative radiochemotherapy and adjuvant chemotherapy with 5-fluorouracil versus preoperative radio-chemotherapy and adjuvant chemotherapy with 5-fluorouracil combined with oxaliplatin in patients with locally advanced UICC stage II and III rectal cancer (CAO/ARO/AIO-04)  
Funding: German Cancer Aid
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);  
Funding: German Cancer Aid
3. Reducing total radiation dose in the context of a simultaneous radiochemotherapy of head and neck tumors (PacCis-RCT)  
Funding: German Cancer Aid
4. Pancreatic carcinoma: chemoradiation compared with chemotherapy alone after induction chemotherapy (CONKO-007)  
Funding: German Cancer Aid
5. Effects of deep regional hyperthermia in patients with anal carcinoma treated by standard radiochemotherapy (HYCAN)

Phase-II trials:

1. PDR/HDR interstitial brachytherapy alone in patients with pT1/pT2 pN0 breast carcinomas after breast conserving surgery (APBI-IV)
2. 3D conformal, external partial breast irradiation in patients with pT1/2 pN0 breast carcinomas after breast conserving surgery (APBI-V)
3. Neoadjuvant chemoradiation with 5-FU (or capecitabine) and oxaliplatin combined with deep regional hyperthermia in locally advanced or recurrent rectal cancer (HyRec)
4. Dose-painting-Image-guided interstitial brachytherapy based on HistoScanning in patients with prostatic cancer – Phase II-Study (Histo-Scanning)
5. Enhancement of neurocognitive functions by hippocampal sparing radiotherapy (HIPPO-SPARE 01)

6. Efficacy of dose intensified radiotherapy of spinal metastases by hypofractionated radiation and IGRT hfSRT mediated boost (SPIN-MET)
7. De-intensification of postoperative radiotherapy in selected patients with head and neck cancer (DIREKHT)
8. Analysis of CMV Infections in Patients with Brain Tumors or Brain Metastases during and after Radio(Chemo)Therapy (GLIO-CMV-01)
9. Immunophenotyping From Blood of Patients with Malignant Gliomas (IMMO-GLIO-01)
10. Immunophenotyping from Blood of Patients Suffering from Chronic Degenerating Joint Diseases and Receiving LDRT (IMMO-LDRT-01)

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.



*Schematic overview of a detailed immunophenotyping of blood (DloB assay), conducted at the Department within most of the clinical trials*

*The translational and interdisciplinary examination of the therapy response plays a major role in the scientific actions of the Department. (from: Rühle PF et al. Int J Mol Sci. 2016 Aug 11;17(8))*

### Clinical trials office

PI: M. Lang-Welzenbach, Dr. D. Lubgan  
Coordination of the clinical trials is carried out in our in-house clinical-trials office. Our tasks cover all activities that are directly related to:

1. Planning, organizing, leading and controlling of clinical trials (ITT and as participating center)
2. Organization of meetings and international training courses
3. Scientific research.

## Radiation biology

PI: PD Dr. L. Distel

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 gamma-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.

Funding: German Cancer Aid

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 (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

PI: Prof. Dr. C. Bert

1. Quality assurance for hyperthermia treatments (MR spectroscopy, phantom development, IR thermometry)

Funding: ZIM

2. Verification of radiotherapy under influence of organ motion (Prostate-Ca. and Liver-Ca.)

Funding: Dr. R. Pflieger Foundation

3. Development of phantoms for quality assurance of treatments for intra-fractionally moving tumors

Funding: ZIM

4. Geometrical and dosimetric verification for interstitial brachytherapy

5. Automated analysis of clinical data from record and verify (R+V) and treatment planning systems.

## Radiation immunobiology

PI: Prof. Dr. U. Gaipl, Dr.-Ing. B. Frey

Connections between local (DNA damage and DNA repair) and systemic, immune-mediated effects of ionizing radiation alone and in combination with immunotherapy (vaccination, immune checkpoint blockade) and the underlying immune mechanisms are examined. Further, detailed immunomonitoring of radiation-exposed patients is performed in the framework of clinical trials (IMMO-LDRT, IMMO-GLIO, CONKO, GLIO-CMV, DIREKHT) and respective biomaterial is stored in the in-house biobank.

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

Funding: BMBF, GREWIS network

2. Modulation of inflammation by low and moderate dose of ionizing radiation; ModInr

Funding: EU, DoReMi network of excellence

3. Validation in vivo of immune biological indicators of radiation exposure to use for emergency situations, the determination of health effects and molecular epidemiology, VIBRATO

Funding: EU, Open Project for the European Radiation Research Area (OPERRA)

4. Role of dendritic cells and T cells in the local and systemic anti-tumor immune response induced by fractionated radiotherapy in combination with immunotherapy

Funding: DFG, GK 1660

## 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 collaboration with the University Cancer Centre (CCC). In the context of this course, students complete an online-module. This module was in part prepared by employees of the Department of Radiation Oncology in collaboration with the Bavarian Virtual University. Students learn by these clinical case studies the interdisciplinary approach in oncology. A course in radiation protection including practical teaching sessions for students that is recognized by the 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. New teaching course "prevention, diagnostics, therapy and after-care of cancer" was offered to the students of the degree program Medical Process Management. The practical and theoretical training of Bachelor and Master students takes place within the basic training "Infections Immunology" and the specialization module "Immunobiology". Laboratory rotations are offered for fast-track students of GK 1660 (compare own report).

Students have the opportunity to work on the Bachelor's or Master's theses and graduates are supervised during their PhD and MD projects, all embedded in the research focus of the Department.

## Selected Publications

Schwegler M, Wirsing AM, Dollinger AJ, Abendroth B, Putz F, Fietkau R, Distel LV. Clearance of primary necrotic cells by non-professional phagocytes. *Biol Cell*. 2015 Oct;107(10):372-87

Lubgan D, Ziegau A, Semrau S, Lambrecht U, Lettmaier S, Fietkau R. Effective local control of vertebral metastases by simultaneous integrated boost radiotherapy: preliminary results. *Strahlenther Onkol*. 2015 Mar;191(3):264-71

Hartmann J, Wölfelschneider J, Stache C, Buslei R, Derer A, Schwarz M, Bäuerle T, Fietkau R, Gaipl US, Bert C, Hölsken A, Frey B. Novel technique for high-precision stereotactic irradiation of mouse brains. *Strahlenther Onkol*. 2016 Nov;192(11):806-814

Müller J, Hartmann J, Bert C. Infrared camera based thermometry for quality assurance of superficial hyperthermia applicators. *Phys Med Biol*. 2016 Apr 7;61(7):2646-64

Goerig NL, Frey B, Korn K, Fleckenstein B, Überla K, Schmidt MA, Dörfler A, Engelhorn T, Eyüpoglu I, Rühle PF, Putz F, Semrau S, Gaipl US, Fietkau R. Frequent occurrence of therapeutically reversible CMV-associated encephalopathy during radiotherapy of the brain. *Neuro Oncol*. 2016 Dec;18(12):1664-1672

Derer A, Spiljar M, Bäumler M, Hecht M, Fietkau R, Frey B, Gaipl US. Chemoradiation Increases PD-L1 Expression in Certain Melanoma and Glioblastoma Cells. *Front Immunol*. 2016 Dec 22;7:610

## International Cooperations

Dr. K. Luminczy, Prof. G. Safrany, Frédéric Joliot-Curie National Research Institute for Radiobiology and Radiohygiene (NRIRR), Budapest: Hungary

Prof. Dr. C. Fournier, Dr. S. Ritter, Prof. Dr. G. Kraft, Dr. C. Graeff, GSI Helmholtzzentrum für Schwerionenforschung, Darmstadt: Germany

Prof. Dr. C. Polgár, Center of Radiotherapy, National Institute of Oncology, Budapest: Hungary

Prof. Dr. S. Hagdoost, Center for Radiation Protections Research, Stockholm University, Stockholm: Sweden

Erasmus Medical Center, Daniel den Hoed Cancer Center, Department Radiation Oncology, Rotterdam: The Netherlands

# Department of Surgery

## Chair of Surgery

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### Research Focus

- Evaluation of prognosis of gastrointestinal tumors
- Randomized trials for gastrointestinal tumors
- Outcomes research of complex surgery with hospital discharge data
- Pathophysiologic role of vascular effects of IFN- $\gamma$  in gastrointestinal diseases
- Tumor-micromilieu induced plasticity of tumor endothelial cells in colorectal carcinoma
- Genome editing of pancreatic tumor models
- Organoid models in pancreatic cancer

### Structure of the Department

Professorships: 4  
Personnel: 207  
• Doctors (of Medicine): 41  
• Scientists: 6 (thereof funded externally: 4)  
• Graduate students: 44

### Clinical focus areas

- Oncological surgery
- Surgery of the gastrointestinal tract
- Metabolic and bariatric surgery
- Endocrinological surgery
- Minimally invasive surgery
- Transplantation
- Outpatient surgery
- Surgical emergency

### Research

Clinical research at the Department of Surgery mainly consists of the clinical cancer registry, randomized trials of gastrointestinal tumors and evaluation of nationwide hospital discharge data. The translational research is focused on colorectal cancers/inflammatory bowel diseases and pancreatic cancer. Groups of young investigators focusing on tumor micromilieu and sepsis are connecting the main research topics.

### Evaluation of prognosis of gastrointestinal tumors

PI: Prof. Dr. R. Grützmann, Prof. Dr. S. Merkel  
Since 1978, a clinical cancer registry has been prospectively maintained for organ specific tumor documentation. At present, more than 28,000 patients are registered. Main foci are on colorectal cancer with over 12,000 and pancreatic cancer with over 2,500 documented cases. Patients are followed for life with only 1% of patients lost to follow-up. The scientific evaluation of this data focuses on health services research, quality management, the improvement of tumor classification, the identification of prognostic factors, the definition of quality indicators, and quality of life research. The documentation of specific diagnostics and multimodal treatment strategies in many patients results from an interdisciplinary cooperation of clinicians and scientists of numerous departments and institutes of the Faculty of Medicine.

### Randomized trials for gastrointestinal tumors

PI: Prof. Dr. R. Grützmann, Dr. H. Golcher  
The Department of Surgery respectively the interdisciplinary Colorectal Cancer Center/ Modul Pancreas Cancer took part in different multicenter trials about gastrointestinal tumors, inter alia "Pancreatoduodenectomy with or without prophylactic Ligamentum teres hepatis wrap around the gastroduodenal artery stump for prevention of pancreatectomy hemorrhage" or "International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (T-Rex)". Patients were screened during the interdisciplinary tumor board for gastrointestinal tumors, assigned to the studies and further attended by the study team (e.g. timely sending of quality of life questionnaires). 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.

### Outcomes research of complex surgery with hospital discharge data

PI: Dr. C. Krautz  
A variety of surgical procedures in general surgery are associated with varying perioperative outcomes due to their complexity. Analyses of nationwide hospital discharge data provide the possibility to examine the underlying causes. Currently, we are assessing the effects of volume-based referral on perioperative outcomes in complex surgery in order to give recommen-

dations for the future hospital market structure in Germany.

### Pathophysiologic role of vascular effects of IFN- $\gamma$ in gastrointestinal diseases

PI: Prof. Dr. Dr. M. Stürzl, Dr. N. Britzen-Laurent  
Previously we showed that an IFN- $\gamma$  dominated Th1-immunomicromilieu in colorectal carcinoma is associated with intratumoral angiostasis and improved prognosis of the patients. This is mediated through the GTPase guanylate binding protein-1 (GBP-1). In the reporting period we could confirm that also in inflammatory bowel diseases an IFN- $\gamma$ /GBP-1 mediated endogenous angiostasis is present, but interestingly in this case associated with a worsened course of disease and increased microvessel permeability. Ongoing work analyses the role of the IFN- $\gamma$  activity on different cell types in gastrointestinal diseases and the structure function relation of GBP-1 activity.

Funding: DFG, Emerging Fields Initiative of the FAU, W. Lutz Foundation

### Tumor-micromilieu induced plasticity of tumor endothelial cells in colorectal carcinoma

PI: PD Dr. E. Naschberger, Prof. Dr. Dr. M. Stürzl  
Anti-angiogenic therapy is only effective in a fraction of patients with colorectal carcinoma (CRC). Our hypothesis was that different tumor-micromilieus (TMM) may induce different phenotypes in blood vessel endothelial cells and via this may affect the responses to anti-angiogenic therapy. To investigate this we isolated tumor endothelial cells from CRC with good and bad prognosis and compared the transcriptomes of the isolated cells. With this approach we could show for the first time a TMM-dependent heterogeneity of the tumor endothelial cells in CRC. The matricellular protein SPARCL was identified as a central regulator of the differential endothelial cell activities. In addition, we obtained evidence that blood vessel endothelial cells in tumors which are associated with good prognosis are actively counteracting tumor progression.

Funding: German Cancer Aid, IZKF, DFG, Cancer Research UK Erlangen

### Genome editing of pancreatic tumor models

PI: Prof. Dr. C. Pilarsky  
Pancreatic cancer is the fourth most frequent cause of cancer in the western world. Only 7% of patients survive five years after diagnosis. This

is caused by chemoresistance of the tumor. In this project we are trying to understand more precisely which mechanisms influence such a chemoresistance and which genes are involved. Based on the well-known changes in the tumor genome, we are targeting specific genes, especially gene involved in DNA repair, with CRISPR/Cas9 technology and are testing whether our tumor cell models are becoming more sensitive to the application of standard chemotherapeutic agents. This allows an adaptation of the various chemotherapeutic regimens to the mutation pattern of the individual tumor within the framework of modern precision medicine.

### Organoid models in pancreatic cancer

Project manager: Prof. Dr. C. Pilarsky

In this project we will test the influence of the culture conditions on the chemosensitivity of pancreatic carcinomas. For this purpose, pancreas tumor cells are grown in a special tissue culture process, the organoid culture, and treated with standard chemotherapeutic agents. This allows us to examine how the individual models can be treated in a tissue substitute by the chemotherapeutic agents. This allows a better understanding of the necessary dosage of chemotherapeutic agents and a possible better preclinical testing of new chemotherapies.

## Teaching

The Department of Surgery is offering courses for students of human medicine and dentistry. The Dr. House colloquium is an interdisciplinary lecture in cooperation with internal medicine. With the implementation of a surgical skills lab, surgical residents as well as medical students (e.g. within the scope of the "Blockpraktikum") benefit from learning different surgical approaches and may acquire basic surgical skills using modern laparoscopic simulators. MD and PhD theses are supervised.

### Selected Publications

Waddell N et al. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature*. 2015 Feb 26;518(7540):495-501

Naschberger E, Liebl A, Schellerer VS, Schütz M, Britzen-Larent N, Kölbel P, Schaal U, Haep L, Regensburger D, Wittmann T, L. Klein-Hitpass, Rau TT, Dietel B, Meniel VS, Clarke AR, Merkel S, Croner RS, Hohenberger W, Stürzl M. Matricellular protein SPARCL1 regulates tumor microenvironment-dependent endothelial cell heterogeneity in colorectal carcinoma. *J Clin Invest*. 2016 Nov 1;126(11):4187-4204

Merkel S, Weber K, Matzel KE, Agaimy A, Göhl J, Hohenberger W. Prognosis of patients with colonic carcinoma before, during and after implementation of complete meso-colic excision. *Br J Surg*. 2016 Aug;103(9):1220-9

Bailey P et al. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature*. 2016 Mar 3;531(7592):47-52

Werner K, Lademann F, Thepkaysone ML, Jahnke B, Aust DE, Kahlert C, Weber G, Weitz J, Grutzmann R, Pilarsky C. Simultaneous gene silencing of KRAS and anti-apoptotic genes as a multitarget therapy." *Oncotarget*. 2016 Jan 26;7(4):3984-92

Nimptsch U, Krautz C, Weber GF, Mansky T, Grützmann R. Nationwide In-hospital Mortality Following Pancreatic Surgery in Germany is Higher than Anticipated. *Ann Surg* 2016; 264: 1082–90

### International Cooperations

Prof. Dr. Noo Li Jeon, Seoul National University, School of Mechanical and Aerospace Engineering, Seoul Republic of Korea: South Korea

Dr. V. Meniel, European Cancer Stem Cell Research Institute, Cardiff University, Cardiff: UK

F. K. Swirski, Massachusetts General Hospital, Harvard Medical School, Boston: USA

D. Tuveson, Cold Spring Harbor Laboratory, Cold Spring Harbor: USA

Prof. T. Holm, Karolinska Institutet, Stockholm: Sweden



# Department of Surgery

## Division of Pediatric Surgery

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### Head of Division

Prof. Dr. med. Roman T. Carbon

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### Research Focus

- Preliminary results of enteral surface stimulation (ESS/EOS) in constipation in children and adolescents
- Device-support in ESCR of congenital chest wall deformities
- Protective negative pressure wound therapy in open correction of chest wall deformities
- Quantification of costal arch eversion in congenital pectus excavatum (PE)

### Structure of the Division

Professorships: 1  
Personnel: 24

- Doctors (of Medicine): 3
- Graduate students: 5

### Clinical focus areas

- Surgical treatment of congenital malformations, especially in the thoracic, abdominal, skeletal, and integumental areas in newborn and children
- Surgical treatment of chest deformities (pectus excavatum and carinatum)
- Special techniques to resolve recurrences after chest wall repair
- Minimally invasive pediatric surgery (laparoscopy, thoracoscopy, rendez-vous procedures)

### Research

#### Preliminary results of enteral surface stimulation (ESS/EOS) in constipation in children and adolescents

PI: Dr. M. Besendörfer

Constipation is a common problem in children and adolescents. Short-term and mild episodes can mostly be treated effectively. In contrast, a long-term course of constipation can frequently not be sufficiently treated. Since cur-

ative therapies are rarely available, treatment algorithm is usually the same, irrespectively of etiology. It is based on a multi-level algorithm which is stepwise escalated until the respective treatment phase shows effects. In terms of chronic constipation, even the highest treatment phase is often not sufficient. Hence, it seems advisable to present a new therapy option which complements and extends the so far existing therapies. Enteral Surface Stimulation (ESS/EOS) therapy aims at supporting intestinal activity and improving constipation through exposing the abdomen to local electromagnetic fields. This therapy principle, known as neuromodulation, was first introduced by Dr. E. Tanagho (San Francisco) for urological reasons and further developed by Prof. Dr. K. Matzel (Erlangen) for enteric indications. Up to now, neuromodulation for pediatric patients with chronic constipation still has not been established.

A self-adhesive electrode was applied ventrally to the left lower abdominal quadrant, another in the right paravertebral-lumbar region. Both were connected to a stimulation device which generated an electromagnetic field (voltage between 5V and 8V at a frequency of 15 Hz) in order to improve intestinal peristalsis and relieve constipation. 18 patients were chosen for the study, aged 3 – 13 years who were treated between 2013 - 2015. Symptomatic changes were evaluated by using questionnaires and observing changes in clinical examination. At a median stimulation magnitude of 5.9 V for an average of 9.6 hours daily over a medium period of 13.2 weeks, satisfaction levels of 67% were achieved. 77% of patients experienced a persisting improvement of constipation after their EOS-treatment had finished. The average patient was aged 8.3 and male. Chronic constipation of unknown origin was the most common etiology. 83% of patients had already been treated with other therapies, 21.4% previously had gastrointestinal tract surgery. 27.3% of patients experienced minor complications which can all be attributed to local problems with self-adhesive electrodes. ESS-application represents an innovative non-invasive therapy option for chronic pediatric constipation which shows high symptomatic improvement at a low complication rate. High efficiency seems to occur particularly in school-children until puberty, because after a phase of a few weeks, stimulation leads to a lasting learning effect with reconditioning of enteral and perineal muscular mobility. Given its efficiency, its uncomplicated application and high subjective levels of satisfaction, ESS/EOS seems to be a new auspicious therapy, completing and enriching the existing options.

#### Device-support in ESCR of congenital chest wall deformities

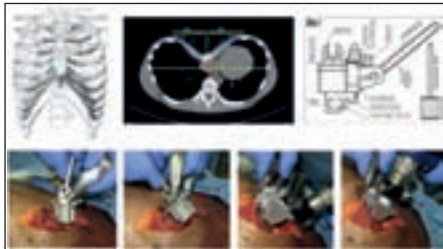
PI: Prof. Dr. S. Schulz-Drost

Major questions are epidemiology and therapeutic options of congenital and acquired deformities of the anterior chest wall, e.g. the pectus excavatum and carinatum as well as their recurrences. Special challenges are complex and extended deformities with regard to surgical correction. Elastic Stable Chest Repair (ESCR) which had been developed at the Division of Pediatric Surgery has already shown numerous clinical findings in stabilization of the corrected chest wall which show excellent results from this method. Titanic implants, especially developed for ESCR in collaboration with partners of industry, have meanwhile been internationally validated and are available on the market. The working group is currently conducting an observation study on long-term results.

Furthermore, an additional key point was the operative correction of breast deformities - the actual corrections on the ribs and the sternum. For example, a standardized CT-based, preoperative operation planning had been developed and validated on the basis of previous patients. This planning concept has been discussed worldwide and is under consideration for further development. The clinical challenge, however, is to be able to implement the planned incisions precisely onto the human surgical anatomy. Therefore, in collaboration with surgical instrumental developers (Lettenbauer, Erlangen), we created an angle-accurate thoracic saw-cutting gauge TCD (thoracic cutting device) for the sternum and the ribs. This allows the precise incision for the osteo- and chondrotomies with safe protection of the underlying thoracic organs. The saw aid for the sternum is aligned with the curvature apex, the sternum thickness, and the corpus deviation which may be corrected, and then temporarily fixed at the sternum. In the case of pectus carinatum deformity, a posteriorly open bone wedge is performed by means of a so-called zero-point undercut while maintaining the depth limit. On the ribs, a fast and easy positioning of the saw gauge at the curvature crest is achieved by an integrated elevator in the subperiosteal layer. The saw cut is also made possible by means of pre-assembled angle positioning devices with depth limitation and with protection of the inner rib cortex.

In this connection, the foundations for a precisely plannable and optimally operable breast wall correction were created, analogous to the usual practice of orthopedic correction osteotomies e.g. on the long bones.





Strategy of ESCR (CT-planning combined with analysis of cutting angles, thoracic Cut-Device by Schulz-Drost)

### Protective negative pressure wound therapy in open correction of chest wall deformities

PI: Dr. K. Simon

Following denudation of tissues and trouble in perfusion, open surgery in chest wall deformities can cause tremendous wound healing complaints. Purpose of this study was to determine if preventive negative pressure wound therapy could reduce wound complications after open pectus surgery. Retrospectively, 100 patients after open procedure for the treatment of pectus excavatum or pectus carinatum in 2010-2012 were analyzed. 50 patients, treated by vacuum technology (PREVEBA™) were compared with 50 patients whose wounds were covered by transparent dealing foil (OPSITE™). Wound closure was performed following a standard procedure as well as the placement of subcutaneous drains. Therefore two comparable groups of patients were formed and analyzed by standardized parameters. The wound dressing was placed epicutaneously immediately after wound closure in the operating room and removed in each case after five days. Follow-ups were performed immediately after removal of the wound dressing, at the time of discharge from hospital as well as six and 12 weeks after operation. The wounds were checked for tenderness, pain, secretion, redness and fistulas. The vacuum-group showed 10% wound complications which needed operative treatment, whereas the foil-group showed complications in 24%. Some patients who were treated by vacuum showed superficial skin lesions at the rim of the foam and the film. All of these lesions healed well. Postoperative wound management with the preventive measure of negative pressure wound therapy showed a remarkable reduction of wound complications ( $p=0.074$ ) following open pectus surgery.

### Quantification of costal arch eversion in congenital pectus excavatum (PE)

PI: Prof. Dr. S. Schulz-Drost

Regarding indication for correction of PE, indices are used to scale severity with Haller

index (HI) being the most popular one. HI should be investigated and compared with the newer Correction index (CI). Costal arch eversion is a frequent comorbidity of PE and shows a major esthetic problem. Therefore, a measuring method was searched with a derived index of costal arch which could separate deformed from not deformed archs. A costal arch index (RI) for diagnostics and indication has been inaugurated.

Considering the HI, the overlapping of values between PE-patients and controls was higher than with CI. Concerning the measurement of the costal arch, a reliable and independent method from the basic shape of the thorax has been found. The cartilage-bone transition zones of costa VIII which can be found more medial at the anterior chest wall in PE than in controls served as a lateral fixation point. A statistically significant negative correlation was found between the RI and CI: Higher CI tends to lower RI. Patients with recurrent PE without former correction of the costal arch showed higher values of costal arch height and RI compared to patients with primary PE.

The CI is more appropriate in evaluating PE as it separates more sharply patients with PE from controls. It is suitable for diagnosis as well as operative planning and pre/postop comparison. The theory of PE-origin in shifted relation between the cartilaginous and bony portion of the ribs is supported. Excessive growth of the bony portion appears to be an elementary part of PE-origin. The extent of eversion of costal arch correlates inversely with the severity of CI. Origin of eversion of costal arch can be derived: Stronger pathological growth of the caudal costal pairs in connection with less deformed sternum and cranial ribs. Furthermore, eversion plays an important role in development of PE-recurrences: RI shows the recommendation of simultaneously performed costal arch correction. For preoperative diagnostics the calculation of RI is recommended and index of 0.9 can be the guideline for correction.

### Teaching

The Division of Pediatric Surgery engages in the curricular teaching according to IMPP (general guidelines for medical studies in Germany). Academic events take place in cooperation with vocational schools at FAU (pediatric nursing, pediatric intensive care medicine, School for operational and technical assistants, physiotherapy, massage), as interdisciplinary lectures and seminars, and in form of practical education in phan-

tom-courses for minimally invasive pediatric surgery in skills lab and hands-on courses. The Division of Pediatric Surgery supervises PhD theses.

### Selected Publications

Bachmann L, Besendörfer M, Carbon R, Lux P, Agaimy A, Hartmann A, Rau TT. Immunohistochemical panel for the diagnosis of Hirschsprung's disease using antibodies to MAP2, calretinin, GLUT1 and S100. *Histopathology* 2015, 66: 824-835

Dimova V, Lötsch J, Hühne K, Winterpacht A, Heesen M, Parthum A, Weber PG, Carbon R, Griessinger N, Sittl R, Lautenbacher S. Association of genetic and psychological factors with persistent pain after cosmetic thoracic surgery. *J Pain Res* 2015, 8: 829-844

Simon K, Schulz-Drost M, Besendörfer M, Carbon RT, Schulz-Drost S. Use of negative pressure wound therapy on surgical incisions (PREVENA) after surgery of pectus deformities reduces wound complications. *Zentralbl Chir* 2015, 140: 156-162

Schulz-Drost S, Syed J, Besendoerfer M, Mauerer A, Blanke M, Schulz-Drost M, Carbon RT. Elastic stable chest repair as a means of stabilizing the anterior chest wall in recurrent pectus excavatum with sternocostal pseudarthrosis: An innovative fixation device. *Thorac Cardiovasc Surg* 2015, 63: 419-426

Schulz-Drost S, Oppel P, Grupp S, Schmitt S, Carbon RT, Mauerer A, Hennig FF, Buder T. Surgical fixation of sternal fractures: Preoperative planning and a safe surgical technique using locked Titanium plates and depth limited drilling. *J Vis Exp* 2015, 95, e52124

Haller F, Knopf, Ackermann A, Bieg M, Kleinheinz K, Schlesner M, Moskalev EA, Will R, Satir AA, Abdelmagid IE, Giedl J, Carbon R, Rompel O, Hartmann A, Wiemann S, Metzler M, Agaimy A. Paediatric and adult soft tissue sarcomas with NTRK1 gene fusions: a subset of spindle cell sarcomas unified by a prominent myopericytic/haemangiopericytic pattern. *J Pathol* 2016, 238: 700-710

### International Cooperations

Prof. Dr. A. Fisher, Biochemical Center of Research, Weizman Institute of Science, Rehovot: Israel

Prof. Dr. G. Berci, Endoscopic Research, Cedars-Sinai Medical Center, Los Angeles: USA

AO Foundation. TK Thoracic Surgery Expert Group, Davos: Switzerland

M. Gasparri, MD, Froedtert Hospital, Cardiothoracic Surgery, Milwaukee: USA

J. Edwards, MD, PhD, Northern General Hospital, Department of Thoracic Surgery, Sheffield: UK

# 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
- Immunological 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

Professorships: 1

Personnel: 9

- Doctors (of Medicine): 6
- Scientists: 6 (thereof funded externally: 0)
- Graduate students: 2

### Research

The focus research of the Division of Thoracic Surgery is to research innovative therapies for operative pulmonary and thoracic diseases to develop new clinical treatment concepts. Furthermore, experimental immunological projects with samples from the lung and human lymphoid organs are carried out within the framework of the cooperation with other departments.

### Surgical therapy of hyperhidrosis – a prospective quality control study

PI: 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 heterogeneous. In this trial, we analyze the long term patient satisfaction with a questionnaire specially designed by the Division of Psychosomatics and Psychotherapy.

### Surgical management of pulmonary metastases from colorectal cancer

PI: Prof. Dr. H. Sirbu, Dr. W. 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

PI: 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

PI: Prof. Dr. H. Sirbu, Dr. M. Würfel (Nürnberg)

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.

### Immunological and molecular characterization of malignant lung tumors

PI: Prof. Dr. H. Sirbu, Dr. D.I. Trufa

The aim of this research project is to investigate immunological and molecular basis in cooperation with the Division of Molecular Pneumology (Prof. Dr. S. Finotto). 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

PI: 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 radio-chemotherapy followed by surgery

PI: Prof. Dr. H. Sirbu, Dr. W. Schreiner

In this trial, we compare in cooperation with the Department of Radiation Oncology (Prof. Dr. R. Fietkau) 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

PI: Dr. W. Schreiner, W. Dudek

The trial includes patients in good clinical condition, younger than 60 years without signifi-

cant 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**

PI: 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**

PI: Prof. Dr. H. Sirbu, W. Dudek

Prospective randomized multicenter clinical trial which compares two established surgical procedures (WOPP-study). The aim of the study is to analyze the pneumothorax recurrence rate within the first 24 months after surgical procedure: parietal pleurectomy with apical lung resection (WRPP) or parietal pleurectomy (PP).

Funding: DFG

### **Functional analysis of human Dendritic cell subpopulations**

PI: Prof. Dr. H. Sirbu

In a collaborative research project with the Department of Dermatology (Prof. Dr. D. Dudziak), comparative analyses of the development of different immune cells were extended to other human organs, such as lymph nodes, blood, lungs, and adult thymus. The latter shows residual activity of T cell development, despite a progressed thymic involution. The analysis of the phenotype and function of the DC subpopulations in various human tissues of the very same donor is of high value, in order to account for the high degree of inter-individual variance. Basis for this cooperation is the scientific work of the research group of Prof. Dr. D. Dudziak (Department of Dermatology), focusing on the characterization of Dendritic cells (DC) and the initiation of specific T cell immune

responses. These studies are being conducted both in the murine and the human setting. First detailed phenotypic and functional analyses of DC subpopulations have been performed with various human lymphoid tissues (spleen, blood, thymus, bone marrow, cord blood, tonsils) and were recently published.

## **Teaching**

For medical students, the Division of Thoracic Surgery offers current lectures on relevant topics, an interactive EKM course and the possibility of hospitalization on the station, in the ambulance and in the operation room of thoracic surgery. Students can apply to spend their elective in our Division.

Furthermore, the Division of Thoracic Surgery supervises Bachelor's, Master's and MD theses.

## **Selected Publications**

Schreiner W, Dudek W, Sirbu H. Combined Clagett procedure, negative pressure therapy, and thoracomyoplasty for treatment of late-onset postpneumectomy empyema necessitates. *Kardiochir Torakochirurgia Pol.* 2015 Sep; 12(3): 259–261

Schreiner W, Dudek W, Sirbu H. Is salvage surgery for recurrent non-small-cell lung cancer after definitive non-operative therapy associated with reasonable survival? *Interact Cardiovasc Thorac Surg.* 2015 Nov;21(5):682-4

Andreev K, Trufa ID, Siegemund R, Rieker R, Hartmann A, Schmidt J, Sirbu H, Finotto S. Impaired T-bet-pSTAT1 and perforin-mediated immune responses in the tumoral region of lung adenocarcinoma. *Br J Cancer.* 2015 Sep 15;113(6):902-13

Schmitz M, Sirbu H, Horch RE. Interdisciplinary treatment of extensive chest wall defects due to irradiation. *Chirurg.* 2015 Sep; 86(9):889-91

Schreiner W, Dudek W, Lettmaier S, Fietkau R, Sirbu H. Should salvage surgery be considered for local recurrence after definitive chemoradiation in locally advanced non-small cell lung cancer. *J Cardiothorac Surg.* 2016; 11: 9

Sirbu H, Stapel P. Pilzinfektionen, Echinokokkose und andere parasitäre Erkrankungen. In: Müller MR, Watzka SB (Hrsg). *Expertise Thoraxchirurgie.* Thieme Verlagsgruppe 2016

# Department of Surgery

## Division of Transfusion Medicine and Hemostaseology

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(until 30.9.2017)

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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)
- 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

Professorships: 1  
Personnel: 76  
• Doctors (of Medicine): 6  
• Scientists: 6 (thereof funded externally: 0)  
• Graduate students: 20

### Clinical focus areas

- Clinical transfusion medicine
- Blood component supply
- Immunohaematological and hemostaseological diagnostics
- Outpatient and inpatient coagulation counseling
- Production and storage of stem cell preparations

### Research

Research in the Division of Transfusion Medicine and Hemostaseology focuses on the characterization of specific blood components, stem cell concentrates and new experimental cellular preparations. Clinical problems with respect to hemotherapy and coagulation management are also investigated. In the GMP laboratory of the

Division, interdisciplinary experimental preparations for innovative clinical trials are produced and tested (Advanced Therapy Medicinal Products, ATPM).

### Preparation and characterization of white cell-poor platelet concentrates by apheresis

PI: 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)

PI: Prof. Dr. E. Strasser  
Circulating monocytes are precursors of DC which play a key role in the immune system's function by presenting antigens to specific lymphocytes. The collection and cultivation of these cells enables the development of new strategies in the treatment of malignant diseases. Members of the Division of Transfusion Medicine and Hemostaseology cooperate with colleagues from the Department of Dermatology to adjust the collection procedures optimally to the specific clinical and experimental demands of procedures aimed at the cultivation, expansion, and priming of DC.

### Clinical research related to hemostaseology

PI: Prof. Dr. 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 erythematosus, and other currently relevant topics.

### Clinical research related to hemotherapy

PI: Prof. Dr. V. Weisbach, Prof. Dr. R. Zimmermann, Prof. Dr. J. Ringwald, Prof. Dr. E. Strasser

We examine antibodies against red cell antigens, characterize factors influencing the quality of stored red cell concentrates, and study the complex dysfunctions of the coagulation system.

### Mesenchymal stromal cells (MSC)

PI: Prof. Dr. V. Weisbach, 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 expected that MSC will play a major role in future applications of regenerative medicine. The main focus of the working group is the preparation, characterization, and expansion of MSC especially from placental tissues.

### Optimization of collection procedures to get regulatory T cells (Tregs)

PI: 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 to optimally adjust the collection procedures to the specific clinical and experimental demands of procedures aimed at the cultivation and expansion of Tregs. In the context of cell preparation, analysis of factors responsible for cell damage (cell apoptosis and necrosis) is relevant to optimize the quality of leukocyte products.

### Legislation of transfusion

PI: Prof. Dr. R. Zimmermann  
Under the auspices of the Legal Counsel and Managing Director of the UK Erlangen, Dr. A.W. Bender, the Division of Transfusion Medicine and Hemostaseology is involved in publications on the legislation and law of blood transfusion in Germany. In the center of attention is the book "Transfusion Law", published by the Wissenschaftliche Verlagsgesellschaft Stuttgart, that has become the benchmark in this field of law



and has found its way into the jurisdiction of the German Federal High Court of Justice. Alongside, book contributions and articles on different aspects of the legislation and law of blood transfusion are published.

### **Platelet-derived growth factors for wound healing and angiogenesis**

PI: 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 is involved in compulsory and optional courses in the curricular teaching of human and dental medicine. Particularly noteworthy is the interdisciplinary teaching of laboratory diagnostics and clinical pathology together with the Department of Medicine 5 and the Clinical Chemistry Laboratory and the participation in the block training in surgery. We supervise MD and PhD theses.

### **Selected Publications**

Eckstein M, Zimmermann R, Roth T, Hauck-Dlimi B, Strasser EF, Xiang W. The effects of an overnight holding of whole blood at room temperature on haemoglobin modification and in vitro markers of red blood cell aging. *Vox Sang* 2015; 108: 359-67

Kraemer L, Raczat T, Weiss DR, Strobel J, Eckstein R, Ringwald J. Correlation of the hypotonic shock response and extent of shape change with the new ThromboLUX™. *Vox Sang* 2015; 109: 194-6

Strobel J, Moellmer I, Zingsem J, Hauck-Dlimi B, Eckstein R, Strasser E. T-cell subsets in autologous and allogeneic peripheral blood stem cell concentrates. *Vox Sang* 2015; 109: 375-86

Hauck-Dlimi B, Ruppel R, Zimmermann R, Strobel J, Reil A, Eckstein R, Zingsem J. Transfusion-related alloimmune neutropenia with no pulmonary complications: one donor - five cases. *Transfusion* 2016; 56: 84-90

Heider S, Strobel J, Mempel W, Eckstein R, Weisbach V. Measuring lymphocyte proliferation in response to specific antigen and mitogen stimuli using flow cytometry. *Clin Lab* 2016; 62: 1857-78

Kraus M-J, Seifert J, Strasser E, Gawaz M, Schäffer T, Rheinländer J. Comparative morphology analysis of live blood platelets using scanning ion conductance and robotic dark-field microscopy. *Platelets* 2016; 27: 541-6

# 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
- Mechanisms of chondrocyte differentiation and ossification
- Cartilage and meniscus repair
- Magnetic resonance imaging of joint structures
- Traumatic lesions of thoracic bone structures

### Structure of the Division

Professorships: 2

Personnel: 88

- Doctors (of Medicine): 19
- Scientists: 2 (thereof funded externally: 2)
- Graduate students: 6

### Clinical focus areas

- Polytrauma and treatment of severe injuries
- Extremity and joint surgery
- Total joint arthroplasty of all large joints (primary and revision)
- Spine surgery
- Sports trauma and arthroscopic surgery
- Pediatric trauma surgery

### Research

The Division of Trauma Surgery covers a broad spectrum of research activities including novel diagnostic technologies and innovative strategies for the treatment of musculoskeletal pathologies. Novel three-dimensional motion analyses and imaging methods contribute to earlier detection of injuries and pathologies as well as a better definition of the underlying pathomechanisms. In a therapeutic point of view, research projects are focused on the establishment of joint-preserving and joint-replacing therapeutic concepts. As a supraregional trauma

center with a focus on the treatment of severely injured patients, health services research also plays an essential role for the Division of Trauma Surgery.

### Validation of a ceramic total knee replacement system

PI: 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). Two-year results also demonstrate a high durability of the total ceramic implant system which encourages the continuation of long-term studies focusing on wear and loosening.

### Gait and motion analysis

PI: 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.

### Mechanisms of chondrocyte differentiation and ossification

PI: Prof. 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. 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. Transcriptome analyses (RNA-Seq) in chondrocytes demonstrated that PEDF stimulates the expression of cartilage-degrading

enzymes (among those MMP13), but simultaneously suppresses the expression of typical chondrocyte-specific genes. These results indicate that PEDF is importantly involved in remodeling processes during endochondral ossification and repair.

### Cartilage and meniscus repair

PI: Prof. 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. This study outlines the highly limited endogenous repair capacity of adult articular cartilage and the prerequisite of an additional cell population. A further project 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. However, repopulation of repair cells was only observed at the surface and the meniscal basis. Current experiments investigate the potential of different chemotactic stimuli to enhance migration of endogenous repair cells into defects or tissue. In this respect, platelet-rich plasma (PRP), PDGF and TGF $\beta$ 3 proved to be very efficient chemotactic factors.

### Magnetic resonance imaging of joint structures

PI: Dr. M.L. Pachowsky

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 Magnetic Resonance (MR)-techniques. In experimental models, healthy articular cartilage was compared with degenerated articular cartilage and cartilage repair tissues. Additionally, biochemical MR-methods were used to assess the associated joint structures in a multiparametric approach (i.e. meniscus tissue). 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 proteoglycan content, 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. These approaches are applied in the course of postoperative follow-up investigations in combination with innovative surgical procedures, in sports medicine attendance and for the individual care of patients at all ages. The aim of future studies will be the expansion of the techniques on other tissues, i.e. vertebral discs.

### **Traumatic lesions of thoracic bone structures**

PI: 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 Trauma register DGU® and the prevalence of fractures of the ribs and sternum were determined in the cohort of severely injured trauma patients. The different types of sternal fractures were characterized, and different methods for operative treatment were analyzed using cadaver models. This led to the establishment of definitive treatment recommendations. For this purpose, specific locking plates were developed in cooperation with AO Foundation for fixation of different fracture types. Additionally, surgical concepts for correcting and stabilizing the chest wall were optimized based on the clinical relevance of instable injuries of thoracic bone structures with severely restricted respiration biomechanics. Furthermore, the influence of locking plates for stabilization of combining sterno-vertebral injuries and the possibilities for minimizing surgical approaches to the chest wall were evaluated in human anatomical studies. Basic recommendations could be incorporated into the S3-guidelines for polytrauma treatment. Currently, recommendations for the classification of injuries of the bony chest wall are established and evaluated based on the present knowledge.

### **Teaching**

The Division of Trauma Surgery participates with elective and compulsory courses in the curricular teaching of students of medicine, dental medicine and of medical engineering. The interdisciplinary teaching for the purposes of preparation for examinations has to be outlined.

The Division of Trauma Surgery supervises numerous MD theses.

### **Selected Publications**

Gelse K, Riedel D, Pachowsky M, Hennig FF, Trattinig S, Welsch GH. Limited integrative repair capacity of native cartilage autografts within cartilage defects in a sheep model. *J Orthop Res.* 2015;33(3):390-7

Meier E, Gelse K, Trieb K, Pachowsky M, Hennig FF, Mauerer A. First clinical study of a novel complete metal-free ceramic total knee replacement system. *J Orthop Surg Res.* 2016;11:21

Zingler C, Carl HD, Swoboda B, Krinner S, Hennig F, Gelse K. Limited evidence of chondrocyte outgrowth from adult human articular cartilage. *Osteoarthritis Cartilage.* 2016;24(1):124-8

Golditz T, Welsch GH, Pachowsky M, Hennig FF, Pfeifer K, Steib S. A multimodal approach to ankle instability: Interrelations between subjective and objective assessments of ankle status in athletes. *J Orthop Res.* 2016 Mar;34(3):525-32

Schulz-Drost S, Oppel P, Grupp S, Krinner S, Langenbach A, Lefering R, Mauerer A. Bony injuries of the thoracic cage in multiple trauma : Incidence, concomitant injuries, course and outcome. *Unfallchirurg.* 2016;119(12):1023-1030

Schulz-Drost S, Oppel P, Grupp S, Taylor D, Krinner S, Langenbach A, Hennig F, Mauerer A. The oblique fracture of the manubrium sterni caused by a seatbelt—a rare injury? Treatment options based on the experiences gained in a level I trauma centre. *Int Orthop.* 2016 Apr;40(4):791-8

# 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
- Biomarker-supported MRI-TRUS-fusion guided biopsies for the diagnosis of prostate cancer
- Multifactorial models in uro-tumorpathology

### Structure of the Department

Professorships: 2

Personnel: 46

- Doctors (of Medicine): 13
- Scientists: 1 (thereof funded externally: 0)
- Graduate students: 13

### Clinical focus areas

- Urologic polyclinic and children's urology ward in the UK Erlangen
- Minimal invasive urology including robotics
- Kidney transplantation unit in cooperation with the Department of Medicine 4
- Kidney transplantation unit focused on children in cooperation with the Department of Pediatric and Adolescent Medicine
- Ambulant uro-oncologic therapy center (AURONTE) in cooperation with the Department of Medicine 5
- Certified center for prostate cancer with kidney- and bladder cancer as part of the Oncology Center
- Certified continence and pelvic floor center
- Adult's urologic ward, therapy center for private insurance patients within Waldkrankenhaus St. Marien
- Trial documentation center within Waldkrankenhaus St. Marien

### Research

The research activities of the Department of Urology comprise key aspects of the basic re-

search as well as of translational research at following high quality standards in statistical evaluation. Our research is based on a well annotated tissue and data bank and also covers the active participation and design of clinical studies for treatment of urologic tumor patients.

### Continuous extension of an annotated tumor tissue repository containing urologic tumors

PI: 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, SOP, and quality management).

### Systemic tumor therapy, clinical trials

PI: 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 truly execute an interdisciplinary decision path.

Thus, it can be assured that all currently activated and planned clinical trials are open to all common patients. Currently open clinical trials mainly focus on new therapeutic options for patients with bladder or prostate cancer:

- Exploratory, randomized, double-blind, placebo-controlled evaluation of efficacy, tolerability, and safety of intravesical instillation of GRT6010 compared to placebo in subjects with bladder pain syndrome
- A randomized, double-blind, placebo-controlled Phase III study of ODM-201 versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone-sensitive prostate cancer
- A randomized, double-blind, multicentric, parallel-grouped Phase III study to evaluate the efficacy and security of DCVAC/PCa versus placebo in metastasized castration resistant prostate cancer patients suited for first line chemotherapy
- A Multinational, Phase 3, Randomized, Double-blind, Placebocontrolled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC)
- A randomized, open label, multicenter study of Cabazitaxel versus an Androgen Receptor (AR)-targeted agent (abiraterone or enzalutamide) in mCRPC patients previously treated with Docetaxel and who rapidly failed a prior AR-targeted agent (CARD)
- A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab with or without Platinum-Based Combination Chemotherapy versus Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma
- Exploratory, randomized, double-blind, placebo-controlled evaluation of efficacy, tolerability, and safety of intravesical instillation of GRT6010 compared to placebo in subjects with bladder pain syndrome
- A Phase 2, Two-arm Multicenter, Open-Label Study to Determine the Efficacy and the Safety of Two Different Dose Regimens of a pan-FGFR Tyrosine Kinase Inhibitor JNJ-42756493 in Subjects with Metastatic or Surgically Unresectable Urothelial Cancer with FGFR Genomic Alterations

### Tumor genetic research with focus on identification of biomarkers

PI: 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 pri-



mary tissue samples retrieved from the CCC biobank, we were able to identify a collection of proteins and RNA 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.

#### **Biomarker-supported MRI-TRUS-fusion guided biopsies for the diagnosis of prostate cancer**

PI: 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 suspicious 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 MRITRUS-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**

PI: 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 physicians in identifying urological tumor patients and finding the right therapy stratification and therapy monitoring and in further expanding the basic molecular knowledge for urological cancers.

#### **Teaching**

Medical students are taught in the lecture series of emergency medicine and in general and specialized urological lectures. Students also conduct a block practical in the Department of Urology or one of the associated teaching hospitals. The Department also allows additional education for achievement of the title medical specialist for urology. Additionally, specialized training courses are offered for Systemic Drug Tumor Therapy and the qualification 'Urologic Diagnostic Radiology'. For acquisition and improvement of specialized surgical techniques, the Department of Urology uses patient simulators. These include models for practicing sterile placement of catheters or laparoscopic methods including a simulator at the da Vinci® operating system for minimally invasive surgery. In addition, practical trainings for basic and advanced techniques in molecular urology are offered. We supervise Bachelor's and Master's theses as well as MD and PhD theses.

#### **Selected Publications**

Keck B, Wach S, Taubert H, Zeiler S, Ott OJ, Kunath F, Hartmann A, Bertz S, Weiss C, Hönscheid P, Schellenburg S, Rödel C, Baretton GB, Sauer R, Fietkau R, Wullich B, Krause FS, Datta K, Maders MH. Neupilin-2 and its ligand VEGF-C predict treatment response after transurethral resection and radiochemotherapy in bladder cancer patients. *Int J Cancer*. 2015 Jan 15;136(2):443-51

Taubert H, Wach S, Jung R, Puglia M, Keck B, Bertz S, Nolte E, Stoehr R, Lehmann J, Ohlmann CH, Stöckle M, Wullich B, Hartmann A. Piv1 2 expression is correlated with disease-specific and progression-free survival of chemotherapy-treated bladder cancer patients. *Mol Med*. 2015 May 13;21:371-80

Wach S, Al-Janabi O, Weigelt K, Fischer K, Greither T, Marcou M, Theil G, Nolte E, Holzhausen HJ, Stöhr R, Huppert V, Hartmann A, Fornara P, Wullich B, Taubert H. The com-

bined serum levels of miR-375 and urokinase plasminogen activator receptor are suggested as diagnostic and prognostic biomarkers in prostate cancer. *Int J Cancer*. 2015 Sep;137(6):1406-16

Grampp S, Platt JL, Lauer V, Salama R, Kranz F, Neumann VK, Wach S, Stöhr C, Hartmann A, Eckardt KU, Ratcliffe PJ, Mole DR, Schödel J. Genetic variation at the 8q24.21 renal cancer susceptibility locus affects HIF binding to a MYC enhancer. *Nat Commun*. 2016 Oct 24;7:13183

Hedegaard J et al. Comprehensive Transcriptional Analysis of Early-Stage Urothelial Carcinoma. *Cancer Cell*. 2016 Jul 11;30(1):27-42

Stoehr CG et al. Homozygous G/G variant of SNP309 in the human MDM2 gene is associated with earlier tumor onset in Caucasian female renal cell carcinoma patients. *Oncogenesis*. 2016 Feb 29;5:e205

#### **International Cooperations**

Prof. Dr. T. Ørntoft, Department of Molecular Medicine, Århus University Hospital, Århus: Denmark

Prof. Dr. S. Subramanian, Department of Surgery, University of Minnesota Medical School, Minneapolis: USA

Dr. B.S. Nielsen, Molecular Histology, Bioneer A/S, Hørsholm: Denmark

Prof. Dr. Z. Culig, Universitätsklinik für Urologie, Medizinische Universität Innsbruck, Innsbruck: Austria

# 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 glassceramic dental materials
- Study of hydrothermal degradation mechanisms in zirconium dioxide
- Material properties self-adhesive cements
- Polymerization properties of bulk-fill composites

## Structure of the Department

Professorships: 1

Personnel: 50

- Doctors (of Medicine): 20
- Scientists: 3 (thereof funded externally: 1)
- Graduate students: 3

## Clinical focus areas

- Restoration
- Endodontic treatment
- Systematic periodontal treatment
- Pediatric dentistry

## Research

The main focus is on dental materials research with fields of expertise in basic science of operative and 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.

### Clinical fractography on dental ceramic restorations

PI: 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 ob-

served. 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. International workshops on dental fractography were successfully organized in 2015/16.

### Residual stress profiles in veneered dental zirconia frameworks

PI: 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 glass-ceramic dental materials

PI: 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 ap-

proach has potential for application with lithium disilicate (LS2) glass-ceramics which contain needle-form  $\text{Li}_2\text{Si}_2\text{O}_5$  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 has joined forces with the Department of Materials Science (Faculty of Engineering) to investigate specific material responses using state-of-the-art mechanical testing.



Scanning electron microscopy image of lithium disilicate glass-ceramic crystals for dental restorations. The fracture behavior of such materials is governed by how cracks interact with the microstructure (b).

### Study of hydrothermal degradation mechanisms in zirconium dioxide

PI: Dr. R. Belli, Prof. Dr. U. Lohbauer

Fully crystalline zirconium dioxide ( $\text{ZrO}_2$ ) ceramics offer moderate translucency and high mechanical performance for use as an alternative to metal-based dental prostheses. The crystalline structure of  $\text{ZrO}_2$  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  $\text{ZrO}_2$  for dental use. In dentistry  $\text{ZrO}_2$  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- $\text{ZrO}_2$  restorations are now exposed to the wet oral environment and contact damage. The scientific evidence regarding the mechanical behavior of  $\text{ZrO}_2$  in such conditions is very scarce and must be urgently addressed. With that in mind, the research laboratory for dental biomaterials within the Department 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-ZrO<sub>2</sub> 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 of self-adhesive cements

PI: Dr. J. Zorzin, Prof. Dr. U. Lohbauer

Self-adhesive cements enable the luting of indirect dental restorations without pretreatment of the tooth substrates. This is possible due to an acid-modified methacrylate-based chemistry. The aim of the research is to investigate the material properties of self-adhesive cements (adhesion, strength, swelling, expansion stress) and the factors which can influence them (pH neutralization, hydrophilicity, chemical composition).

### Polymerization properties of “bulk-fill” composites

PI: PD Dr. M. Taschner, Dr. J. Zorzin

Direct conventional, light-curing, dental filling resin composites have a limited depth of cure and polymerization shrinkage. Thus, these materials must be placed in thin layers into the tooth cavity which is very time consuming. Modern „bulk-fill“ composites claim to have a higher depth of cure and lower polymerization shrinkage. The aim is to investigate the polymerization properties of “bulk-fill” composites and to compare them with conventional composites (degree of polymerization, hardness, shrinkage and shrinkage stress) and its influence on the restored tooth cavity (marginal integrity and bond strength).

## Teaching

The Department of Operative Dentistry and Periodontology is involved in curricular teaching in the frame of the dental students' degree program. Interdisciplinary lectures are held at the Department of Materials Science and Engineering (Faculty of Engineering).

The Department offers supervision of Bachelor's and Master's theses as well as MD and PhD theses in conjunction with the Departments of Medical Engineering and Materials Science and Engineering.

## Selected Publications

Zorzin J, Maier E, Harre S, Fey T, Belli R, Lohbauer U, Petschelt A, Taschner M. Bulk-fill resin composites: polymerization properties and extended light curing. *Dent Mater.* 2015;31:293-301

Belli R, Wendler M, Zorzin JI, da Silva LH, Petschelt A, Lohbauer U. Fracture toughness mode mixity at the connectors of monolithic 3Y-TZP and LS2 dental bridge constructs. *Journal of the European Ceramic Society*, 2015;35:3701-3711

Wendler M, Belli R, Petschelt A, Lohbauer U. Spatial distribution of residual stresses in sphero-cylindrical glass-ZrO<sub>2</sub> bilayers. *Journal of the Mechanical Behavior of Biomedical Materials*, 2016;60:535-546

Roedel L, Bednarzig V, Belli R, Petschelt A, Lohbauer U, Zorzin J. Self-adhesive resin cements: pH-neutralization, hydrophilicity, and hygroscopic expansion stress. *Clin Oral Investig.* 2016, Sep 23

Belli R, Wendler M, Zorzin JI, Petschelt A, Tanaka CB, Meira J, Lohbauer U. Descriptions of crack growth behaviors in glass-ZrO<sub>2</sub> bilayers under thermal residual stresses. *Dent Mater* 2016;32:1165-1176

Belli R, Petschelt A, Hofner B, Hajtő J, Scherrer SS, Lohbauer U. Fracture rates and lifetime estimations of CAD/CAM all-ceramic restorations. *Journal of Dental Research*, 2016;95:67-73

## International Cooperations

Prof. H. Peterlik, Institut für Physik, Universität Wien, Vienna: Austria

Prof. R. Danzer, Institut für Struktur- und Funktionskeramik, Montan Universität Leoben, Leoben: Austria

Prof. P. F. César, University of Sao Paulo, Sao Paulo: Brazil

Prof. S. Scherrer, University of Geneva, Geneva: Switzerland

# 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

- Tumor research
- Infection and inflammation
- Biomedical techniques

## Structure of the Department

Professorships: 1  
Personnel: 100  
• Doctors (of Medicine): 18  
• Scientists: 1 (thereof funded externally: 0)  
• Graduate students: 20

## Clinical focus areas

- Tumor surgery of the oral cavity and the face
- Trauma surgery of the facial skull
- Surgery of facial malformations
- Orthognathic surgery of the facial skull
- TMJ surgery
- Dentoalveolar surgery

## Research

The research at the Department of Oral and Cranio-Maxillofacial Surgery focuses on the field of tumor research as well as on the investigation of infections and inflammations in the facial area. Another focus is biomedical research.

### Tumor research

Microsurgical tissue transfer for the reconstruction of extensive hard and soft tissue defects of the mouth, jaw and facial region represents a standard procedure in clinical routine. A challenge exists with the application of the microsurgical tissue transfer in the pre-irradiated hard and soft tissue, since thromboembolic events and wound healing compromise the clinical success of free transplants. Since more than 30% of the patient's microvasculature treated patients have pre-irradiation in the head and

neck region, we investigate mechanisms and methods that reduce the rate of irradiation-associated vascular complications and wound healing disorders. In a clinical study it is investigated whether thromboembolic complications due to irradiation of vessel, vessel thickening and the expression of inflammatory parameters in the irradiated vessel wall predict the likelihood of a thromboembolic complication. After applying for and approval in the DFG large-scale program, an operation microscope with integrated infrared-based perfusion measurement of microvascular structures was obtained. These intraoperative perfusion measurements enable intraoperative blood flow control and are correlated with the biological, histopathological parameters of the perfusion.

Another focus was the influence of the immune system on tumor progression. Tumor progression can be understood as immunologically mediated processes in the sense of a tolerance induction against the tumor. For the condition of tolerance of the tumor, macrophages are of particular importance. Macrophages can occur in the tissue in two different functional states - also known as polarization: M1 polarized macrophages activate other immune cells and promote inflammation. M2 macrophages inhibit the immune response and can even support cancer cells by delivering growth factors. We were able to show that there is a convergence between increased malignancies of the tumors with enhanced M2 polarization of the macrophages. In addition, there is already a link between M2 polarization of the macrophages and the occurrence of recurrences in early stages.

We further worked on the development of a minimally invasive method for the diagnosis, prognosis and clinical monitoring of the squamous cell carcinoma of the oral cavity (PECM) and oral leukoplakia. For this purpose, genes and miRNA are to be identified by means of the method of the next generation sequencing (NGS) which is directly involved in the malignant transformation of precursors of cancer, in particular of the oral leukoplakia (OLP) and therefore in the development of a tumor as so-called „key players“. At the same time, miRNA mRNA networks are to be developed in order to further elucidate this process. We hope to identify miRNA and genes that directly control the transition from premalignant to malignant lesion. This could ultimately contribute to the identification of prognostic markers for the imminent development of a tumor from its precursors. In addition, the basis for the development of new approaches for new, effective therapies could be laid which specifically counteract

the malignant transformation and thus the development of the PECM.

### Infection and inflammation

Research addresses etiology, pathogenesis, and therapeutic options of inflammatory reactions of the facial skeleton. Furthermore the osseous regeneration of bone defects in sites displaying compromised wound healing is investigated. A relevant focus is on the medication-related osteonecrosis of the jaw (MRONJ).

As MRONJ 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 MRONJ.

### Biomedical techniques

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 bio-functional surfaces in implant dentistry.

In a further project for the guided soft tissue regeneration, the temporal sequence of the reperfusion and vascularization of free mucosal grafts and collagen matrices is quantitatively examined. Within this clinical patient study, perfusion measurements of the tissue are carried using a Laser-Doppler-spectrophotometer.

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 nerve structures during surgery, such as the mandibular nerve 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

The Department of Oral and Cranio-Maxillofacial Surgery is involved in the curricular teaching of human and dental medicine with compulsory and elective subjects. Particularly noteworthy is the training of dental students in dental implantology as part of the elective course ilect®. Furthermore MD and PhD theses are supervised.

## Selected Publications

Lutz R, Berger-Fink S, Stockmann P, Neukam FW, Schlegel KA. Sinus floor augmentation with autogenous bone vs. a bovine-derived xenograft - a 5-year retrospective study. Clin Oral Implants Res, 2015, 26, 644-8

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 Investig 2015, 19:1289-1298

Weber M, Möbius P, Büttner-Herold M, Amann K, Preidl R, Neukam FW, Wehrhan F. Macrophage polarisation changes within the time between diagnostic biopsy and tumour resection in oral squamous cell carcinomas-an immunohistochemical study. Br J Cancer. 2015, 113(3):510-9

Weber M, Iliopoulos C, Moebius P, Büttner-Herold M, Amann K, Ries J, Preidl R, Neukam FW, Wehrhan F. Prognostic significance of macrophage polarization in early stage oral squamous cell carcinomas. Oral Oncol 2016, 52:75-84

Schmitt CM, Moest T, Lutz R, Wehrhan F, Neukam FW, Schlegel KA. Long-term outcomes after vestibuloplasty with a porcine collagen matrix Mucograft®) versus the free gingival graft: comparative prospective clinical trial. Clinical Oral Implants Research. 2016 Nov;27(11):e125-e133

von Wilmowsky C, Schlegel KA, Baran C, Nkenke E, Neukam FW, Moest T. Peri-implant defect regeneration in the diabetic pig: A preclinical study. J Craniomaxillofac Surg, 2016, 44, 827-34

## International Cooperations

Dr. E. Felszeghy, EARC (kft), Semmelweis-Universität, Budapest: Hungary

Prof. Dr. Dr. E. Nkenke, Medizinische Universität, Vienna: Austria

# 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

Professorships: 1  
Personnel: 24  
• Doctors (of Medicine): 9  
• Graduate students: 4

## Clinical focus areas

- Malformations of the upper and/or lower jaw
- Dentofacial disorders
- Craniofacial anomalies and syndromes
- Orthodontic treatment of cleft lip and/or palate
- Treatment of newborn babies with cleft lip and/or palate

## Research

The evolution of methods for digital evaluation in orthodontic differential diagnosis and therapy offers 3D metric assessments of dental and skeletal disorders. As a consequence, this questions the 3D validity and reliability of those data and

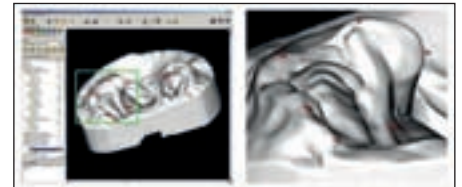
the appropriateness of x-ray exposure with MSCT or CBCT. As a result of the technical improvement of MRT imaging, the morphology of cranial hard tissues can now be presented in a way that assessments of validity and reliability also are in reach for the first time.

## 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 internet 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

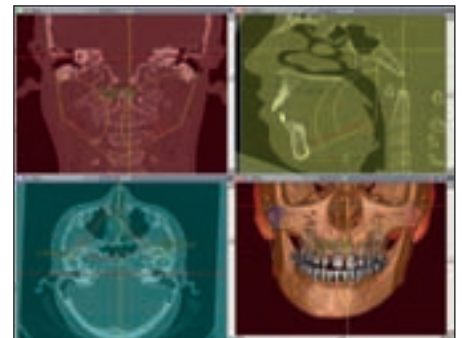
Aim of this study is the development of a platform to examine the practicability of three-dimensional (3D) MRI imaging in orthodontic issues due to the statement of the German society of Orthodontics (DGKFO) on the indication of 3D-imaging and the evaluation of MRI as an alternative imaging technique 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.



Three dimensional measurement of maxillary casts of newborn children with unilateral cleft lip and palate

## 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 19<sup>th</sup> 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.



Metrical analysis of a case with craniofacial asymmetry

## Investigation of the reproducibility of skeletal maxillary landmarks in CT-scans

The skeletal landmarks anterior and posterior nasal spine show 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.

### **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.

### **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.

### **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.

### **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**

For training within the scope of orthodontic analysis and treatment, the curriculum comprises comprehensive clinically based material. Skills lab work enables the students to collect and evaluate diagnostic data and to control the clinical application of orthodontic devices. MD and PhD theses are supervised.

### **Selected Publications**

Detterbeck AM, Kaiser J, Hirschfelder U. Electronic transfer of sensitive patient data. *Int J Comput Dent.* 2015;18(1): 45-57

Hirschinger V, Hanke S, Hirschfelder U, Hofmann E. Artifacts in orthodontic bracket systems in cone-beam computed tomography and multislice computed tomography. *J Orofac Orthop.* 2015;76(2): 152-60, 162-3

Detterbeck A, Hofmeister M, Hofmann E, Haddad D, Weber D, Hölzing A, Zabler S, Schmid M, Hiller KH, Jakob P, Engel J, Hiller J, Hirschfelder U. MRI vs. CT for orthodontic applications: comparison of two MRI protocols and three CT (multislice, cone-beam, industrial) technologies. *J Orofac Orthop.* 2016;77(4): 251-261

Ebert T, Elsner L, Hirschfelder U, Hanke S. Shear bond strength of brackets on restorative materials : Comparison on various dental restorative materials using the universal primer Monobond(®) Plus. *J Orofac Orthop.* 2016;77(2): 73-84

Hofmann E, Fimmers R, Schmid M, Hirschfelder U, Detterbeck A, Hertrich K. Landmarks of the Frankfort horizontal plane : Reliability in a three-dimensional Cartesian coordinate system. *J Orofac Orthop.* 2016;77(5): 373-83

Hofmann E, Schmidt M, Steinhäuser-Andresen S, Hirschfelder U. Three-dimensional CT evaluation of orofacial spectrum patients use of Katsumata's asymmetry index. *J Orofac Orthop.* 2016;77(3): 176-184

# 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
- Prosthodontics and implant therapy based on 3D-imaging

## Structure of the Department

Professorships: 1

Personnel: 50

- Doctors (of Medicine): 19
- Scientists: 13 (thereof funded externally: 0)
- Graduate students: 10

## Clinical focus areas

- Implant prosthetics
- Fixed and removable prosthetic
- Diagnosis and treatment of temporomandibular joint dysfunction (TMJD)
- Hypnosis and acupuncture treatment
- Esthetic dentistry
- Prosthetic rehabilitation with epithesis
- Prosthetic rehabilitation of children

## Research

Due to the high demands and quality standards of research projects, synergistic effects of highly qualified specialists are mandatory. This is reflected in the general orientation and a focus on future demands as well as in extensive cooperation with other fields of research. One key focus of research is the aging population and the resulting demographic changes and the investigation of the relationship between oral and general health.

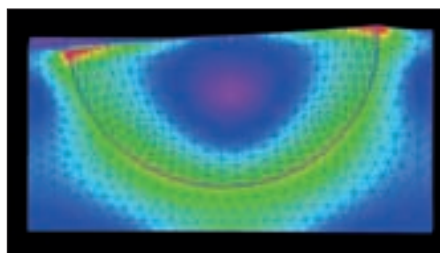
## Dental biomechanics

PI: PD Dr. M. Karl

Mechanical parameters of the components used 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

PI: 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

PI: Dr. R. Matta, L. Wolf

Quantitative assessment of biomechanical effects in vivo intraorally required highly complex research set-ups due to lack of adequate measurement technology in the past. The aim of the research group is to establish and evaluate full-field three-dimensional (3D) optical inspection systems for clinical application in biomechanical research. The system will allow 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 and facilitate verification and iteration of models that cannot be used solely to draw general conclusions regarding specific questions related to biomechanics. The system available at 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

PI: Dr. R. Matta, Z. 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 qual-



ity and precision, product aligned process routes are a mandatory prerequisite. The research group focuses on segmenting CAD/CAM processes and assessment of the impact on the overall quality. In addition to recently developed methodologies for 3D-display and analysis of microgaps in conventional dental restorations, new protocols are in development for a clinical assessment of fit of implant retained superstructures. The research laboratories are equipped with state-of-the-art industrial non-contact scanners and necessary analytical software programs. As high strength oxide ceramics are applied more frequently as framework materials in dentistry, several research projects assess the clinical application and factors influencing long-term success.

### **Prosthodontics and implant therapy based on 3D-imaging**

PI: Dr. R. Matta, L. Wolf, Dr. C. Motel

The three dimensional imaging becomes more and more important for the modern implant and prosthodontic therapy plan. This includes the Computer Tomography (CT), the Cone Beam Computer Tomography (CBCT) and the intraoral digital impression.

Two research groups handle this research topic; the first one is concerned with the digital intraoral impression taking and compares it with the conventional method. The second group focuses on the three dimensional accuracy of the X-ray imaging. In addition the impact of different dental implant materials on the appearance of artifacts in the three-dimensional virtual model is investigated by this group.

In this context a new method for the three-dimensional evaluation of CT and CBCT images has been developed.

The research in this area is of great importance and interest because the long-term clinical success of prosthodontic and implant restorations depends on the accuracy of the three dimensional transfer of oral structures in "virtual" illustrations.

## **Teaching**

The main focus of traditional prosthodontic education has shifted from a technically oriented towards an interdisciplinary treatment approach. Prophylaxis and biology are in the focus as well as minimally invasive treatment concepts. Clinically relevant topics are introduced into the preclinical curriculum, focusing on biologic interactions and material properties. While theoretical knowledge remains integral part of dental education, manual manufacture

of dental restoration will be taught only exemplarily.

A unique opportunity for all dental students at the FAU Dental School 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 passed successfully their examination in 2012 and finished their i.Lect pre-graduate program and started the post-graduated program which is also provided in cooperation with the Department of Oral and Cranio-Maxillofacial Surgery.

The Department of Prosthodontics supervises MD theses.

### **Selected Publications**

Karl M. In vitro studies on CAD/CAM restorations fabricated with Procera technology: an overview. *Quintessence Int.* 2015; 46(7): 561-574

von Wilmowsky C, Bergauer B, Nkenke E, Neukam FW, Neuhuber W, Lell M, Keller A, Eitner S, Matta RE. A new, highly precise measurement technology for the in vitro evaluation of the accuracy of digital imaging data. *J Craniomaxillofac Surg.* 2015; 43(8):1335-1339

Nickenig HJ, Wichmann M, Eitner S, Zöller JE, Kreppel M. Lingual concavities in the mandible: a morphological study using cross-sectional analysis determined by CBCT. *J Craniomaxillofac Surg.* 2015; 43:254-259

Matta RE, von Wilmowsky C, Neuhuber W, Lell M, Neukam FW, Adler W, Wichmann M, Bergauer B. The impact of different cone beam computed tomography and multi-slice computed tomography scan parameters on virtual three-dimensional model accuracy using a highly precise ex vivo evaluation method. *J Craniomaxillofac Surg.* 2016 ; 44(5):632-636

Nkenke E, Agaimy A, Vairaktaris E, Lell M, von Wilmowsky C, Eitner S. Case History Report: Immediate Rehabilitation with a Prefabricated Fibula Flap Following Removal of a Locally Aggressive Maxillary Tumor. *Int J Prosthodont.* 2016 Jan-Feb;29(1): 53-58

Schmitt CM, Matta RE, Moest T, Humann J, Gammel L, Neukam FW, Schlegel KA. Soft tissue volume alterations after connective tissue grafting at teeth: the subepithelial autologous connective tissue graft versus a porcine collagen matrix - a pre-clinical volumetric analysis. *J Clin Periodontol.* 2016; 43(7):609-617

### **International Cooperations**

Prof. T.D. Taylor, Prof. J.R. Kelley, PhD, University of Connecticut, Farmington: USA

Dr. H. Leblebicioglu, PhD, Erciyes University, Kayseri: Turkey

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### Research Focus

- Preventing overdiagnosis in primary care – the network Pro Pricare
- Pilot project MVZ Eckental – Clinical quality control
- Competence development in general practice trainees and medical students
- Medical decision-making in general practices
- Classification of diseases in primary care

### Structure of the Institute

*Institute of General Practice:*

Professorships: 1

Personnel: 8

- Doctors (of Medicine): 3
- Scientists: 3 (thereof funded externally: 3)
- Graduate students: 20

*Medical care center (MVZ) Eckental:*

- Doctors (of Medicine): 5
- Medical assistants: 6

### Clinical focus areas

Primary care in MVZ Eckental

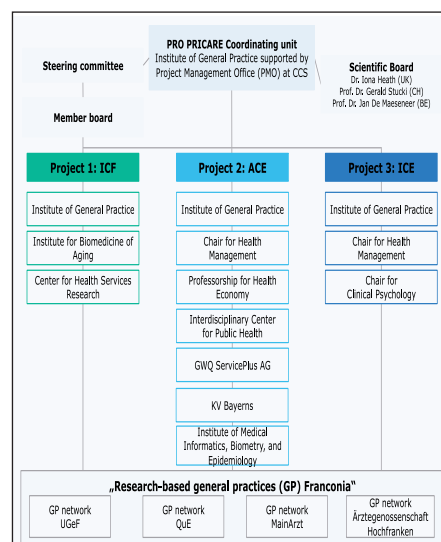
### Research

Our area of investigation is health services research. In our projects, we analyze use, risks and benefits of diagnostic and therapeutic methods as well as health services in “everyday life” connecting our research closely to real healthcare. Our main area of interest is primary care and health care delivered in general practices. Our research focuses on overdiagnosis in primary care and on competence development.

### Preventing overdiagnosis in primary care – the network Pro Pricare

Pro Pricare is the acronym for PREventing Overdiagnosis in PRImary CARE. Pro Pricare will focus

on implementing feasible tools to identify areas of overtreatment and to prevent medical overuse. Pro Pricare is a consortium of academic institutions of FAU and UK Erlangen. A partner in ambulatory care will be the research-based practice network “Forschungspraxen Franken” comprising of four practice networks located in rural and urban areas of Franconia (a region in Northern Bavaria). Also, the GWQ ServicePlus AG representing company health insurance funds (Betriebskrankenkassen) and the Bavarian Association of Statutory Health Insurance Physicians (Kassenärztliche Vereinigung Bayerns, KVB) are involved. The network will receive funding of 2.1 million Euro by BMBF.



It is mostly elderly people who experience a growing amount of health problems and disabilities. Medicine's reaction to this is an increasing amount of medical procedures, leading into a situation where medical intervention might do more harm than good. This requires a rational choice of the most effective interventions. However, medical overuse affects not only old patients. The lack of clear distinction between risk factors, pre-disease and disease in combination with advancing medical technology, entrepreneurship and a cultural focus on health all carries the risk of “disease inflation”. To address these problems, three projects will be conducted:

**1. ICF:** International Classification of Functioning. Development of an ICF core set to place the person as the watershed between necessary and unnecessary medicine into the center of medical thinking.

**2. ICE:** Ideas, Concerns, Expectations. Can patient-centered communication reduce the number of medical interventions in self-limited illness (here: acute low back pain)?

**3. ACE:** Adverse Cascade Effects. Understanding and describing the starting points and drivers of detrimental clinical pathways ending with unnecessary medical interventions (here: for thyroid disorders).

### Pilot project MVZ Eckental – Clinical quality control

Young general practitioners (GP) prefer flexible working hours as well as team work, reconciling family and work and work-life-balance. Practice networks, as for example MVZ, already provide the required structural conditions: However, working conditions and procedures need to be adapted. Comprehensive information on patients' diagnostic and therapeutic treatment must be accessible continuously for all team members. Until now, information on treatment process was insufficiently documented. Furthermore, therapeutic concepts were not organized for team work. The aim of our project is to create a comprehensive and detailed documentation. Therefore, we use routine data derived from electronic health records and added by additional information. Furthermore, we will develop concepts for inter-professional work in patient care, in particular collaboration between GP and specialists.

Funding: Bavarian State Ministry of Health and Care

### 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 need to be developed and tested. In our project, we want to examine whether financial and ideological support of medical students during their one-year internship and working in a GP in rural areas would help to make the profession general practitioner more attractive. A qualitative cohort-study was conducted. Medical students were interviewed in order to explore career choices of medical students and to gather more information about their perception and rating of a GP's work. We also wanted to know whether funding initiatives will aim at successfully reducing the shortage of GP.

Funding: Bavarian State Ministry of Health and Care, Bavarian Association of General Practitioners, Oberfranken Offensiv e.V.

## Medical decision-making in general practices

The main workload of GP comprises illnesses with vague symptoms, presented at early stages and in an undifferentiated way. To deal with diagnostic uncertainty is hence a major challenge for a 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. Routine data provided by the KVB were analyzed.

## 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). There are cooperations with Radboud University in Nijmegen (The Netherlands) and Ghent University (Belgium).

## Teaching

The Institute's teaching activities entail lectures, internships and various elective courses within the medical curriculum. Two interprofessional courses can be highlighted: The elective course "Arzt und Unternehmer" and the "Anamnese-gruppen an der Medizinischen Fakultät der FAU".

The elective course "Arzt und Unternehmer" is based on a cooperation with the KVB, the Verein Aktivsenioren Bayern e.V. and the Deutsche Apotheker- und Ärztebank. Within the course students learn how to develop a business plan for a practice aiming at reducing students' economic fears to establish an own practice in the future.

Furthermore the Institute of General Practice supports a students' initiative called „Anamnese-gruppen an der Medizinischen Fakultät der FAU". Students learn to consult with emphasis on a bio-psycho-social model, patient-centered communication, handling of subjective percep-

tions of patients, reflection on communication skills and interprofessional teamwork. Students from all medical degree programs (medicine, dentistry, logopedics, psychology) are invited. This project was awarded the prize of the Deutsche Balint-Gesellschaft e.V. (DBG) in 2016. We also provide supervision of Bachelor's and Master's theses as well as MD theses.

## Selected Publications

Roos M, Hartleb L, Langbein S. Der Hausarztmangel auf dem Land ist angekommen. *Z Allg Med.* 2015, 03:131-136

Maenner M, Schneider D, Schaffer S, Kühlein T, Roos M. Welche Argumente motivieren für eine Landarztstätigkeit? *Z Allg Med* 2015, 04:11-16

Roos M, Pfisterer D, Krug D, Ledig T, Steinhäuser J, Szece-nyi J, Goetz K. Adaptation, psychometric properties and feasibility of the Professionalism Scale Germany. *Z Evid Fortbild Qual Gesundhwes.* 2016, 113:66-75

Nittritz C, Schaffer S, Kühlein T, Roos M. Consultation skills training as an element of general practice training in Germany - a qualitative survey. *Z Evid Fortbild Qual Gesundhwes.* 2016, 117:57-64

Kühlein T, Madlo-Thiess F, Wambach V, Schaffer S. 10 Years of Quality Management: Perception and Importance from GPs' Point of View. *Gesundheitswesen.* 2016, Oct 25

Schrans D, Avonts D, Christiaens T, Willems S, de Smet K, van Boven K, Boeckxstaens P, Kühlein T. The search for person-related information in general practice: a qualitative study. *Fam Pract.* 2016, Feb;33(1):95-9

## International Cooperations

Prof. Dr. J. de Maeseneer, Department of Family Medicine and Primary Health Care, Ghent University, Ghent: Belgium

Dr. I. Heath, London: UK

Prof. Dr. G. Stucki, Department of Health Sciences and Health Policy, University of Lucerne, Lucerne: Switzerland

# Institute of Radiology

## Chair of Diagnostic and Interventional Radiology

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### Director

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### Research Focus

- Optimization of radiation dose and image quality in computed tomography
- Functional and metabolic MRI
- Interventional radiology
- Cardiovascular imaging
- Breast imaging and gynecological radiology
- Information technology in radiology
- Experimental radiology and small animal imaging
- Musculoskeletal imaging research
- MR-physics

### Structure of the Institute

Professorships: 4

Personnel: 156

- Doctors (of Medicine): 33
- Scientists: 11 (thereof funded externally: 11)
- Graduate students: 13

### Clinical focus areas

- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Angiography (including therapies)
- Conventional radiography
- Imaging
- Ultrasound
- Mammography
- Biopsies with imaging guidance

### Research

Scientific focus of the Radiological Institute is clinical and translational research. Within different study groups and research projects, the clinical impact of various imaging procedures or novel technical developments is evaluated. Furthermore, the Imaging Science Institute (ISI; compare own report) is operated in cooperation with Siemens Healthcare to integrate new developments in diagnostic imaging and novel IT-solutions into the clinical routine and the academic research. Finally, experimental and pre-

clinical studies are well-established in our scientific activities.

### Optimization of radiation dose and image quality in computed tomography

PI: PD Dr. M. May, Dr. M. Brand, PD Dr. W. Wüst, Prof. Dr. M. Lell, Prof. Dr. M. Uder  
CT is the major contributor to overall medical x-ray exposition. Radiation induced DNA-double-strand-breaks (DSB) can be detected by immunofluorescence microscopy. Recent studies have shown a strong correlation between DSB levels and the dose deposited in blood lymphocytes of patients. A different approach for radiation dose estimations is the mathematical Monte-Carlo-Simulation that provides detailed dose distribution for each individual. The knowledge from these monitoring techniques is used to establish methods for optimization of radiation dose and image quality. Studies evaluate the performance of modern technological developments for modulation of the x-ray spectra (organ based tube current modulation, tube voltage adaptation, spectral shaping, dual energy), for rapid examinations (high-pitch), for image reconstruction (iterative reconstructions, metal artifact reduction) and post-processing (dual energy techniques, anatomic landmark detection). Moreover, the potential protective effect of radical forming agents on DSB-induction is evaluated in vivo and in vitro.

### Functional and metabolic MRI

PI: Prof. Dr. M. Uder, Prof. Dr. R. Janka, PD Dr. M. Hammon, Prof. Dr. A. Cavallaro, Prof. Dr. F. Laun, Prof. Dr. A. Nagel

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

PI: Dr. A. Schmid, PD Dr. W. Wüst, Prof. Dr. M. Uder, Prof. Dr. R. Janka

Clinical studies are performed in cooperation with the departments of Surgery, Nuclear Medicine, Medicine 1, Medicine 4 and the divisions of Vascular Surgery and Nephropathology.

Research foci include the establishment of endovascular radiofrequency ablation of sympathetic nerve fibers 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

PI: PD Dr. W. Wüst, Prof. Dr. R. Janka, PD Dr. M. May, Dr. M. Scharf, Prof. Dr. M. Lell, Prof. Dr. F. Laun, Prof. Dr. A. Nagel

Close cooperation exists with the departments of Medicine 2 and of Pediatrics and Adolescent Medicine, the Institute of Medical Physics, and the divisions of Pediatric Cardiology and Pediatric Cardiac Surgery.

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 Leading Edge Cluster. 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

PI: Prof. Dr. R. Schulz-Wendtland, PD Dr. E. Wenkel, Prof. Dr. R. Janka, Prof. Dr. F. Laun

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 hybrid systems). 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. Finally, we are cooperating with Prof. Dr. W.A. Kalender (Institute of Medical Physics) to develop a breast CT scanner.

### Information technology in radiology

PI: Prof. Dr. A. Cavallaro, PD Dr. M. Hammon, Dr. P. Dankerl, Dr. H. Seuß

Aims of this group include the development of novel and intelligent medical databases as performed within the collaborative project 'Clinical Data Intelligence' of the BMWI (Federal Ministry for Economic Affairs and Energy). Important tasks of our group are the optimization of automatic algorithms for segmentation and characterization (e.g. for breast cancer) as well as the inclusion of clinical data and information from the genome. Modern mathematical algorithms such as 'deep learning' or 'ANN' together with methods of pattern recognition from radiological data may help to obtain disease-specific parameters. By connecting data from the electronic health record and genome analysis we furthermore assess the impact on diagnosis and image interpretation for therapeutic management of patients. For the resulting big amount of relevant data, our research group optimizes the automatization of information extraction and data anonymization.

### Experimental radiology and small animal imaging

PI: Prof. Dr. T. Bäuerle, Dr. C. Gillmann, Dr. S. Ellmann

Dedicated preclinical scanners are available for the imaging modalities MRT, CT, PET, SPECT, ultrasound and optical imaging 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 noninvasively 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.

### Musculoskeletal imaging research

PI: PD Dr. F. Roemer, Prof. Dr. T. Bäuerle

The focus of musculo-skeletal is the characterization of osteoarthritis by magnetic resonance imaging. This includes tissue evaluation in os-

teoarthritis through comprehensive joint assessment and the development and validation of quantitative and semiquantitative evaluation tools for application in cross-sectional and longitudinal fashion. One of the major research interests is the application of such MRI-based instruments to better understand the natural history of degenerative joint diseases and particularly focus on prediction models to isolate patients at high risk for disease incidence and progression. A close collaboration with the Department of Radiology at Boston University School of Medicine is on-going and has enabled active involvement in the largest on-going epidemiologic osteoarthritis studies including the Multi-center Osteoarthritis Study (MOST) and the Osteoarthritis Initiative (OAI), both with several thousand participants that are being followed over many years. The Institute is participating member of the recently launched Applied Public-Private Research enabling OsteoArthritis Clinical Headway (APPROACH) consortium of the European Commission's Innovative Medicines Initiative.

### MR-physics

PI: Prof. Dr. F. Laun, Prof. Dr. A. Nagel

The focus of the MR physics group is on the development of new image acquisition, image reconstruction and post-processing techniques for magnetic resonance imaging. These techniques are evaluated in close collaboration by physicists and clinicians. The aim is to provide improved clinical radiological diagnostics. Among others, techniques are developed to acquire in vivo images of the sodium ( $^{23}\text{Na}$ )-, potassium ( $^{39}\text{K}$ )-, chloride ( $^{35}\text{Cl}$ )-, or phosphorous ( $^{31}\text{P}$ ) distribution. These nuclei play an important role in many physiological processes. For example, the  $^{23}\text{Na}$ -,  $^{39}\text{K}$ - and  $^{35}\text{Cl}$ -concentrations are closely related to the physiological status of the cells. An additional focus is on the development of new methods to measure susceptibility and diffusion of water molecules in vivo. The measurement of diffusion coefficients provides information about the tissue structure and integrity. Clinical applications of diffusion-weighted imaging are, for example, the diagnostics of ischemic stroke and prostate carcinomas.

### Teaching

Besides the standard lectures and practical courses, innovative clinically orientated courses are regularly offered including interactive discussions of clinical cases. In these courses the

students are taught a much more analytic and clinical rather than a systematic approach towards the interpretation of radiologic images. A new online course was established for students to prepare effectively for the state examination. Students of the degree program Medicine can always perform clinical electives or internships at our Institute. Students striving for a doctor's degree are supervised closely when writing their experimental or clinical thesis. Furthermore, the Institute of Radiology participates in degree programs Medical Process Management and Molecular Medicine (Faculty of Medicine) as well as Medical Technology (Faculty of Engineering).

### Selected Publications

Brand M, Ellmann S, Sommer M, May MS, Eller A, Wuest W, Engert C, Achenbach S, Kuefner MA, Baeuerle T, Lell M, Uder M. Influence of Cardiac MR Imaging on DNA Double-Strand Breaks in Human Blood Lymphocytes. *Radiology*. 2015 Nov;277(2):406-12

Jantsch J et al. Cutaneous Na<sup>+</sup> storage strengthens the antimicrobial barrier function of the skin and boosts macrophage-driven host defense. *Cell Metab*. 2015 Mar 3;21(3):493-501

Lurz M, Lell MM, Wuest W, Eller A, Scharf M, Uder M, May MS. Automated tube voltage selection in thoracoabdominal computed tomography at high pitch using a third-generation dual-source scanner: image quality and radiation dose performance. *Invest Radiol*. 2015 May;50(5):352-60

Roemer FW, Kwok CK, Hannon MJ, Hunter DJ, Eckstein F, Wang Z, Boudreau RM, John MR, Nevitt MC, Guermazi A. Can Structural Joint Damage Measured with MR Imaging Be Used to Predict Knee Replacement in the Following Year? *Radiology* 2015; 274(3):810-20

Ellmann S, Kammerer F, Brand M, Allmendinger T, May MS, Uder M, Lell MM, Kramer M. A Novel Pairwise Comparison-Based Method to Determine Radiation Dose Reduction Potentials of Iterative Reconstruction Algorithms, Exemplified Through Circle of Willis Computed Tomography Angiography. *Invest Radiol*. 2016 May;51(5):331-9

Häberle L, Fasching PA, Brehm B, Heusinger K, Jud SM, Lohberg CR, Hack CC, Preuss C, Lux MP, Hartmann A, Vachon CM, Meier-Meitingen M, Uder M, Beckmann MW, Schulz-Wendtland R. Mammographic density is the main correlate of tumors detected on ultrasound but not on mammography. *Int J Cancer*. 2016 Nov 1;139(9):1967-74

### International Cooperations

Prof. A. Bogdanov, PhD, University of Massachusetts, Worcester: USA

Prof. D.R. Enzmann, MD, UCLA, Los Angeles: USA

Prof. W.E. Fahl, PhD, University of Wisconsin-Madison, Madison: USA

Prof. R. Frobell, Lund University, Lund: Sweden

Prof. A. Guermazi, MD, PhD, Boston University School of Medicine, Boston: USA

# Institute of Radiology

## Division of Neuroradiology

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### Research Focus

- Clinical and experimental validation of flat-panel volume CT
- Multimodal imaging of cerebrovascular diseases
- 7 Tesla high-field-neuroimaging
- Preoperative multimodal 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

Professorships: 1

Personnel: 45

- Doctors (of Medicine): 15
- Scientists: 7 (thereof funded externally: 7)
- Graduate students: 4

### Clinical focus areas

- Diagnostic and interventional neuroradiology
- Multimodal diagnostics in cerebrovascular diseases, brain tumors and epilepsy
- Functional and metabolic neuroimaging

### Research

The scientific focus of the Division of Neuroradiology is on multimodal imaging, especially in stroke, brain tumors and focal epilepsies. Hereby, a paramount scientific focus is on the evaluation of new imaging modalities, in particular „interventional imaging“. In cooperation with various partners, validation and optimization of

intravenous and intraarterial flat detector angiography, flat detector volume CT and high-field MRI are performed. In addition, there are several third-party research collaborations, among others with Siemens Healthineers, Bayer Pharma AG and the Faculty of Engineering of the FAU.

### Clinical and experimental validation of flat-panel volume CT

Projects are funded in part by the Bayerisches Förderprogramm Medizintechnik “Stroke Machine” and the EU-grant EIT Health “P3 Stroke – Predictive prevention and personalized multimodal interventional stroke therapy”. “Stroke Machine” evaluates the potential of multimodal angiography as “one-stop-shopping” tool for acute stroke. In “P3 Stroke” together with Siemens Healthineers and the Pattern Recognition Lab we develop, implement and validate an integrated hybrid Angio-MRI system. In cooperation with Siemens Healthineers and the Pattern Recognition Lab, we further evaluate and further develop intravenous and intraarterial flat-panel volume CT, angiographic techniques, and postprocessing algorithms in cerebrovascular disease. Hereby, a focus is set on the optimized visualization of cerebral microimplants, such as stents, coils, clips, new perfusion techniques, and 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. Here, a main focus is on 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.

### 7 Tesla high-field neuroimaging

Within the scope of a research collaboration on a clinical 7T prototype installation with Siemens Healthineers, various scientific research projects are carried out in close cooperation with the Department of Neurology and the Institute of Radiology for the validation and optimization of X-nuclear spectroscopy, high-resolution structur-

al imaging, diffusion tensor imaging and fMRI in epilepsy, multiple sclerosis, brain tumors and neurodegenerative diseases.

### Preoperative comprehensive imaging of epilepsy

In cooperation with the Epilepsy Center, we evaluate different multimodal imaging strategies in the preoperative workup of patients with focal seizures refractory for best medical treatment. A major focus is put on high-resolution 3T and 7T morphologic and functional MR imaging (MR spectroscopy, diffusion tensor imaging, functional MRI, perfusion- and diffusion-weighted MRI, MR volumetry/voxel-based morphometry) in conjunction with physiological parameters (EEG, MEG, WADA test, SPECT, PET).

### Functional and metabolic MR-imaging

There are several ongoing research projects in cooperation with departments and institutes at the Faculty of Medicine (Department of Psychiatry and Psychotherapy, Division of Child and Adolescent Mental Health, Division of Psychosomatics and Psychotherapy, Department of Medicine 3, Department of Neurology, Institute of Physiology and Pathophysiology, Institute of Experimental and Clinical Pharmacology and Toxicology) and at the Faculty of Business, Economics, and Law (Institute of Marketing) involving functional and metabolic MR-imaging (e.g. patients with major depressive disorders, anxiety and eating disorders, chronic pain syndromes, and rheumatoid arthritis). Together with the Department of Neurosurgery and funded by the DFG, we evaluate and optimize multimodal imaging protocols to distinguish diffuse tumor cell spread in glioma patients.

### Holistic assessment of optical tract in glaucoma patients using diffusion tensor imaging

In cooperation with the Department of Ophthalmology and the Computer Science Department 5 (Pattern Recognition Lab; Faculty of Engineering) and funded by the IZKF, we evaluate diffusion tensor imaging (DTI) using 3 and 7 Tesla MRI to assess quantitative and qualitative changes within the optical fiber tracts in glaucoma patients at a very early stage. Disorders in optical fiber tracts result in reduced fractional anisotropy (FA) and atrophy of the tracts which can be used for non-invasive and fast screening, staging and to evaluate therapeutic strategies in glaucoma. Moreover, 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 and optimize multimodal imaging and new therapy strategies in experimental brain gliomas, using micro-CT, high-field and ultra-high-field MRI (3 and 7 Tesla), and micro-PET. Additionally, using an elastase-induced and a surgical aneurysm 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), the Institute of Fluid Mechanics (both Faculty of Engineering) and Siemens Healthineers, 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 new endovascular microimplants, such as stents, flow diverter stents, bifurcation devices and coils. Medium-term strategy is to develop and clinically implement an automated software-platform that can be used within the perinterventional setting.

## **Teaching**

The Division of Neuroradiology is widely involved in the training of medical students. In

addition, we train residents in neuroradiology and general radiology and radiological technicians.

### **Selected Publications**

Struffert T, Deuerling-Zheng Y, Kloska S, Engelhorn T, Lang S, Mennecke A, Manhart M, Strother CM, Schwab S, Doerfler A. Dynamic Angiography and Perfusion Imaging Using Flat Detector CT in the Angiography Suite: A Pilot Study in Patients with Acute Middle Cerebral Artery Occlusions. *AJNR Am J Neuroradiol*. 2015 Oct;36(10):1964-70

Rösch J, Hamer HM, Mennecke A, Kasper B, Engelhorn T, Doerfler A, Graf W. 3T-MRI in patients with pharmacoresistant epilepsy and a vagus nerve stimulator: a pilot study. *Epilepsy Res*. 2015 Feb;110:62-70

Ghoochani A, Schwarz MA, Yakubov E, Engelhorn T, Doerfler A, Buchfelder M, Bucala R, Savaskan NE, Eyüpoglu IY. MIF-CD74 signaling impedes microglial M1 polarization and facilitates brain tumorigenesis. *Oncogene*. 2016 Dec 1;35(48):6246-6261

Rösch J, Ott M, Heismann B, Doerfler A, Engelhorn T, Sembritzki K, Grodzki DM. Quiet diffusion-weighted head scanning: Initial clinical evaluation in ischemic stroke patients at 1.5T. *J Magn Reson Imaging*. 2016 Nov;44(5):1238-1243

Eckert M, Göllitz P, Lücking H, Struffert T, Knossalla F, Doerfler A. Optimized Flat-Detector CT in Stroke Imaging: Ready for First-Line Use? *Cerebrovasc Dis*. 2016;43:9-16.

Göllitz P, Struffert T, Hoelter P, Eyüpoglu I, Knossalla F, Doerfler A. Flow-diverting stents allow efficient treatment of unruptured, intradural dissecting aneurysms of the vertebral artery: An explanatory approach using in vivo flow analysis. *Interv Neuroradiol*. 2016 Feb;22(1):76-83

### **International Cooperations**

Prof. C. Strother, Department of Radiology, University of Wisconsin, Madison: USA

Dr. A. Bose, Department of Radiology and Neurology, Lenox Hill Hospital New York, New York: USA

Prof. Dr. Anton Valavanis, Klinik für Neuroradiologie, Universitäts-Spital, Zurich: Switzerland

Prof. Dr. Marco Essig, Department of Radiology, University of Manitoba, Winnipeg: Canada

Prof. Dr. A. El-Rafei, Faculty of Engineering, Ain Shams University, Cairo: Egypt

# Medicine

## Dean for Student Affairs

Prof. Dr. med. Hans Drexler

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## Figures and Structure

In the winter term 2015/2016, 2,555 students were enrolled in the degree program medicine (among them 175 students in the 1<sup>st</sup> term) and in the summer term 2016, 2,554 students studied medicine at the FAU (among them 182 students in the 1<sup>st</sup> term). In the academic year 2015/2016, 58.4 % of the enrolled students were female. The percentage of women studying medicine decreased as compared to the winter term 2013/2014 by 1.3 %.

According to statistics of the FAU, 7.1 % of the students enrolled in the degree program medicine in the above mentioned academic year were foreigners.

Applicants for this degree program are chosen according to the criteria of the "Stiftung für Hochschulzulassung" (foundation for higher education admission) through the corresponding online platform. Applicants for the degree program medicine are able to improve their chances of receiving a program place at 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 the 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 among the Institutes and Departments belonging to the UK Erlangen according to the results of the online course 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 teach-

ing 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 (terms 5 – 10) of the degree program medicine receive grants of 5,000, 3,000, and 2,000 Euro, respectively. For the degree programs Dentistry, Molecular Medicine, and Medical Process Management, the best instructors receive 5,000 Euro 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 students' evaluations are awarded a total of 165,000 Euro. 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 learn and 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, taking 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), the practical year (Praktisches Jahr) as well as practical examination. Skills Lab PERLE, fully funded by student fees, is a visible enrichment of the medical education in Erlangen. Practical courses using different training models as well as simulators can be attended by all students during the term. Additionally, PERLE offers special training hours during the term and structured courses during the lecture free time. In addition, practicing in PERLE within the frameworks of the Introduction into Clinical Medicine (EKM) course, the practical training in urology as well as surgery is a part of the teaching curriculum. The course "PERLE International" has been introduced to meet the special learning needs of the foreign students and is being offered on a regular basis.

## Medical State Examination

In 2015 the Medicine students in Erlangen ranked the fifth place in Germany and the second place in Bavaria in the First State Medical Examination (first part of the physician exam). In the Second State Medical Examination the Medicine students have reached the third place in Bavaria and the fourth place in the general ranking of Germany. In 2016 the Medical stu-

dents in Erlangen have topped their results in the First State Medical Examination by achieving the second place in German ranking and the remarkable first place in the Bavarian one. In the Second State Medical Examination the students in Erlangen finished seventh in the general German ranking and second in Bavaria.



# Dentistry

## Speaker

Prof. Dr. med. dent. Anselm Petschelt

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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.



*Phantom head (photo: S. Krikava)*

# Molecular Medicine

## Speaker

Prof. Dr. rer. nat. Michael Wegner

## Coordination

Dr. rer. nat. Simone Reiprich  
(as from 1.8.2017)

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## Aims and Structure

The consecutive bachelor/master degree program Molecular Medicine combines the subjects of experimental medicine with the approaches of molecular biology, biochemistry, and genomics. 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 degree program Molecular Medicine addresses the need to teach knowledge from both, medicine and natural sciences. An interdisciplinary curriculum optimally prepares the students for the changing requirements in biomedical research. With the master's degree, the students acquire the ability to do research independently.

Graduates of this research-oriented program can work as biomedical scientists in universities, industry and public administration.

During their studies, our students are closely supervised. New bachelor students, for example, are welcomed with a symposium introducing the study program and the different research activities at the Faculty of Medicine. In the mentoring program, each student is assigned a mentor from among the teaching staff of the program. The participation of student representatives in the program committee ensure that students are actively involved in decision-making and further development of the study programs.

### Bachelor program Molecular Medicine

Each winter semester, 37 new students are chosen from among 800-1000 applicants. The B.Sc. degree program spans six semesters in which a solid education in all basic disciplines of Molec -

ular Medicine is achieved. The core curriculum in Molecular Medicine is mainly taught by pre-clinical and theoretical institutes. In the first two years, there is a focus on basic sciences and human biology (e.g. chemistry, physics, cell biology) as well as the preclinical disciplines anatomy, biochemistry and physiology. These courses are complemented by further modules in pathogenesis and experimental therapies (e.g. human genetics, pathology, pharmacology) and practical lab work. The degree program concludes with a 2-months experimental thesis.



Participants of the graduation ceremony on 17 October 2015. (Photo: FAU)



Participants of the graduation ceremony on 15 October 2016. (Photo: FAU)

### Master's program Molecular Medicine

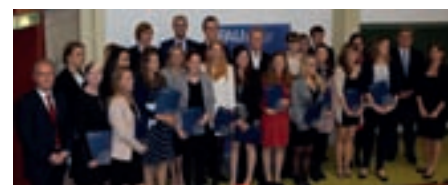
The main goal of the consecutive two year master degree program is to enable students to do independent scientific research. The master program is highly research oriented. While the B.Sc. curriculum teaches the basics of single disciplines, the M.Sc. degree program focuses on interdisciplinary courses. These link theoretical concepts with extensive lab practice and analysis and discussion of current and classical research publications. The master degree program ends with a thesis of six months. A mobility window in the third semester gives students an opportunity to gain lab experience abroad or in an industry context.

The curriculum of the master's program was changed significantly as of winter semester 2016/2017. The language of teaching (including examinations) was switched to English, taking into consideration that English is the lingua franca in biomedical science. This change opens the program for qualified international appli-

cants. Furthermore, the student body's wish for more freedom of choice was addressed by the introduction of elective compulsory and elective modules. Students and alumni were strongly involved in the development of the curriculum.



Participants of the graduation ceremony on 17 October 2015. (Photo: FAU)



Participants of the graduation ceremony on 15 October 2016. (Photo: FAU)

## Perspectives

The master degree Molecular Medicine offers the opportunity to pursue a high-quality doctoral program at FAU and other universities. 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 is 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 seek university graduates experienced in molecular diagnostics, DNA and protein diagnostics for medical and biotechnological applications.

Molecular Medicine graduates who have gone on to obtain a doctoral degree currently have positions in national and international research institutions (e.g. Harvard Medical School, Karolinska Institute) and in industry (e.g. Novartis or Roche). Graduates of the first generation are already holding professorships.

# Medical Process Management

## Speaker

Prof. Dr. med. Dr. h.c. Jürgen Schüttler

## Coordination

Prof. Dr. med. Harald Mang, MHBA

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medical-process-management

## Aim and Structure

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.

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 time needed for writing the master's thesis. The degree program starts in the winter term only. For successful completion of the degree program, 120 ECTS credit points must be obtained.

This degree program provides medical knowledge, deep proficiencies of the German healthcare system, 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, hospital and care management, strategic leadership, and psychology of communication. In this way, the degree program con-

nects medicine and healthcare to business process management and information technology. Strengthening patient-orientation, improving the quality of medical care, and increasing efficiency in healthcare are the topics that make up the curriculum's key focus.

## The situation of the students

In the first place, the 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 2015 and 2016 140 and 120 students, respectively, applied for admission to MPM (80 % female). In both years half of the applicants were admitted after passing the qualification assessment exam. 60 percent of the students who were admitted finally accepted the university place. This means that the student cohort of the eighth year contains 42 students, whereas the cohort of ninth year comprises 36 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, the length of the study can be organized flexibly between three and six terms. Moreover, 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 at external institutions – with an additional supervisor of the university. The students of each academic year elect 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 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 35

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 an innovative approach to tackle the challenges faced by healthcare systems in industrialized countries. No other university in Germany offers so far an equal 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 large group practices, as case managers for health insurers, and as managers of health 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

## Speaker

Prof. Dr. med. Christopher Bohr

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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 degree program 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 (2021) and will then acknowledge both, B.Sc. and the professional title of state-approved speech and language therapist, as equal qualifications.



*Lip strength measurement*



*Voice formation and training*



*Lecture (explaining the larynx with the help of a model)*



# Interdisciplinary Center for Clinical Research (IZKF)

## Chairman

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## Aims and Structure

The Interdisciplinary Center for Clinical Research (IZKF) is the central intramural structure of research development at the Faculty of Medicine. Its aim 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. The IZKF is funded by the Faculty of Medicine itself with additional contributions from FAU. All focal research areas and interdisciplinary fields of the Faculty participate in IZKF, ensuring that nearly all institutions of the Faculty of Medicine can submit grant applications to the IZKF. In 2016, the two separate funding instruments of the Faculty of Medicine - IZKF and ELAN-Fonds (compare own report) - were consolidated under the umbrella of IZKF. The new IZKF comprises the following programs:

## Research grants

IZKF offers single and joint research grants with 30 month duration and funding for two personnel positions (e.g. one or two graduate students or one technician) and for consumables. Project leaders are expected to have an active publication record and own external funding. Innovative and original ideas and concepts are especially valued; the same applies to the clinical relevance and interdisciplinary approaches. It is expected that projects are successfully transferred into external funding following IZKF funding. If project leaders apply for external funding by the end of the funding period, an extension for another six months is provided.

IZKF is a high risk funding program starting at an early phase of a project. It is nevertheless reassuring that most of the projects are successful and thus likely to be transferred into extramural funding. Within the last funding period (2013 – 2016) all projects submitted third party funds applications and therefore received the six month funding extension. When considering

the last two funding periods (2010 – 2016), 47 projects were funded by IZKF, 44 (94%) of which submitted third party funds applications. Of these, 34 projects (77%) were granted extramural funding, 3 (7%) are still under review and only 7 (16%) were not funded. This impressive success is also reflected by the fact that IZKF funding resulted in the acquisition of more extramural funds than what was originally spent. Apart from external funding, the publication output is of importance when evaluating IZKF's performance in advancing clinically oriented research at the Faculty of Medicine. Various parameters are used, with scientific publications and academic success of young scientists being the most obvious and straightforward ones. Furthermore, patents, scientific prizes, and offers of professorships are relevant parameters. In 2016, the 75 funded projects altogether published 69 original articles with a cumulative impact factor (IF) of 495.939. The high quality of these publications is reflected in the fact that 19 articles (28%) were published in highly visible journals with an IF above 10.

## Career development

Support and development of young scientists have been central goals of the IZKF since its inception. Two junior research groups offer attractive career development opportunities for outstanding young scientists with a training in medicine or natural sciences and 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 P. Ceppi, PhD, (junior research group 1) is working on the topic "Understanding the plasticity of cancer cells". The group of Dr. D. Dulin (junior research group 2), located at the Optical Imaging Center Erlangen (OICE), is engaged in the field "Physics and Medicine". The junior research group 3 (Prof. Dr. B. Winner) successfully completed its work on "Modeling neurodegenerative diseases using stem cells" in 2016. Prof. Dr. B. Winner was recently appointed professor at the Institute of Human Genetics and is now head of the division of stem cell biology.

In addition, IZKF supports up to eight positions for a laboratory rotation and 18 MD-thesis scholarships. Since 2009, IZKF has also been offering 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. Funding for a technician or a doctoral student and consumables for 2.5 years is provided. 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, IZKF provides positions for laboratory rotation for up to twelve months full-time or 24 months part-time.

## Start-up support (ELAN)

The aim of ELAN is to prepare scientific projects for successful application for external funding (start-up projects), to support newly established working groups, to develop new innovative ideas (pilot projects) or act as interim funding if temporary gaps arise between individual extramural funding periods. ELAN supports young scientists up to 38 years of age from the entire Faculty of Medicine with up to 50,000 Euro for a period of up to twelve months.

## 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 offering 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 approaches have access to these technologies and also ensure that students get acquainted with these modern developments. IZKF offers an initial funding of core facilities for up to five years. Further supporting activities include the "Visiting Professor Program" and a biennial international scientific meeting. In addition, central funds for participating in scientific meetings, publications charges and particularly cost-intensive experiments (High Tech Pool) provide additional support for funded projects.



# Preclinical Experimental Animal Center (PETZ) at the Franz-Penzoldt-Center (FPZ)

## Speaker

Prof. Dr. med. Stephan von Hörsten

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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 in studies on large or small animals. The center provides state-of-the-art phenotyping services for neurobiological, hematological, neuroendocrine, and immunological characterization of mice and rats. Already as early as at 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, 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.

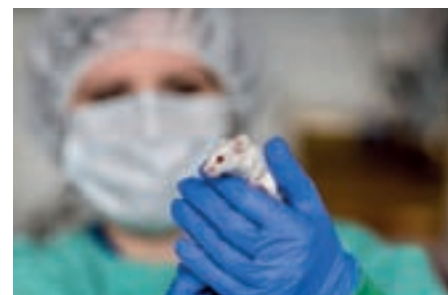


## Research

The superior goal of PETZ is the continuous implementation of the principles of reduction and refinement being part of the 3R principles of humane animal research and experimentation. PETZ takes over responsibility for continuous optimization of the housing conditions for the benefit of both, animal welfare and quality of scientific results. Though primarily representing a service unit, PETZ runs independent research projects, acquires external funding, and is a source of exciting lectures, seminars, and practical courses on animal experimentation and ethics. Thus, central function of PETZ is to provide services and an environment of responsible and ethical breeding and treatment of animals in accordance with the local and national law. These constant achievements are combined with continuous optimization and standardization processes related to animal housing, including, but not limited to implementation of additional core services in animal phenotyping, quality management and strategic facility management aiming at providing highest service quality also in the future.

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 2017, a variety of different research projects representing over 92 working groups are realized in PETZ. These researchers originate from 43 institutes, academic chairs, or departments. Most of these working groups belong to the Faculty of Medicine.



## Teaching

PETZ is a source of exciting lectures, seminars, and practical courses on animal experimentation and ethics. The 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 commerce and industry (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

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## Aims and Structure

In 2008, the Center for Clinical Studies (CCS) was founded as a service unit shared by the Faculty of Medicine 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 UK Erlangen for the conception, planning, conduct, and analysis of clinical studies, taking into account the relevant legal and regulatory requirements;
2. Support to 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 participated in about 420 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 four projects involving the first administration to humans of novel medicinal products (first-in-man trials).

CCS is structured into the areas of study management and clinical monitoring, quality management, and pharmacovigilance.

## Counseling and support for clinical studies

### Counseling

Each year, CCS 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 UK Erlangen. CCS 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 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 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 helps identify and develop the relevant SOP.

If requested by the sponsor or the project leader, CCS performs audits of study sites or other institutions involved in a clinical study to assess their compliance with regulatory requirements. On request, CCS 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 UK Erlangen, CCS ensures the documentation and timely notification of serious adverse events according to legal and regulatory requirements. For this task, CCS uses a dedicated and certified database.

### Administration of the insurance for participants in clinical studies

CCS administers the insurance for participants in clinical studies initiated by members of the Faculty of Medicine and staff of UK Erlangen. This comprises obtaining insurance offers and accompanying the project until its conclusion.

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 in collaboration with the Institute of Clinical Pharmacology and Clinical Toxicology has currently conducted more than 40 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 800 physicians from UK Erlangen and the associated academic teaching hospitals have attended the courses.

## Research

### Clinical studies database of the Faculty of Medicine

The clinical studies database serves to present the clinical research efforts of the Faculty of



# Comprehensive Cancer Center Erlangen-EMN

## Director

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## Aims and Structure

The Comprehensive Cancer Center Erlangen – European Metropolitan Region of Nuremberg (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.

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. Cooperation agreements with Bamberg hospital (Sozialstiftung Bamberg), Bayreuth hospital (Klinikum Bayreuth, GmbH) and Amberg hospital (Klinikum St. Marien Amberg) were established. All four 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 18 certified organ cancer centers, eleven focal points and 24 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 personalized 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."

In 2016 a molecular tumor board was established. Patients suspected to have a complex oncological syndrome or with advanced/metastatic solid cancers are presented in the board and can be tested with a comprehensive cancer-/genpanel. The results improve clinical decision making of innovative therapies.

## 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; compare own report) 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 three clinical cancer registries. 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 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, CCC ER-EMN provides a series of lectures for physicians and scientists in the field of cancer research.



**CCC** Comprehensive  
Cancer  
Center   
**Erlangen-EMN**  
Europäische Metropolregion Nürnberg



## Emil-Fischer-Center (EFC)

### Speaker

Prof. Dr. med. Andreas Ludwig

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### Aims and Structure

The Emil Fischer Center (EFC) aims at promoting and implementing interdisciplinary research and educational projects in pharmaceutical sciences, food chemistry, and molecular medicine. The center constitutes an association of eight chairs from the Faculty of Medicine and the Faculty of Sciences. The EFC includes the full and associate professors from the chairs of Biochemistry and Pathological Biochemistry, Biochemistry and Molecular Medicine, Pharmacology and Toxicology, Clinical Pharmacology and Clinical Toxicology (Faculty of Medicine), and the chairs of Pharmaceutical Chemistry, Pharmaceutical Technology, Food Chemistry, and Bioinorganic Chemistry (Faculty of Sciences). The EFC promotes collaborative research activities 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 interdisciplinary training of post-graduates is accomplished by the associated Emil-Fischer-Graduate School (EFS; compare own report).

### Research and Teaching

The EFC studies biomedically relevant target proteins which are controlled by biologically active substances including drugs, hormones, neurotransmitters, 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, by SFB 796, GK 1910 und 2162, 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 shortly after foundation of the EFC and includes currently 42 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,
- one LC-tandem quadrupole-MS/MS,
- two LC-triple quadrupole-MS/MS,
- three NMR 360, 400 and 600 MHz,
- one CD spectrometer,
- NMR for small animals (4,7 Tesla),
- various electrophysiological setups, and
- a bioinformatics computer cluster.



# Erlangen Center for Infection Research (ECI)

## Speaker

Prof. Dr. rer. nat. Steffen Backert  
(Faculty of Sciences)

## Scientific Coordinator

Dr. rer. nat. Sonja Pötzsch

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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. K. Überla (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 1181, SFB 796, SFB/TRR 130), several research training groups (GK 1660, GK within SFB1181 and GK within SFB 796) as well as in the application for a Cluster of Excellence at the FAU within the framework of the federal excellence initiative 2017. 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) and master students in cell and molecular biology, but also the invitation of national and international infectious disease researchers for guest lectures.

## Selected lectures

23.2.2015 Dr. R. Bückner, Charité Berlin  
Colonization and virulence mechanisms of the gastrointestinal pathogens *Helicobacter*, *Campylobacter* and *Arco-bacter*

20.2.2015 Prof. Dr. T. Stradal, Helmholtz Centre for Infection Research  
Cytoskeletal rearrangements during infection and pathogen defense

6.10.2015 Dr. D. Gruber, University of Zurich  
*Helicobacter pylori* type IV secretion-induced double-strand DNA breaks in gastric epithelial cells are introduced by nucleotide excision repair endonucleases and promote NF- $\kappa$ B target gene expression

9.10.2015 R. Kapetanovic, PhD, The University of Queensland  
Of mice and men... Studying genes differentially regulated between mammals

16.10.2015 Prof. Dr. K. Rottner, Technical University Braunschweig  
Actin dynamics in host cell motility and bacterial infections

27.11.2015 Dr. S. Bartfeld, University of Würzburg  
Infection, innate immune signaling and cancer in the stomach – stem cell derived organoids as new host cell model

3.6.2016 Prof. G. Zanotti, Department of Biomedical Sciences University of Padua  
Do protein crystal structures always reveal function? The case of *Helicobacter pylori*

13.6.2016 PD Dr. R. Bückner, Charité Berlin  
Induktion von fokalen Läsionen und epithelialer Barriereförderung durch Enteropathogene: das Leaky Gut Konzept

11.7.2016 Univ.-Prof. Dr. T. Alter, FU Berlin  
Molekulare Epidemiologie lebensmittelassoziierter Zoonoseerreger

7.12.2016 Prof. Dr. R. Tsolis, University of California  
ER stress: a pattern of pathogenesis during *Brucella* infection of the mononuclear phagocyte system and placenta



# Imaging Science Institute (ISI)

## Speakers

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Dr. med. Patrick Amarteifio (Siemens Healthcare)

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[imaging-science-institute](http://imaging-science-institute)

## Aims and Structure

The Imaging Science Institute (ISI) was founded in 2005 as a cooperation project between Siemens Healthcare and the Institute of Radiology. Its location within the UK Erlangen allows optimizing modern imaging systems to improve quality and efficiency of diagnostic analysis as well as treatment methods. ISI provides the prerequisites to transfer new developments regarding imaging methods and data processing systems into the clinical setting. Aside from scientific activities, ISI provides training courses for users and technicians to operate new hard- and software services in the field of biomedical imaging. Moreover, 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 twelve years since its establishment, roughly 40,000 people from all over the world have visited ISI, among them numerous leaders of medical centers as well as representatives of public healthcare systems and politicians.

## ISI partners:

- Siemens AG
- Fujitsu Technology
- Medtronic
- Medrad, INC.
- Barco
- Federal Ministry for Economic Affairs and Energy
- BMBF
- Medical Valley EMN e.V.

## Research

Research projects aim at translating preclinical developments from industrial partners into im-

proved patient care. New concepts of examinations and medical products are created by a direct and mutual dialogue between clinical users and industrial developers as well as technicians. These cooperations often result in corporate patents, underlying the competence of ISI. New medical products are further evolved and optimized. The BMBF funded Leading Edge Cluster Medical Valley EMN connects ISI to a strong regional network. Main research focus is:

- Radiological information technology  
Increasing radiology data are structured in „Big Data“-projects and future artificial intelligence algorithms are aimed at improving patient care. After finalization of the „Medico“-project of the Federal Ministry for Economic Affairs and Energy, the next funded research project „Klinische Datenintelligenz“ was recently started.

- Pediatric radiology  
Clinical usability and impact on the clinical patient care of fast Computed Tomography techniques (High Pitch) are evaluated. Adult techniques of Magnetic Resonance Imaging are adapted to pediatric patients.

- Radiography  
Next generation X-ray systems use industrial robotic arms to standardize examination protocols and to establish new examinations like weight bearing imaging and 3D images. Usability, dose performance and image quality are evaluated in comparison to conventional systems.

- Computed tomography  
Technological developments are evaluated for the use in clinical patient collectives and new indications are established (i.e. low kV, tin prefiltration, iterative reconstructions, Dual Energy). New concepts of mobile interfaces are used to economize the daily workflow and to improve patient compliance.

## Teaching and advanced training

Offering a wide range of courses and workshops for physicians, technicians, engineers, and radiographers, ISI enjoys a very high national and international reputation owing to the professional competence of the course instructors and the excellent training conditions. Since its foundation ISI in 2005, more than 20,000 people have already participated in advanced training courses.



# Interdisciplinary Center for Aging Research (ICA)

## Speaker

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## Aims and Structure

Since its foundation in 2003, the Interdisciplinary Center for Aging Research (ICA) has been active in the fields of biological, medical, psychiatric, psychological, behavioral, humanistic, economic, and technological aging research. ICA initiates and supports interdisciplinary collaboration on aging research at the FAU. ICA is also actively collaborating with communal institutions of medical care and with nursing homes of the region. Currently ICA has 29 members from four different faculties and five associated institutions.

## Research

Research of the members of 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.

## Nutrition

Quantity and quality of our daily diet are of major importance for health, functionality, and well-being until very old age. At a higher 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. These relations were investigated within the framework of the Professorship of Clinical Nutrition in the Elderly at the Institute for Biomedicine of Aging (IBA) in national and international projects in interdisciplinary cooperation. Within the Bavarian nutrition competence cluster enable, for example, electronic gadgets were developed in cooperation with the Institute for Psychogerontology (IPG) with the aim to improve drinking behavior of nursing home residents. Recruitment and phenotyping of an enable elderly cohort at the IBA will hereafter allow comparisons of the nutritional situation with younger age-groups which were assessed in Freising using identical methods. In the European joint project DEDIPAC (Determinants of Diet and Physical Activity), IBA contributed to the development of a complex framework of determinants of nutrition and

eating (DONE framework). One of the aims of the European joint project MaNuEL (Malnutrition in the Elderly Knowledge Hub) is to identify the most relevant modifiable determinants of malnutrition in older persons by systematic literature reviews and secondary data analysis of longitudinal cohort studies. As a result, a better understanding of the etiology and complex network of determinants of malnutrition is expected which is important for effective prevention and treatment of malnutrition. In the worldwide nutritionDay project, current use of nutritional interventions was not associated with six month mortality in nursing home residents who are malnourished or at risk of malnutrition. The reasons for these findings need to be clarified.

## 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: GESTALT I and II; Standfest im Alter 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 long-term changes in physical activity behavior is the affective attitude towards physical activity (project: KASPAD). 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 as-

sets 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).

## 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. 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 for Health Technology Assessment (HTA) and Public Health (IZPH)

## Speaker

Prof. Dr. med. Hans Drexler

## Contact

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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). As a multidisciplinary research center, the primary objective of the IZPH 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 region Medical Valley EMN, 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 IZPH 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 1.3 million Euro. With its emphasis on Health Technology Assessment (HTA) and market access, health promotion and preventive medicine, and federal health monitoring, IZPH acts as the scientific platform for outcomes research at the FAU and as the main regional promoter.



*IZPH provides support to the Faculty of Medicine of the Cairo University to establish research infrastructure and capacity building in Health Technology Assessment (HTA). From left to right: S. Mosaad (research analyst of Healthcare Governance and Transparency Association, HeGTA), Dr. M. Hunter (CEO of HeGTA), Prof. Dr. Dr. h.c. J. Schüttler (Dean), Prof. T. Anis, (Vice-Dean for Research, Kasr Alainy Faculty of Medicine, Cairo University), Prof. Dr. P. Kolominsky-Rabas (IZPH) (photo: E. Malter)*

## 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” (compare own report).

# Interdisciplinary Center of Ophthalmic Preventive Medicine and Imaging (IZPI)

## Speakers

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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 Engineering" 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) was 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. Several peer-reviewed articles and a book chapter were published and two patents were accomplished. This project is finished.

(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). Several peer-reviewed articles were published.

## Projects funded within funding program of ZIM (the Central Innovation Program for small and medium-sized enterprises) by the Federal Ministry for Economic Affairs and Energy (BMWi)

Based on the results of the above mentioned project „Telemedical LowCost-Fundus Camera System“, new technologies for illumination, patient guidance, imaging, image processing and image qualification are used to realize a fundus camera for mass screening. Here methods are analyzed that allow a later transfer into a compact medical device.

## 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 PhD-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.

## 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 the degree program Medical Engineering, we offer the lectures "Biological and Technical Vision" and "Medical Applications of Photonics".

# Medical Immunology Campus Erlangen

## Speaker

Prof. Dr. med. Christian Bogdan

## Scientific Coordinator

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www.mice.uni-erlangen.de

## Aims and Structure

The Medical Immunology Campus Erlangen, an interdisciplinary center at the Faculty of Medicine, 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, departments, 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 (MPL) 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, plans to establish a new Master's degree program in immunology and coordinates the participation in competitive federal funding initiatives. Currently, the campus, in close cooperation with the Faculty of Sciences and the MPL, is focusing on an application for a Cluster of Excellence on the topic "Immunophysics" within the framework of the German Excellence Initiative. The scientific goal of the planned Excellence Cluster is to elucidate the biophysical and physicochemical factors that contribute to the development of chronic inflammatory diseases.

Three times a year, the Campus publishes a newsletter on exciting publications, honors, and awards of the Campus' almost 100 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 SFB together with an integrated GK which in its first phase will be funded by the DFG from Juli 2015 until June 2019 (SFB 1181 „Checkpoints for Resolution of Inflammation" and IRTG 1181, compare 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 Research Institute for Genetic Diseases in Paris (France), Prof. Dr. A. Fischer on December 1, 2015, and the directress of the Kennedy Institute at Oxford University (UK), Prof. Dr. F. Powrie, on November 8, 2016.

## Lectures

Scientists of the Medical Immunology Campus Erlangen organized the international conference „Infectious Disease Immunology Meets Molecular Microbiology" which took place at the Institute in April 2016. More than 100 scientists from eight different countries attended this conference. In 2015 and 2016, 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.

13.1.2015 D. Sancho, PhD, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid  
Novel aspects on Regulation of Th1 immunity by Dendritic cells

14.4.2015 Prof. M. Dustin, Kennedy Institute, Oxford  
Role of immunological synapse in T cell tolerance and priming

23.2.2015 Prof. S. Ghosh, Columbia University  
Regulation of NF- $\kappa$ B in inflammation and Immunity

12.5.2015 Prof. W. Strober, National Institute of Allergy and Infectious Diseases (NIAID), Bethesda  
The Role of E-Proteins in Th17 and Regulatory T cell induction

18.5.2015 Prof. B. Alarcón, Universidad Autónoma de Madrid  
Clustering, Conformational Changes and Cooperativity in the T-cell Receptor

9.6.2015 Prof. A. Macpherson, Gastroenterology & Mucosal Immunology, Bern  
When and where are our bodies influenced by our intestinal microbes?

30.6.2015 Prof. T. Decker, Max F. Perutz Laboratories, Wien  
From Cosmos to Chaos-interferon signaling gets messy

27.10.2015 Prof. A. Hidalgo, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid  
Functional interactions of neutrophils with the bone marrow

12.1.2016 F. Swirski, PhD, Harvard Medical School, Boston  
Growth factors link B cells with macrophages in inflammation and metabolism

3.5.2016 Prof. E. Pearce, Max-Planck-Institut für Immunbiologie und Epigenetik, Freiburg  
Metabolic reprogramming in innate immune cell activation

14.10.2016 Prof. J. Miller, Walter and Eliza Hall Institute of Medical Research, Parkville  
Thymus function revealed

18.10.2016 Prof. J. J. Lee, Mayo Clinic, Scottsdale  
Eosinophils in Health and Disease: Regulators of Local Tissue Immune Responses

25.10.2016 Prof. N. Harris, École polytechnique fédérale de Lausanne  
The multifaceted roles of B cells in helminth immunity

6.12.2016 Prof. P. Crocker, School of Life Sciences, University of Dundee  
Regulation of neutrophil and macrophage functions by the murine inhibitory lectin, Siglec-E

13.12.2016 Prof. N. Fasel, Center for Immunity and Infection, University of Lausanne  
Metastatic leishmaniasis



# Medical Technology Test and Application Center (METEAN) of the Fraunhofer Institute for Integrated Circuits IIS

## Speaker

Dipl.-Inf. Christian Weigand, Fraunhofer IIS

## Contact

PD Dr.-Ing. Thomas Wittenberg, Fraunhofer IIS

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## Research

Intention and main focus of METEAN, located at the Faculty of Medicine inside facilities of UK Erlangen, 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.

## Vital parameter study

PI: C. Sauter

A study for the measurement of vital parameters with subjects was conducted by METEAN. During the study, employees of METEAN undertook the tasks of study manager and study monitor and were responsible for the general set-up like the vote of the ethics committee and insurance. The study focused on the evaluation of wearables in comparison to medical reference devices during everyday life movements.

## MedTech Business Design Bootcamp

PI: N. Chrobok-Pensky

The goals of the annual MedTech Business Design Bootcamp are to elaborate a project idea in the field of medical engineering within a team and to gain feedback of experts, entrepreneurs and investors. In 2015, the experts of METEAN undertook the coaching concerning regulatory affairs and gave an insight into Medical Device Legislation.

## Med-Hackathon

PI: N. Chrobok-Pensky

A different approach to current challenges in medical engineering was chosen during the first Med-Hackathon. This event was hosted in the METEAN facilities in cooperation with the Department of Medicine 3, Spirit Link Medical and

the Medical Valley. For 24 hours, electronic engineers, programmers and doctors dedicated themselves to the measurement of physical activity of patients with inflammatory joint disease by using activity trackers. Within the focus of the event was the longtime data logging.

## Ambient assisted living

PI: N. Chrobok-Pensky

In several projects with care facilities, METEAN researches on useful application scenarios of available assistance devices and the consequent best possible combination of different application fields. Within the focus is checking the range of functions, safety and technical viability of new systems.

## INSYDE

PI: C. Sauter

The project develops a nursing bed with industrial partners and FAU that varies the distribution of pressure across the patient's body using sensors and actuators to prevent the development of pressure ulcers. METEAN is advising the project consortium on regulatory questions that arise during the development process, is training the consortium and providing it with standardized documentation tools.



*Distribution of pressure in various positions*

## Computer assisted microscopy

PI: PD Dr.-Ing. T. Wittenberg

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.

## Decision support systems

PI: PD Dr.-Ing. T. Wittenberg

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-funded 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. First promising tests in the clinic were performed with the developed software.

## Teaching

Employees of METEAN contribute to various lecture courses of the Faculties of Medicine and Engineering, e.g. the certificate of the Advanced Studies in Medical Device Law and hands-on-courses for students.

METEAN employees supervise Bachelor's and Master's theses as well as MD theses.



# Nikolaus-Fiebiger-Center of Molecular Medicine (NFZ)

## Speaker

Prof. Dr. med. Thomas Brabletz

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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 Oncology, respectively), the Division of Molecular Immunology, a division of the Chair of Genetics (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
- 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: Dr. P. Ceppi
  - Group 3: Prof. Dr. B. Winner (until 30 September 2016)
- Clinical research groups
  - Prof. Dr. A. Bozec (Department of Medicine 3 – Rheumatology and Immunology)
  - Prof. Dr. J. Winkler (Division of Molecular 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 (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. In August 2015, Dr. P. Ceppi started as a leader of the IZKF junior research group 2.

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.



# Translational Research Center (TRC)

## Speakers

Prof. Dr. med. Kai-Uwe Eckardt

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## Aims and Structure

In 2014 the Translational Research Center (TRC) with an exemplary concept and infrastructure was inaugurated at the Faculty of Medicine. 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. Important aims of the TRC are the dynamic development of present and the integration of new research areas especially in the framework of career development for younger scientists. An important structure component to achieve these tasks are the C modules. These laboratories are distributed between the modules of the core groups (A modules) which represent the main research focuses. C modules are allocated transiently and preferably to junior researchers

who are sponsored by external third party agencies in order to enable them an optimal connection to all instruments, equipment and expertise available in the TRC. In 2017, all existing C modules will be filled with research units from the Departments of Medicine 3 and 4, the Department of Surgery and the Institute of Radiology. Furthermore, a laboratory for pregnant women was established in order to provide separately from the multiuser concept of the TRC a laboratory where certain techniques can be carried out under strictly controlled conditions excluding exposure to harmful chemicals during the pregnancy. At the end of 2016, the staff of the TRC consisted of 135 employees from 15 different nations.

## Research

The TRC assembles research groups of the Departments of 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 expanded the methodological spectrum and allows for additional joint re-

search strategies. Another innovative, interdisciplinary approach includes the analysis of extracellular vesicles which function as intercellular communication units.

The high research quality of the TRC is documented by six research articles published in 2016 under the first and last authorship of TRC members in internationally high-ranking journals, such as Journal of Clinical Investigation, Nature Communications, Leukemia and Blood.



Photo: UK Erlangen

# Central Institute of Medical Engineering (ZiMT)

## Speaker

Prof. Dr. Björn Eskofier

## Executive Committee

Prof. Dr. Björn Eskofier

Prof. Dr. Ben Fabry

Prof. Dr. med. Dr. h.c. Jürgen Schüttler

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## Aims and Structure

Medical engineering is one of the scientific focuses of FAU and the Faculty of Medicine. More than 100 scientists, medical doctors and lecturers from the field of medical engineering are connected through the Central Institute of Medical Engineering (ZiMT). The core tasks of ZiMT include the coordination of the numerous cooperation partners' competences as well as enhancing the national and international visibility. ZiMT strengthens the medical engineering profile of FAU and UK Erlangen and improves the framework of the interdisciplinary collaboration in the diversified research area of medical engineering.

ZiMT is directed by an interdisciplinary executive committee, consisting of Prof. Dr. B. Eskofier (Faculty of Engineering), Prof. Dr. h.c. J. Schüttler (Faculty of Medicine) and Prof. Dr. B. Fabry (Faculty of Sciences). On an operative level, ZiMT is managed by the administrative office under the direction of Dr. S. Reiprich and T. Zobel.

## Research

ZiMT acts in close interaction with Medical Valley EMN (Nuremberg Metropolitan Region; compare own report) which has been assigned as German cluster of excellence in medical engineering. Within the internationalization of clusters of excellence - again funded by the BMBF - ZiMT and Medical Valley EMN e.V. reach out to Brazil, China and the USA. Another milestone for the regional research infrastructure in medical engineering is the participation in the consortium EIT Health: As part of the 8<sup>th</sup> European Union Research Program Horizon2020, the European Institute of Innovation and Tech-

nology (EIT) has extended its focus to "Healthy Living and Active Ageing". During the consortium's founding phase, ZiMT has been representing the interests of FAU, UK Erlangen and Medical Valley EMN e.V. in numerous Europe-wide work groups. Thanks to this initiative, FAU has established itself as a core partner of EIT Health and is eligible for all comprehensive EIT Health funding measures. ZiMT represents FAU and UK Erlangen in projects and applications for EIT Health as a representative and offers advisory services and networking platforms.

By distributing about 80 millions Euro worth of funding over the next seven to 15 years, the European consortium aims to establish excellent medical engineering research networks, support creative entrepreneurship, develop joint innovations for healthy living and active aging, and therefore providing opportunities for European citizens for more health, improved well-being and higher quality of life.

With a total venture volume of more than two billions Euro, of which up to 700 millions Euro are intended for funding purposes, EIT Health is one of the largest publicly funded initiatives in the field of healthcare worldwide.

## Teaching

At FAU, the relevance of medical engineering as a scientific focus is not only visible in the research sector, but also in the educational sector. The Bachelor and Master degree programs Medical Engineering have received very high numbers of applications from the very beginning and have a steady enrollment of 700 - 800 students, establishing itself as one of the largest degree programs at the Faculty of Engineering. The constantly high amount of enrolled students and the goal of keeping the percentage of students dropping out as low as possible were the reasons for the introduction of qualification assessment processes. Despite the elevated workload, this procedure enables ZiMT to offer a valuable individual advisory service before the start of a degree 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 Bachelor's degree program of Medical Engineering. Another outstanding feature about the Medical Engineering degree program is the high percentage of female students with more than 50 %. Until today, no other engineering degree program has reached those figures.

The Master's degree program Medical Engineering was established in the winter term 2011/2012 and offers three different specialization possibilities: Medical Electronics (focus on electrical engineering), Medical Imaging and Data Processing (focus on computer sciences), and Medical Production Technology, Device Engineering and Prosthetics (focus on mechanical engineering/ material sciences).

The Central Institute of Medical Engineering offers separate lectures and seminars and therefore provides an early interfaculty exchange for students. Offers like the Innovation Research Lab (IRL), which is funded by Siemens Innovation Think Tank, the colloquium for research and industry and various other seminars allow the Medical Engineering students to realize their own ideas at an early stage and analyze their topics considering entrepreneurial aspects. One of our most innovative teaching concepts is the Scientific Speed-Dating that is directed towards projects with participants from the fields of medicine and engineering.



# Collaborative Research Center 643: Strategies of Cellular Immune Intervention

## Speaker

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## Aims and Structure

The DFG-funded SFB 643 "Strategies of cellular immune intervention" was started in July 2004 and ended after the third successful funding period in June 2016. The goal of the SFB 643 was the successful implementation of immunological knowledge into treatments that are based on the manipulation of the immune system, i.e. on immune intervention. Immunotherapeutic 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 was 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 investigated 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 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 aims to translate the concept of in vivo "antigen targeting" of dendritic cells (DC) into the human system. Thereby, the work focused on the production of antigen-conjugated antibodies targeting DC to analyze T cell responses in tissue culture and the characterization of DC in human tissues. These data are 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 (antibody-dependent cellular cytotoxicity) 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 studied 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 explored 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 was investigated using murine T cells. The functional role of IL-28/IL-29 for the immunopathogenesis of colitis and colitis-associated colon carcinoma was characterized in vivo using murine models.
- PD Dr. B. Schuler-Thurner, PD Dr. N. Schaft, Dr. J. Dörrie, and Prof. Dr. G. Schuler aim to develop new and innovative immunotherapies based on DC especially for the treatment of patients with cancer (melanoma as a prime model). Several clinical phase I and II-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 tumor-reactive T cells and homing to the tumor. Several strategies have been 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 last funding period the adoptive transfer of CMV/EBV-multi-epitopespecific T cells was 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 performed within the last funding period.



# Collaborative Research Center 796: Reprogramming of Host Cells by Microbial Effectors

## Speaker

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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 interfaculty 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.

# Collaborative Research Center 1181: Checkpoints for Resolution of Inflammation

## Speaker

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## Aims and Structure

The SFB 1181 “Checkpoints for Resolution of Inflammation” has been established in July 1, 2015 by the DFG. The SFB 1181 aims to investigate the molecular mechanisms involved in the resolution of inflammation. The DFG supports the SFB 1181 with more than 13 million Euro within four years. The SFB consists of 19 preclinical subprojects, a central imaging project and an integrated research training group. The main focus is on the resolution of inflammation that fails in chronic inflammatory diseases such as arthritis, Crohn’s disease and asthma. Furthermore, a central objective is the rapid translation to clinical applications in order to develop therapeutic strategies to resolve inflammation as well as to rehabilitate immune and tissue homeostasis. The working groups investigate three cellular checkpoints which might be essential for resolution of inflammation:

- The switch from pro- to anti-inflammatory cytokine response,
- The blockade of pro-inflammatory lymphocyte activation and
- Fostering of tissue remodeling by cell death and tissue repair mechanisms.

## Research

A central task of the immune system is the initiation and control of inflammatory responses to contain and therefore prevent organ damage. This process requires a functioning immune system to resolve inflammation after hazards have been eliminated, allowing tissue repair to commence. However, chronic inflammatory diseases often arise from dysregulation of inflammatory processes. It can be assumed that a sequence of linked switches is responsible to regulate the inflammation process. It is established that neutrophil granulocytes dominate early stage of inflammation, whereas macrophages and other granulocytes, especially eosinophils, characterize the phase of resolution. The SFB 1181 will identify and decipher potential molecular dysregulations and checkpoints which are responsible for failure of the resolution of inflammation. So far, scientists of the SFB

1181 already discovered molecular processes leading to a switch from pro- to anti-inflammatory cytokines, regulating the fate to either resolution of inflammation or its chronification.

The groups around Prof. Dr. G. Schett and Prof. Dr. A. Bozec in cooperation with PD Dr. S. Wirtz observed how high-fat diet leads to specific alterations in the bacterial flora of the gut. They described how these alterations activate the metabolic checkpoint molecule PPAR- $\gamma$  leading to an increased production of adipose tissue in the bone marrow and displace the stem cell and bone marrow niche. Prof. Dr. A. Bozec together with the team of Prof. Dr. D. Vöhringer were able to provide evidence that helminth infections lead to an increase of TH2-cells and eosinophils in the synovial fluid of patients with rheumatoid arthritis which in turn blocks chronic inflammation. Astonishingly, here, the immune response responsible to repel worm infections is also able to resolve chronic inflammation like arthritis.

Chronic inflammatory diseases are characterized by a constantly active adaptive immune system and recruitment of B-cells, T-cells and others during the course of the inflammatory response. Often observed is the pro-inflammatory activation of these lymphocytes before the chronification of a disease like rheumatoid arthritis. If this sequence of pathological incidences occurs in Crohn’s disease or ulcerative colitis is not known so far. Crohn’s disease and ulcerative colitis are both inflammatory bowel diseases (IBD), but are well-defined, e.g. via disease characteristic cytokine profiles. The group of Prof. Dr. M. Neurath and Dr. B. Weigmann identified the regulation of transcription factor GATA3 via specific blockade with DNazymes as a novel therapy concept in ulcerative colitis. Why an inadequate immune response is present in CED deciphers the group around Prof. Dr. A. Steinkasserer. Murine Arthritis models showed promising results that sCD83 decreases and/or inhibits inflammatory responses. Thereby, the group focuses on the role of Indoleamine 2,3-Dioxygenase (IDO) and transforming growth factor beta (TGF-beta) in resolution of inflammatory processes.

It can be expected that an important checkpoint deciding chronification or resolution of inflammation is the remodeling of tissue, cell death and tissue repair mechanisms occurring at the side of inflammation. Tissue generation is a crucial process in the body. However, due to dysfunction tissue formation persists in fibrosis diseases. The team of Prof. Dr. J. Distler discovered a new mechanism which is responsible for ongoing activation of renewal processes. They proved that it is able to reactivate the receptor Nr4a1 pharmacologically which inhibits TGF-beta leading to a block of excessive activation of fibrocytes. So it can counteract to excessive production or disturbed tissue necrosis

of extracellular necrosis by fibrosis diseases. Extracellular matrix formation is a certain cell function of neutrophils, so called neutrophil extracellular traps (NET). The groups of Prof. Dr. Dr. M. Herrmann and Dr. M. Hoffmann were able to demonstrate the size dependent induction of NETosis with inert, non-polar nanoparticles – like nanodiamonds or uric acid crystals – in acute gout attacks. This process not only leads to the immobilization of uric acid crystals in gout, but induces the resolution of the originally inflammatory response. A previously unknown type of regulated necrosis in the liver could be described by the team of Prof. Dr. C. Becker. Here, they provided evidence that cytotoxic activity of the pro-inflammatory cytokine IFN- $\gamma$  is closely connected with expression of MLLKL. Together, these proteins regulate necrosis independently of the RIPK3 receptor. Cytokines play an important role in all phases of inflammation: The teams of PD Dr. C. Neufert and Prof. Dr. R. Atreya deciphered differently expressed levels of IL-36R and its upregulation in IBD. Their study describes how the IL-36R signaling pathway is activated upon damage which leads to IEC and fibroblast stimulation. This in turn is part of the wound healing of the gut mucosa and therefore an efficient resolution of acute gastro-intestinal inflammation.

Our previous results indicate that defects at the described checkpoints are pivotal for failure of resolution of inflammation. These findings are just a small excerpt of more than 30 recent publications since the founding of the SFB 1181.

## Teaching

The heads of the research groups are involved in the traditional teaching program (lectures, seminars, practica) covering all subjects in the field of medicine and molecular medicine as well as in the PhD/MD programs for basic and translational research. The integrated research training group 1181 (IRTG 1181; compare own report) is affiliated to the SFB 1181.



# 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 that has been funded by the DFG for the first funding period of three years with a total volume of 6.8 million Euro. At the beginning of 2013, SPP 1468 – IMMUNOBONE has been positively evaluated for a second funding period for additional three years with a total volume of 7.1 million Euro. 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- $\kappa$ 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. Some significant results of the project groups in Erlangen can be highlighted as follows: The findings of the different projects prove a close interaction between immune-, bone- and

metabolic system. A connection between unhealthy nutrition and damage of the immune system was shown. This group identified that high-fat diet leads to specific alterations in the bacterial flora of the gut. They described how these alterations activate the metabolic checkpoint molecule PPAR- $\gamma$ , leading to an increased production of adipose tissue in the bone marrow and displace the stem cell and bone marrow niche. It is known that if adipocytes store energy, this leads to inflammation and subsequent damage or destruction of joints and bones.

A group in Erlangen revealed that lack of sialic acid in the glycosylation of immunoglobulin G in synovial fluids of patients with rheumatoid arthritis (RA) leads to an activation of osteoclast formation. Therefore, IgG complexes are a key component of inflammatory bone loss. This mechanism is directly involved in the induction of an autoimmune disease – rheumatoid arthritis – and was recently described in more detail. The lack of sialic acid in the glycosylation of proteins involved in RA induction seemed to be the key element. The group was able to show the direct involvement of TH17 cells on the immunologic memory that - by a simple variation of the glycosylation structure of autoantibodies - led to the provocation of RA.

In all inflammatory and renewal processes immune cells interact with pathogens and endogenous cells. An IMMUNOBONE group discovered a new mechanism which is responsible for ongoing activation of renewal processes. They were able to reactivate the receptor Nr4a1 pharmacologically which inhibits TGF-beta leading to a block of excessive activation of fibrocytes. This reactivation can counteract excessive production or disturbed tissue necrosis of extracellular necrosis in fibrotic diseases. Neutrophil extracellular trap (NET) formation is a cell function of neutrophils. One of our groups was able to demonstrate the size dependent induction of NETosis with inert, non-polar nanoparticles – like nanodiamonds or uric acid crystals, with the latter appearing in acute gout attacks. This process not only leads to the immobilization of uric acid crystals in gout, but induces the resolution of the originally inflammatory response.

All these 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 90 scientific articles published within SPP 1468 – IMMUNOBONE.

## Teaching

The heads of the research groups are involved in the traditional teaching program (lectures, seminars, internships) covering all subjects in the field of medicine and molecular medicine as well as in the PhD/MD programs for basic and translational research.



# BMBF Leading Edge Cluster: Center of Excellence for Medical Engineering – Medical Valley EMN e.V.

## Speaker

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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 January 26, 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. 45 projects were funded until the end of 2015. In total there is a German wide potential for reduction in health expenditure of more than Euro 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 Euro 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. In the frame of the BMBF funding program "Internationalization of leading edge clusters, future projects and similar networks", Medical Valley secured follow-up funding for the leading edge program which terminated in 2015. Since the beginning of 2016, this funding has helped to develop strategic international partnerships with the regions Greater Boston/Connecticut (USA), Hongkong (China) and Rio Grande do Sul (Brazil). As of 2017, selected transnational research and development projects will be funded.

## 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 project "Home monitoring of patients with cardiac insufficiency to avoid decompensation and reduce hospitalization rates" of the Department of Medicine 2 is associated with this core research area.

### 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.

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# BMBF MI-I: MIRACUM

## Speaker

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## Aims and Structure

The MIRACUM Consortium (Medical Informatics in Research and Care in University Medicine) was funded for the nine month conceptual phase of the Medical Informatics Funding Scheme of the German Federal Ministry of Research and Education (August 2016 to April 2017). Based on its successful pilot projects and its compelling and visionary concept, it will be funded with an amount of 32.1 million Euro for the four-year implementation and networking phase from 2018 onwards as well. Prof. Dr. H.-U. Prokosch (Chair of Medical Informatics) is responsible for the coordination of the consortium. Prof. Dr. Dr. h.c. J. Schüttler, Dean of the Faculty of Medicine, is the co-investigator for the Faculty of Medicine and UK Erlangen. MIRACUM: This is eight universities with university hospitals (Erlangen, Frankfurt, Freiburg, Gießen, Magdeburg, Mainz, Mannheim and Marburg), two universities of applied sciences (Hochschule Mannheim (University of Applied Sciences) and THM University of Applied Sciences) and Averbis (Freiburg), the industrial partner of the consortium.

The aim of the project is to make data from numerous heterogeneous IT systems and databases in patient care and medical research accessible for innovative IT solutions and to support translational research as well as diagnostic and therapeutic decisions in health care processes. Together with the Medical Information and Communication Center of the UK Erlangen, the Chair of Medical Informatics will establish the Erlangen Data Integration Center and provide means for integrating this local data integration center into a consortium-wide and federated cross-hospital network that supports various aspects of data sharing.

## Research

The establishment of data integration centers and their federated application in various research scenarios is based on an ecosystem of modular and reusable open source IT tools which will be developed and adapted by the

MIRACUM competence centers at the sites of the respective partners and which will stepwise be integrated into the eight MIRACUM data integration centers. The data flow (strictly adhering to data protection regulations and the patient's consent) originates from the routine IT systems of a university hospital and typically requires data harmonization and the mapping to a jointly defined common data model to then result in a data integration step that comprises various types of research data repositories. The concept of data sharing is based on both a strictly federated approach and the philosophy to „Bring the analysis to the data“. First exemplary analyses with data items of the German core data set (patient demographics, encounters, diagnosis and procedures) have already been pursued on this basis.

In the four years to come MIRACUM will focus on the following three use cases:

1. Alerting in care – IT support for patient recruitment,
2. From data to knowledge – a predictive clinico-molecular knowledge tool,
3. From knowledge to action – support for molecular tumor boards.

Especially for the third use case first pilot projects have already been initiated during the conceptual phase and the respective results have led to joint consortium publications in international journals. We first analyzed the processes and the IT status in the context of molecular/genomic high-throughput analyses as well as the use and the visualization of such results in the molecular tumor boards of all MIRACUM hospitals. The respective structures and processes in our eight hospitals vary widely, but

they have two things in common: The presentation and visualization of data still requires many cumbersome manual steps and data is typically stored in a narrative and unstructured text format. This provides room for improvement that shall be realized by developing and introducing innovative and user-friendly IT tools. In order to define a comprehensive and visionary concept for our work in the development/networking phase we also analyzed the experiences and the attitudes of more than 500 clinicians towards using clinical decision support tools for molecularly-guided therapy decisions in all MIRACUM hospitals. Finally yet importantly, a systematic literature review was pursued in order to learn from developments, applications and experiences of other international research groups.

## Teaching

MIRACUM is also working on the improvement of both education and the advanced training of Biomedical Informatics for clinicians, basic scientists, researchers in medical informatics and computer scientists. To this end first online courses and webinars have been designed and regular online tutorials have been established for members of the MIRACUM team. In the upcoming funding phase MIRACUM aims at establishing the cross-university part-time master program „Biomedical Informatics und Medical Data Science“.



# BMBF-Research Network Musculoskeletal Disorders: METARTHROS – metabolic impact on joint and bone diseases

## Speaker

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## Aims and Structure

METARTHROS is one of nine national consortium projects in the course of the BMBF research network “Musculoskeletal diseases”, investigating clinically relevant key factors in the interaction between inflammation and metabolic diseases. The consortium has been funded by the BMBF for a period of 3,5 years with 4,1 million euros. It aims the definition of pathophysiological processes and the clinical impact of disturbed glucose and energy homeostasis, such as obesity and diabetes on arthritis. METARTHROS consists of eight subprojects and one clinical trial, represented by a strongly interdisciplinary consortium of rheumatologists, diabetologists, epidemiologists, geneticists, imaging physicists, and orthopedics, bridging translational, clinical and health care sciences in the field of arthritis. Furthermore, the consortium combines aspects of medical care, translational and clinical research in the field of arthritis. Due to the cooperation of eight different centers, including the German Diabetes Center Düsseldorf (DDZ) and the German Rheumatism Research Centre Berlin (DRFZ), the consortium disposes of well-characterized patient cohorts, biobanks as well as a range of technical skills, reaching from disease modeling, outcome, research and trial design.

## Research

The main focus of the METARTHROS consortium is the evaluation of the interplay of different molecular mechanisms and factors which are responsible for the development and progress of musculoskeletal disorders and connected to metabolic diseases. It is not known how glucose metabolism affects mechanistically musculoskeletal diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (PsA) and osteoarthritis (OA). Thereby, regulation of inflammation mediated by the adipose tissue might be a key factor affecting the joint-bone-unit.

Preliminary results of prior collaboration „A Network on Clinics and Pathophysiology of Osteophytes and Ankylosis“ (ANCYLOSS) have shown that diabetes is an independent predictor for severe joint diseases. Furthermore, we were able to investigate adipokines – pro-inflammatory mediators originating in adipose tissue – and could show that they are tightly connected to joint inflammation and bone architecture. Diabetes is associated to severe osteoarthritis that could lead to endoprosthetic surgeries. Thus, it seems that arthritis, overweight and diabetes form an alliance, affecting joint- and bone structures destructively. Hallmarks of RA and diabetes include the detection of an increase of markers of inflammation before the actual onset of the disease which indicates subclinical inflammation as a common mechanism. In particular, resistance against insulin is intensified in inflammation. Intriguingly, resistance against insulin is not only present in patients with RA, but observed early in the course of the disease.

The METARTHROS subprojects (TP) 1-3 are investigating pathophysiological aspects that are clinically relevant in arthritis and energy metabolism. TP 4-6 are developing instruments and methods in regard to genetic, serological factors and imaging modalities in order to observe the impact of metabolism on musculoskeletal disorders. TP 7 and 8 analyze the effects of diabetes and overweight on the clinical presentation, changes in bone structure as well as the therapeutic response of patients with arthritis. Additionally, the importance of musculoskeletal diseases in patients with diabetes will be defined. All results will be incorporated into the clinical study in order to establish a strategy for intervention that aims to limit inflammation and improves the resistance against insulin.

Experimental studies revealed a molecular mechanism that substantiates the close alliance of adiposity, resistance against insulin and inflammation. Here, high fat diet led to a specific alteration in the microbacterial flora of the gut. This alteration induced the activation of the peroxisome proliferator-activated receptor PPAR- $\gamma$  which plays an important role in bone formation. It was shown that there was an increase in adipose tissue in the bone marrow replacing stem- and immune cell niches. Another group was able to detect the release of adiponectin from cells involved in the bone reconstruction in arthritic bone tissue. Adiponectin changes the gene expression and cytokine release in osteoblasts and elevates the IL-8 release in osteoclasts. These results support the pro-inflammatory role of adiponectin and indicate that adi-

ponectin is influencing bone remodeling in RA via osteoblasts and osteoclasts.

Analysis of synovial fluids of patients with RA revealed that lack of sialic acid in glycosylation of immunoglobulin G leads to an activation of osteoclast formation. Therefore, IgG complexes are a key component of inflammatory bone loss. This mechanism is directly involved in the induction of an autoimmune disease – as e.g. rheumatoid arthritis – and was recently described in more detail. The lack of sialic acid in the glycosylation of proteins involved in RA induction seemed to be the key element. The group was able to show the direct involvement of TH17 cells on the immunologic memory that by a simple variation of the glycosylation structure of autoantibodies led to the provocation of RA.

The above mentioned findings are an overview of the more than 20 publications of the METARTHROS consortium.

## Teaching

The heads of the research groups are involved in the traditional teaching program (lectures, seminars, practica) covering all subjects in the field of medicine and molecular medicine as well as in the PhD/MD programs for basic and translational research.



# 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 its 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 (iPSC) of Parkinson's disease patients and healthy controls at 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 iPSC 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 an ideal 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 novel treatment strategies.

## Research

The Bavarian Research Network ForIPS focuses on the most prevalent neurodegenerative movement disorders of Western industrial countries, the sporadic PD, first described by James Parkinson in 1817. This disorder is characterized by specific motor deficits, such as bradykinesia, rigidity, resting tremor, and postural instability. Throughout the disease course, in particular, however, in the premotor stage, non-motor symptoms such as hyposmia, autonomic dys-

function, disturbed gut mobility, and cognitive deficits are observed. The goal of the ForIPS network is, based on PD-derived cells, to characterize the molecular and cellular mechanisms which are crucial for the etiology of the disease. To this aim, ForIPS provides the individual projects with primary skin fibroblasts or with iPSC. The projects, headed by Prof. Dr. A. Reis (Institute of Human Genetics) and Prof. Dr. M. J. Riemenschneider (UK Regensburg), are analyzing the genetic and epigenetic stability and alteration of iPSC 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 (Chair of Animal Physiology, Faculty of Sciences), Prof. Dr. J. Winkler, Division of Molecular Neurology), on intracellular organelles such as mitochondria (Dr. D. Vogt-Weisenhorn, Prof. Dr. W. Wurst, TU Munich), on intraneuronal mechanisms such as autophagy (Prof. Dr. J. Klucken (Division of Molecular Neurology), Prof. Dr. D.C. Lie, Professorship of Molecular Medicine with focus on Molecular Imaging) 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 (Chair of Biochemistry and Pathobiochemistry) 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 PD. The functional assessment of astrocytes, underlying specific Parkinson-associated neurodegenerative processes, will be examined by Prof. Dr. M. Götz (LMU Munich). 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 (Division of Stem Cell Biology), 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 PD. 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 UK Erlangen. Novel technologies in life sciences such as the iPSC-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, Faculty of Humanities, Social Sciences, and Theology).

## Teaching

The research network ForIPS, coordinated by Dr. R. Lederer together with J. Burczyk-Schuster (Division of Molecular Neurology), 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 UK Erlangen, the participating scientists are enabled to learn the technology of human iPSC, thus standardizing the cell culture models and transferring this technology to all other Bavarian sites. In addition, two PhD seminars with different topics in stem cell biology and neurodegeneration took place in 2014. In July 2015, an international symposium was held at the Carl-Friedrich-von-Siemens-Foundation (Munich) with numerous outstanding national and international speakers. A public hearing with the topic "Human biobanking for stem cell research" attracted a large audience at the FAU in October 2016.



# Bavarian Research Alliance – Research collaboration: Biomarkers in the fight against infectious diseases (ForBIMed)

## Speaker

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[www.bayfor.org/en/portfolio/research-cooperations/world-of-living/forbimed.html](http://www.bayfor.org/en/portfolio/research-cooperations/world-of-living/forbimed.html)

## Aims and Structure

This research collaboration between universities and companies was funded by the Bavarian Research Alliance from October 2013 until January 2017. The major aim of ForBIMed was the establishment of new, pathogen- and host-specific biomarkers that can serve as a basis for new diagnostics, therapeutics and vaccination strategies. Within this research network the participating universities and companies intensified their collaborative efforts in the field of infectious diseases and thus strengthened the Bio-tech-environment in Bavaria. From the Faculty of Medicine, Prof. Dr. M. Marschall (Institute of Clinical and Molecular Virology) and Prof. Dr. A. Steinkasserer (Division of Immune Modulation) participated as project leaders within this network.

## Research

The subproject of Prof. Dr. M. Marschall focused on the identification of key positions in the virus-specific cellular signaling (VSS) as a marker of therapy, immunity and diagnostics. Within the three year research consortium, new knowledge could be gained in several areas of this project:

1. VSS patterns of cellular signaling were determined for in vitro infections with various herpesviruses and, as a consequence, virus-specific biomarkers were thereby deduced as possible targets of antiviral therapy.
2. VSS kinases of the group DYRK were validated as suitable antiviral target molecules.
3. DYRK inhibitors were nominated as hits in antiviral efficacy and were optimized by means of medicinal chemistry.
4. Additional putative therapy targets, also derived from VSS screenings, were analyzed and further prepared for target-fishing experiments by the generation of linker-coupled compound derivatives.

iments by the generation of linker-coupled compound derivatives.

5. Moreover, new insights were obtained for IFI16, a restriction factor of the intrinsic HCMV immune defense.

6. Finally, interesting preliminary data were obtained on the level of protein expression patterns analyzed in first clinical samples (PBMC isolated under active Epstein-Barr virus infection) in order to identify VSS biomarkers possibly correlating with the pathogenesis of herpesviral infections.

The research project headed by Prof. Dr. A. Steinkasserer focused on the characterization of immunologic biomarkers for the development of new antiviral therapies against HSV-1 infections. Using an in vitro screening system developed by us, in total 60 compounds have been analyzed. Out of these 60 compounds, 13 potentially inhibited viral replication when tested in permissive cell line as well as primary Dendritic Cells (DC). In order to further propagate these compounds for possible clinical use, it is an absolute prerequisite to make sure that they do not interfere with the immune system of the host. Thus, these 13 compounds were further analyzed regarding their influence on DC-phenotype as well their maturation status and their T cell stimulatory capacity. Finally, four compounds have been identified which potentially inhibit viral replication, but did not interfere with DC-maturation and/or their T cell stimulatory function. Thus, these compounds represented very interesting lead candidates for further development. Individual ones have already been tested in PK studies in mice and rats, showing a very good bioavailability profile. Furthermore, after oral application, the reached plasma levels could guarantee a pharmacological efficacy in animal studies. In addition, we showed that one specific compound not only inhibits HSV-1, but - even more important - also neutralizes Acyclovir as well as multi-resistant HSV-1- and HSV-2-isolates derived from patients. Due to these very encouraging results we are currently planning first in vivo studies to further propagate this approach.

## Teaching

The research activities within the ForBIMed network efficiently contributed to the successful development of Bachelor's, Master's and PhD theses projects.





# Bavarian Immunotherapy Network (BayImmuNet): Adoptive Immunotherapy

## Speaker

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www.bayimmunet.de

## 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 Euro, 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 building housing the Center for Internal Medicine (INZ) provides clean-rooms within the Department of Medicine 5 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 principal investigators of BayImmuNet are involved in the teaching program (lectures, seminars, practica) covering all subjects in the field of medicine and molecular medicine. They are also involved in the PhD and MD program for basic and translational research.

# EIT Health

## Speaker

Prof. Dr. med. Dr. h.c. Jürgen Schüttler  
(supervisory board member of the German CLC)  
Dr. rer. nat. Simone Reiprich  
(institutional coordinator and FAU delegate to the partner assembly)

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## Aims and Structure

Created in 2008, the European Institute of Innovation and Technology (EIT) is a unique EU initiative that spurs innovation and entrepreneurship across Europe. Since December 9, 2014, EIT Health is one of six "Knowledge and Innovation Communities" through which EIT addresses societal challenges in different areas of life.

The goal of EIT Health is to contribute to increasing the competitiveness of European industry as well as improving the quality of life of Europe's citizens and the sustainability of healthcare systems. The partnership will promote entrepreneurship and develop innovations in healthy living and active ageing, providing Europe with new opportunities and resources. This will be achieved through delivering products, concepts and services, including educational programs that will nurture talents and train the workforce of tomorrow. EIT Health will overcome the fragmentation of different healthcare systems in Europe and give companies easier access to markets across the EU. The critical mass of partners from business and industry, education, research, healthcare providers and insurance companies within EIT Health opens the path to reduced time-to-market for added-value products and services.

EIT Health consists of more than 50 core partners from leading businesses, research centers and universities from across 14 EU countries. EIT Health has formed six Co-location Centers across Europe (UK/Ireland, Scandinavia, Spain, France, Germany, Belgium/The Netherlands), with headquarters based in Munich. EIT Health also includes 92 associate partners and six

"InnoStars" regions in Wales, Portugal, Poland, Hungary, Italy, and Croatia. FAU and Siemens Healthcare are full members of EIT Health. Medical Valley EMN e.V. and Fraunhofer IIS are associated partners.

Adopting an investor approach, EIT Health is driving the integration of business, research and higher education, boosts innovation, and is a catalyst for new solutions for Europe. EIT Health offers its members additional or follow-up funding of up to 25% for ongoing projects in the pillars "Projects" (research and technology, product or process development), "Accelerator" (services and support for nascent entrepreneurs and young companies) and "Campus" (entrepreneurship education and innovation training for students, researchers and healthcare professionals). All projects and programs address the three overarching themes of the network: promote healthy living, support active ageing and improve healthcare.

## Research

P3 Stroke is the first project funded by EIT Health at FAU. In P3 Stroke, the Division of Neuroradiology, Siemens Healthineers, the Department of Pattern Recognition (Faculty of Engineering) and other European collaborators (University Leuven, University Bordeaux, University Coimbra) develop, implement and validate an integrated hybrid Angio-MRI system. This will improve predictive prevention and personalized interventional acute stroke therapy, resulting in lower healthcare and socioeconomic costs and a unique selling proposition with new business opportunities. Funding of P3-Stroke within EIT was approved 2016 with an estimated funding period of five years and an annual volume of one million euros.

Stroke is a leading cause of mortality and morbidity worldwide and the leading cause of severe long-term disability, making it a major cost factor in European healthcare systems. Currently, a patient with a suspected stroke receives an initial diagnosis using CT or MRI. Subsequently, the patient is transferred to the interventional unit or angiography suite (gold standard). However, since "time is brain" (the average stroke patient loses up to two million neurons per minute), any possible delays in stroke management should be minimized. Promising approaches are improved imaging-based patient selection, intra-interventional imaging and therapy monitoring as well as speeding-up and optimizing the clinical work-flow. To address this clinical need, the international, cross-sec-

toral and interdisciplinary P3 Stroke consortium will develop a unique integrated hybrid Angio-MRI system by combining state-of-the art MR imaging with interventional flat-panel angiography. Instead of the current workflow, selected stroke patients could be directly referred to the new integrated hybrid Angio-MRI system. This high-end "one-stop shop" stroke machine would dramatically speed up acute stroke management: Initial results indicate time savings of up to one hour, resulting in significant smaller infarction volumes and better outcomes. At the same time, the technology can help prevent strokes by supporting interventional therapy of one of its major risk factors, cardiac arrhythmias. Thanks to the translational approach and consortium, the concept can immediately be tested in a clinical setting and transferred to other areas, like cardiovascular diseases at a later stage of the project with the support of the University of Bordeaux, among others.

Further projects have been initiated within EIT Health. For example, the Department of Urology successfully applied for funding for 2017 as part of a Swedish-led consortium. In the funded study, a new application for individualized prostate cancer risk, the STHLM3 Risk Score application, will be introduced, assessed and refined.

## Teaching

The Central Institute of Medical Engineering (ZiMT; compare own report) co-organized a summer school in Dublin and Barcelona in 2016. Thirty-six students from all over Europe received entrepreneurship training, covering aspects such as idea generation, design thinking, business plan development, project management and financing etc.



# German Chronic Kidney Disease (GCKD-Study): National Cohort Study on Chronic Kidney Disease

## Speaker

Prof. Dr. med. Kai-Uwe Eckardt

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## Aims and Structure

Chronic kidney disease is an increasing health problem, affecting more than 10% of the population. Chronic kidney disease can progress to end stage renal disease with requirement for dialysis or transplantation. Patients suffering from chronic kidney disease also have a disproportionate risk of cardiovascular diseases including myocardial infarction and stroke.

However, the loss of kidney function and the development of cardiovascular disease in the setting of renal disease are highly variable. Factors determining progression and complication rates are to a large extent unknown.

The number of randomized controlled trials in nephrology lags behind all other medical disciplines. This is partly due to the fact that the knowledge about the natural course of chronic kidney disease is limited.

To address this problem, the FAU is coordinating a large prospective observational cohort study in Germany together with the universities of Aachen, Berlin, Freiburg, Hannover, Heidelberg, Innsbruck, Jena, München, Regensburg, and Würzburg and a network of approximately 150 nephrologists from different regions all over Germany.

The study aims at gaining important insights on the heterogeneity of disease courses by 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 for 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 enrolled between 2010 and

2012 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 other bioanalytical approaches 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 and progression. It will also provide novel insights to the question why patients with kidney disease have a tremendously increased risk of cardiovascular diseases.

Another research focus of the GCKD study 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 hopefully help to improve the overall prognosis, and to postpone or avoid onset of dialysis.



The map shows all centers involved in the multicentric study.

GEFÖRDERT VOM



Bundesministerium  
für Bildung  
und Forschung

# Horizon 2020: CloSed

## Sprecher

Prof. Dr. rer. nat. Antje Neubert

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## Aims and Structure

Most critically ill children admitted to Paediatric Intensive Care Units (PICU) require potent analgesic and sedative drugs to facilitate treatments and recovery, but also to reduce anxiety and distress. To date, this is commonly achieved by combining benzodiazepines and opioids, such as midazolam plus morphine. The sedative drug midazolam is already authorized for these purposes, but causes significant adverse reactions, such as withdrawal symptoms or respiratory depression.

A promising alternative could be the treatment with clonidine, a drug used throughout the EU and the USA as a centrally acting hypotensive agent and a treatment for migraines (in adults only). Despite this drug already being recommended for the treatment of children by guidelines in various countries, the optimal dose requirements, the safety of clonidine and its efficacy when used for sedation in PICU have not been fully studied in pediatrics.

For this reason clonidine was included in the European Medicines Agency – Paediatric Committee's (EMA-PDCO) priority list of off-patent medicines for which further clinical development are urgently needed.

The project CloSed (Clonidine for Sedation of Paediatric Patients in Paediatric Intensive Care Units) has been funded by the European Commission to generate data on the pharmaceutical quality, safety and efficacy of clonidine and to obtain a license in the pediatric population. It has commenced in December 2013 and has a duration of five years. Overall the project is being funded with 6 mio Euro of which 1,3 mio Euro are foreseen for UK Erlangen.

The CloSed consortium comprises ten European partners (five clinical centers, one non-profit foundation, one patient organization, one industry partner and two scientific partners) from seven different countries: Czech Republic, Estonia, Germany, Italy, Sweden, The Netherlands and United Kingdom (compare list). The con-

sortium brings together a group of clinicians, pharmacologists and researchers representing a highly skilled, multi-national, interdisciplinary team with a wide range of expertise all focused on developing appropriate medicines for children.

The Department of Pediatric and Adolescent Medicine is the coordinator of the project and responsible for the scientific conduct and the reporting towards the European commission. In addition, the pharmacy of UK Erlangen is manufacturing the study drug; the Center for Clinical Studies is responsible for all pharmacovigilance activities and provides guidance in various aspects for the conduct of a multicenter clinical trial.

## Research

The heart of the project is the conduct of a double-blind, randomized, multicenter clinical trial to compare intravenous clonidine with midazolam for sedation in critically ill children until the age of 18. All research will be conducted in line with the ethical requirements in the pediatric population, considering risk minimization for patients and avoiding unnecessary studies. There are four foci of our research:

1. Develop an age-appropriate intravenous clonidine formulation at three different strengths in order to accurately administer the drug based on dose per volume and patient weight;
2. Generate safety and efficacy data on clonidine in children and adolescents from birth to <18 years;
3. Use the project results to apply for a Paediatric Use Marketing Authorization (PUMA);
4. Develop guidelines for sedation of critically ill newborns and children in PICU within the European Society of Paediatric Neonatal Intensive Care (ESPNIC).

The aim of our research is to

- Make a licensed clonidine product available for sedation in PICU
- Contribute to and extend the experience in conducting clinical research in the vulnerable pediatric population
- Represent a new model of international and interdisciplinary collaboration of high level experts in the field of sedation
- Increase the scientific knowledge regarding the use of clonidine in PICU by bringing academic expertise together and by using modern clinical trial methodologies
- Contribute to harmonized future therapeutic approaches through the development of international guidelines for sedation in PICU/NICU.



Beneficiary	Country
Universitätsklinikum Erlangen	Germany
University College London	United Kingdom
Therakind Ltd	United Kingdom
Erasmus MC: University Medical Center Rotterdam	The Netherlands
Gianni Benzi Pharmacological Research Foundation	Italy
Karolinska Institute	Sweden
University of Tartu	Estonia
Charles University Prague	Czech Republic
Vereniging Samenwerkende Ouder- en Patiëntenorganisaties	The Netherlands
Bambino Gesù Children's Hospital	Italy



Members of the CloSed-consortium on the occasion of the kick-off meeting in December 2013 in Erlangen



# Horizon 2020: EuroHYP-1

## Speaker

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## Aims and Structure

EuroHYP-1 trial is a pan-European, open, randomized, phase III clinical trial which will assess the benefit of therapeutic cooling in adult patients with acute ischemic stroke. In addition to efficacy and safety, the economic impact of therapeutic hypothermia will be also evaluated.

The trial is based on the EuroHYP-1 consortium, a collaboration of more than 30 renowned European research institutions with outstanding experience in the development and conduct of large clinical trials. EuroHYP-1 is funded by the European Union from 2012-2017 within the seventh framework program (FP7, Grant agreement 278709). UK Erlangen, represented by the Dean of the Faculty of Medicine, resumed the sponsor function for the trial. The Department of Neurology and the Center for Clinical Studies Erlangen both contribute substantially to the leadership of the trial. Overall more than 49 well-known neurovascular centers in more than 15 European countries will participate in this trial. EuroHYP-1 is furthermore supported by the „European Clinical Research Infrastructure Network (ECRIN)“, the „Stroke Alliance for Europe (SAFE)“, the „European Stroke Organisation (ESO)“ and the „European Stroke Network (ESN)“.

## Research

Despite major advances in diagnostic and therapeutic procedures, ischemic stroke still represents one of the leading causes of death or dependency in industrialized countries. Up to date, the majority of patients with acute ischemic stroke are not eligible for established evidence-based treatment options, like intravenous thrombolysis or mechanical thrombectomy, due to contraindications. Stroke is a threatening condition for every single patient affected and at the same time causes substantial damage to the whole society as a result of permanent dependency on nursing care and occupational dis-

ability. Mild therapeutic hypothermia is one of the most promising novel treatment options for stroke. During therapy, the patient's body temperature is lowered to a target of  $< 35^{\circ}\text{C}$  under controlled conditions. The procedure has been used for several years in survivors of cardiac arrest and in newborns with hypoxic brain injury. Several pilot clinical trials have shown feasibility of therapeutic hypothermia also among spontaneously breathing stroke patients in the absence of mechanical ventilation.

The EuroHYP-1 trial is investigating the efficacy of therapeutic hypothermia in a large number of patients with acute ischemic stroke. Participants are randomized 1:1 either to an active or to a control group. The active group receives hypothermia treatment for twelve hours at a target temperature between  $34^{\circ}\text{C}$  to  $35^{\circ}\text{C}$ , followed by controlled rewarming at a rate of  $0,2^{\circ}\text{C}/\text{hour}$  until normothermia is established. The control group receives standard treatment without targeted changes in body temperature. The primary end point is the functional status of the patient after three month, measured on the modified Rankin Scale. Until present (April 2017), 77 patients have been included into the trial, of whom eleven were treated at the UK Erlangen. The final recruitment target is 800 patients. After the first interim analysis of the Data Safety Monitoring Board, led by Prof. Dr. P. Bath (University of Nottingham) after inclusion of 64 patients in June 2016, it was unanimously recommended to continue with recruitment. Therefore an application for an 18-months trial extension was submitted to the European Union.



# MelEVIR – Melanoma, Extracellular Vesicles, and Immune Response

## Speaker

Prof. Dr. Julio Vera-González

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## Aims and Structure

The aim of the project is the development, testing and translation into clinical practice of a systems biology-based diagnostic tool. The tool uses the profiling of miRNA, lncRNA and proteins contained in plasma extracellular vesicles (pEV) to assess the probability of tumor relapse in melanoma patients.

The project is conducted by an interdisciplinary team including biomedical and translational researchers (Prof. Dr. L. Heinzerling and Prof. Dr. A. Baur, Department of Dermatology), medical informaticians (Prof. Dr. H.U. Prokosch and PD Dr. T. Ganslandt, Chair of Medical Informatics), bioinformaticians (Prof. Dr. O. Wolkenhauer, Department of Systems Biology and Bioinformatics, Universität Rostock) and mathematical modelers (Prof. Dr. J. Vera-González, Department of Dermatology).

The project started on April 1, 2016, has duration of three years and is funded with 1.3 million Euro by the BMBF.

## Research

Experimental results indicate that macroscopic tumors can produce and load into the blood

large amounts of extracellular vesicles (pEV). Our preliminary results indicate that the minimal residual disease (MRD), the small amount of disperse tumor cells and micrometastases left after the tumor resection, cannot be the origin of the high levels of pEV that are found in high risk patients. Rather, large amounts of pEV are produced by the immune system upon detection of circulating tumor cells. We hypothesize that these pEV are part of the systemic immune response against the micrometastases and participate in the immune control of the MRD. In order to test our hypothesis, we will development, test and translate into clinical practice a software diagnostic tool which uses the profiling of pEV.

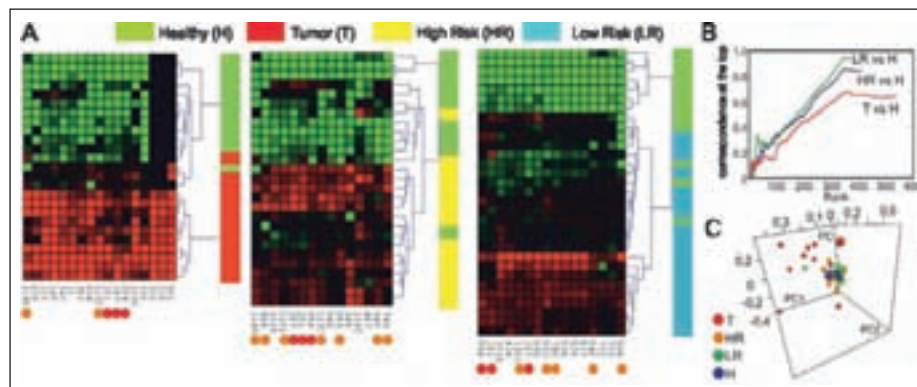
Precisely:

1. We will collect and quantify samples for primary tumors and pEV from melanoma patients.
2. We will perform experiments to elucidate the role of pEV in the tumor-immunity interaction.
3. We will use the obtained data to generate and characterize a mathematical model describing the tumor-immunity interaction.
4. The model and patient data will be used to make individualized simulations assessing the risk of tumor relapse in the patients.
5. The developed predictive model will be integrated in the clinical routine and in the electronic records of the patient.

Through the integration of clinical records, high throughput data analysis, network reconstruction and mathematical modelling, we will select a small set of microRNA, long non-coding RNA and proteins to be measured in the pEV taken from the patient blood samples. This information will be used to assess

a) the activation of the immune system response against the MRD and  
b) the risk of tumor relapse.

The data used includes measurements of miRNA, lncRNA and cytokines levels in patient pEV as well as the expression profile of samples from the primary tumor. The aim is to develop and test a diagnostic tool to assess in an individualized manner the risk of tumor relapse in melanoma patients.



pEV miRNA from melanoma patients separate into distinct clusters.

Hierarchical clustering analysis of miR from all patient groups against healthy controls based on Euclidean distance. The 15 most relevant miR for each patient group compared to controls were determined by SAM (significance analysis of microarrays).

# Thematic network: Translational kidney research – from physiology to clinical application (TRENAL)

## Speaker

Prof. Dr. med. Kai-Uwe Eckardt

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## Aims and Structure

TRENAL („Translational kidney research – from physiology to clinical application“) is an interdisciplinary network project that aims at leveraging the achievements of basic kidney research and translating them into novel diagnostic and therapeutic strategies. TRENAL unites nephrologists, physiologists, nephropathologists and basic researchers from FAU, Yale University and University College London (UCL) and the Max Planck Institute for the Science of Light.

TRENAL was selected as one of the winners of the DAAD's "Strategic Partnerships and Thematic Networks" call 2014, a program funded by BMBF. The "Thematic Networks" branch of the program supports networking with selected international universities based on shared interest in the same subjects and topics, and aims at helping German universities to position themselves as leaders in international research by creating specialist centers. TRENAL is funded from 2015-2018 (total funding: 917,302 Euro).

## Research

TRENAL supports the mobility of students, researchers, physicians in training and professors interested in doing translational kidney research at one of the partner institutions. It furthermore provides financial support for selected conferences and educational events.

From July 3-5, 2015, more than 100 clinicians and scientists from FAU, Yale, UCL and other research institutions met in the medieval town of Bamberg to discuss mechanisms of adaptation and dysfunction of the renal tubule. Talks by leading kidney researchers were complemented by a poster session and networking opportunities. The junior investigators and emerging phy-

sician-scientists from the TRENAL partner institutions made good use of the opportunity to liaise with senior faculty and discuss novel research directions in the context of their own interests.

## Teaching

TRENAL places a strong emphasis on the career development of medical students and young researchers. In 2015 and 2016, five medical students and five junior researchers and physicians from FAU and UK Erlangen have spent up to six months at the partner institutions in London and New Haven for research and training. Teaching at the partner institutions was further enhanced through lectures given by visiting professors from the TRENAL network.

Moreover, the project team hosted an international summer school. Around 120 scientists and physicians from different European countries, the US and Brazil met in Erlangen from July 6-9, 2016, to take part in the Summer School "Translational kidney research – from physiology to clinical application" with the aim of contributing to the translation of research results into new treatment methods in the area of kidney disease. The group of participants ranged from medical students to highly reputed emeritus professors. On the first two days, the speakers focused on the scientific aspects of kidney function, whereas on the last two days, the focus was on clinical questions and case discussions. The talks of the summer school were recorded and can be watched on the TRENAL website.



TRENAL summer school 2016 in Erlangen



# Clinical Research Unit 257:

## Molecular pathogenesis and optimized therapy of chronic inflammatory bowel disease (CEDER)

### Speaker

Prof. Dr. med. Markus F. Neurath

### Head

Prof. Dr. rer. nat. Christoph Becker

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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. The second assessment of the KFO took place in October 2014 and the research unit was approved for further three years until 31.1.2018 with 4,8 Mio Euro. Topics of the research center are the molecular pathogenesis and optimized treatment of inflammatory bowel diseases (IBD; Ulcerative Colitis and Crohn's disease). KFO 257 includes researchers from the departments of Dermatology (Derma), Surgery (Surg), Medicine 1 (Med 1) and 3 (Med 3) and from the Division of Immune Modulation (DIM). 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 immune system to the intestinal microbiota, 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 aimed at.

### Research

In 2015/2016 KFO 257 was structured into the following subprojects:

- Cytokine mediated mechanisms in the immune-pathogenesis of IBD  
Project managers: Prof. Dr. C. Becker / PD Dr. S. Wirtz (Med 1)
- Neutrophil extracellular traps orchestrate the immune response in IBD  
Project managers: Prof. Dr. M. Herrmann / Dr. M. Leppkes (Med 3 / Med 1)
- Functional analysis of the immune modulator sCD83 in the pathogenesis and therapy of IBD  
Project managers: Prof. Dr. A. Steinkasserer / PD Dr. M. Lechmann (DIM)
- Immune regulation of angiogenesis in IBD  
Project managers: Prof. Dr. M. Stürzl / Dr. M. Waldner (Surg / Med 1)
- Neuropeptides and TRP receptors as effectors of immune cell activation in IBD  
Project manager: PD Dr. M. Engel (Med 1)
- Functional characterization of prenylated Rho proteins in the pathogenesis of IBD (new project)  
Project manager: Dr. I. Atreya (Med 1)
- Analysis of the molecular mode of action of cyclosporine A in IBD  
Project manager: PD Dr. B. Weigmann (Med 1)
- Characterization and expansion of regulatory T cells for cell-based therapy of IBD  
Project managers: Prof. Dr. M.F. Neurath / Dr. C. Bosch-Voskens (Med 1 / Derma)
- In vivo endoscopic molecular imaging to predict therapeutic response to anti-adhesion molecule therapy in Crohn's disease patients  
Project manager: Prof. Dr. R. Atreya (Med 1)
- Central project to coordinate the scientific program of KFO 257  
Project manager: Prof. Dr. C. Becker (Med 1)

### Teaching

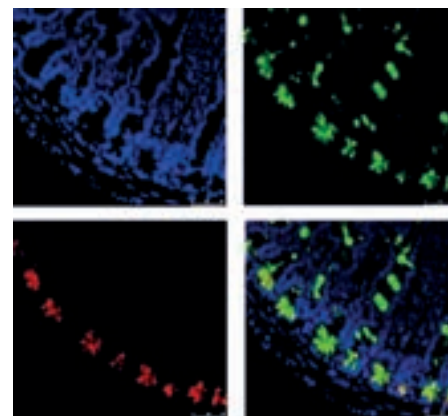
Seminars on IBD:

- Immune pathogenesis and treatment of IBD
- 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)

On October 12, 2015 a meeting was held at Schloss Atzelsberg in Erlangen in which the project leaders presented and discussed their scientific results. On October 24-25, 2016, a joint meeting between researchers of KFO 257 and colleagues from Berlin took place at Schloss Atzelsberg.



Immunofluorescence staining of paneth cells in the small intestine



# Research Unit 1228: Molecular Pathogenesis of Myofibrillar Myopathies

## Speaker

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## Aims and Structure

The multilocation research unit (FOR) 1228 was funded by the DFG from November 2009-2015. This research unit aimed at clarifying the molecular processes that lead to progressive skeletal muscle and cardiac damage in myofibrillar myopathies. FOR 1228 combined the scientific expertise of physicians, biologists, and biochemists and was 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 summed up to 3.6 million Euro for a six year term of funding.

## Research

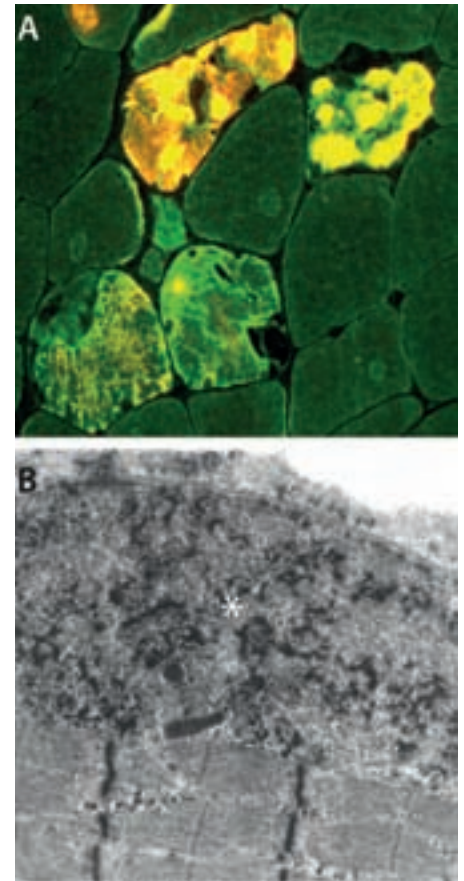
Myofibrillar myopathies (MFM) are progressive and devastating diseases of human skeletal and cardiac muscles that often lead to premature death. MFM are histopathologically characterized by desmin-positive protein aggregates and myofibrillar degeneration. While about half of all MFM are caused by mutations 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 focused 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 offered 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 therefore not only provided deeper mechanistic and preclinical insight into the pathogenesis of MFM, but also aimed at paving the way to novel targeted treatment concepts. As translational approach we therefore studied the therapeutic effect of drugs and compounds that directly target pathological protein aggregation processes. In addition, gene replacement strategies by AAV-mediated gene transfer were evaluated.

## Teaching

The participating groups of FOR 1228 were supervising PhD and/or medical theses. The principal investigators of individual projects were 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.

# Research Unit 2438: Cell Plasticity in Colorectal Carcinogenesis

## Speaker

Prof. Dr. med. Florian Greten  
(Georg-Speyer-Haus, Frankfurt)

## Deputy Speaker and Contact Faculty of Medicine

Prof. Dr. med. Markus Neurath

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## Aims and Structure

Since July 2016, the DFG has been funding a new research group on colorectal cancer with 3.5 million Euro for three years. Scientists from the Universities of Erlangen, Frankfurt and Regensburg jointly investigate fundamental mechanisms for the development of colorectal cancer within the research group „Cell Plasticity in Colorectal Carcinogenesis“ (FOR 2438). Speaker of the research group is Prof. Dr. F.R. Greten, Director of the Georg-Speyer-Haus in Frankfurt, Deputy Speaker is Prof. Dr. M.F. Neurath, Director of the Department of Medicine 1. FOR 2438 comprises nine subprojects, four of which are headed by members of the Faculty of Medicine. Another subproject is a cooperation between Erlangen and Frankfurt, and the central project is jointly led by Prof. Dr. F.R. Greten and Prof. Dr. M.F. Neurath. In addition to the Department of Medicine 1, scientists from the Department of Surgery and the Chair for Experimental Medicine I are also involved.

## Research

Colorectal cancer is still one of the most common tumors in adulthood. Despite major advances in diagnosis and therapy, colorectal cancer has so far been insufficiently treatable. It is now known that not only the actual tumor cells, but also immune cells and connective tissue cells which directly surround the tumor cells and jointly form the so-called tumor micro-milieu have a decisive influence on tumor growth. The cellular composition of this micro-milieu and the nature of the cells involved are very variable and influence each other: Certain mutations in tumor cells can alter the composition of the tumor stroma. On the other hand, cells from the tumor stroma have a great influence on the

growth of the actual tumor cells as well as the response of therapies. The scientists of this research group are investigating the complex molecular and cellular interrelations in the micro-milieu of colorectal cancer by means of complementary approaches in order to derive new therapeutic concepts from these.

The research projects within FOR 2438 investigate the following topics:

- Project 1: The functional role of VEGFR2-signaling in CD4+ T cells in the pathogenesis of colorectal cancer  
PI: Prof. Dr. M. Waldner (Department of Medicine 1)
- Project 2: Endothelial cell-derived SPARCL1 as a regulator of tumor cell dormancy in colorectal cancer  
PI: PD Dr. E. Naschberger, Prof. Dr. M. Stürzl (Department of Surgery)
- Project 3: Functional analysis of pathways mediating intestinal stem cell plasticity  
PI: Prof. Dr. F.R. Greten (Georg-Speyer-Haus, Frankfurt)
- Project 4: The role of the EMT-inducer Zeb1 in the invasive tumor stroma during colon cancer progression  
PI: Dr. H. Farin (Georg-Speyer-Haus, Frankfurt), Prof. Dr. T. Brabletz (Chair of Experimental Medicine I)
- Project 5: Functional role of Smad7 on intestinal epithelial homeostasis and colorectal cancer development  
PI: Prof. Dr. C. Becker, Dr. E. Martini (Department of Medicine 1)
- Project 6: The cell-specific role of Interferon regulatory factor-5 for tumor cell plasticity and tumor progression during ulcerative colitis-associated and spontaneous colon tumorigenesis  
PI: Dr. R. Kesselring, Prof. Dr. S. Fichtner-Feigl (Universitätsklinikum Regensburg)
- Project 7: Tumorigenic cytokine networks during colon carcinogenesis depend on sphingosine-1-phosphate receptor signaling  
PI: PD Dr. A. Weigert, Prof. Dr. B. Brüne (Goethe-Universität Frankfurt)
- Project 8: The role of the IL-6/STAT3 axis in tumor fibroblasts during colorectal carcinogenesis  
PI: Dr. C. Neufert, Prof. Dr. M.F. Neurath (Department of Medicine 1)
- Central project: Central collaboration project that aims to systematically collect and link data from the individual projects and to perform unbiased bioinformatical cluster analysis  
PI: Prof. Dr. F.R. Greten (Georg-Speyer-Haus, Frankfurt), Prof. Dr. M.F. Neurath (Department of Medicine 1)



# Integrated Research Training Group 130: B Cells and beyond

## Speaker

Prof. Dr. rer. nat. Hans-Martin Jäck

## Coordination

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## Aims and Structure

The DFG has been supporting the collaborative research center Transregio 130 (TRR130) „B cells: Immunity and Autoimmunity“ since 2013. The intercity research consortium assembles B cell immunologists from the Faculties of Medicine and Sciences (FAU) as well as the Albert-Ludwigs University Freiburg, the Charité Berlin, the Deutsches Rheuma-Forschungszentrum, the Max Planck Institute for Infection Biology and 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 research training group (IRTG) “B cells and beyond” with a strong research and training program as well as mentoring and career development concept has been established within the TRR130. Common retreats, laboratory rotations within the TRR130 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 TRR130 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

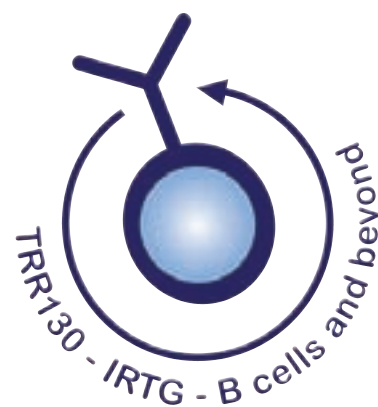
affinity antibodies for long periods of time. A second scientific topic of the TRR130 is to understand how B cells with autoreactive antigen receptors are activated to produce autoantibodies that attack the body's own tissue. Autoantibodies can be involved in the pathogenesis of autoimmune diseases, 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-TRR130 is based on four pillars: research, education, mentoring and career development. Each PhD student is supervised by a thesis advisory committee. It consists of the supervisor and two additional group leaders of the TRR130. The annual B cell winter school provides a platform for the PhD students to present their research in front of a larger audience and to discuss the progress of their PhD 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 TRR130 investigators. A student exchange program allows optional visits in laboratories within the TRR130 to broaden the range of methods of the PhD 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 PhD 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 PhD students' national and international networks and to discuss their projects in a broader context, they have the possibility to participate at network meetings with other GK and organize the bi-annual international GK symposium and one session of the international TRR130 symposium. To promote public awareness about the importance of immunological research, the IRTG-TRR130 PhD students also participate in local public relations projects. Finally the IRTG-TRR130 covers the costs to attend scientific congresses and the three immunology schools of the “Academy of Immunology” within the German Society for Immunology (DGfI).



Participants of the B cell winter school 2016 (Photo: Dr. A. Giniewski)



# Integrated Research Training Group within SFB 643: Strategies of Cellular Immune Intervention

## Speaker

Prof. Dr. rer. nat. Dr. med. habil.  
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## Aims and Structure

The GK was integrated in the SFB 643 "Strategies of Cellular Immune Intervention". It trained the doctoral candidates to become highly qualified scientists. With a structured educational and support program, it prepared purposefully for the job. Our offer to the students included a bi-weekly regular meeting, workshops on communication and GMP-production, project-related workshops that allowed students to spend time in labs outside of Erlangen. Additionally, each student got 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 streamlined and focused each research project and thus facilitated 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 was funded for three periods, running out in 2015. The goal of the SFB 643 was 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. Fortunately, concepts were successfully adapted and enhanced in the IRTG 1181.

The research program was 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 not only resulted in better trained doctoral students, but also made them independent scientists early in their career. Our goal was based upon the following mentoring and educational units: Every graduate student was accompanied by a support commission. It consisted of the direct supervisor and two sub-project-leaders of the SFB 643. In a biweekly regular meeting the candidates discussed literature, methodical problems, and their own research-data. Internal report symposia and network meetings with other topically relevant and external GK trained the candidates to present their research in front of a larger council. Workshops imparting the following skills were held: Knowledge of the different industrial occupational fields and the improvement of the students' presentation and scientific writing skills. The SFB 643 emphasized on translating experimental data into clinical practice. Therefore, courses were offered that dealt 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 taught 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" were detected at an early stage and the education of the candidates was streamlined.



# Integrated Research Training Group within SFB 796: Erlangen School of Molecular Communication

## Speaker

Prof. Dr. rer. nat. Andreas Burkovski

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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 FAU as well as 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  
Expiration of funding: 2016 - 2017

## 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 ef-

fector 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, is also provided on student request.

# Integrated Research Training Group 1181: Checkpoints for Resolution of Inflammation

## Speaker

Prof. Dr. rer. nat. Dr. med. habil.  
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www.sfb1181.forschung.fau.eu/integrated-research-training-group-2

## Aims and Structure

The integrated GK 1181 (GK 1181), funded by the DFG for four years (2015-2019), has the objective to offer a highly qualified, translational training with focus on life sciences to graduate students in parallel to their dissertation.

Medical research is not only related to either clinics or laboratory – medical science is both. Thus all graduates within the GK 1181 receive a structural education and mentoring program to be prepared for a scientific career in life sciences. The graduates have received a comprehensive qualification in the field of basic and clinical research by completion of the dissertation. They have learned to think outside the box, have taken active part to an interdisciplinary research network and have acquired comprehensive knowledge about inflammation from molecular mechanism up to diseases. In addition, national and international scientific collaborations are essential for the current and future path of the graduates. The close networking of the GK 1181 with other graduate schools (GK 1160 (Erlangen), TRR 130 (Erlangen, Berlin, Freiburg, Göttingen), IRTG 914 (München), CiM/IMPRS (Münster)) already led to joint scientific symposia.

In February 2017, the GK 1181 consisted of 46 graduates (23 full members, five GK-supported medical stipends, seven alumni and eleven associated doctorates).

## Research

Inflammation is a part of the elaborate human defense system. This process needs a functioning immune system to allow the defense against dangers such as mechanical, chemical and biological signals or at least to contain and therefore prevent organ damage. The human body responds rapidly to dangers by an inflammatory response, which is also rapidly resolved after the

dangers have been removed allowing for tissue repair to begin. How resolution of inflammation functions is still inadequately researched and will thus be researched by the SFB 1181.

The SFB 1181 (Checkpoints for Resolution of Inflammation; compare own report) has been funded by the DFG since 1 July 2015 and was established to investigate the molecular mechanisms involved in the resolution of inflammation. Our main focus is on why resolution of inflammation fails in chronic inflammatory diseases such as arthritis, Crohn's disease and asthma which are characterized by chronic inflammation of the inner surfaces of the body, usually having serious health implications for its patients.

The research program is conceptually structured in three closely interconnected checkpoints:

**Checkpoint A:** Switch from pro- to anti-inflammatory cytokine response

**Checkpoint B:** Blockade of pro-inflammatory lymphocyte activation

**Checkpoint C:** Fostering of tissue remodeling by cell death and tissue repair mechanisms.

## 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:

- Mentoring commission and annual report  
Each graduate student of the GK 1181 is accompanied by a mentoring commission besides their direct supervisor. This commission will ensure the unobstructed progress of their thesis, suggests constructive enhancements and assists with problem of all forms.

- Bi-weekly „Jour fixe“

Every other week, the graduates organize a meeting discussing literature, their own research data or methodological problems and much more.

- Interdisciplinary training workshops and method seminars

These workshops and seminars will not only teach state of the art methods, but also introduce other areas such as industry, techniques of rhetoric or scientific writing.

- Seminars and mini symposia

These seminars are arranged by small groups of graduates, highlighting the wishes and requirements of the graduates. Furthermore, mini symposia are organized to generate stimuli by presentations of recent findings of inter-

national guest speakers in the multi-faceted research areas of the SFB 1181.

- Clinical rounds of life science researchers in the daily grind of a clinician

The graduates can get an impression of the clinical routine and state-of-the-art treatments of patients suffering of chronic diseases.

- Annual retreats and participation in national and international conferences and symposia  
During annual retreats of the SFB 1181 the graduates have the opportunity to present their data to the members of the SFB and will be trained to present their work on international congresses.

- Publicity

An important aspect within SFB 1181 is scientific communication. The GK 1181 is closely involved in scientific events such as the Lange Nacht der Wissenschaften in Erlangen and will inform about their respective field of study and career possibilities in life sciences as well as the current work of the SFB.



# Research Training Group 1660: Key Signals of Adaptive Immune Response

## Speaker

Prof. Dr. rer. nat. Hans-Martin Jäck

## Coordination

Dr. rer. nat. Anja Glanz

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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 laboratory abroad), 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 Euro 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 identi-

fication 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 and the first funding period of the GK 1660:

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 are mentored by a three member thesis advisory committee. To internationally position our doctoral students, they organized the 5<sup>th</sup> International GK Symposium on "Regulators of Adaptive Immunity" in 2016.

Our research and innovative training concept resulted in a reduction in the time required to finish a doctoral program, but it also provides a high-quality training environment for young scientists at an internationally competitive level.



# Research Training Group 2162: Neurodevelopment and Vulnerability of the Central Nervous System

## Speaker

Prof. Dr. Dieter Chichung Lie

## Coordination

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## Aims and Structure

The GK 2162 „Neurodevelopment and Vulnerability of the Central Nervous System“ aims to investigate the pathophysiological links between neurodevelopment and adult-onset of neuropsychiatric and -degenerative disorders. In the GK 2162, eleven groups of the Faculty of Medicine (FM) and the Faculty of Sciences (FS) combine forces to train a total of 48 PhD and MD students over the next 4.5 years in the novel concept that neurodevelopment constitutes a major determinant for the individual's vulnerability to neuropsychiatric and -degenerative diseases in later life.

The GK 2162 is composed of basic and physician-neuroscientists with expertise in the areas of CNS development, genetics of CNS disorders and modeling of neuropsychiatric and -degenerative diseases. Project leaders of the GK 2162 are Prof. Dr. K. Friedland (Professorship of Molecular and Clinical Pharmacy, FS), Prof. Dr. C. Alzheimer (Institute of Physiology and Pathophysiology, FM), Prof. Dr. J.H. Brandstätter and PD Dr. H. Regus-Leidig (Chair of Animal Physiology, FS), Prof. Dr. M. Wegner and Prof. Dr. D.C. Lie (Institute of Biochemistry, FM), Prof. Dr. J. Winkler (Division of Molecular Neurology, FM), Prof. Dr. B. Winner (Division of Stem Cell Biology, MF), Prof. Dr. R. Linker (Department of Neurology, FM), Prof. Dr. J. Kornhuber (Department of Psychiatry and Psychotherapy, FM), Prof. Dr. A. Reis and PD Dr. C. Zweier (Institute of Human Genetics, MF).

## Research

Development of the central nervous system (CNS) is a complex sequence of patterning, proliferation, migration, differentiation, and synapse formation steps. These events ultimately lead to the formation of neural circuits - the

structural basis for behavior, learning, and cognition. Failure to form precise neural circuits has long been known to result in neurodevelopmental disorders, such as CNS malformations, intellectual disability, and autism, which manifest at birth or in early childhood. Evidence has emerged indicating that the pathogenesis of neuropsychiatric and -degenerative disorders which typically show an onset of disease during adulthood may be linked to perturbation of neurodevelopmental processes. The goal of the GK 2162 is to significantly promote the understanding of the interconnection between neurodevelopment and adult CNS disorders. Research projects address three central topics:

- 1) What is the overlap in genetics and disease pathways between neurodevelopmental and adult-onset CNS disorders?
- 2) What are developmental functions of neuropsychiatric and -degenerative disease genes?
- 3) What is the impact of neurodevelopmental factors and processes on vulnerability versus resilience to disease-precipitating insults in later life?

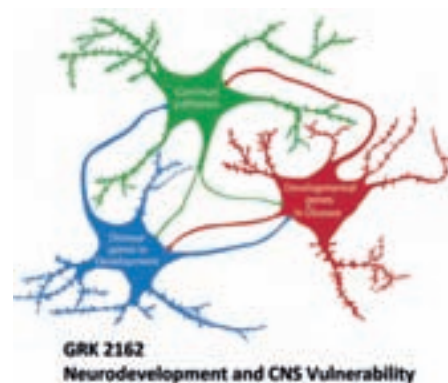
## Training

The interdisciplinary qualification program of the GK 2162 aims to endow its graduate students with comprehensive education and key qualifications in the field of neuroscience. They acquire a broad overview of current key questions and pitfalls in a lecture about the development and pathophysiology of the central nervous system and learn how to approach solutions in a theoretical and experimental manner. The program places a major emphasis on graduate students taking initiative and establishing scientific networks already at a very early stage of their career. To promote that purpose, graduate students are encouraged to regularly invite experts in their field of research as guest speakers, to organize an international symposium, and to present at national and international conferences.

To achieve close supervision of the doctoral students, progress reports and meetings with individually tailored thesis advisory committees are regularly held. One retreat per year gives additionally room and time for scientific exchange, evaluation and discussion of the single projects. A particular concern of the GK 2162 is to provide excellent training across all levels and biomedical disciplines to ensure a high degree of translational and interdisciplinary research. One focus is to encourage medical students and physicians to pursue a physician-scientist career

by offering them stipends and fully paid rotation positions. In parallel to their experimental doctoral thesis, the medical students pass an intense neuroscientific training while physicians can pursue full-time research in translational topics of the GK focus and develop their own scientific profiles.

Additionally, six postdoctoral researchers are associated to the GK who receive intensive mentoring and support to promote the development of their academic career and the establishment of their independent research profile and scientific network.





# Emil Fischer Graduate Program of Pharmaceutical Sciences and Molecular Medicine (EFS)

## Speaker

Prof. Dr. rer. nat. Markus Heinrich

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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 at the Faculty of Sciences in 2013.

## Research and Teaching

The graduate program provides a framework of activities, including seminars and counseling, in order to allow the PhD students to acquire interdisciplinary skills that reach far beyond the

particular topic of their PhD thesis. Throughout the graduate program, all PhD 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 PhD 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 PhD students to present and discuss their methods and data in an interdisciplinary framework.

Since the start of the program in December 2008, 155 PhD students have enrolled in the program. Until February 2017, already 72 candidates successfully completed the program with a PhD and a program certificate.



# Erlangen Graduate School in Advanced Optical Technologies (SAOT)

## Speaker

Prof. Dr.-Ing. Michael Schmidt

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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 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, of Sciences, and of Medicine and is embedded into an international network of distinguished experts in their respective fields of optical technologies. The scientific topics of SAOT are optical metrology, optical material processing, optics in medicine, optics in communication and information technologies, optical materials, and systems and computational optics.

## Research

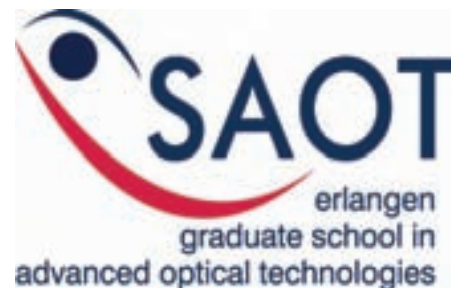
Intensive research work is carried out in each of the SAOT topics which are partly overlapping. This in particular is true for the topic "Optics in Medicine" which can be considered to form an application field of the other topics. It is inherently interdisciplinary, covering e.g. optical diagnostics 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 diagnos-

tics, 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.



# Emerging Fields Initiative: CYDER

## Speaker

Prof. Dr. rer. nat. Felix B. Engel

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## Aims and Structure

CYDER is an international, interdisciplinary consortium of cell cycle experts from the Faculty of Medicine (Prof. Dr. K. Amann, Prof. Dr. F. Engel, PD Dr. C. Daniel, Division of Nephropathology; Prof. Dr. J. Behrens, Chair of Experimental Medicine II; Prof. Dr. R. Schneider-Stock, Institute of Pathology; Prof. Dr. Dr. M. Stürzl, Department of Surgery; Prof. Dr. M. Wegner, Institute of Biochemistry; PD Dr. C. Neufert, Department of Medicine 1), the Faculty of Sciences (Prof. Dr. R. Slany, Department of Genetics) and the three international members Prof. Dr. B. Edgar ((DKFZ/University of Utah), Prof. Dr. E. Nigg (Biozentrum, University of Basel) and Prof. Dr. S.J. Shankland (University of Washington School of Medicine). CYDER has been funded since January 2015 for three years by the Emerging Fields Initiative (EFI) with 1,25 Mio Euro.

## Research

The cell cycle is a strictly regulated sequence of events that governs the proliferation of cells. Usually one associates errors in cell cycle control mechanisms with cancer. However, it is less known that there are a variety of incurable diseases in which cell cycle activity is induced in non-proliferative cell types (such as heart disease and renal disease which are not explicitly considered as cell cycle disorders). Our goal is to better understand the effects of cell cycle activation in such diverse processes as cancer, regeneration and chronic organ failure. Ultimately, CYDER strives to identify common cell cycle-associated paradigms between apparently unequal disease states in order to accelerate the development of new prevention, treatment and healing methods of cell cycle-associated diseases. In addition, CYDER has the goal of supporting the internationalization efforts of the FAU and of promoting junior scientists.

Since the start of the EFI-CYDER consortium, we have

- 1) identified novel molecular circuitries governing cell cycle control in development and disease;
- 2) revealed that cell cycle activation in terminal differentiated cells during chronic disease is directly correlated with the severity of the disease, and
- 3) established novel mouse animal models to determine the role of cell cycle activation in development and disease. The consortium has contributed so far to 23 original publications as well as six reviews.

Highlights of our research results are for example:

- 1) The tumor microenvironment (TME) influences plasticity of tumor and stromal cells that affects the progression and malignancy of tumors. The analysis of tumor endothelial cells (TEC) from human colorectal carcinomas that exhibited TME with either improved or worse clinical prognosis showed a TME-dependent intertumoral TEC heterogeneity in colorectal carcinomas. Further, it could be demonstrated that TEC heterogeneity is regulated by SPARCL1, a protein of the extracellular matrix. SPARCL1 promotes cell quiescence and vessel homeostasis.
- 2) During the late embryonic development of mammals, but not zebrafish, proteins of the pericentriolar matrix are translocated in cardiomyocytes from the centrosome to the nuclear envelope. This causes the inactivation of the centrosomes and contributes to the cell cycle arrest in cardiomyocytes. Our data provide a novel mechanism underlying the post-mitotic state of mammalian cardiomyocytes and a potential explanation for why zebrafish, but not mammals, can regenerate their heart.
- 3) Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine which are induced by a misregulation of the immune response. Here we have shown that the function of the IL-36 receptor plays an important role in intestinal wound healing. Normally ligands of the IL-36 receptor are released after mucosal injury which promotes wound healing by activating fibroblasts and stimulating the proliferation of intestinal epithelial cells. Moreover, we could demonstrate in animal experiments that the healing of intestinal wounds after treatment with IL-36 receptor ligands was significantly accelerated.
- 4) Podocytes are non-proliferative cells of the glomerulus that are of importance for the filtration function of the kidney. Activation of the cell cycle in these cells results in binucleation (cells

with two nuclei) and to significant ultrastructural changes like footprocess widening. Further, cell cycle-activated podocytes, preferentially binucleated podocytes, exhibit a lower survival rate upon stress. Accordingly, a significant correlation was found between "induction of cell cycle re-entry in podocytes" and "severity of the disease" as well as between "kidney function" and "the number of binucleated podocytes".

## Teaching

Seminars for all consortium members and for interested students and researchers of FAU take place monthly. In addition, CYDER regularly organizes symposia and scientific presentations with invited speakers (for details see homepage). Members of the consortium supervise Master's, MD and PhD theses.

# Emerging Fields Initiative: Human Rights in Healthcare

## Speakers

Prof. Dr. med. Andreas Frewer, M.A.

(Faculty of Medicine)

Prof. Dr. phil. Dr. h.c. Heiner Bielefeldt (Faculty of Humanities, Social Sciences, and Theology)

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human-rights-in-healthcare

## Aims and Structure

The Emerging Fields Initiative (EFI) of FAU aims at funding innovative ideas and research projects that are interdisciplinary, can be implemented and further the structure and teaching at FAU. Thus, it is intended to enable excellent research and to enhance the profile of FAU.

The project „Human Rights in Healthcare“ has been funded by EFI since 2014 for a period of three years with a total amount of 660,000 Euro. Twelve professors and four fellows from three faculties cooperate within the project: Faculty of Medicine, Faculty of Humanities, Social Sciences, and Theology, and Faculty of Business, Economics, and Law.

## Research

This EFI project focuses on highly relevant issues in the intersection of human rights, medicine and medical ethics. The project is based on the assumption that in order to be able to lead autonomous lives and take autonomous decisions concerning far-reaching health questions, human beings often need facilitating structures. It deals with conflicting claims to receive such support for personal autonomy in health care. 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 which will be studied intensively include issues of dialysis, transplantation, new conflicts arising from international patient mobility, „health literacy“ education, contributions to „health-empowerment“ of vulnerable groups in developing countries 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.

The project focuses on the following aspects:

1. Foundations of human rights in healthcare  
In this focus legal and normative implications of the human right to the highest attainable standard of health are interdisciplinarily analyzed and questioned about their concrete possibilities of measures which should be operationalized on different levels of health care. In this context different ethical concepts, as for example vulnerability – which is conceptualized in different ways –, relational autonomy, human dignity and justice are used in a hermeneutical way to approach urgent questions of the field from a legal as well as an ethical and a clinical perspective (human rights based approach). Thus not only national obligations of respecting, protecting and fulfilling the right to the highest attainable standard of health will be discussed along the parameters of availability, accessibility, acceptability and quality (AAAQ), but also questions of extraterritorial obligations between states accounting to standards of international solidarity for the sake of the other to fulfil certain core standards of public health.

2. Medicine and human rights for migrants  
The human right to the highest attainable standard of health should be available and accessible for all humans alike – unconditionally. However, this right is restricted and sometimes even withheld when it comes to the treatment of refugees, undocumented migrants and/or children sans papiers; which is both medically as well as ethically highly problematic. Connecting essential considerations about the vulnerability and dignity of these groups of persons and about concrete national and social obligations turns the attention e.g. to the medical healthcare in Germany. One question might be whether healthcare meets the requirements claimed by AAAQ and – if not – how this can be changed.

3. Human rights for patients in vulnerable situations

Starting with various kinds of vulnerability – inherent, situational and pathogenic – different groups of patients whose situations are characterised by distinct dependencies on and special kinds of openness towards institutions and the personnel of the healthcare system build the focus of this research area. Especially the situation of children, persons with dementia or transplantation-patients in hospital – to name but a few – is highly precarious and in danger of falling prey to misuse of power imbalances and to infringements of autonomy and dignity. Using the concept of vulnerability and the human rights based approach as a kind of hermeneutical tool to understand situational structures, the purpose is to name deficits (and positive resources) in public and clinical treatment-practice, to propose possible solutions and to cautiously evaluate new technologies.

4. Autonomy and human rights at the end of life  
The rights and needs of older patients are mainly analyzed in this project area: Taking ac-

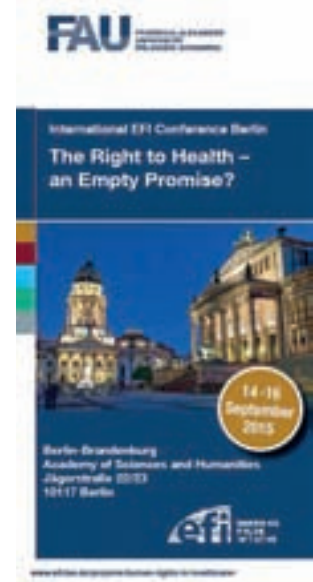
count of the dignity and autonomy of older patients, the question to be answered is whether the healthcare system is able to treat them fairly and justly according to the normative implications of equity and equality. In this context palliative care might be used as a paradigm of person-oriented medical treatment which on the one hand dedicates itself to help very vulnerable patients in extreme situations to save their dignity and autonomy and to experience them in daily treatment. On the other hand palliative care also helps to prevent or at least attenuate the misuse of power over older patients and their life-world in clinical settings or long-time care institutions. Complementary laws about changing therapeutic goals and about instruments of advance care planning, as e.g. advance directives and health care proxies etc., shall be analyzed relating to their ethical content and their practical relevance. Which significance shall they have when it comes to realize the human right to the highest attainable standard of health and to protect older persons from being treated against their will and life-worldly based values?

Large-scale projects in close contact with the project „Human Rights in Healthcare“:

- Bavarian dementia-survey „BayDem“ (Bavarian Ministry of Health and Care)
- BMBF project „MRSA in End-of-Life Care“
- GK „OptiDem“ – Optimizing Strategies for Dementia (Carstens Foundation)

## Teaching

The project leaders of all three faculties involved supervise Master's and PhD theses. In September 2015, an international conference on „The Rights to Health - an Empty Promise?“ took place at the Berlin-Brandenburg Academy of Sciences and Humanities.





# Emerging Fields Initiative: Ludwig Demling Center

## Speaker

Prof. Dr. med. Markus F. Neurath

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ludwig-demling-center

## Aims and Structure

The Emerging Fields Initiative (EFI) funded project „Ludwig Demling for endoscopic molecular imaging“ aims to visualize the molecular cellular structure of a tissue to detect disease specific alterations. This imaging modality should enable an earlier detection of these lesions, thereby influencing our currently used diagnostic and therapeutic algorithms. Scientific findings regarding the immunopathogenesis of specific diseases are being clinically utilized by the in vivo detection of the corresponding changes in the molecular signature of the diseases cells. Endoscopic molecular imaging should enable the prediction of the therapeutic response to biological treatments and realize the detection of diminutive changes in neoplastically transformed tissue. This interdisciplinary approach further strengthens the Faculty's core research areas Infection and Immunology as well as Tumor. The translational approach of the project takes up the immunological core research area of the Faculty of Medicine and broadens the area inflammation research which has established itself as one of the main areas within the field of immunology.

The interdisciplinary character of the project creates valuable synergistic effects between different departments and theoretical and basic science institutes at the Faculty that lead to the implementation of novel methods for the endoscopic molecular imaging of inflamed or neoplastic diseases. The interdisciplinary cooperation of the different institutions (Department of Medicine 1, Pharmacy of UK Erlangen, Institute of Biochemistry, Center for Clinical Studies, Institute of Pathology, Division of Genetics, Institute of Medical Informatics, Biometry, and Epidemiology, Department of Urology, Department of Otorhinolaryngology, Department of Surgery, Department of Anesthesiology, Division of Transfusion Medicine and Hemostaseology) enables the envisioned pre- and clinical studies. This consortium represents an established and proven basis for the conception and conduct of studies re-

garding endoscopic molecular imaging. The production of the fluorescent labeled probes is possible as the Pharmacy is allowed and certified to create GMP-conform products.

This novel endoscopic imaging modality of molecular imaging is done in remembrance and in honor of Prof. Dr. L. Demling who held the Chair of Internal Medicine and was director of the Department of Medicine 1, in the newly found „Ludwig Demling Center for Molecular Imaging“.

## Research

Improved detection of mucosal lesion through the identification and visualization of molecular target structures represents a promising area within the medical field. This approach was already successfully implemented and conducted in an phase 1 trial with Crohn's disease patients in the Ludwig Demling Center. We have already proven that visualization of mTNF positive cells with a topically applied fluorescent anti-TNF antibody is possible in an endoscopic in vivo molecular imaging procedure in Crohn's disease patients. It could be demonstrated that there was a significant correlation between the therapeutic efficacy of anti-TNF therapy and prior in vivo detected mucosal mTNF expression. To the best of our knowledge, this was the first report on the use of GMP-conform, fluorescent antibody for in vivo imaging. Apart from facilitating medical care and avoiding unnecessary treatment and side-effects, this approach also has substantial implications and impact from a socioeconomic point of view. Our consortium would like to follow this vision and establish similar molecular imaging procedures to predict therapeutic response to other approved biological therapies in the field of inflammatory bowel diseases (IBD) and other disease entities. Translational transfer of scientific findings into the endoscopic molecular imaging procedure is also undertaken in the oncology field. The visualization of molecular structures in neoplastic tissue through topical application of specific fluorescent labeled probes that are directed against them is another major aim of the group.

## Teaching

Another aim of the Ludwig Demling Center is the transfer of knowledge regarding this novel imaging procedure to students and physicians. This is realized by special lectures and teaching activities of experienced endoscopists within their respective departments.

Furthermore, the “Ludwig-Demling-Medal” for outstanding endoscopic work has already been awarded twice to internationally renowned endoscopists in special symposia for physicians. This special event will be conducted every two years.



*Presentation of the Ludwig-Demling-Medal 2016 (from left: Prof. Dr. O. Pech, Prof. Dr. J. Riemann, Prof. Dr. R. Kiesslich (laureate 2016), Prof. Dr. M.F. Neurath, Prof. Dr. J. Pohl, Prof. Dr. C. Ell (laureate 2014), Prof. Dr. R. Atreya, Prof. Dr. M. Waldner. Photo: Department of Medicine 1)*

# Emerging Fields Initiative: Moves

## Speaker

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## Aims and Structure

The overall goal of the project is to implement a sensor-based gait analysis system as an objective diagnostic readout of gait impairment for patients with Parkinson's disease (PD) and Osteoarthritis (OA) paralleled by different intervention paradigms. Inertial sensor units attached to the patient's shoes measure spatio-temporal gait parameters that objectively support the clinical work-up by identifying PD- and OA-specific gait characteristics reflecting rater-independent disease progression and therapeutic efficacy measures. In order to show the sensitivity-to-change of these gait parameters, two proof-of-concept interventions were tested: PD patients underwent an eight-week training on a perturbation treadmill in order to improve gait and balance; OA patients received standard knee surgery and joint replacement. The ability of instrumented movement assessment to generate clinically relevant target parameters was evaluated prior and after the intervention. Therefore, a comprehensive assessment strategy was generated to show the clinical applicability of sensor-based gait analysis in a multidisciplinary approach from different faculties at the FAU. The partners of the consortium are: Divisions of Molecular Neurology (Prof. Dr. J. Winkler, Prof. Dr. J. Klucken) and of Traumatology (Prof. Dr. F. Hennig), Institute of Radiology (Prof. Dr. M. Uder; all Faculty of Medicine), Pattern Recognition Laboratory (Prof. Dr.-Ing. B. Eskofier, Faculty of Engineering) and Institute of Sport Science and Sport (Prof. Dr. K. Pfeifer, Faculty of Humanities, Social Sciences, and Theology). This project has been funded since 2014 by the Emerging Fields Initiative of FAU with a total of 1,060,000 Euro.

## Research

Motor symptoms in PD were assessed during a randomized, controlled treadmill intervention study. Patients were stratified into an experi-

mental group (EG; treadmill training with constantly applied perturbation) or control group (CG; training on the identical treadmill without perturbations). The intervention consisted of an eight week treadmill training program (twice per week, 40 minutes/session) on a worldwide unique treadmill prototype (zebris Medical GmbH, Isny, Germany). The innovative intervention paradigm for PD patients allows an advanced gait therapy by training dynamic postural stability for the patient during walking. Motor impairment was rated by neurologists using the Unified Parkinson Disease Rating Scale part III (UPDRS-III) and Hoehn and Yahr (H&Y) disease staging at baseline, after eight weeks of intervention, and after three months follow-up visit. Sensor-based gait analysis was used to evaluate effects on gait impairment in standardized walking tests (10 m walk, 2 minutes walk test, Timed up and go (TUG)), and an instrumented force plate assessed balance. Immediate effects directly after one training session and intermediate effects after eight weeks of intervention were analyzed. We observed that EG significantly increased overground walking speed immediately after intervention as compared to CG. Furthermore, gait variability decreased more dominantly after treadmill walking with these perturbations as compared to treadmill walking without. After eight weeks of intervention both groups improved motor symptoms using the UPDRS-III and H&Y disease staging. EG showed more marked effects on balance (part of UPDRS-III and instrumented force plate), gait (part of UPDRS-III), gait variability (sensor-based gait analysis), maximum walking distance in the 2 minutes walk test, and TUG test. In conclusion, the study revealed three major findings:

- (1) Perturbed treadmill training is feasible in mild to moderate affected PD patients
- (2) Gait and balance improve after eight weeks of perturbation treadmill training
- (3) The sensor-based gait analysis system allows gait assessment under standardized and supervised laboratory test conditions.

Currently, this interdisciplinary study will be analyzed and prepared for publication. In OA, we investigated if a mobile gait analysis system is able to reliably detect osteoarthritic gait dysfunction. Therefore, gait patterns from end-stage knee osteoarthritis patients and from age and gender matched healthy controls were collected. Gait parameters that are related to gait variability (stride-to-stride fluctuations) including stance time variability, swing time variability, stride length variability and stride time

variability are the most relevant parameters in discriminating between OA and controls (classification accuracies up to 92 %).

In addition, an innovative MR imaging method (T2-mapping) for high resolution has been validated in patients with an increased risk to develop ankle OA and established as a quantitative marker for compositional joint status. The effects on gait assessment before and after surgery are currently under investigation.



Image source: UK Erlangen

## Teaching

The multidisciplinary team offers different students and researchers from the three Faculties participating in the project the possibility to work together within their training programs achieving numerous insights and understandings that are required for the successful development of medical-technologies in future digital health applications. Not only students from the degree program Medical Engineering, but also medical students, sport scientists, Master and PhD students of physiotherapy, engineering, computer science, physics and biology were included in the different aspects of this project.



# ERC Starting Grant: Sorting of Self (SOS)

## Awardee

Prof. Dr. med. Gerhard Krönke  
Professorship for translational immunology

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## Aims and Structure

The European Research Council (ERC) was set up by the European Commission. ERC starting grants are funded with 1.5 million Euro and provide funding for top researchers for a time period of five years in order to promote basic research and visionary projects, and to enable new interdisciplinary fields to be explored.

The ERC awards starting grants to promising young researchers to give them the chance to establish their own research groups and to independently pursue research projects with great innovative potential.

Prof. Dr. G. Krönke finished medical school in Vienna before he spent two years as postdoc at the University of Virginia (USA). After moving to UK Erlangen in 2006, he started as clinical fellow at the Department for Internal Medicine 3 and in addition as research group leader at the Nikolaus Fiebiger Center for Molecular Medicine (in 2009). Since 2012 he is attending physician and was appointed as Professor of Translational Immunology in 2016. The ERC grant enabled him to recruit additional personal for his laboratory and to establish novel techniques to analyze and understand autoimmune diseases.

## Research

Aim of the project is the investigation of mechanisms that allow a segregated clearance of dying cells and pathogens during inflammation. The non-immunogenic clearance of dying cells is vital to dispose autoantigens and prevent autoimmunity. A defective clearance eventually results in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematoses. Insights into underlying mechanisms should foster novel therapeutic approaches for the treatment of such diseases.

## Teaching

Prof Dr. G. Krönke is engaged in teaching medical students and students of molecular medicine.

He supervises Bachelor's and Master's theses as well as MD and PhD theses.



Photo: Erich Malter

# 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 German Council of Science and Humanities and the Conference of the Ministers of Education and Cultural Affairs to support clinical research and teaching. A total of 1.3 million Euro 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.

In 2016, ELAN was integrated under the umbrella of IZKF (compare own report). Due to financial support by FAU (ETI program), the ELAN program could be opened for all young researchers of the Faculty of Medicine.

## 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 2016, a total of 979 grant applications were received (2015: 36, 2016: 27), 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. Whereas the average funding per project increased to 44,000 Euro in both years, the total amount of granted money decreased to 1.58 and 1.2 million Euro annually due to a lower number of grants. External peer review of grant proposals is required for funding requests above 20,000 Euro. 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 core research areas, infection and immunology research (half of all applications) and the growing core research area tumor research (up to one third of all applications).

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 two to three 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 four to five years after approval of the grant.

All except one project of 2012 are completed and documented by a final report. 60 % of the grants led to at least one accepted publication and 25 % led to external funding. External funding following an ELAN funding amounts to more than 1.7 million Euro, thus indicating a higher income than investment. Parental leave and change of jobs account for missing reports and/or a lack of results in terms of publications or external funding.

In conclusion, the ELAN program has successfully stimulated high quality research projects from all clinical departments. The lower number of applications due to a restriction to younger researchers (the age limit is 38 years) was wanted as the amount distributed per grant increased whereas the total budget was pared at the same time.

The majority of finished projects resulted in a visible success. This emphasizes the value of this program as a tool to dynamically improve clinical research within the Faculty of Medicine.



# Jakob-Herz-Prize

## Speaker

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

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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 2016, the Faculty of Medicine elected Professor Dr. F.H. Gage for the Jakob-Herz-Prize. Prof. Dr. F.H. Gage is director of the Gage Lab, a laboratory of genetics at the renowned Salk Institute for Biological Studies in La Jolla, California. He holds the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases at the Department of Neurosciences of the University of California in San Diego.

Prof. Dr. F.H. Gage was the first to show that the human hippocampus generates new neurons. Following this basic observation, his work concentrated on the ability of the brain to change not only its structural characteristics, but also its function, a process defined in neuroscience as plasticity. In general, plasticity reflects the brain's capacity to adapt to environmental stimuli. In particular, his findings showed that environmental and cognitive enrichment as well as physical exercise have a tremendous influence on adult hippocampal neurogenesis. Prof. Dr. F.H. Gage's efforts continue to this day as he tries to dissect the molecular and genetic foundations that regulate hippocampal neurogenesis in order to define the nature of these newborn neurons and potentially to use this knowledge as a window to repair damaged or aged nerve cells. His current work also aims at answering basic questions, such as how genes, in concert with the environment, shape the central nervous system leading to the evolution of the human brain, to individual differences in how we think, memorize and behave or suffer from different neurological or psychiatric diseases.

Prof. Dr. F.H. Gage has published more than 750 articles and his work has been quoted more than 66,000 times. He received three honorary doctorates and multiple awards.



*Prize-giving ceremony 2016  
from left to right: Prof. Dr. J. Hornegger (President), Prof.  
Dr. F.H. Gage (awardee), Prof. Dr. Dr. h.c. J. Schüttler  
(Dean)*

# Cord-Michael Becker-Prize

## Speaker

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

## Address

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Phone: +49 9131 8524638  
Fax: +49 9131 8522224  
molmed-info@fau.de  
[www.med.fau.eu/faculty/honors-and-prizes](http://www.med.fau.eu/faculty/honors-and-prizes)

## Announcement and Aim

Since 2013, the Faculty of Medicine and the Research Foundation of Medicine (compare own report) 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 (compare own report) at FAU. The prize is endowed with 5,000 Euro. It is awarded to graduates of all degree 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.

## Awardee of 2015

In 2015, Dr. S. Ganai-Vonarburg was awarded the Cord-Michael Becker-Prize for her dissertation entitled "Role of the commensal microbiota and environmental signals in calibrating the responsiveness of non-mucosal immune cell populations". Dr. S. Ganai-Vonarburg studied Molecular Medicine at Albert-Ludwigs-University Freiburg. After finishing her diploma, she started her doctoral research at the Spemann Graduate School of Biology and Medicine at Albert-Ludwigs-University Freiburg. She investigated how microorganisms naturally occurring on the body affect the development and maturation of different types of immune cells. Her research helps to better understand the effects of changes in the microbial milieu through hygiene, lifestyle or antibiotics on the immune system. Currently, Dr. S. Ganai-Vonarburg is a post-doctoral researcher at the Department of Clinical Research - Gastroenterology/ Mucosal Immunology at the University of Berne (Switzerland).



(Left to right) Prof. Dr. C.-M. Becker (in front), Prof. Dr. B. Fleckenstein (Research Foundation of Medicine), Prof. Dr. Dr. h.c. J. Schüttler (Dean), Prof. Dr. A. Diefenbach (eulogist), Dr. S. Ganai-Vonarburg (awardee), Prof. Dr. D. Werner (Research Foundation of Medicine) (Photo: FAU)

# Advancement of women and gender research promotion

## Speaker

Prof. Dr. med. Kerstin Amann

## Deputies

Prof. Dr. rer. nat. Ursula Schlötzer-Schrehardt  
Prof. Dr. (TR) Yesim Erim

## Address

Women's Representative Office of the  
Faculty of Medicine  
Division of Nephropathology  
Krankenhausstraße 8-10  
91054 Erlangen  
Phone: +49 9131 8522291  
Fax: +49 9131 8524724  
kerstin.amann@uk-erlangen.de  
www.frauenbeauftragte.med.fau.de

## Aims and Structure

The women's representative of the Faculty of Medicine was placed at the disposal of academic staff of 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 March 20, 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 from 11 % (2011) to 15 % (2017)
- Increase in the number of female W3-professors 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  
ARIADNEmed mentoring program, aimed at potential young female researchers in the postdoctoral and postgraduate phase, started in October 2008 as one part of the target agreement for the promotion of women in science. The core of the program is 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. The fourth round with 15 mentees ended in May 2015 and initiated the fifth round, with 16 new mentees partici-

pating, including six physicians, seven scientists, one pedagogue, one psychologist and one sports scientist.

## Gender mainstreaming

Building on the FAU efforts to raise the number of female professors by headhunting and gender appropriate appointment proceedings, ARIADNEmed mentees are furthermore involved in the relevant appointment committee, exercising an advisory function. To make appointment processes more transparent, one further female expert is – in addition to the woman's representative – 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 FAU monitors the appointment process in order to achieve a consequent, systematic, and consistent integration of gender aspects.

## 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 field 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 2015 and 2016, five applications were supported with a total funding of 3,600 Euro.

## Public relations

Since October 2016 the woman's representative of the Faculty of Medicine has her own website. The website offers detailed information on the target agreement and gives further information on topics, such as sexual harassment.

### Gender Lectures

Vortragsreihe für Studentinnen und Mitarbeiterinnen an der Medizinischen Fakultät und am Klinikum

**Dienstag, 23. Februar 2016 um 17.30 Uhr**

**OÄ Dr. med. Petra Zöbelein**  
Betriebsärztliche Dienststelle, FAU Erlangen-Nürnberg

**„Wissenswertes für Schwangere am Arbeitsplatz Krankenhaus“**

**Veranstaltungsort**  
Pathologisches Institut  
Bibliothek (Raum Nr. 02.134), 2. OG  
Krankenhausstraße 8-10, 91054 Erlangen  
Bitte benutzen Sie den Eingang gegenüber der Anatomie

Benötigen Sie eine Kinderbetreuung für die Dauer der Veranstaltung?  
Melden Sie sich beim Familienservice der FAU und des Universitätsklinikums.  
(www.familien-service.fau.de)

[www.gender-and-diversity.fau.de](http://www.gender-and-diversity.fau.de)




### Gender Lectures

Vortragsreihe für Studentinnen und Mitarbeiterinnen an der Medizinischen Fakultät und am Klinikum

**Dienstag, 13. Dezember 2016 um 17.30 Uhr**

**Dr. med. Maya Niethard**  
OÄ am HELIOS Klinikum Berlin-Buch und Initiatorin des Projekts OPIDS (Operieren in der Schwangerschaft)

**„Operieren in der Schwangerschaft - Möglichkeiten und Hindernisse“**

**Bitte melden Sie sich für den kostenfreien Vortrag an:**  
[www.frauenbeauftragte.med.fau.de/2016/10/vortrag/](http://www.frauenbeauftragte.med.fau.de/2016/10/vortrag/)

**Veranstaltungsort**  
Bibliothek (Raum Nr. 02.134), 2. OG, Pathologisches Institut  
Krankenhausstraße 8-10 (Eingang gegenüber Anatomisches Institut)

Benötigen Sie eine Kinderbetreuung für die Dauer der Veranstaltung?  
Melden Sie sich beim Familienservice der FAU und des Universitätsklinikums  
Erlangen.  
(www.familien-service.fau.de)

[www.frauenbeauftragte.med.fau.de](http://www.frauenbeauftragte.med.fau.de)

# Research Foundation of Medicine

## Speaker

Prof. Dr. med. Werner G. Daniel

## Address

Research Foundation of Medicine  
at the UK Erlangen  
Ulmenweg 18  
91054 Erlangen  
Phone: +49 9131 8535301  
Fax: +49 9131 8535303  
forschungsstiftung@uk-erlangen.de  
www.forschungsstiftung.uk-erlangen.de

## Donation 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 Faculty of Medicine. The initial capital stock of almost 150,000 Euro was given by 36 founder members – mainly directors of departments and institutes – out of their personal assets. The Research Foundation of Medicine at the UK Erlangen 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,
- Benevolence within the medical care of patients in need.

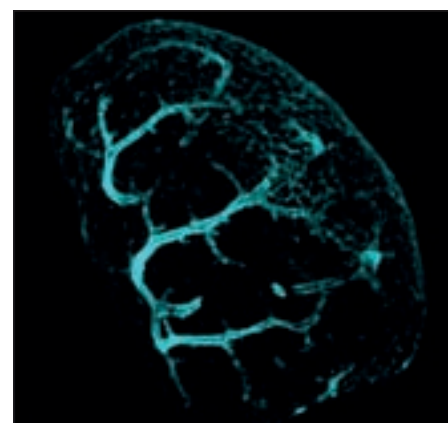
## Development

The Research Foundation of Medicine provides attractive honors and stimulations for sponsors: Donators of 10,000 Euro 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 Euro it becomes possible to establish an separate foundation bearing one's name within the Research Foundation of Medicine, and in certain cases a lecture hall may be named after a particularly generous sponsor (e.g. the RudolfWöhrl-Hörsaal and Ernst-Freiberger-sen.-Hörsaal). 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 converted Euro sum) contributed to the successful development. Thus, between 2011 and 2016 the Research Foundation of Medicine was able to distribute approximately 3.7 million Euro 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 donors for funding immensely. This concept is successfully practiced in other countries, as e. g. USA and UK.

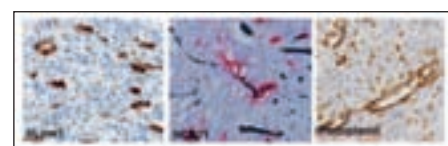
The Research Foundation of Medicine at the UK Erlangen has meanwhile supported a large number of projects. This is true for many clinical or basic research projects as well as for the "Erlanger Medizinische Bürgervorlesung", a series of 12 – 14 lectures on up-to-date medical topics, initiated in 2007 and addressed each term to interested citizens. During the last 20 terms, the "Erlanger Medizinische Bürgervorlesung" has reached a large audience (200 – 400 participants each lecture), numerous lectures were also broadcasted by television, and in 2012 the "Erlanger Medizinische Bürgervorlesung" was awarded with the Erlanger Medizinpreis. For the fourth time, the Research Foundation of Medicine – together with the Faculty of Medicine – has given the Jakob-Herz-Prize (compare own report) to an outstanding researcher in the field of medicine: In 2016, Prof. Dr. F. H. Gage, Salk Institute for Biological Studies, La Jolla, California, was the awardee. Since 2013, the Research Foundation of Medicine and the Faculty of Medicine award the Cord-Michael Becker-Prize (compare own report) for an outstanding doctoral research study in Molecular Medicine. In 2015, the prize was received by Dr. S. Ganai-Vonarburg (Freiburg and Bern). 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 2015, Dr. M. Müller (Institute of Pathology) and Dr. T. Jobst-Schwan (Department of Medicine 4), and in 2016, Dr. D. Wolff (Institute of Human Genetics) and Dr. M. Schüler (Institute of Physiology and Pathophysiology) were awarded this prize for their outstanding theses.

Figures from research projects funded by the Research Foundation of Medicine:



3D-reconstruction of arterial vessels in an embryonic mouse kidney using 200 confocal laser microscopy scans. PD Dr. C. Daniel, Division of Nephropathology. Project title: Aquisition of a continuous license of a "Voloom-Software" for 3D-reconstruction, based on histologic slices or confocal microscopy images



Development of new blood vessels and lymphatic vessels in the AV-loop model of the rat. Blood vessels (CD31) and lymphatic vessels (Lyve and Podoplanin). Dr. A.M. Boos, Prof. Dr. Dr. h.c. R.E. Horch, Department of Plastic and Hand Surgery. Project title: Development of an autonomous lymphatic system for use in regenerative medicine and as a model for research of lymphangiogenesis and anti-lymphangiogenesis



# Johannes and Frieda Marohn-Foundation

## Head of the Scientific Board (since October 2015)

Prof. Dr. Christian Alzheimer

## Contact

Vasiliki Ikonomidou

Johannes and Frieda Marohn-Foundation –  
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Universitätsstraße 19

91054 Erlangen

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vasiliki.ikonomidou@fau.de

## 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 of 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 co-operation costs between scientific and clinical departments.

Grant applications should be sent to the head of the scientific board. The rules of the Foundation are available at the office of the Johannes and Frieda Marohn-Foundation.

## Accepted projects (Time of funding 2015 – 2016)

Financial year	Budget	Number of accepted applications
2015	303.673,09 €	2 (23.199,37 €)
2016	403.406,27 €	13 (352.391,96 €)

## Finalized projects (Time of funding 2015 – 2016)

Number of projects	Number of publications	Continued funding by other foundations*
19	28	8

\* DFG: Five projects

Other foundations: Three projects

Eleven 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. Furthermore, every three years, a reputed physician engaged in meritorious surgical medicine is awarded the Dr. Fritz Erler Research Award.
- 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.
- The Ria Freifrau von Fritsch Foundation endows a prize for young investigators in cancer research.
- 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.
- 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.
- The Dr. Ernst and Anita Bauer Foundation is an independent foundation based in Nuremberg. 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.
- The Thiersch Prize is awarded annually for the best and most concise postdoctoral qualification (Habilitation). In 2016, Dr. C. Beyer (Department of Medicine 3) was awarded with the Thiersch-Preis for his outstanding habilitation dissertation.
- The Staedtler Prize, provided by the Staedtler-Foundation, honors outstanding doctoral theses. The Staedtler-Foundation furthermore provides generous support for research project.
- 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 H2 – Körperschaft und Stiftungen, provides further details upon request.

# Physico-Medical Society Erlangen

## Managing Committee

Prof. Dr. med. Christian Bogdan  
(Chairman)

Prof. V. Sandoghdar, PhD  
(Vice Chairman)

Prof. Dr.-Ing. Dr. rer. med. Ulrich Hoppe  
(Secretary)

Prof. Dr. med. Friedrich Paulsen  
(Treasurer)

## Contact

Prof. Dr. med. Christian Bogdan  
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and Hygiene  
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Fax: +49 9131 85 22573  
christian.bogdan@uk-erlangen.de  
www.physicomedica-erlangen.de

## Aims and Structure

The Physico-Medical Society Erlangen (PMSE), also known as Societas physico-medica Erlangensis, was founded on March 20, 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 18, 2008, the PMSE celebrated its 200<sup>th</sup> birthday in a ceremony at the castle of the FAU. In the year of the 200<sup>th</sup> birthday of the PMSE, the Medical Society which had separated from the PMSE in 1958 after the 150<sup>th</sup> birthday celebration of the Societas physico-medica Erlangensis merged again with the PMSE.

As of June 8th, 2016, the Society has 344 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

10.3.2015 Prof. Dr. M. Schäfer-Korting, Freie Universität Berlin  
Innovative Techniken in der Pharmakologie und Toxikologie - Krankheitsmodelle und „Human-on-the-Chip“

10.6.2015 Prof. Dr. G. J. Hämmerling, German Cancer Research Center (DKFZ)  
Strategic manipulation of the tumor microenvironment for efficient immunotherapy of cancer

15.7.2015 em. Univ.-Prof. Dr. M. Heller, Klinik für Diagnostische Radiologie, UKSH  
Virtuelle Autopsie in Forensik und Klinik

8.6.2016 Prof. C. H. Contag, PhD, Stanford University School of Medicine  
Insertable, implantable and wearable micro-optical devices for the early detection of cancer

20.6.2016 Prof. Dr. T. Moser, Universitätsmedizin Göttingen  
Hören mit Licht – Entwicklung eines optischen Cochlear Implants

22.6.2016 Professor K. N. Dahl, PhD, Carnegie Mellon University  
Nuclear biomechanics and cellular phenotype

27.6.2016 Prof. Dr. G. Koenderink, FOM Institute for Atomic and Molecular Physics (AMOLF)  
Physics of cellular form and function

13.7.2016 Prof. A. C. Rowat, PhD, University of California  
Cancer cell mechanotype: from screening to disease biophysics

7.12.2016 Prof. C. Yang, California Institute of Technology  
Focusing light into biological tissues with wavefront engineering

30.11.2016 Prof. Seok-Hyun Yun, Harvard-MIT Health Sciences and Technology  
Bio-lasers for imaging



# Selection of Honors and Prizes

## 2015

### **Honorary professor of the Huazhong University of Science and Technology, Wuhan, China**

**Prof. Dr. Dr. h.c. Jürgen Schüttler**

Department of Anesthesiology

### **Honorary professor of the State Medical University of Turkmenistan**

**Prof. Dr. Dr. h.c. Raymund E. Horch**

Department of Plastic and Hand Surgery

### **Honorary professor of the State Medical University of Turkmenistan**

**Prof. Dr. Dr. h.c. Klaus Tschaiakowsky**

Department of Anesthesiology

### **Member of the Academy of Sciences and Literature (Mainz), mathematic and scientific class**

**Prof. Dr. Kai-Uwe Eckardt**

Department of Medicine 4 – Nephrology and Hypertension

### **Honorary member of the French Neurological Society**

**Prof. Dr. Dr. h.c. Stefan Schwab**

Department of Neurology

### **Honorary member of the European Pain Federation**

**Prof. Dr. Dr. h.c. Hermann O. Handwerker**

Institute of Physiology and Pathophysiology

### **Honorary member of the German Society for Radiation Oncology**

**Prof. Dr. Dr. h.c. Werner Hohenberger**

Department of Surgery

### **Honorary member of the Associazione Italiana per lo Studio del Sistema NeuroVegetativo**

**Prof. Dr. Max-Josef Hilz**

Department of Neurology

### **Adolf-Wallenberg award**

**Prof. Dr. Hagen Huttner**

Department of Neurology

### **Commemorative Medal of the Comenius-University Bratislava**

**Prof. Dr. Friedrich Paulsen**

Chair of Anatomy II

### **Gold Medal (Society of Cardiovascular Computed Tomography)**

**Prof. Dr. Stephan Achenbach**

Department of Medicine 2 – Cardiology and Angiology

### **Paul-Ehrlich-und-Ludwig-Darmstaedter junior award**

**Prof. Dr. Raja Atreya**

Department of Medicine 1 –

Gastroenterology, Lung Diseases, and Endocrinology

### **Karl-Heinrich-Bauer award**

**Prof. Dr. Roland S. Croner**

Department of Surgery

### **Sertürner award**

**Dr. Matthias Engel**

Department of Medicine 1 –

Gastroenterology, Lung Diseases, and Endocrinology

### **Alfred-Breit award**

**Prof. Dr. h.c. Willi A. Kalender, PhD**

Institute of Medical Physics

### **Eugenie-und-Felix-Wachsmann award**

**Prof. Dr. Rolf Janka**

Institute of Radiology

### **Carol-Nachman award**

**Prof. Dr. Georg Schett**

Department of Medicine 3 – Rheumatology and Immunology

### **Eugen-Rehfish award**

**Dr. Verena Huppert**

Department of Urology

### **Otto-von-Guericke medal**

**Prof. Dr. Dr. h.c. Raymund E. Horch**

Department of Plastic and Hand Surgery

### **Chugai Science award**

**Dr. Ulrike Harre**

Department of Medicine 3 – Rheumatology and Immunology

### **bioMérieux diagnostics award**

**Dr. Jürgen Held**

Institute of Clinical Microbiology, Immunology, and Hygiene



## 2016

**Honorary member of the British Institute of Radiology**  
**Prof. Dr. Stephan Achenbach**

Department of Medicine 2 – Cardiology and Angiology

**Honorary member of the British Anatomical Society**  
**Prof. Dr. Friedrich Paulsen**

Chair of Anatomy II

**Honorary member of the German Society of Surgery, the  
 Amercian Society of Colorectal Surgeons and the European  
 Society of Coloproctology**

**Prof. Dr. Dr. h.c. Werner Hohenberger**

Department of Surgery

**Honorary member of the German Society of Anesthesiology  
 and Intensive Care Medicine**

**Prof. Dr. Dr. h.c. Jürgen Schüttler**

Department of Anesthesiology

**Vice-chairman of section 23 of the National Academy  
 of Sciences Leopoldina**

**Prof. Dr. Karl-Heinz Leven**

Institute of the History of Medicine and Medical Ethics

**Martin-Gülzow award**

**Dr. Rocío López-Posadas, Dr. Imke Atreya**

Department of Medicine 1 –

Gastroenterology, Lung Diseases, and Endocrinology

**Wilhelm-Feuerlein research award**

**Dr. Eva Hoch, PD Dr. Bernd Lenz, Prof. Dr. Christian P. Müller,**

**Prof. Dr. Johannes Kornhuber**

Department of Psychiatry and Psychotherapy

**Ritter-von-Frisch award**

**Prof. Dr. Bernd Wullich**

Department of Urology

**von-Langenbeck award**

**PD Dr. Georg Weber**

Department of Surgery

**Award for clinical studies (German Cancer Society)**

**Prof. Dr. Rolf Sauer**

Department of Radiation Oncology

**Junior research award (German Parkinson Association)**

**Ben Ettle**

Division of Molecular Neurology

**Research award (German Ophthalmological Society)**

**Dr. Martin Schicht**

Chair of Anatomy II

**Award to promote rehabilitation research**

**Prof. Dr. Wolfgang Kemmler**

Institute of Medical Physics

**Young Scientist Award (Competence Network Stroke)**

**Dr. Joji Kuramatsu**

Department of Neurology

**Research award (German Society for Vascular Surgery  
 and Vascular Medicine)**

**Dr. Alexander Meyer**

Department of Surgery

**Heinricht-Pette award**

**Prof. Dr. Ralf Linker**

Department of Neurology

**GIST-award**

**Prof. Dr. Abbas Agaimy**

Institute of Pathology

# International mobility of scientists

## Visiting scientists \*

### Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology

- Project title: Gada 4  
PI: Prof. Dr. C. Becker  
Dr. J. Patankar from Canada (since 2016)
- Project title: The regulation and pathophysiological role of epithelial cell death in the gut  
PI: Prof. Dr. C. Becker  
Yueqiang Yu from China (since 2015)

### Department of Medicine 3 – Rheumatology and Immunology

- Project title: Antimodified protein antibody response pattern influences the risk for disease relapse in patients with rheumatoid arthritis tapering disease modifying antirheumatic drugs  
PI: Prof. Dr. G. Schett  
Dr. C. P. Figueiredo from Brazil (2014-2016)
- Project title: Effects of DMARD on citrullinated peptide autoantibody levels in RA patients – A longitudinal analysis  
PI: Prof. Dr. G. Schett  
Dr. I. D'Oliviera from Brazil (2014-2017)
- Project title: Arthritis and immune-mediated bone loss  
PI: Prof. Dr. G. Schett  
Dr. C. Engdahl from Sweden (2015-2017)
- Project title: Revealing the interaction between inflammation and bone loss  
PI: Prof. Dr. G. Schett  
Dr. O. Yasunuri from Japan (2015-2017)
- Project title: Immunomodulation durch apoptotische und nekrotische Zellen und Annexine  
PI: Prof. Dr. G. Schett  
R. Bilyy, PhD, from Ukraine (2015-2016)
- Project title: Microbiota from Obese Mice Regulate Hematopoietic Stem Cell Differentiation by Altering the Bone Niche  
PI: Prof. Dr. G. Schett  
Dr. Y. Luo from China (2012-2016)

### Department of Medicine 4 – Nephrology and Hypertension

Project title: Tissue sodium storage  
PI: Dr. F. Knauf  
Dr. R. Evans from UK (2016-2017)

### Department of Neurology Division of Molecular Neurology

- Project title: Feasibility of normal and pathological gait assessment by using smart devices in unconstrained circumstances  
PI: Prof. Dr. J. Winkler  
Dr. S. Šprager from Slovenia (2016)
- Project title: Wearable sensors for personal health recordings  
PI: Prof. Dr. J. Winkler  
Prof. Dr. C. A. da Costa from Brazil (2016)

### Department of Operative Dentistry and Peridontology

Project title: Eigenspannungen in dentalen Keramiken  
PI: Prof. Dr.-Ing. U. Lohbauer  
Dr. M. Wendler from Chile (2013-2017)

### Department of Plastic and Hand Surgery

Project title: Tumorangiogenese und -vaskulogenese beim Mammakarzinom  
PIs: Dr. A. Weigand / Dr. A. Boos  
Dr. R. An from China (2016–2018)

### Department of Urology

Project title: Effect of heart glycosides in urological tumor cells  
PIs: Prof. Dr. H. Taubert / Prof. Dr. W. Kreis  
Dr. I. Thais da Silva from Brazil (2015)

### Institute of Biochemistry Professorship of Bioinformatics

Project title: Conformational control of ion channels  
PI: Prof. Dr. H. Sticht  
Prof. Dr. H.-G. Bretinger from Egypt (2015, 2016)

### Institute of Clinical and Molecular Virology

Project title: Functional analysis of human cytomegalovirus (HCMV) pp71, elucidating the roles in lytic infection and latent infection  
PI: Prof. Dr. T. Stamminger  
T. Maeki, MD, from Japan (2014-2016)

### Institute of Pathology

- Project title: Hospitation for immunohistochemical evaluation of CRC-samples  
PI: Prof. Dr. R. Schneider-Stock  
Dr. A. Vial Roehe from Brazil (2016)
- Project title: p21 and colorectal cancer stem cells  
PI: Prof. Dr. R. Schneider-Stock  
Prof. Dr. P. Chanvorachote from Thailand (2015, 2016)

### Institute of Pathology Division of Nephropathology

Project title: Training in nephropathology  
PI: Prof. Dr. K. Amann  
Dr. T. Chuva from Portugal (2016)

### Institute of Physiology and Pathophysiology

- Project title: Photosensation (ALA, PpIX, 7-DHC); TRPV4  
PI: Prof. Dr. P. Reeh  
Prof. A. Babes from Romania (2015, 2016)
- Project title: GABA receptor function  
PI: Prof. Dr. C. Alzheimer  
Dr. H. van Brederode from the USA (2015)

## FAU scientists going abroad \*

### Department of Medicine 2 – Cardiology and Angiology

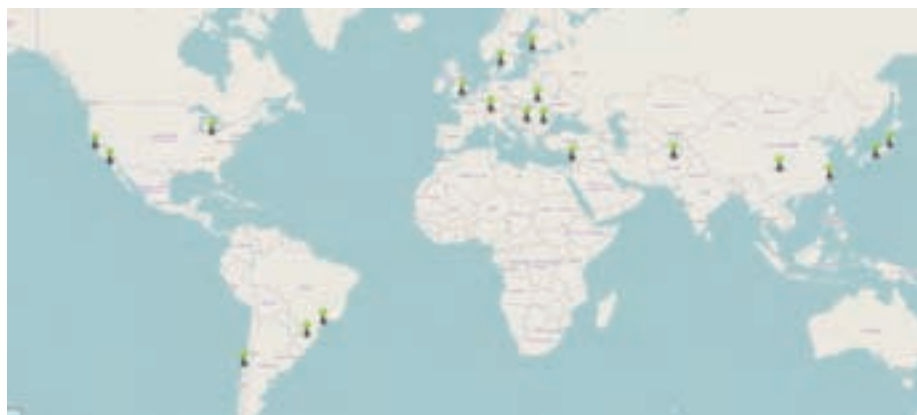
Project title: Coronary CTA  
PI: Prof. Dr. S. Achenbach  
Dr. D. Bittner in the USA (2015-2016)

### Department of Medicine 4 – Nephrology and Hypertension

- Project title: Mechanisms of cyst development  
PI: Dr. F. Knauf  
Dr. M. Krappitz in the USA (2015-2016)
- Project title: Genetic basis of the nephrotic syndrome  
PI: Prof. Dr. K.-U. Eckardt  
Dr. T. Jobst-Schwan in the USA (2016)

### Department of Neurology

- Project title: Invasive EEG-derivative in humans  
PI: Prof. Dr. H. Hamer  
Dr. S. Gollwitzer to UK (2014-2015)
- Project title: PhD Program  
PI: Prof. Dr. H. Huttner  
Prof. Dr. H. Huttner to Sweden (2015, 2016)



# Doctorates theses, habilitations\*, board qualifications, additional qualifications

## Institute of Anatomy

### Chair of Anatomy I

#### Doctorate theses 2015

**Beuscher, Nicholas**, Dr. med.: Was für Neuroonen werden durch Calretinin-Immunreaktivität im menschlichen Darm markiert?

#### Doctorate theses 2016

**Bermel, Christina**, Dr. med.: Vaskularisation der dorsalen Basis des zweiten Mittelhandknochens – Eine anatomische Studie unter Verwendung von C-Arm Cone Beam Computertomographie

**Hermann, Franz**, Dr. med.: Untersuchungen zu einer möglichen zirkadianen Rhythmik bei Intrinsic Choroidalen Neuronen am Hühnerauge

**Keylen, Piet van der**, Dr. rer. biol. hum.: Katecholaminerge Innervation der quergestreiften Muskulatur im Mäuse- und Rattenösophagus

**Strauß, Vanessa**, Dr. med. dent.: Topografische Beziehung chemisch definierter Neuronenpopulationen zu mukosalen Stammzellen im Magen der Maus

## Institute of Anatomy

### Chair of Anatomy II

#### Doctorate theses 2015

**Hoffmann, Kathrin**, Dr. med.: Charakterisierung der Expression von Osteopontin und damit assoziierter Rezeptorproteine an der Augenoberfläche

**Schob, Stefan**, Dr. med.: The Detection of Surfactant Proteins A, B, C and D in the Human Brain and their Regulation in Cerebral Infarction, Auto-immune Conditions and Infections of the CNS

**Wild, Katharina**, Dr. med.: Strategien gegen Burnout und Angststörungen in der medizinischen Lehre – Einführung und Beurteilung eines neuen Kurses zum Erlernen von Entspannungstechniken (Relacs) für Studierende der Medizin

#### Doctorate theses 2016

**Ackermann, Philipp**, Dr. med.: Isolation und Charakterisierung adulter Tränendrüsenstammzellen

**Henker, Robert**, Dr. med.: Morphologische Eigenschaften der Tränendrüse des Schweins und ihre Eignung als Xenotransplantat für den Menschen

#### Habilitation 2016

**Hampel, Ulrike**, PD Dr. med.: Untersuchungen zur kornealen Wundheilung und der Meibom-Drüsen Dysfunktion

#### Board qualification 2015

**Eichhorn, Michael**, Prof. Dr. med.

**Hampel, Ulrike**, Dr. med.

#### Additional qualification 2016

**Garreis, Fabian**, Dr. rer. nat.: Fachanatom Anatomische Gesellschaft

**Hammer, Christian**, Dr. rer. nat.: Fachanatom Anatomische Gesellschaft

## Institute of Biochemistry –

### Emil-Fischer-Center

#### Chair of Biochemistry and Pathobiochemistry

#### Doctorate theses 2015

**Arter, Juliane**, Dr. rer. nat.: Einfluss von Sox-Proteinen auf transkriptionelle Elongation und Homöostase in Säuger-Gliazellen

**Bischof, Melanie**, Dr. rer. biol. hum.: Beitrag des Brg1-abhängigen Chromatin-remodellierenden Komplexes zur oligodendroglialen Differenzierung in Mus musculus

**Hoffmann, Stephanie**, Dr. rer. nat.: Die Rolle der Transkriptionsfaktoren Sox2 und Sox3 für die Entwicklung von Oligodendrozyten in Mus musculus

#### Doctorate theses 2016

**Fröb, Franziska**, Dr. rer. nat.: Das Zusammenspiel der Transkriptionsfaktoren Sox10 und Myrf und des Chromatin-Remodellierers p400 in myelinisierenden Gliazellen der Maus

#### Habilitation 2015

**Eulenburger, Volker**, PD Dr. rer. nat.: Differenzierte Funktion von Glycintransportern exprimiert in Neuronen und Gliazellen

## Institute of Biochemistry –

### Emil-Fischer-Center

#### Professorship of Bioinformatics

#### Doctorate theses 2015

**Stump, Joachim**, Dr. rer. nat.: Computational study of herpesviral proteins involved in host-pathogen interaction

#### Habilitation 2016

**Jardin, Christophe**, PD Dr.: Prediction of protein interactions using molecular docking

## Institute of Physiology

### and Pathophysiology

#### Chair of Physiology

#### Doctorate theses 2015

**Hartmann, Elisabeth**, Dr. med.: Psychophysik und fMRT bei histaminergem und nicht-histaminergem Juckreiz

**Kallenberger, Stefan**, Dr. med.: Separating visual fusion from binocular rivalry by fMRI

**Link, Andrea**, Dr. rer. nat.: Activating signaling as a molecular target in antidepressant therapy

**Schüler, Markus**, Dr. med.: Extrakranielle Projektion meningealer Afferenzen von Ratte und Mensch und ihr Einfluss auf die meningeale Nozizeption

**Schuy, Theresa**, Dr. med.: Resurgent Na<sup>+</sup>-Strom in Nav1.6-überexprimierenden Neuroblastomzellen

**Tröltzsch, Matthias**, Dr. med.: Seltene Ursachen des Kopf-, Kiefer- und Gesichtsschmerzes – ein Überblick über Pathogenese, Diagnostik und Therapie ausgewählter Krankheitsbilder anhand von Originalarbeiten und Fallstudien

**Übner, Michael**, Dr. med.: Aktivitätsabhängige Modulation mechanisch evozierter Entladungen meningealer Afferenzen der Ratte

#### Doctorate theses 2016

**Eberhardt, Esther**, Dr. med.: Funktionelle Charakterisierung spannungsabhängiger Natriumkanäle in humanen stammzell-abgeleiteten Nozizeptoren

**Kageneck, Charlotte Gräfin von**, Dr. med.: Eine neue Methode zur Freisetzung von Calcitonin gene-related peptide aus Hirnstamm-schnitten der Maus zeigt hemmende Effekte von Naratriptan und Kynurensäure am spinalen Trigemuskern

**Müller-Tribbensee, Sonja**, Dr. med.: Die Rolle der sensorischen Ionenkanäle TRPA1, TRPV4 und TRPM8 bei der Schmerzverarbeitung im Colon der Maus

**Schick, Maximilian**, Dr. med. dent.: Unterschiedliche Sensibilisierung von mechano-insensitiven und mechano-sensitiven Nozizeptoren des Menschen durch Prostaglandin E2

**Wild, Vanessa**, Dr. med. dent.: Schwefelwasserstoff als limitierender Faktor bei der HNO-induzierten Stimulation von trigeminalen Afferenzen

#### Habilitation 2015

**Huth, Tobias Ingo**, PD Dr. med. Dr. rer. nat.: Interaktion von  $\beta$ -site APP-cleaving enzyme 1 (BACE1) und Neuropharmaka mit Ionenkanälen

#### Board qualification 2016

**Fischer, Michael**, Prof. Dr.

**Huth, Tobias Ingo**, PD Dr. med. Dr. rer. nat.

## Institute of Cellular and Molecular Physiology

### Chair of Physiology (Systems Physiology)

#### Doctorate theses 2016

**Frost, Fabian**, Dr. med.: Der Effekt von Syntaxin 2, 3 und 4 auf die Funktion des epithelialen Natriumkanals (ENaC) in Xenopus laevis Oozyten

**Hörner, Christian**, Dr. med.: Koexpressionsstudie in Xenopus laevis Oozyten zur Charakterisierung der funktionellen Interaktion zwischen dem Chloridkanal Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) und dem humanen epithelialen Natriumkanal (ENaC) in der  $\delta\gamma$ -Konfiguration

**Nacken, Regina**, Dr. rer. nat.: Mechanismen von Funktionsstörungen des epithelialen Natriumkanals (ENaC)

#### Additional qualification 2016

**Korbmacher, Christoph**, Prof. Dr. med.: Fachphysiologe (DPG)

**Volk, Tilmann**, Prof. Dr. med.: Fachphysiologe (DPG)

\* Postdoctoral qualification showing ability to lecture and do research at professorial level

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

**Doctorate theses 2015**

**Fersch, Anna**, Dr. med.: Burnout bei jungen Ärzten – eine Längsschnittuntersuchung zu möglichen Ursachen in Studium und Arbeitsleben  
**Flüh, Greta**, Dr. med.: Erfahrung bei der Durchführung eines betrieblichen Präventionsprogramms am Beispiel eines Screenings auf Osteoporose bei Beschäftigten eines Universitätsklinikums

**Weisbrich, Ruth**, Dr. med.: Untersuchungen zu Impfstatus und zum Antikörperstatus bei Beschäftigten einer Universitätskinderklinik

**Institute of Clinical and  
Molecular Virology**  
Chair of Clinical Virology

**Doctorate theses 2015**

**Niemann, Ina**, Dr. rer. nat.: The human cytomegalovirus-encoded G protein-coupled receptor pUS27 – a regulatory switch for canonical NF- $\kappa$ B activation

**Otto, Victoria**, Dr. med.: Funktionale Analyse der Interaktion des cytomegaloviralen Regulatorproteins IE1 mit SUMO-Proteinen

**Wagenknecht, Nadine**, Dr. rer. nat.: Analysis of the role of the subnuclear structure ND10 for latent and lytic replication of human cytomegalovirus

**Habilitation 2016**

**Gramberg, Thomas Hans Wolfgang**, Prof. Dr. rer. nat.: Die Rolle von SAMHD1 als Restriktionsfaktor der retroviralen Infektion  
**Milbradt, Jens Wilfried Rolf**, PD Dr. rer. nat.: Human Cytomegalovirus Nuclear Egress

**Institute of Clinical Microbiology,  
Immunology, and Hygiene**  
Chair of Microbiology and Immunology  
of Infection

**Doctorate theses 2015**

**Mahnke, Alexander**, Dr. med.: Der Einfluss von Sauerstoff auf die antimikrobielle Immunantwort

**Schulz, Theresia**, Dr. med.: Etablierung und Anwendung von Echtzeit-PCR Verfahren zur quantitativen Bestimmung der Parasitenbelastung bei kutaner und viszeraler Leishmaniose in vitro und in vivo

**Doctorate theses 2016**

**Knoll, Karin**, Dr. med.: Autochtone Leishmaniose in Bayern: Epidemiologische Untersuchungen zur Existenz tierischer Reservoirs

**Habilitation 2015**

**Lührmann, Anja**, PD Dr. rer. nat.: Modulation von Phagozyten durch Virulenzfaktoren intrazellulärer Erreger

**Institute of Clinical Microbiology,  
Immunology, and Hygiene**  
Division of Infection Biology

**Doctorate theses 2015**

**Oeser, Katharina**, Dr. rer. nat.: Role of T cells and innate immune cells as producers of IL-4 and IL-13 during helminth infections

**Schwartz, Christian**, Dr. rer. nat.: Basophil-mediated protection against gastrointestinal helminths

**Institute of Experimental and  
Clinical Pharmacology and Toxicology**  
Chair of Pharmacology and Toxicology

**Doctorate theses 2015**

**Hummel, Regina**, Dr. med.: Evaluierung des kardioprotektiven Potentials von Candesartan in zwei transgenen Mausmodellen mit dilatativer Kardiomyopathie

**Nguyen, Huong**, Dr. rer. nat.: Calcium-abhängige Mechanismen der Schrittmacheraktivität im murinen Sinusknoten

**Wank, Isabel**, Dr. rer. nat.: Neurobiologie der Schmerzchronifizierung: Korrelative Analysen strukturspezifischer funktioneller Änderungen der fMRT-BOLD-Antwort am Mausmodell

**Institute of Experimental and  
Clinical Pharmacology and Toxicology**  
Chair of Clinical Pharmacology and  
Clinical Toxicology

**Doctorate theses 2015**

**Hartmann, Nina**, Dr. med.: Evaluation von allgemeinen Patientensicherheitsindikatoren (PSI) in einer nicht-traumatischen medizinischen Notaufnahme

**Kittel, Anja**, Dr. rer. nat.: In vitro- und in vivo-Charakterisierung der Alanin-Glyoxylat-Aminotransferase 2 (AGXT2) als Enzym des Dimethylargininstoffwechsels: Untersuchungen am Zell- und Tiermodell sowie an gesunden Freiwilligen

**Pfistermeister, Barbara**, Dr. rer. nat.: Untersuchung zu Erkennung und Vermeidung von Risiken im Medikationsprozess  
**Ringel, Reingard**, Dr. med. dent.: Zahnärztliche Prozeduren bei Patienten, die Thrombozytenaggregationshemmer oder Antikoagulantien einnehmen – Umfrageergebnisse vom Deutschen Zahnärztetag 2011

**Doctorate theses 2016**

**Strobel, Joachim**, Dr. rer. nat.: Der proteinvermittelte Transport des kardiovaskulären Risikofaktors asymmetrisches Dimethylarginin und strukturähnlicher Substanzen

**Institute of Human Genetics**  
Chair of Human Genetics

**Doctorate theses 2015**

**Bauer, Judith**, Dr. med.: Identifizierung neuer Gene für autosomal rezessive Mentale Retardierung

**Popp, Bernt**, Dr. med.: De novo missense mutations in the NAA10 gene cause severe non-syndromic developmental delay in males and females

**Schanze, Denny**, Dr. rer. nat.: Systematische Analysen zur Identifikation der genetischen Ursache der Periodischen Katatonie

**Wolff, Dorit**, Dr. med.: Analyse des Kandidatengens SMARCA2 als Kandidatengen für mentale Retardierung

**Doctorate theses 2016**

**Al-Kaisi, Nadine**, Dr. med.: Gastrointestinale Stromatumoren bei Patienten unter 40 Jahre

**Buchert, Rebecca**, Dr. rer. nat.: Identifizierung und Charakterisierung der Kandidatengene FAR1, EDC3, FRRS1L, und HMG20A bei Individuen mit autosomal rezessiver mentaler Retardierung

**Eberlein, Caroline**, Dr. med.: Identifizierung von Genen für autosomal rezessive vererbte Intelligenzminderung

**Habilitation 2016**

**Pasutto, Francesca**, PD Dr. rer. nat.: Genetic basis of glaucoma

**Institute of Medical Informatics,  
Biometry, and Epidemiology**  
Chair of Medical Informatics

**Doctorate theses 2015**

**Patapovas, Andrius**, Dr. rer. biol. hum.: Stufenkonzept zur Alarmierung von Gefährdungssituationen bei Arzneimittelinformationssystemen

**Vollmer, Anne-Maria**, Dr. rer. biol. hum.: Entwicklung und Testung eines Modells zur Untersuchung soziotechnologischer Faktoren am Beispiel der elektronischen Pflegedokumentation

**Wagner, Stefan**, Dr. med.: Analyse, Modellierung und Optimierung der Dokumentations-, Diagnostik- und Therapieprozesse für verschiedene Tumorerkrankungen am Universitätsklinikum Erlangen

**Doctorate theses 2016**

**Gantner-Bär, Marion**, Dr. rer. biol. hum.: Konzeptionelle Modellierung für komplexe Situationen für Entscheidungsunterstützung im Gesundheitswesen

**Newe, Axel**, Dr. rer. biol. hum.: Ein generischer Algorithmus zur Erkennung temporaler Koinzidenzen zwischen Medikamentenapplikationen und Laborwertveränderungen

**Sedlmayr, Brita**, Dr. rer. biol. hum.: Benutzerzentrierte Entwicklung eines Navigations- und Visualisierungskonzepts für Entscheidungsunterstützungssysteme zur Verordnungsprüfung

**Habilitation 2016**

**Ganslandt, Thomas Herbert Ernst**, PD Dr. med.: Voraussetzungen, Rahmenbedingungen und Potentiale einer nachhaltigen Nutzung klinischer Routinedaten für die Forschung



## Institute of Medical Physics

Chair of Medical Physics

### Doctorate theses 2015

**Kellermeier, Markus**, Dr. rer. biol. hum.: Physical assessment of a novel concept for computed tomography with a stationary source ring of fixed X-ray anodes for medical imaging

**Rößler, Ann-Christin**, Dr. rer. biol. hum.: Patientenlagerung bei dedizierter Brust-CT

**Ruile, Georg**, Dr. rer. biol. hum.: Bewertung medizintechnischer Innovationen in der Frühphase der Produktentwicklung

**Saboori, Mohammadsaeed**, Dr. rer. biol. hum.: Development of a daily dosimetric control for radiation therapy using an electronic portal imaging device (EPID)

**Saltybaeva, Natalia**, Dr. rer. biol. hum.: Radiation dose calculation and optimization in Computed Tomography

**Steiding, Christian**, Dr. rer. biol. hum.: Verfahren zur automatisierten und objektiven Bildqualitätssicherung in der Kegelstrahlcomputertomographie

### Doctorate theses 2016

**Kuttig, Jan David**, Dr. rer. biol. hum.: Bildqualitätsuntersuchungen verschiedener Detekortechnologien für die dedizierte Brust-CT

**Paulus, Daniel**, Dr. rer. biol. hum.: Attenuation Correction in Integrated PET/MR Hybrid Imaging

## Institute of Neuropathology

Chair of Neuropathology

### Board qualification 2015

**Coras, Roland**, Dr. med.

## Institute of Pathology

Chair of General Pathology and Pathological Anatomy

### Doctorate theses 2015

**Knobloch, Katharina**, Dr. med.: Sessil serra-tierte Adenome als Subgruppe kolorektaler Polypen – eine Studie zu Häufigkeiten, diagnostischen Kriterien und Tumorgenetik

**Pimenta, Daniela**, Dr. med.: Human epidermal growth factor receptor 2 und Topoisomerase II a als prädiktive Marker für das Ansprechen auf eine neoadjuvante, anthrazyklinhaltige Chemotherapie beim Mammakarzinom und deren Bedeutung als prognostische Faktoren

**Spiegelberg, Christine**, Dr. med.: Frequenz aktivierender Mutationen im Exon 7 des FGFR2-Gens bei Patienten mit Urothelkarzinom der Harnblase

**Weisflog, Anna-Monika**, Dr. med.: Expression der Prognosemarker MIB-1, p53, Ck20 und E-Cadherin in Korrelation zur Hormonrezeptor Expression im Urothelkarzinom der Harnblase

### Doctorate theses 2016

**Bachmann, Leonhard**, Dr. med.: Immunohistochemical panel diagnostics of Hirschsprung's disease with Map2, Calretinin, Glut1 and S100

**Erber, Ramona**, Dr. med.: Predictive role of HER2/neu, Topoisomerase-II-alpha and Tissue Inhibitor of Metalloproteinases (TIMP-1) for response to adjuvant taxane-based chemotherapy in patients with intermediate risk breast cancer: results from the WSG-AGO EC-Doc Trial

**Hauck, Franziska**, Dr. med.: Prävalenz der HPV-Infektion in Kopf-Hals-Karzinomen: Vergleichende Analyse in Deutschland und Brasilien

**Pülhorn, Heinke**, Dr. med.: Apoptotic cells and clonally expanded T cells in bone marrow trephines of patients with myelodysplastic syndrome

### Habilitation 2015

**Rau, Tilmann Johannes**, PD Dr. med.: Genetik in Vorläuferläsionen von gastrointestinalen Tumoren

**Wachter, David Lukas**, PD Dr. med.: Neue prognostische und prädiktive Marker beim Mammakarzinom

### Habilitation 2016

**Söder, Stephan**, PD Dr. med.: Degenerative DNA-Veränderungen in der Arthrose

### Board qualification 2015

**Giedl, Johannes**, Dr. med.

### Board qualification 2016

**Brunner, Kathrin**, Dr. med.

## Institute of Pathology

Division of Nephropathology

### Doctorate theses 2015

**Schaffert, Johannes**, Dr. med.: Unterschiede in der glomerulären Architektur und in der renalen Kapillarisation nach intrauteriner Wachstumsrestriktion an der Ratte: Einfluss der Wurfreduktion

### Doctorate theses 2016

**Auer, Claudia**, Dr. med.: Auswirkung von niedrigem Geburtsgewicht und reduzierter Nephronenzahl auf die Hochsalz-induzierte Progression renaler Schädigung im tiereperimentellen Modell der GDNF+/- -Maus

**Königer, Laura**, Dr. med.: Einfluss einer Coronin 1a-Defizienz auf die frühe Phase der Anti-GBM-Glomerulonephritis in der Maus

**Schlote, Julia**, Dr. med.: Cardiovascular and renal effects of high salt diet in GDNF +/- Mice with low nephron number

## Institute of the History of Medicine and Medical Ethics

Chair of the History of Medicine

### Doctorate theses 2016

**Tannenbaum, Jessica**, Dr. med.: Medizin im Konzentrationslager Flossenbürg 1938 bis 1945 – eine lokale Studie

## Institute of the History of Medicine and Medical Ethics

Professorship for Medical Ethics

### Doctorate theses 2015

**Emrich, Inken Annegret**, Dr. rer. biol. hum.: Patientenorientierung im stationären Sektor Analysen und medizinethische Implikationen zur Beratungsarbeit des Patientenführersprechers

**Fröhlich-Güzelsoy, Leyla**, Dr. med.: Medizinethik und klinische Erfahrung – die Macht der Kommunikation Untersuchungen zur Patientenperspektive im Gesundheitswesen

**Hübner, Constanze**, Dr. phil.: Aktive Sterbehilfe – ein unbekanntes Terrain

**Jentsch, Nadine**, Dr. med.: Forschung und Heilung für das gelbe Kind. Historische und ethische Probleme von Icterus neonatorum und Phototherapie

### Doctorate theses 2016

**Schenk, Michael**, Dr. med.: Eine Anti-Aging-Pille auf Rezept? Ethische Perspektiven der Langlebigkeit

## Nikolaus-Fiebiger-Center of Molecular Medicine

Chair of Experimental Medicine I (Molecular Pathogenesis Research)

### Doctorate theses 2015

**Golovchenko, Svitlana**, Dr. rer. nat.: Funktionsanalyse von beta-Catenin in hypertrophen Chondrocyten durch gewebespezifische Gendelektion

## Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

Chair of Orthopedics and Orthopedic Surgery

### Doctorate theses 2015

**Haaker, Jan**, Dr. med.: Orthopedic management of patients with Pompe disease: a retrospective case series of 8

**Kleyer, Birte**, Dr. med.: CT-gestützte Osteodensitometrie zur Untersuchung der tibialen und spongiosen knöchernen Reaktion nach Implantation einer kondylären Knieprothese bei Patienten mit degenerativer Gonarthrose in vivo – eine prospektive Studie

**Wagner, Benedikt**, Dr. med.: Migrationsmessungen mittels Radiostereometrie des unzementierten Cerafit-Hüftschafes der Firma Ceraver innerhalb der ersten zwei postoperativen Jahre  
**Wierer, Thomas**, Dr. med.: Radiostereometrische Migrationsanalyse des Lubinus SP II Hüftprothesenschafes: follow-up von 59 Hüftimplantaten über 2 Jahre

### Doctorate theses 2016

**Beck, Andrea**, Dr. med.: Klinische und radiologische Ergebnisse nach Implantation eines dynamischen Neutralisationssystems (DYNESYS) bei multisegmentaler lumbaler Stenose mit Instabilität

**Dankerl, Peter**, Dr. med.: Effects on posture by different neuromuscular afferent stimulations and proprioceptive insoles: Rasterstereographic evaluation

**Henkel, Matthias**, Dr. med.: Sterilisationsverhalten einer antibakteriell wirksamen CuTiO<sub>2</sub>-Beschichtung

**Nordmeyer, Matthias**, Dr. med.: Negative Pressure Wound Therapy zur Vermeidung von Serombildung nach chirurgischer Versorgung von Wirbelsäulenfrakturen

**Reinhardt, Maximilian**, Dr. med.: Epiphyseolysis capitis femoris: Langzeitergebnisse und Remodeling nach Kirschner-Draht-Fixation

**Schilling, Lisa**, Dr. med.: Orthopädische Manifestationen bei Myotoner Dystrophie Typ 1: eine klinische Studie mit 21 Patienten

**Schropp, Vivian**, Dr. med.: Orthopädische Aspekte der Gliedergürteldystrophien

**Tschunko, Franz**, Dr. med.: Translations- und Rotationsverhalten des Cerafit-Prothesenschaftes: Eine Radiostereoanalyse von 26 Patienten, untersucht über 10 Jahre

#### Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH Division of Orthopedic Rheumatology

##### Doctorate theses 2015

**Reiß, Lena**, Dr. med.: Gelenkfunktion nach bikondylärer Knieendoprothese – Unterschiedlicher Verlauf bei Patienten mit Gonarthrose und rheumatoider Arthritis

**Stolle, Jeska**, Dr. med.: Langzeitverlauf des postoperativen Ergebnisses beim endoprothetischen Knie-Gelenkersatz bei präexistierenden degenerativen Gonarthrose im Vergleich zum vorbestehenden entzündlich-rheumatischen Kniegelenkprozess bei rheumatoider Arthritis

##### Additional qualification 2016

**Weiß, Julian**, Dr. med.: Manual Medicine/Chirotherapie

#### Institute for Biomedicine of Aging Chair of Internal Medicine (Geriatrics)

##### Doctorate theses 2015

**Goisser, Sabine**, Dr. rer. biol. hum.: Einfluss der Ernährungssituation auf die klinische und funktionelle Rehabilitation bei geriatrischen Patientinnen und Patienten mit Hüftfraktur

**Kümpflein, Peter**, Dr. med.: Migration im Kontext der Pflegebegutachtung: inwieweit unterscheiden sich Personen mit bzw. ohne Migrationshintergrund in medizinischer Sicht – gibt es kulturspezifische Unterschiede?

**Purucker, Katja**, Dr. med.: Vergleich von Mini Nutritional Assessment und Nutritional Risk Screening 2002 bei unfallchirurgischen Patienten  $\geq 75$  Jahre hinsichtlich Übereinstimmung, Korrelation zu prognoserelevanten Parametern und Praktikabilität

**Zenk, Philipp**, Dr. med.: Prädiktive Aussagekraft zweier Screening-Instrumente – „Identification of Seniors at Risk (ISAR)“ und „Inter Residents

Assessment Instrument Emergency Department (interRAI ED)“ – in einer deutschen Notaufnahme

##### Doctorate theses 2016

**Eberl, Tanja**, Dr. med.: Ernährungsstatus und Appetit regulierende Hormone bei geriatrischen Krankenhauspatienten

**Salb, Johannes**, Dr. rer. biol. hum.: Sturzprävention bei Menschen mit geistiger Behinderung

**Thrun, Jan-Marc**, Dr. med.: Vergleich von Blutdruckmesswerten mittels automatisiertem Handgelenksmessgerät und automatisiertem Oberarmmessgerät bei Patienten  $> 80$  Jahren

##### Habilitation 2015

**Drey, Michael**, PD Dr. med.: Neurodegenerative Aspekte der Sarkopenie

#### Department of Anesthesiology Chair of Anesthesiology

##### Doctorate theses 2015

**Fischer, Mathias**, Dr. med.: Vergleich des Verlaufes der neuromuskulären Blockade zwischen dem Musculus adductor pollicis und dem Musculus flexor hallucis brevis nach Applikation von Mivacurium

**Köckeritz, Julia**, Dr. med.: Perioperativer Schmerzmittelverbrauch bei Patienten mit Morbus Crohn

**Müller, Christiane**, Dr. med.: Differenzierte Auswirkungen auf sensorische Funktionen und Messwerte der epidermalen Nervenfaserdichte nach der Anwendung von Lidocain-Pflaster (5%) auf gesunder menschlicher Haut

**Schäfer, Simone**, Dr. med.: Nachweis der analgetischen und antihyperalgetischen Effekte von inhalativem Stickoxydul auf die durch Remifentanyl induzierte Hyperalgesie in einem Probanden-Schmerzmodell

**Schmidt, Christian**, Dr. med.: Entwicklung und Implementierung einer Checkliste zur Steigerung der Patientensicherheit bei der i.v. Medikation

##### Doctorate theses 2016

**Abusafieh, Mohammed**, Dr. med.: Vergleich der Effektivität der Schmerztherapie nach Oberflächenersatz des Kniegelenks zwischen lumbaler Periduralanalgesie und der Kombination einer kontinuierlichen Femoralisblockade mit einem single shot Ischiadicusblock

**Huber, Tobias**, Dr. med.: Untersuchung der Notfallkompetenz Erlanger Zahnmedizinstudenten – Multiperspektivische Bedarfsanalyse für eine curriculare Neugestaltung

**Huberth, Sandra**, Dr. med.: Distale Ischiadikusblockade bei Patienten mit Charcot-Marie-Tooth-Erkrankung

##### Habilitation 2015

**Breuer, Georg**, PD Dr. med.: Curriculumsentwicklung und Lernprozessunterstützung im Bereich Anästhesiologie, Intensiv- und Notfallmedizin

##### Habilitation 2016

**Heinrich, Sebastian**, PD Dr. med.: Versorgungsforschung in der Anästhesiologie und Intensivmedizin: Erhöhung von Patientensicherheit und Behandlungsqualität durch Aggregation klinischer Patientendaten

##### Board qualification 2015

**Mertens, Christian**, Dr. med.

**Pröttengier, Johannes**, Dr. med.

##### Board qualification 2016

**Hoyer, Evelyn**, Dr. med.

**Richter, Ute**, Dr. med.

**Weiß, Marina**, Dr. med.

**Weller, Konrad**, Dr. med.

##### Additional qualification 2015

**Birkholz, Torsten**, PD Dr. med.: Intensive Care Medicine

**Krischke, Frederick**, Dr. med.: Emergency Medicine

**Niedermirtl, Florian**, Dr. med.: Emergency Medicine

**Wiernik, Michaela**, Dr. med.: Emergency Medicine

##### Additional qualification 2016

**Freund, Robert**, Dr. med.: Intensive Care Medicine

**Gottfried, Angelina**, Dr. med.: Emergency Medicine

**Maier, Jan-Niklas**: Emergency Medicine

**Maiwald, Thomas**: Emergency Medicine

**Mayr, Lucia**, Dr. med.: Emergency Medicine

**Münster, Tino**, Prof. Dr. med.: Intensive Care Medicine

**Singler, Boris**, Dr. med.: Intensive Care Medicine

**Wagner, Sören**, Dr. med.: Intensive Care Medicine

#### Department of Anesthesiology Division of Palliative Medicine

##### Doctorate theses 2015

**Drukarczyk, Laura**, Dr. med. dent.: Quantitative Analyse zur Thematisierung von unheilbaren Erkrankungen in populären Filmen

##### Doctorate theses 2016

**Denk, Julia**, Dr. med.: Frühe Integration von Palliativmedizin in das Behandlungskonzept von Patienten mit fortgeschrittenen Tumorleiden

**Fraundorf, Tobias**, Dr. med.: Patientencharakteristika in der spezialisierten ambulanten Palliativversorgung (SAPV) im Raum Fürth? Versorgungsrelevante Daten unter besonderer Berücksichtigung der Krankenhauseinweisungen, Versorgungsräume und Diagnosegruppen.

**Kötzsch, Franziska**, Dr. med.: Versorgungsrealität von Patienten nach Entlassung aus der spezialisierten stationären Palliativversorgung

**Matthies, Dominik**, Dr. med.: Tumor- und Nichttumorpatienten unter stationärer, palliativ-

medizinischer Behandlung im Vergleich; eine Symptom- und Problemclusteranalyse

#### Additional qualification 2016

**Huberth, Sandra:** Palliative Medicine

#### Department of Cardiac Surgery

Chair of Cardiac Surgery

#### Doctorate theses 2016

**Ballazhi, Fatos,** Dr. med.: Epikardiale Ablation des Vorhofflimmerns beim herzchirurgischen Patienten – Langzeitergebnisse und Bedeutung der medikamentösen Therapie

**Engel, Anna,** Dr. med.: Analyse herzchirurgischer OP-Verfahren bei Patienten mit akuter Aorta Ascendens-Dissektion. Eine retrospektive Untersuchung am Universitätsklinikum Erlangen unter besonderer Berücksichtigung geschlechtsspezifischer Unterschiede

**Heindl, Felix,** Dr. med.: Die Rolle des Chemokinrezeptors CCR7 bei der murinen Trachea-transplantation

#### Board qualification 2016

**Nooh, Ehab,** Dr. univ. cairo

**Ballazhi, Fatos,** Dr.med.

#### Department of Cardiac Surgery

Division of Pediatric Cardiac Surgery

#### Doctorate theses 2015

**Walk, Jana,** Dr. med.: Mittelfristige Ergebnisse nach Conduit-Implantation in subpulmonaler Position bei kongenitalen Herzfehlern

#### Doctorate theses 2016

**Pollari, Francesco,** Dr. med.: Better outcome and costs reduction by using sutureless valves: a propensity-matched score analysis sutureless valves and healthcare costs

#### Habilitation 2015

**Rüffler, André,** Dr. med.: Chirurgische Korrektur von Aortenbogenfehlbildungen: Kardiale Protektion und hämodynamische Optimierung

#### Department of Dermatology

Chair of Skin and Veneral Diseases

#### Doctorate theses 2016

**Angelovska, Irena,** Dr. med.: Palmoplantare Psoriasis im Erwerbsleben: Eine Fallserie aus der Praxis unter Berücksichtigung der S1-Leitlinie zur berufsdermatologischen Begutachtung von Psoriasis

**Hiller, Julia,** Dr. med.: Beruflich bedingtes Handekzem: Nachuntersuchung zur leitlinienkonformen Therapie und Lebensqualität im Kollektiv der Berufssprechstunde 2010 der Hautklinik Universitätsklinikum Erlangen

**Krammer, Ramona,** Dr. med.: Therapiepräferenzen in der Melanombehandlung - Wert der Therapie und Präferenz von Lebensqualität versus Lebensdauer von Patienten, Ärzten und gesunden Kontrollpersonen

**Orthmann, Jens,** Dr. med.: Laserbehandlung der Onychomykose Vergleich eines Niedrigenergielasers mit einem 1.064nm-Diodenlaser

**Wörner, Antonia,** Dr. med.: Verbreitung und Bedeutung von Typ I-Sensibilisierungen auf Hausstaub- und Speichermilbenallergene im Kollektiv der Hautklinik Universitätsklinikum Erlangen

#### Doctorate theses 2016

**Behling, Juliane,** Dr. med.: Evaluation von HIV-Präventionsprogrammen: Herpes simplex Virus Typ 2- Antikörper als Biomarker für sexuelles Risikoverhalten bei jungen Erwachsenen in Entwicklungsländern

**Hofmann, Lars,** Dr. med.: Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy

**Kickinger-Lörsch, Anja,** Dr. med.: Nickel und Kobalt in Metalllegierungen von Werkzeugen - eine Ist-Analyse

#### Habilitation 2015

**Hartmann, Anke,** PD Dr. med.: Hautregeneration und Pigmentierung: in vitro Modelle und neue klinische Strategien

**Zinser, Elisabeth,** PD Dr. nat. tech.: Modulation des Immunsystems bei Autoimmunität und Transplantation

#### Board qualification 2015

**Brauner, Kathrin,** Dr. med.

#### Department of Dermatology

Division of Immune Modulation

#### Habilitation 2015

**Dörrie, Jan,** PD Dr. rer. nat.: Therapeutic Cancer Vaccination

#### Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology

Chair of Internal Medicine I

#### Doctorate theses 2015

**Al Hussin, Nuhad,** Dr. med.: Die Durchführung der Dual X-Ray-Absorptiometrie und der Bioelektrischen Impedanzanalyse zur Detektion einer Mangelernährung bei hospitalisierten Patienten

**Bal, Zeynep,** Dr. med.: Klinik, Manometrie- und pH-Metrie-Befunde einschließlich Impedanzmessung bei Patienten mit eosinophiler Ösophagitis

**Behm, Barbara,** Dr. med.: Additive Tumorantwort auf die Kombination von Radiofrequenzablation und Stimulation des Toll like 9-Rezeptors im VX2-Lebertumormodell

**Frigowitsch, Emilie,** Dr. med.: Ernährungsversorgung stationär liegender internistischer Patienten – Bedeutung von Mangelernährung und künstlicher Ernährungsintervention

**Gerlach, Thomas,** Dr. med.: Molekulare Analyse des Immunsuppressivums Cyclosporin A

**Helmschrott, Peter,** Dr. med.: Palliative Therapie von malignen Stenosen im Gastrointestinaltrakt mit selbstexpandierenden Stents: Erfolgsraten, Komplikationen und klinischer Verlauf

**Klinger, Ursula,** Dr. med.: Stellenwert der Coceptinanalyse in der Zentralen Notaufnahme zum raschen Ausschluss eines akuten Koronarsyndroms

**Knieling, Ferdinand,** Dr. med.: Anti-angiogenetische Therapie bei Lebertumoren: Quantitative dynamische kontrastmittelverstärkte Sonographie zur frühzeitigen Analyse des Therapieansprechens

**Krischke, Frederick,** Dr. med.: Nahrungsmittelallergie bei Patienten mit Reizdarmsyndrom: Prävalenz, moderne Diagnose und Einfluss einer Eliminationsdiät

**Malinger, Adam,** Dr. med.: Strategies for the development of a preclinical humanized mouse model of experimental colitis

**Pfeiffer, Hella,** Dr. med.: Bestimmung der Oberflächenmarker und des Aktivierungsgrades von CD14+ Zellen aus humanem Blut nach Stimulation und Reifung mit IL-4/GM-CSF oder IL-15/GM-CSF

**Steindorf, Claudia,** Dr. med.: Die klinische Signifikanz der Histondeacetylasen 1, 2, 3 und 7 im hepatozellulären Karzinom

**Sturm, Jörg,** Dr. med.: Stellenwert der ARFI (Acoustic Radiation Force Impulse) Elastometrie in der Diagnostik der Leberfibrose bei chronischen Lebererkrankungen und im Therapieverlauf

#### Doctorate theses 2016

**Blank, Beate,** Dr. med.: Prospektive Evaluation der Patientenzufriedenheit bei endoskopischen Eingriffen in Abhängigkeit der Sedierungsart

**Gallitz, Julia,** Dr. med. dent.: Maßnahmen zur Erhöhung der Koloskopiebereitschaft – führt das Angebot von advanced endoscopic imaging Verfahren zu einer verbesserten Vorsorge?

**Neuber, Martin,** Dr. med.: Stellenwert der kombinierten pH-Metrie/Impedanzmessung bei Patienten mit einer extraösophagealen Manifestation der Refluxkrankheit

**Widder, Michael,** Dr. med.: Ein systematischer Ansatz zur Untersuchung von Zytokinfunktionen in vivo – Fokus auf Typ 2-Zytokin-vermittelte Regulation antimikrobieller Faktoren im Darm

#### Habilitation 2015

**Hagel, Alexander Fritz Karl,** PD Dr. med.: Komplikationsmanagement in der modernen Endoskopie

**Neufert, Clemens,** PD Dr. med.: Die Wirkung von Zytokinen und weiteren Botenstoffen auf die intestinale Homöostase bei chronisch entzündlichen Darmerkrankungen und Kolitis assoziierten Karzinomen

**Neumann, Helmut,** PD Dr. med.: Innovative Verfahren zur optimierten Diagnostik von gastrointestinalen Erkrankungen



**Habilitation 2016**

**Engel, Matthias**, PD Dr. med.: Die duale Rolle peptiderger sensorischer Neurone des Dickdarms bei Schmerz und Entzündung

**Gahr, Susanne Gertraud**, PD Dr. med.: Wirkung von Histondeacetylaseinhibitoren in gastrointestinalen Tumoren

**Wildner, Dane**, PD Dr. med.: Quantifizierende Verfahren in der Sonographie des Abdomens zur Beurteilung von Gewebepfusion und -elastizität

**Board qualification 2015**

**Engel, Matthias**, PD Dr. med.: Internist

**Neumann, Helmut**, Prof. Dr. med.: Internist and Gastroenterologist

**Board qualification 2016**

**Fürst, Julia**, Dr. med.: Internist

**Zoicas, Flavius**, Dr. med.: Internist

**Additional qualification 2016**

**Görtz, Rüdiger**, PD Dr. med.: Emergency Medicine

**Quast, Stefan**, Dr. med.: Allergology

**Department of Medicine 2 –  
Cardiology and Angiology**

Chair of Internal Medicine II

**Doctorate theses 2015**

**Cranach, Moritz von**, Dr. med.: Wirksamkeit eines paclitaxel-beschichteten Ballonsystems zur Therapie der Restenose von Drug-Eluting-Stents verglichen mit unbeschichteten Ballonkathetern

**Dechant, Katharina**, Dr. med.: Einfluss der Schulbildung auf das Gesundheitsbewusstsein und die Sekundärprävention von Patienten nach akutem Myokardinfarkt

**Gundlach, Ulrike**, Dr. med.: Evaluation des Koronarvenenstatus bei Patienten mit Koronararterienanomalien: Retrospektive Analyse anhand der CT-Angiographie von 14488 Patienten

**Loders, Sabrina**, Dr. med.: Vergleich der transapikalen mit der transfemoralen interventionellen Aortenklappenimplantation bei Patienten mit hochgradiger Aortenklappenstenose und stark erhöhtem Operationsrisiko

**Osinski, Daniela**, Dr. med.: Die Rolle von endothelalem RGSS bei der ERK 1/2-Aktivierung in der arteriosklerotischen Inflammation

**Schaefer, Marcella**, Dr. med.: Prädiktoren des Bildschadens bei einer CT-Koronarangiographie

**Seybold, Katrin**, Dr. med.: Inflammatorische und anti-inflammatorische Mechanismen des infarzierten und chronisch ischämischen Myokards am Tiermodell der Ratte sowie deren therapeutische Beeinflussbarkeit durch Interleukin-10

**Tragl, Yvonne**, Dr. med. dent.: Untersuchung zur Veränderung der klinischen Charakteristika der bakteriellen Endokarditis über einen Zeitraum von zehn Jahren

**Doctorate theses 2016**

**Gerlach, Andreas**, Dr. med.: Regionale Verteilung von Post-systolic motion bei Patienten

nach Myokardinfarkt – Ein direkter Vergleich zwischen Gewebedopplerechokardiographie und Magnetresonanztomographie

**Lichtenstern, David**, Dr. med.: Assoziation von CRP-Rezeptor-Polymorphismen mit akutem Myokardinfarkt als Erstmanifestation einer koronaren Herzkrankheit

**Lonke, Sandra**, Dr. med.: Wirksamkeit eines Paclitaxel-beschichteten Ballonsystems zur Therapie der Restenose von Drug-Eluting-Stents im Vergleich mit unbeschichteten Ballonkathetern bei komplexen Läsionen – eine Subgruppenanalyse der PEPCAD-DES Studie

**Scharl, Stefanie**, Dr. med.: Prospektive Evaluation der Lebensqualität bei Patienten nach kathetergestütztem Aortenklappenersatz

**Schmidt, Elke**, Dr. med.: Genauigkeit der Dual Source CT Koronarangiographie bei Patienten nach koronarem Bypass: Vergleich mit der invasiven Angiographie bei 78 Patienten

**Simon, Hans Michael**, Dr. med.: Veränderungen von inflammatorischen Zytokinen und EKG bei Profi-Fußballspielern

**Steinhoff, Alina**, Dr. med.: Assoziation des epikardialen Fettvolumens mit Markern der systemischen Inflammation

**Wild, Johannes**, Dr. med.: Der Einfluss von Kochsalz auf die endotheliale Aktivierung durch nicht-uniforme Scherkräfte

**Habilitation 2016**

**Marwan, Mohamed Ibrahim Kamel**, PD Dr. med.: Analyse von koronaren atherosklerotischen Läsionen mittels CT-Angiographie

**Regenfus, Matthias Georg Jakobus**, PD Dr. med.: Die kontrastverstärkte Magnetresonanztomographie in der Diagnostik der koronaren Herzerkrankung

**Board qualification 2015**

**Beckendorf, Claudia**, Dr. med.

**Graf, Verena**, Dr. med.

**Heigl, Ariane**, Dr. med.

**Tröbs, Monique**, Dr. med.

**Board qualification 2016**

**Anneken, Lars**, Dr. med.

**Layritz, Christian**, Dr. med.

**Sarkar, Nathalie**, Dr. med.

**Additional qualification 2016**

**Gundlach, Ulrike**, Dr. med.: Adults with congenital heart disease (EMAH)

**Hell, Michaela**, Dr. med.: Emergency Medicine

**Pichl, Carolin**, Dr. med.: Emergency Medicine

**Department of Medicine 3 –  
Rheumatology and Immunology**

Chair of Internal Medicine III

**Doctorate theses 2015**

**Chen, Zhu**, Dr. med.: Suppression of inflammatory arthritis by Th2 responses and eosinophil activation

**Hecht, Carolin**, Dr. med.: Additive Wirkung von Antikörpern gegen citrullinierte Proteine und dem Rheumafaktor auf Knochenerosionen bei Patienten mit rheumatoider Arthritis

**Kleyer, Arnd**, Dr. med.: Liver X receptors orchestrate osteoblast/osteoclast crosstalk and counteract pathologic bone loss

**Krämer, Marlene**, Dr. med.: Fibroblasten-Aktivierung und Fibroseinduktion durch Hemmung der Histon-Methylierung von H3K27

**Meßbacher, Maria-Elena**, Dr. med.: Interleukin-36alpha in der Pathogenese entzündlicher Arthritiden

**Teufel, Stefan**, Dr. rer. biol. hum.: Inhibierung der Knochengewebe-Remodellierung durch anti-resorptive Medikamente verlagert die Plasmazellnische in die Milz

**Zeller, Barbara**, Dr. med.: Die Rolle von ATF3 bei der Pathogenese der Systemischen Sklerose

**Zirngibl, Matthias**, Dr. med.: Loading of nuclear autoantigens prototypically recognized by SLE sera into late apoptotic vesicles requires intact microtubules and MLCK activity

**Doctorate theses 2016**

**Aschermann, Sarah**, Dr. med.: Presence of HLA-B\*27 is associated with changes of serum levels of mediators of the Wnt and hedgehog pathway

**Dogan, Volkan**, Dr. med.: Die Rolle des „retinoic-acid-receptor-related orphan receptor  $\alpha$ “ ROR $\alpha$  bei der Systemischen Sklerose

**Fickentscher, Christoph**, Dr. med.: Die Pathogenität von anti- $\beta$ 2GP1-Autoantikörpern wird von deren Fc-Glykosylierung bestimmt

**Layritz, Florian**, Dr. med. dent.: Die Bedeutung Adenosin-abhängiger Signalkaskaden in präklinischen Modellen der systemischen Sklerose

**Petsch, Christina**, Dr. med.: Prevalence of monosodium urate deposits in a population of rheumatoid arthritis patients with hyperuricemia

**Rauscher, Veronika**, Dr. med.: Adhärenz bezüglich der antirheumatischen Medikation bei Patienten mit rheumatoider Arthritis

**Regensburger, Adrian**, Dr. med.: A comparative analysis of magnetic resonance imaging (MRI) and high-resolution peripheral quantitative computed tomography (HR-pQCT) of the hand for the detection of erosion repair in rheumatoid arthritis

**Weber, Christian**, Dr. med.: Bedeutung molekularer Chaperone bei der Pathogenese von Autoimmunerkrankungen

**Habilitation 2015**

**Beyer, Christian**, PD Dr. med.: Translationale Forschung in fibrosierenden Autoimmunerkrankungen

**Habilitation 2016**

**Hueber, Axel**, PD Dr. med.: Die Rolle von Zytokinen im zellulären Netzwerk entzündlich-rheumatischer Erkrankungen

**Board qualification 2015**

**Hueber, Axel**, PD Dr. med.

**Board qualification 2016**

**Beyer, Christian**, PD Dr. med.



## Department of Medicine 3 – Rheumatology and Immunology

Division of Molecular Immunology

### Doctorate theses 2015

**Peeß, Carmen**, Dr. rer. nat.: Entwicklung von Antikörpern gegen den Domäne II beta-Hairpin des HER3-Rezeptors unter Verwendung der Thermus thermophilus SlyD-Scaffoldtechnologie  
**Schmittnägels, Martina**, Dr. rer. nat.: Rekombinante Viruspeptid-MHCI-Antikörperfusionen zur Induktion von Tumorzelllyse durch Zytomegalievirus-spezifische, zytotoxische T-Zellen

### Doctorate theses 2016

**Stein, Merle**, Dr. rer. nat.: A defined mitochondrial metabolic state in pre-B cells contributes to B cell homeostasis and is modulated by Swiprosin-2/EFhd1

## Department of Medicine 4 – Nephrology and Hypertension

Chair of Internal Medicine IV

### Doctorate theses 2015

**Barhoum, Fatima**, Dr. med.: ABO-inkompatible versus ABO-kompatible Lebendnierentransplantation am Transplantationszentrum Erlangen-Nürnberg in den Jahren 2006-2010 – ein Subgruppenvergleich  
**Deutsch, Birgit**, Dr. med.: Die circadiane Rhythmik und Tag-zu-Tag-Variabilität von Kalium und Cystatin C im Serum  
**Hartmann, Roswitha**, Dr. med.: Einfluss des Inhibitors EHT 1857 auf CTGF und das Zytoskelett in proximalen Tubuluszellen  
**Heiß, Rafael Ulrich**, Dr. med.: Molekulare Mechanismen der gestörten ischämieinduzierten Angiogenese bei Niereninsuffizienz  
**Preißer, Felix**, Dr. med.: Einfluss von Prolyl-Hydroxylase Inhibitoren auf den TGF-beta/Smad-Signalweg und die Migration humaner primärer Tubulusepithelzellen  
**Prignitz, Antonina**, Dr. med.: Inzidenz der BK-Virämie und Polyomavirus BK-Nephropathie bei 352 Nierentransplantatierten am Transplantationszentrum Erlangen-Nürnberg in den Jahren 2008-2012 – Risikofaktoren und Bedeutung der mTOR Inhibition  
**Siegle, Michaela**, Dr. med.: Blutdruckunabhängiger Einfluss von Mineralokortikoid-Rezeptor-Blockade mit Eplerenone auf die Größe des linken Vorhofs bei Patienten mit therapieresistenter Hypertonie – Evaluation des linksatrialen Volumens mittels einfacher Flächen-Längen-Methode in der kardialen Magnetresonanztomographie  
**Thieme, Stefan**, Dr. med.: Die Regulation von Survivin durch das von Hippel-Lindau-Tumorsuppressorprotein in Abhängigkeit von p53  
**Walker, Stefanie Elke**, Dr. med.: Der Effekt des Angiotensinrezeptorblockers Olmesartan auf die Pulswellengeschwindigkeit und den zentralen systolischen Blutdruck bei Patienten mit metabolischem Syndrom  
**Zühlke, Jonathan**, Dr. med.: Polarized distal and proximal epithelial cells

### Doctorate theses 2016

**Fiedler, Christian**, Dr. med.: Die Reinnervation von sympathischen efferenten und peptiderg afferenten perivaskulären Nervenfasern in der Rattenniere nach einseitiger chirurgischer Denervierung  
**Großkopf, Leonore**, Dr. med.: Wirkung des Kalziumantagonisten Manidipin auf den zentralen Blutdruck bei Patienten mit essentieller Hypertonie  
**Jäger, Martin**, Dr. med.: Änderungen der vaskulären und renalen Hämodynamik nach renaler Denervation  
**Rotter, Marie-Therese**, Dr. med.: Doppelnierentransplantation am Transplantationszentrum Erlangen-Nürnberg: Zentrumsanalyse und Vergleich mit postmortalen Einzelnierentransplantationen sowie Lebend-Nierentransplantationen mit älteren Spendern  
**Wilhelm, Katharina**, Dr. med.: Neue Biomarker bei akutem Nierenversagen und Sepsis

### Habilitation 2016

**Knauf, Felix**, PD Dr. med.: Molekulare Mechanismen der hyperoxalurischen Nierenerkrankungen

### Board qualification 2015

**Akimov, Irina**: Internal Medicine  
**Fortenbacher, Silke**, Dr. med.: Internal Medicine  
**Friedrich, Stephanie**, Dr. med.: Internal Medicine and Nephrology  
**Kopp, Christoph**, Dr. med.: Internal Medicine and Nephrology

### Board qualification 2016

**Braun, Tobias**, Dr. med.: Internal Medicine  
**Heigl, Johannes**: Internal Medicine and Nephrology  
**Kannenkeril, Dennis**, Dr. med.: Internal Medicine  
**Pfau, Anja**, Dr. med.: Internal Medicine and Nephrology  
**Rath, Utina**: Internal Medicine  
**Roth, Simon**, Dr. med.: Internal Medicine  
**Schmidt, Stephanie**, Dr. med.: Internal Medicine  
**Schödel, Johannes**, Dr. med. Dr. phil.: Internal Medicine and Nephrology

## Department of Medicine 5 – Hematology and Oncology

Chair of Hematology and Oncology

### Doctorate theses 2015

**Feulner, Julian**, Dr. med.: Rekrutierung humaner T-Lymphozyten durch CD33xCD3 bispezifische Antikörper des BiTE-Formates gegen Myeloblasten bei akuter myeloischer Leukämie  
**Geisler, Konrad**, Dr. med.: Anti-Tumor-Immunität unter Tyrosinkinase-Inhibitor Behandlung  
**Thaller, Martina**, Dr. med. dent.: Stellenwert des konventionellen Röntgen-Thorax in der Diagnostik von Infektionen bei ambulanten Patienten nach Chemotherapie und Niedrigrisiko-Neutropenie

### Doctorate theses 2016

**Finkel, Patrick**, Dr. med.: Die Rolle der NK-Zelle bei Tumormimmunisierung  
**Möckel, Jennifer**, Dr. med.: TKI-Immunmonitoring – Untersuchung zellulärer Veränderungen unter Therapie mit Tyrosinkinase-Inhibitoren

### Board qualification 2015

**Angerer, Moritz**, Dr. med.: Internist

### Board qualification 2016

**Bezhad, Ali**, Dr. med.: Internist  
**Mougiakakos, Dimitrios**, Dr. med.: Internist and Haematologist and Oncologist  
**San Nicolo, Katja**, Dr. med.: Internist

## Department of Neurology

Chair of Neurology

### Doctorate theses 2015

**Bolwerk, Anne**, Dr. rer. biol. hum.: Funktionelle Ruhekonnektivitäten im menschlichen Gehirn: Veränderungen beim Komplex-Regionalen Schmerzsyndrom und Effekte von produktiver und rezeptiver Kunstintervention bei gesunden Probanden  
**Erlmeier, Franziska**, Dr. med.: Personalized Medicine in Screening for Malignant Disease: A Review of Methods and Applications  
**Hofmann, Vanessa**, Dr. med.: Glykogenphosphorylase Isoenzym BB als neuer Biomarker bei akuter zerebraler Ischämie  
**Kahl, Nicolas**, Dr. med.: Know your pulse: Periphere Pulsmessung nach ischämischem Schlaganfall – Eine prospektive Pilotstudie  
**Kriza, Christine**, Dr. rer. biol. hum.: Health Technology Assessment: Systematische Bewertung von Krankheitskosten bei Darmkrebs sowie der Kosten-Effektivität von Koloskopie und virtueller Kolonographie  
**Kurka, Natalia**, Dr. med.: Reliability and limitations of automated arrhythmia detection in telemetric monitoring after stroke  
**Möhringer, Susanne**, Dr. med.: Differenzielle Effekte der Allgemeinnarkose mit Propofol, Remifentanyl und Esketamin auf die Schmerzverarbeitung im transdermalen elektrischen Schmerzmodell  
**Möller, Sebastian**, Dr. med.: Schlafbezogene Atemstörungen und eingeschränkte Arousal-Funktion bei Patienten mit Familiärer Dysautonomie  
**Pfenninger, Jasmin**, Dr. med.: Endogene Schmerzmodulation bei Morbus Parkinson  
**Richter, Jörg**, Dr. med.: Effizienz neurolinguistischer Teletherapie bei zerebralem Insult mit Aphasie – eine prospektive Längsschnittstudie  
**Schmidt, Tamara**, Dr. med.: Einfluss zerebraler Läsionen auf somatosensorische Profile bei Schlaganfallpatienten  
**Teuber, Linda**, Dr. med.: Neuroendokrine Veränderungen bei Patienten mit spontaner, supratentorieller intracerebraler Blutung  
**Zöpfel, Nadine**, Dr. med.: Zerebrale autonome Verarbeitung von Schmerz und Schmerzverarbeitung

**Doctorate theses 2016**

**Aurnhammer, Felix**, Dr. med.: Der Bulbusdruckversuch zeigt kardiovaskulär-autonome Störungen bei Patienten nach stattgehabtem leichten Schädel-Hirn-Trauma

**Crodel, Carl**, Dr. med.: Prävalenz erektiler Dysfunktion nach ischämischen Schlaganfall

**Gerner, Stefan**, Dr. med.: Anämie bei Krankenhausaufnahme stellt einen unabhängigen Prognosefaktor bei intrazerebralen Blutungen dar

**Hoog, Jana**, Dr. med.: Erfassung der Patientenpräferenz und deren Gründe für eine orale und parenterale Darreichungsform von krankheitsmodulierenden Medikamenten für die Multiple Sklerose

**Leichtl, Sibylle**, Dr. med.: S100B nach Hirnschädigung – ein eingeschränkt geeigneter Prognosemarker für das funktionelle Patiententoutcome, bei langfristiger Freisetzung jedoch wichtiger Hinweis für eine fortdauernde Neuroregeneration

**Noack, Natalie**, Dr. med.: Aberrante endogene Schmerzmodulation bei Migräne

**Reindl, Caroline**, Dr. med.: Neuromodulation elektrisch induzierter Hyperalgesie im trigeminovaskulären System

**Schmidt, Ariana**, Dr. med.: Experimentelle Ansätze zur Anwendung von Granulozyten-Kolonie-stimulierendem Faktor als Therapie bei intrazerebraler Blutung an der Ratte

**Wahlster, Philip**, Dr. rer. biol. hum.: Health Technology Assessment: Multi-Criteria Decision Analysis (MCDA) zur Bewertung medizinischer Technologien im Innovationsprozess

**Wolf, Rebecca**, Dr. med.: Effects of CDP-choline on macrophages and oligodendrocytes in neuroinflammation

**Habilitation 2015**

**Kiphuth, Iris-Christine**, PD Dr. med.: Neue Ansätze zur Prognoseabschätzung in der neurologischen Intensivmedizin

**Lee, De-Hyung**, PD Dr. med.: Neuroprotektion im tierexperimentellen Modell der autoimmunen Demyelinisierung

**Habilitation 2016**

**Bayas, Antonios Georgios**, PD Dr. med.: Aktuelle Konzepte zur Pathogenese und Therapie der Multiplen Sklerose

**Kallmünzer, Bernd**, PD Dr. med.: Neurokardiale Interaktionen bei zerebrovaskulären Erkrankungen

**Board qualification 2015**

**Blinzler, Christian**, Dr. med.

**Breuer, Lorenz**, Dr. med.

**Gollwitzer, Stephanie**, Dr. med.

**Stark, David**, Dr. med.

**Board qualification 2016**

**Jukic, Jelena**, Dr. med.

**Kallmünzer, Bernd**, Dr. med.

**Möbius, Cornelia**, Dr. med.

**Volbers, Bastian**, Dr. med.

**Additional qualification 2015**

**Fraunberger, Britta**, Dr. med.: Special pain therapy

**Hagge, Mareike**, Dr. med.: Epileptologist DGfE  
**Marxreiter, Franz**: Clinical electromyography certificate (EMG-Zertifikat, DGKN)

**Seifert, Frank**, PD Dr. med.: Neurologische Ultraschalldiagnostik (ultrasound diagnostics in neurology), DEGUM

**Department of Neurology****Division of Molecular Neurology****Doctorate theses 2015**

**Grimm, Thomas**, Dr. med.: Charakterisierung der adulten Neurogenese im akuten MPTP-Mausmodell des idiopathischen Parkinson-Syndroms

**Mishra, Himanshu Kumar**, Dr. rer. nat.: Untersuchung der Neuronalentwicklung und kortikalen Dysfunktion der SPG11 assoziierten Hereditären Spastischen Paraplegie unter Zuhilfenahme von humanen pluripotenten Stammzellen

**Paus, Marie**, Dr. med.: Verstärkte Dendritogenese und Axogenese in hippocampalen Neuroblasten von LRRK2 knockout Mäusen

**Vogelsgang, Jonathan Samuel**, Dr. med.: Der Effekt von humanem  $\alpha$ -Synuclein auf die Stammzellbiologie neuraler Stamm- und Vorläuferzellen

**Doctorate theses 2016**

**Ettle, Benjamin**, Dr. rer. nat.: Der Einfluss von alpha-Synuclein Anreicherung auf die Oligodendrozytenreifung und die Myelinisierung in der Multisystematrophie

**Habilitation 2016**

**Kohl, Zacharias**, PD Dr. med. dent.: Einfluss der Proteinaggregation auf neuronale Stammzellen bei der Huntington- und Parkinson-Erkrankung

**Department of Neurosurgery****Chair of Neurosurgery****Doctorate theses 2015**

**Chen, Juan**, Dr. med.: The role of MIF and xCT in pituitaryadenomas

**Fleischhauer-Johannssen, Rolf**, Dr. med.: Behandlungsergebnisse nach CT-gesteuerter Punktion von Sakralzysten

**Thaler, Christian**, Dr. med.: Proteinkonzentrationsverläufe von S100B, Neuronenspezifischer Enolase,  $\beta$ -Trace und Albumin im ventrikulären Liquor cerebrospinalis nach Anlage einer externen Ventrikel – Drainage und intraindividuellem Konzentrationsgradientenvergleich im ventrikulären und lumbalen Liquor cerebrospinalis

**Wolf, Ines**, Dr. med.: Histondeacetylase-Inhibition mittels SAHA/Vorinostat normalisiert die Mikroumgebung bei Gliomen über Äquilibration des xCT-Transporters

**Wolfschmidt, Anna**, Dr. med.: Studie zum Outcome von Patienten mit niedriggradigen Gliomen, die mit Hilfe von intraoperativer Magnetresonanztomographie operiert wurden

**Doctorate theses 2016**

**Bucher, Norbert**, Dr. med.: Vergleich der klinischen Ergebnisse des Einsatzes zervikaler Bandscheibenprothesen gegenüber einer Distraktionsspondylodese im 2-Jahres Verlauf

**Friedlein, Katharina Sofia**, Dr. med. dent.: Ein neues System mit prognostischer Aussagekraft zur Klassifizierung des Gesamtüberlebens von Glioblastom-Patienten

**Hock, Stefan**, Dr. med.: Analyse von Tumorstadium und Tumor-induzierter Angiogenese in einem organotypischen Hirnschnittmodell

**Manava, Panagiota**, Dr. med.: Korrelation neurovaskulärer Kompression bei arterieller Hypertonie mit klinisch prospektiven Daten

**Xu, Tengfei**, Dr. med.: Identification of two novel Chlorotoxin derivatives CA4 and CTX-23 with chemotherapeutic and anti-angiogenic potential

**Zhao, Xi**, Dr. med.: Diffusion tensor magnetic resonance imaging before and after release of visual pathway compression by pituitary tumors

**Habilitation 2015**

**Savaskan, Nicolai Engin**, PD Dr. med.: Untersuchungen zur Rolle des Tumormikromilieus bei malignen Gliomen

**Board qualification 2016**

**Merkel, Andreas**

**Sommer, Björn**, Dr. med.

**Department of Nuclear Medicine****Chair of Clinical Nuclear Medicine****Doctorate theses 2015**

**Haferkamp, Jens**, Dr. med.: Der Stellenwert des FDG-PET/CT bei der kurativen Behandlung des Iod-negativen, lymphogen metastasierten Schilddrüsenkarzinoms

**Lehenmeier, Andreas**, Dr. med.: Untersuchung des möglichen Zugewinns durch die SPECT/CT bei der Untersuchung von Schilddrüsenknoten mit  $^{99m}\text{Tc}$ -MIBI im Vergleich zur planaren Szintigraphie

**Doctorate theses 2016**

**Adamek, Oliver**, Dr. med.: Eine longitudinale Verlaufskontrolle szintigraphisch kalter Schilddrüsenknoten an der Friedrich Alexander Universität Erlangen-Nürnberg im Zeitraum von 2007 bis 2009

**Andrassy, Grégory Jean**, Dr. med.: Vergleich zwischen Skelettszintigraphie und SPECT in Referenz zu SPECT/CT

**Habilitation 2015**

**Hocke, Carsten**, PD Dr rer. nat.: Entwicklung von F-18 markierten Subtyp-selektiven, dopaminergen D3-Rezeptorliganden und deren in vivo Evaluierung mittels Micro-PET

**Board qualification 2016**

**Beck, Michael**, Dr. med.

**Erdinger, Mathias**, Dr. med.

**Seiffert, Carolin**, Dr. med.

## Department of Obstetrics and Gynecology

Chair of Obstetrics and Gynecology

### Doctorate theses 2015

**Algermissen, Niels Henrik**, Dr. med. dent.: Einflussfaktoren der chemotherapie-induzierten oralen Mukositis bei Patientinnen mit Mammakarzinom

**Bodewald, Anne Wiebke**, Dr. med.: Zusammenhänge zwischen Mammographischer Dichte und Hormonrezeptorstatus bei Patientinnen mit invasivem Mammakarzinom

**Brunel-Geuder, Lisa**, Dr. med.: Ist die Betreuung von Frauen mit einem familiären Mammakarzinomrisiko finanzierbar? Gesundheitsökonomische Betrachtung der genetischen Testung, intensivierte Früherkennung und präventiver Maßnahmen aus der Sicht des Gesundheitswesens und des Leistungserbringers

**Correll, Carla**, Dr. med.: Die Rolle der PCOS Diagnosekriterien bei der Identifizierung des metabolischen Risikos - Ergebnisse eines phänotyp-bezogenen Vergleichs

**Dietl, Anna**, Dr. med.: Schwangerschaft, Geburt und fetal Outcome bei fortgeschrittenem maternalen Alter

**Engel, Anne**, Dr. rer. biol. hum.: Methoden der Statistik zur Analyse von Single Nucleotide Polymorphismen (SNP) anhand der Auswertung von Genotypdaten aus einer neoadjuvanten Chemotherapie

**Finsterwalder, Petra**, Dr. med.: Der Proliferationsmarker Ki-67 und die mammographische Dichte in einer prospektiven Kohorte von Mammakarzinompatientinnen

**Habermeyer, Markus**, Dr. med.: Einfluss der Zytostatikakombinationen Epirubicin/Cyclophosphamid + Paclitaxel und Carboplatin/Paclitaxel auf die in vitro Oxidation von LDL bei Frauen mit Mammakarzinom

**Hofmann, Sebastian**, Dr. med.: Einfluss von Polymorphismen in Östrogen- und Progesteronrezeptoren auf Tumorcharakteristika und Prognose bei Ovarialkarzinompatientinnen

**Jonas, Kathleen**, Dr. med.: Sterilität und Frühaborte bei Patientinnen mit Endometriose

**Knetzger, Sandra-Maria**, Dr. med.: Wissenstand und Einstellungen gynäkologischer Patientinnen zu medizinischen Studien

**Kotziabassis, Efstratios**, Dr. med.: Finanzierung zertifizierter Zentren – eine willingness-to-pay-Analyse

**Lang, Michaela**, Dr. med. dent.: Einfluss von hormonellen und reproduktiven Faktoren auf die Entstehung und Prognose eines Ovarialkarzinoms

**Ozan-Mergner, Sevil Julia Katharina**, Dr. med.: Hinzunahme der mammografisch dichten Fläche zur prozentualen mammografischen Dichte als Risikofaktor für das Mammakarzinom – Ergebnisse einer Fall-Kontroll-Studie

**Rödl, Melanie**, Dr. med.: Molekulargenetische Marker zur Prädiktion des Präeklampsie-Risikos bei Schwangeren

**Schwab, Stefanie**, Dr. med.: Korrelation gynäkologischer Anamnese Faktoren mit der Erkrankung Endometriose anhand einer Fall-Kontrollstudie

**Stephan, Liana**, Dr. med.: Diagnostik hormoneller Veränderungen und Korrelation mit dem Phänotyp bei Patientinnen mit dem Mayer-Rokitansky-Küster-Hauser Syndrom

**Weber, Meike**, Dr. med.: Untersuchung der Wirkung von Dienogest auf die uterine Kontraktilität im Schweineuterus-Perfusionsmodell und Vergleich mit natürlichem Progesteron

**Whitehead, Lisa**, Dr. med.: Veränderung von Insulin- und Glukosewerten bei PCOS-Patientinnen unter Metformin und oralen Kontrazeptiva

### Doctorate theses 2016

**Faschingbauer, Cornelia**, Dr. med.: Der Einfluss des Zeitintervalls zwischen Untersuchung und Entbindung auf die Genauigkeit der fetalen sonographischen Gewichtsschätzung

**Meier, Kirstin**, Dr. med.: Soziale und ökonomische Faktoren und deren Einfluss auf Depression in und nach der Schwangerschaft

### Habilitation 2015

**Haas, Dietmar**, PD Dr. med.: Moderne Aspekte in der Klassifikation der Endometriose

**Rauh, Claudia**, PD Dr. med.: Einfluss genetischer und nicht-genetischer Risikofaktoren auf die Prognose gynäkologischer Malignome

### Habilitation 2016

**Hein, Alexander**, PD Dr. med.: Methoden zur Prognose- und Therapiebeurteilung beim Mammakarzinom

### Board qualification 2015

**Bayer, Christian**, Dr. med.

**Burghaus, Stefanie**, Dr. med.

**Heimrich, Jutta**, Dr. med.

**Koch, Martin**, Dr. med.

**Renner, Simone**, Dr. med.

### Board qualification 2016

**Hack, Carolin**, Dr. med.

**Hackl, Janina**, Dr. med.

**Sell, Charlotte**, Dr. med.

### Additional qualification 2015

**Bani, Mayada**, PD Dr. med.: Gynecological Oncology

**Burghaus, Stefanie**, Dr. med.: Hygiene officer

**Engel, Julia**, Dr. med.: Special Obstetrics and Perinatal Medicine

**Hack, Carolin**, Dr. med.: Naturopathic Methods

**Hildebrandt, Thomas**, Dr. med.: Gynecological Endocrinology and Reproductive Medicine

**Lermann, Johannes**, Dr. med.: Special Obstetrics and Perinatal Medicine

**Löhberg, Christian**, PD Dr. med.: Special Obstetrics and Perinatal Medicine

**Lux, Michael Patrick**, Prof. Dr. med.: Special Obstetrics and Perinatal Medicine

**Rauh, Claudia**, PD Dr. med.: Gynecological Oncology

**Schrauder, Michael**, PD Dr. med.: Special Obstetrics and Perinatal Medicine

### Additional qualification 2016

**Bayer, Christian**, Dr. med.: Diploma in Mountain Medicine

**Beckmann, Matthias W.**, Prof. Dr. med.: Senior surgeon Mamma

**Burghaus, Stefanie**, Dr. med.: Qualification AGUB I Urogynecology and Pelvic Reconstructive Surgery

**Burghaus, Stefanie**, Dr. med.: Diploma in colposcopy

**Heusinger, Katharina**, PD Dr. med.: Gynaecological Endocrinology and Reproductive Medicine

**Jud, Sebastian**, PD Dr. med.: Senior surgeon Mamma

**Jud, Sebastian**, PD Dr. med.: Gynecological Oncology

**Lux, Michael Patrick**, Prof. Dr. med.: Senior surgeon Mamma

**Rauh, Claudia**, PD Dr. med.: Senior surgeon Mamma

**Renner, Stefan**, Prof. Dr. med.: Gynaecological Endocrinology and Reproductive Medicine

**Schrauder, Michael**, PD Dr. med.: Senior surgeon Mamma

**Schrauder, Michael**, PD Dr. med.: Diploma in colposcopy

## Department of Ophthalmology

Chair of Ophthalmology

### Doctorate theses 2015

**Bilger, Angelika**, Dr. med.: Der Einfluss der Häufigkeit von Papillenrandblutungen auf die Progressionsrate bei chronischem Offenwinkelglaukom

**Cirkovic, Aleksandar**, Dr. med.: Clinical and ultrastructural characteristics of graft failure in Descemet membrane endothelial keratoplasty (DMEK): One year results after repeat DMEK

**Kopschillis, Nikolaos**, Dr. med.: Vernetzung des cornealen Stromas in einem künstlichen Hornhautmodell durch Induktion von Tissue Transglutaminasen

**Otto, Juliane**, Dr. med.: Repetitive tests of visual functions improved visual acuity in young subjects

**Schwarz, Martin**, Dr. med.: Einfluss der Chlo-roquineinnahme als Malariamedikation auf das mfERG – Untersuchung an einer brasilianischen Population mittels portablen mfERG

**Steyskal, Kerstin**, Dr. med.: Intravitreale Therapie bei Makulaödem nach retinalem Venenverschluss

**Treutlein, Eric**, Dr. med.: Klinisch-pathologische Befunde bei erworbenen Tränenwegsstenosen

### Doctorate theses 2016

**Heck, Saskia**, Dr. med.: Endoskopische Cyclophotokoagulation in der Behandlung von therapieresistenten Glaukomen

**Kurz, Julia**, Dr. med.: Prävalenz von Demodex folliculorum bei Patienten mit Keratokonjunktivitis sicca – Ergebnisse von 73 Patienten aus der Erlanger Sicca-Sprechstunde

### Habilitation 2015

**Tourtas, Theofilos**, PD Dr. med.: Optimierung und Weiterentwicklung der hinteren lamellären Keratoplastik



**Board qualification 2015**

**Frosz, Michaela**, Dr. med.  
**Rudolph, Michael**, Dr. med.

**Board qualification 2016**

**Beck, Christina**, Dr. med.  
**Queck, Susanne**  
**Weller, Julia**, Dr. med.

**Department of Otorhinolaryngology –  
 Head and Neck Surgery**  
 Chair of Otorhinolaryngology

**Doctorate theses 2015**

**Bauer, Conrad Niklas**, Dr. med. dent.: Artikulationsstörungen und Sprechverständlichkeit bei Patienten mit orofazialen Spaltbildungen  
**Frank, Friedrich**, Dr. med.: Analyse der Stimmklappen-Oberflächenschwingung im Hemilarynx-experiment: Künstliche Stimmklappen mit Elastizitätsmodul 9kPa  
**Hebel, Florian**, Dr. med. dent.: Instrumente zur Erfassung der stimmbezogenen Lebensqualität bei Patienten nach Kehlkopfteilresektion – ein Methodenvergleich  
**Hohm, Julian**, Dr. med. dent.: Einfluss von Fo und Sequenzlänge von Audio- und EGG-Signalen auf Perturbationsmaße (Jitter- und Shimmer-Parameter) bei der Stimmanalyse  
**Jesus Goncalves, Miguel de**, Dr. med.: Methodenvergleich zur Bestimmung der glottalen Mittelachse bei endoskopischen Hochgeschwindigkeitsvideoaufnahmen von organisch basierten pathologischen Stimmgebungsprozessen  
**Klipphahn, Nicole**, Dr. med.: Kontrastverstärkte sonografische perfusionsdynamische Dignitätsuntersuchungen bei Tumoren der Glandula parotis mit immunhistochemischer Auswertung der Gefäßstruktur  
**Nöller, Natalie**, Dr. med. dent.: Evaluation von Nasometrie im Vergleich mit perzeptiven Nasalitätsbeurteilungen bei deutschsprachigen Kindern mit Lippen-Kiefer-Gaumenspalte  
**Ogadzhanov, Anna**, Dr. med.: Die chirurgische Therapie des Vestibularisschwannoms  
**Plack, Sarah**, Dr. med.: Dreidimensionale Stimmklappenschwingungen: Einfluss von Symmetrie und subglottalem Druck  
**Ryzek, Don-Felix**, Dr. med.: Early-Stage Oropharyngealkarzinome: Ein Vergleich der Lebensqualität bei unterschiedlichen Behandlungsmodalitäten  
**Schulz, Aneliya**, Dr. med. dent.: Validierung der automatischen Sprechanalyseverfahrens mit Sprechproben von Kindern und Jugendlichen mit einer isolierten Gaumenspalte  
**Schumann, Annette**, Dr. rer. biol. hum.: Computer-based auditory phoneme discrimination training improves speech recognition in noise in experienced adult cochlear implant listeners  
**Sege, Anja**, Dr. med. dent.: Einfluss der zeitlichen Aufnahmezeit von endoskopischen Hochgeschwindigkeitsaufnahmen auf darauf berechnete Perturbationsmaße während gehaltener Phonation  
**Zdrojek-Fernandez, Magdalena**, Dr. med. dent.: Analyse der Stimmklappen-Oberflächenschwingung im Hemilarynxexperiment: Künstliche Stimmklappen mit Elastizitätsmodul 5kPa

**Doctorate theses 2016**

**Bellanova, Martina**, Dr. rer. biol. hum.: Development of a Logatome Test for the Evaluation of Signal Processing Algorithms in Hearing Aids on a Microscopic Level  
**Mangold, Elisabeth**, Dr. med.: Outcome und Prognosefaktoren bei T4a-Oropharynxkarzinomen, inklusive der Rolle einer HPV-Infektion  
**Petermann, Simon**, Dr. rer. biol. hum.: Quantitative Analysis of the Pitch-Shift Reflex  
**Pinhack, Hanna**, Dr. med.: Dreidimensionale Bewegung gesunder humaner Stimmklappen  
**Tomppert, Andrea**, Dr. med.: Epidemiologie und Überleben von HPV-assoziierten Tonsillenzinomen  
**Wagner, Johannes**, Dr. med.: Evaluierung von Thyreoplastiken Typ 1 nach Isshiki  
**Wasielewski, Elisabeth**, Dr. med.: Die Therapie des Hörsturzes – profitieren Patienten von einer intratympanalen Glukokortikoidtherapie?

**Habilitation 2016**

**Mantsopoulos, Konstantinos**, PD Dr. med.: Reduzierung der chirurgischen Invasivität bei Tumoren der Glandula parotis

**Board qualification 2016**

**Angerer, Florian**, Dr. med.: Ear-Nose-Throat Specialist  
**Dürr, Stefan**, Dr. med.: Speech, Voice and Paediatric Hearing Disorders – Phoniatrier

**Additional qualification 2016**

**Angerer, Florian**, Dr. med.: Somnolog (QN Somnology according to DGSM)

**Department of Pediatric  
 and Adolescent Medicine**  
 Chair of Pediatrics

**Doctorate theses 2015**

**Binkhoff, Theresa Maria**, Dr. med.: „Kunstfehler“ in der Schwangerenberatung? Eine Analyse von Erfahrungsberichten nach der vorgeburtlichen Diagnose Trisomie 21  
**Bruckmann, Kathrin**, Dr. med.: Klinik und Verlauf der hypothyreoten Autoimmunthyreopathie Hashimoto bei Kindern und Jugendlichen  
**Burger, Kristin**, Dr. med.: Genotyp-Phänotyp-Korrelationen bei Jungen mit X-chromosomal hypohidrotischer ekto-dermaler Dysplasie  
**Dietz, Jasna**, Dr. med.: Lungen- und Augenbeteiligung bei X-chromosomal vererbter hypohidrotischer ekto-dermaler Dysplasie  
**Doyle, Franziska**, Dr. med.: Korrelation der Kurzzeitmortalität von Frühgeborenen mit dem arteriellen Blutdruck sowie der Behandlung der akuten arteriellen Hypertonie innerhalb der ersten Lebenswoche  
**Heydt, Hanna**, Dr. med.: Sind die Effekte einer Therapie mit Wachstumshormon (GH) bei Kindern mit idiopathischem GH-Mangel oder mit neurosekretorischer Dysfunktion der GH-Sekretion unterschiedlich?  
**Hugel, Arnika**, Dr. med.: In-vitro-Studie zur Erfassung komplexer Ringbandrupturen der Finger und anatomischer Parameter mit hochauflösender Sonographie

**Karl, Matthias**, Dr. med.: Identification of the genomic BCR-ABL1 fusion sequence from blood specimen stored on filter paper  
**Kittel, Yamina**, Dr. med.: Welche Rolle spielen die Geburtsmaße bei Kindern mit einer prä-maturen Pubarche?  
**Magh, Johanna**, Dr. med.: Therapie der euthyreoten Autoimmunthyreopathie Hashimoto bei Kindern und Jugendlichen mit L-Thyroxin – Ergebnisse einer randomisierten Untersuchung  
**Meyer, Sarah**, Dr. med.: Angeborene und erworbene Störungen der Lungen und Atemwege bei Kindern und Jugendlichen – Übersicht der Erlanger Krankheitsfälle aus den Jahren 2000 bis 2011  
**Radtko, Susanne**, Dr. med.: Pharmakogenetik der Hochdosis-Methotrexat Therapie bei Kindern mit akuter lymphoblastischer Leukämie im Rahmen der therapieoptimierenden Studie ALL-BFM 2000  
**Schramm, Juliane**, Dr. med.: Klonierung der VEGF-Rezeptoren 1 und 2 mittels linearem lentiviralem Plasmidsystem und Expression in primären humanen T-Zellen  
**Strangl, Felix**, Dr. med.: Kortikale Expression von Brain-derived Neurotrophic Factor und N-Methyl-D-Aspartat-Rezeptor im Low-Protein-Tiermodell intrauteriner Wachstumsrestriktion  
**Studtacker, Julia**, Dr. med.: Stellenwert der Szintigraphie beim Auslassversuch bei Kindern mit primärer angeborener Hypothyreose  
**Wiebe, Diekmann**, Dr. med.: Pränatale Therapie des AGS bei 21-Hydroxylase Defekt  
**Zierk, Jakob**, Dr. med.: Indirect determination of pediatric blood count reference intervals

**Doctorate theses 2016**

**Hermes, Katharina**, Dr. med.: Vorgeburtliche Proteinersatztherapie am Mausmodell – Evaluation intraamniotischer Ektodysplasiegaben zur Behandlung der X-chromosomalen hypohidrotischen ekto-dermalen Dysplasie  
**Kußmann, Franziska**, Dr. med.: Das Schmerzverhalten von Small-for-Gestational-Age (SGA)-Kindern  
**Ostermeier, Christina**, Dr. med.: Schlafverhalten, körperliche Aktivität und Ernährung von Kindern und Jugendlichen mit Adrenogenitalem Syndrom und 21-Hydroxylase-Defekt  
**Queißner, Ellen**, Dr. med.: Therapie mit GnRH-Agonisten bei kleinwüchsigen Kindern unter Therapie mit Wachstumshormon und mit schlechter Endgrößenprognose  
**Speicher, Theresa**, Dr. med.: Infektionskrankheiten bei stationär behandelten Kindern – Spektrum und Therapiestrategien im Abstand von über 40 Jahren

**Habilitation 2015**

**Fahlbusch, Fabian Benedikt**, PD Dr. med.: Regulation von Wachstumsfaktoren und Tumorsuppressoren bei intrauteriner Wachstumsrestriktion

**Habilitation 2016**

**Brecht, Ines Beatrice**, PD Dr. med.: Seltene Tumorerkrankungen in der Pädiatrie  
**Menendez Castro, Carlos**, PD Dr. med.: Mechanismen der fetalen Programmierung kardiovaskulärer und renaler Erkrankungen



**Board qualification 2015**

Brackmann, Florian, Dr. med.  
Kiefer, Alexander, Dr. med.  
Penger, Theresa  
Siebenlist, Gregor, Dr. med.

**Board qualification 2016**

Bauer, Stefanie, Dr. med.  
Bornschelegl, Philipp  
Krickau, Tobias, Dr. med.

**Additional qualification 2015**

Karle-Hess, Stephanie, Dr. med.: Pediatric Nephrology  
Marek, Ines, Dr. med.: Pediatric Nephrology  
Melichar, Volker, Dr. med.: Allergology  
Sauerstein, Katja, Dr. med.: Pediatric Nephrology

**Additional qualification 2016**

Kusnik, Stefan, Dr. med.: Neonatology  
Wolf, Paul, Dr. med.: Neonatology

**Department of Pediatric  
and Adolescent Medicine**

Division of Pediatric Cardiology

**Doctorate theses 2015**

Mösler, Johanna, Dr. med.: Die Anwendung von Flachdetektor-Computertomographie bei der Katheterisierung von angeborenen Herzfehlern  
Treutlein, Christoph, Dr. med.: Beatmungsdauer nach Operationen kongenitaler Herzfehler bei intraoperativer Analgesie mit Fentanyl oder Remifentanyl

**Habilitation 2016**

Toka, Okan, PD Dr. med.: Untersuchungen zur Genetik und Pathophysiologie sekundärer Hypertonie im Kindesalter

**Board qualification 2015**

Herrndobler, Franz, Dr. med.: Pediatric Cardiology

**Board qualification 2016**

Alkassar, Muhannad, Dr. rer. nat.: Pediatric Cardiology  
Halbfaß, Julia, Dr. med.: Pediatric Cardiology  
Reif, Fabian, Dr. med.: Pediatrician  
Stec, Dagmara: Pediatric Cardiology

**Additional qualification 2016**

Berzel, Simon, Dr. med.: Genetic counselor  
Raake, Michael, Dr. med.: Genetic counselor  
Reif, Fabian, Dr. med.: Genetic counselor

**Department of Plastic  
and Hand Surgery**

Chair of Plastic Surgery and Hand Surgery

**Doctorate theses 2015**

Bitto, Franz-Ferdinand, Dr. med.: Myogenic differentiation of mesenchymal stem cells in a newly developed neurotized AV-Loop model  
Bührer, Gregor, Dr. med.: Signifikant vermehrte Knochenbildung durch die Kombination von MSCs und BMP2 im arteriovenösen Loop-Modell der Ratte  
Hilgert, Johannes, Dr. med.: Hämodynamik und Angiogenese im Modell der Arteriovenösen Schleife und Etablierung des Arterioarteriellen Modells  
Jost, Matthias, Dr. med.: Bestimmung von Moxifloxacin-Gewebespiegeln bei vakuumversiegelten Wunden  
Maktabi, Tarek, Dr. med.: Modifizierte kranio-medial gestielte Mammareduktionsplastik Eine retrospektive Analyse des Erlanger Patientenkollektivs aus dem Zeitraum 2005 bis 2012  
Müller-Seubert, Wibke, Dr. med.: Extrakorporale Perfusion und Oxygenierung des Musculus rectus abdominis im Schweinmodell  
Saalabian, Katharina, Dr. med.: Klinische Evaluation der Wundheilung bei Anwendung von titanbeschichteten Nahtmaterial beim chirurgischen Wundverschluss  
Weigel, Linda, Dr. med.: Kombination von extrinsischer und intrinsischer Vaskularisation im arteriovenösen Loop Modell der Ratte zur Erzeugung axial vaskularisierter Gewebekonstrukte

**Doctorate theses 2016**

Lutz, Brigitta, Dr. med.: Prospektive Studie zur Beurteilung der psychischen Entwicklung und des Wohlbefindens von postbariatrischen Patienten im prä- und postoperativen Vergleich  
Seuß, Hannes, Dr. med.: Technische Entwicklung eines dreidimensionalen Mappings des arteriovenösen-loop Modells unter Verwendung von zweidimensionalen histologischen Verfahren

**Board qualification 2015**

Boos, Anja, Dr. med.

**Board qualification 2016**

Ludolph, Ingo, Dr. med.

**Department of Psychiatry  
and Psychotherapy**

Chair of Psychiatry and Psychotherapy

**Doctorate theses 2015**

Fleischmann, Johanna, Dr. med.: Veränderung der Expression von mTOR, Orexin 1 und NGF bei Patienten mit akuter Suizidalität  
Hübschmann, Lukas, Dr. med.: Mortalität von dementiellen Syndromen nach Diagnostik in einer regionalen Gedächtnissprechstunde  
Kinzel, Olga, Dr. med.: Einfluss des Genotyps der sauren Sphingomyelinase auf die Höhe des

Carbohydrat-defizienten Transferrins bei alkoholabhängigen Patienten

Kübler, Janina, Dr. med.: Vergleichende Untersuchung elektrophysiologischer Parameter bei Patienten mit Tako-Tsubo Kardiomyopathie und Depression

Reich, Karin, Dr. rer. biol. hum.: Kurzfristige psychische und physiologische Effekte unterschiedlicher physischer Aktivität – Eine Untersuchung zu den Effekten verschiedener Bewegungsformen auf Körper und Befindlichkeit bei gesunden Personen

Schamber, Christine, Dr. med.: Einflussfaktoren auf die Plasmakonzentration der Amyloid- $\beta$ -Peptide A $\beta$ 1-40, A $\beta$ x-40, A $\beta$ 1-42 und A $\beta$ x-42 in einem Probandenkollektiv kognitiv unbeeinträchtigter Erwachsener. Eine Untersuchung der Faktoren Body Mass Index, Blutdruck, Glukose-, Triglyzerid- und Kreatininkonzentration im Serum sowie biographischer und familienanamnestischer Daten

Schmidt, Anika, Dr. rer. biol. hum.: Bindung und Liebe: Unterschiede zwischen gesunden und von affektiven Störungen betroffenen Paaren

Zölch, Julia, Dr. med.: Repetitive transkranielle Magnetstimulation (rTMS) zur Behandlung rezidivierender depressiver Episoden – Vergleich der Wirkung bei unterschiedlich gewählter Stimulationsstärke

**Doctorate theses 2016**

Ermann, Natalia, Dr. rer. biol. hum.: Optimierung der Qualitätskontrolle und Interpretation der Neurochemischen Demenzdiagnostik

Hönig, Stefanie, Dr. med.: Entwicklung eines Zellkulturmodells zum Nachweis von Funktion und Substrat der sekretorischen sauren Sphingomyelinase

Loserth, Martina, Dr. med.: Psychopathologische Auffälligkeiten und Persönlichkeitsmerkmale von Patienten mit Tako-Tsubo Kardiomyopathie

Lüke, Katharina, Dr. med.: Basic presynaptic functions in hippocampal neurons are not affected by acute or chronic lithium treatment

Oberstein, Timo, Dr. med.: Astrocytes and microglia but not neurons preferentially generate N-terminally truncated beta amyloid peptides

Röther, Mareike, Dr. med.: Dynamic properties of the alkaline vesicle population at hippocampal synapses

Rümmler, Anne, Dr. med.: Die Effekte von Mitragynin auf Verhaltenssensitivierung und Genexpression in der Maus

Wieser, Erika, Dr. rer. biol. hum.: Psychische Störungen und Partnerschaft. Welche Auswirkungen hat das Vorliegen einer psychischen Störung auf die Partnerschaft, und welche Belastungen erleben die Angehörigen von Menschen mit solchen Störungen?

Wismeth, Barbara, Dr. med.: Unerwiderte und glückliche Liebe im Vergleich – die Suche nach Ursachen, Folgen und Grenzüberschreitungen

**Habilitation 2015**

Reichel, Martin Hans Helmut, PD Dr. rer. nat.: Alkoholassoziierte Veränderungen im Sphingolipid-Stoffwechsel

**Rotter-Neubert, Andrea**, PD Dr. med.: Transkriptionelle und epigenetische Modifikationen bei psychischen Störungen im Rahmen von Abhängigkeit und Depression

#### Board qualification 2015

**Kreil, Sebastian**, Dr. med.  
**Stöckl, Thomas**, Dr. med.

#### Board qualification 2016

**Bergner, Matthias**, Dr. med.  
**Braun, Birgit**, Dr. med.  
**Suttner, Gerald**

#### Additional qualification 2015

**Spitzer, Philipp**, Dr. med.: IPT (trainer and supervisor of interpersonal psychotherapy)

#### Department of Psychiatry and Psychotherapy

Division of Child and Adolescent Mental Health

#### Doctorate theses 2015

**Busch, Katrin**, Dr. rer. biol. hum.: Aufmerksamkeitsprozesse bei Kindern mit ADHS: geringere Ressourcen und/oder höhere Variabilität auf neuronaler Ebene?  
**Tapfer, Ann-Katrin**, Dr. med.: Blickverhalten beim Lesen bei Kindern mit und ohne Lesestörung

#### Doctorate theses 2016

**Irlbauer-Müller, Viktoria**, Dr. rer. biol. hum.: Elterliche Belastung und die Zuverlässigkeit von Elternangaben psychisch und verhaltensauffälliger Kinder und Jugendlicher

#### Board qualification 2015

**Bezold, Mareile**, Dr. med.

#### Board qualification 2016

**Golub, Yulia**, Dr. rer. nat.  
**Horndasch, Stefanie**, Dr. med.

#### Additional qualification 2015

**Irlbauer-Müller, Viktoria**, Dr. rer. biol. hum.: licensed Pediatric Psychotherapist  
**Jonas, Nicola**: licensed Pediatric Psychotherapist

#### Department of Psychiatry and Psychotherapy

Division of Psychosomatics and Psychotherapy

#### Doctorate theses 2015

**Leidinger, Rezvan**, Dr. med.: Iranische und deutsche Patienten in einer psychiatrischen Großstadtpraxis: Gibt es Unterschiede in Bezug auf Häufigkeit und Schweregrad psychischer Störungen?  
**Nowy, Kerstin**, Dr. med.: Prävalenz und Charakteristika der klinischen Präsentation von Patienten mit nicht-kardialen Brustschmerz

#### Doctorate theses 2016

**Sariaslan, Selim**, Dr. med.: Körperliche Erkrankungen und komorbide psychische Belastungen bei türkischstämmigen im Vergleich zu deutschen Patienten in einer Allgemeinanzpraxis. Ein empirischer Vergleich von nicht-kardialen und kardialen Brustschmerzpatienten hinsichtlich Soziodemographie, kardiovaskulärer Risikofaktoren, Schmerz, Beeinträchtigung und Inanspruchnahmeverhalten

#### Board qualification 2016

**Kastel-Hoffmann, Silke**, Dr. med.: Psychosomatic Medicine Specialist and Psychotherapist

#### Additional qualification 2016

**Paslakis, Georgios**, PD Dr. med.: Psycho-Oncologist

#### Department of Radiation Oncology

Chair of Radiotherapy

#### Doctorate theses 2015

**Betz, Anne**, Dr. med.: Multimodale Strahlentherapie des lokal fortgeschrittenen Zervixkarzinoms an der Strahlenklinik des Universitätsklinikums Erlangen von 2000 bis 2011  
**Dorsch, Verena**, Dr. med.: Methodische Untersuchung zum Nachweis zirkulierender Tumorzellen im Blut  
**Frischholz, Birgit**, Dr. med.: Verminderte Sekretion des Zytokins IL-1b durch aktivierte Peritonealmakrophagen strahlensensibler Balb/c Mäuse nach einer Strahlenexposition von 0,5 und 0,7 Gy  
**Gabriel, Stefanie**, Dr. med.: Der Einfluss von fraktionierter Bestrahlung und AnnexinA5 auf Zelltod und immunogenes Potential der murinen kolorektalen Tumorzelllinie CT26  
**Hild, Sebastian**, Dr. rer. biol. hum.: Adaptive treatment of prostate carcinoma in scanned ion beam therapy  
**Hohmann, Nora**, Dr. med.: Untersuchung von Tumorzellen und Hautfibroblasten als nicht-professionelle Phagozyten unter besonderer Betrachtung der Seneszenz  
**Lödermann, Barbara**, Dr. med.: NF- $\kappa$ B abhängige verringerte Sekretion von aktivem IL-1 $\beta$  durch aktivierte Makrophagen nach Niedrigdosisbehandlung mit Röntgenstrahlen bei diskontinuierlicher Dosisabhängigkeit  
**Losensky, Wencke**, Dr. med.: Untersuchung der symptomorientierten Lebensqualität von Patienten mit Rektumkarzinom unter simultaner neoadjuvanter Radiochemotherapie  
**Putz, Florian**, Dr. med.: Ein prädiktives Modell zur Vorhersage der Durchführbarkeit einer simultanen Radiochemotherapie mit Temozolomid bei Glioblastom-Patienten über 65 Jahren  
**Radev, Miroslav**, Dr. med. dent.: Prognostische Bedeutung der M1 CD 68 und M2 CD163 Makrophagen bei drei Kopf-Hals Tumorkollektiven unterschiedlichen Risikos  
**Seliger, Toni**, Dr. med.: Die Quantität der Zell-Zell Strukturen über die Zeit im Vergleich zwischen einer Tumorzelllinie und primären Hautfibroblasten  
**Weiling, Max**, Dr. med.: Lebensqualität bei Patienten mit simultaner Radiochemotherapie

**Winkler, Sebastian**, Dr. med.: Interindividuell unterschiedlich ausgeprägte Induktion der Apoptose und Nekrose bei Bestrahlung, Chemotherapie und Hyperthermie von Lymphozyten im Blut von Tumorpatienten

#### Doctorate theses 2016

**Dege, Sabine**, Dr. med.: Zervixkarzinom- Analyse der Ergebnisse der perkutanen Strahlentherapie und der nicht bildgestützten Brachytherapie  
**Finkel, Patrick**, Dr. med.: Die Rolle von NK-Zellen bei Tumormimmunisierungen  
**Haas, Claudia**, Dr. med.: Ergebnisse der Salvage-Brachytherapie  $\pm$  simultane Chemotherapie und interstitielle Hyperthermie bei vorbestrahlten Hals-Nasen-Ohren-Tumoren  
**Hartmann, Josefin**, Dr. rer. biol. hum.: Quality assurance in hyperthermia  
**Kulzer, Lorenz**, Dr. med.: Einfluss von norm- und hypo-fraktionierter Tumorzellbestrahlung auf die Aktivierung von humanen dendritischen Zellen  
**Loibl, Monika**, Dr. med.: Untersuchung von Normalgewebszellen und Tumorzellen als nicht professionelle Phagozyten im in-vitro Zellmodell und im Gewebe  
**Maier, Valerie**, Dr. med. dent.: Einfluss von Röntgenbestrahlung muriner CT 26 Zellen und von Annexin A5 auf die Phagozytose durch RAW- Makrophagen  
**Ries, Sonja**, Dr. med.: Untersuchung von zytotoxischen Effekt und Wirkmechanismus verschiedener nicht-nukleosidischer Reverse-Transkriptase-Inhibitoren  
**Scheerer, Cora**, Dr. med.: Der nicht-Nukleosidische Reverse-Transkriptase-Inhibitor Efavirenz hemmt Cisplatin-Toxizität gegen Tumorzellen in vitro  
**Stubbe, Franziska**, Dr. med.: Effektive lokale Kontrolle nach neoadjuvanter Radiochemotherapie und Resektion von fortgeschrittenen Weichteilsarkomen – Ergebnisse der unizentrischen Fallsammlung der Strahlenklinik Erlangen  
**Wekenborg, Camilla Alexandra**, Dr. med.: Ergebnisse der Brachytherapie bei Vaginal- und Vulvakarzinom mit Analyse des rezidivfreien Überlebens, des tumorfreien Überlebens und des Gesamtüberlebens unter Evaluation einzelner Prognosefaktoren  
**Wölfelschneider, Jens**, Dr. rer. biol. hum.: 4D Motion Management of Intra-Fractionally Moving Tumors in Radiation Therapy  
**Zoske, Hanno**, Dr. med.: Die prognostische Bedeutung von Tumor assoziierten Makrophagen sowie Tumor infiltrierenden Lymphozyten bei strahlentherapeutisch behandelten Patienten mit einem Adenokarzinom des Pankreas

#### Board qualification 2015

**Onischka, Katharina**: Pharmacological tumor therapy

#### Board qualification 2016

**Schmidtner, Johannes**, Dr. med.: Radiation therapy  
**Sadat, Fahima**: Radiation therapy  
**Wimmer, Caterina**, Dr. med.: Radiation therapy  
**Ziegau, Anke**: Pharmacological tumor therapy

**Additional qualification 2015**

**Yohannes, Indra**, Dr. rer. nat.: Medical Physics Expert

**Additional qualification 2016**

**Serpa, Marco**, MPE

**Hartmann, Josefin**, Dr. rer. biol. hum.: Medical Physics Expert

**Department of Surgery**

Chair of Surgery

**Doctorate theses 2015**

**Dykta, Michael**, Dr. med.: Fehleranalyse nach Rekonstruktion der Rotatorenmanschette – Eine retrospektive Erfassung operativer Revisionen nach offener Rotatorenmanschettenrekonstruktion

**Förtsch, Line**, Dr. med.: Klinische Ergebnisse nach laparoskopischer Operation bei Morbus Crohn mit und ohne Komplikationen

**Kaiser, Armin**, Dr. med.: Der Einfluss von intensivierte Dreifach-Thrombozytapheresen auf systemische Konzentrationen hämatopoetischer Wachstumsfaktoren

**Koch, Mila**, Dr. med.: Analyse der Pankreaspunktionen 2003 – 2008 am Universitätsklinikum Erlangen

**Teufel, Miriam**, Dr. med.: Vergleichsuntersuchung zum Screening auf erythrozytäre Alloantikörper mit Hilfe zweier Festphasensysteme sowie zusätzlich parallele Untersuchung von Testseren mit Röhrchenmethoden

**Tines, Roland**, Dr. med.: „Damage-Control“ Verfahren mit intrathorakaler Tamponade – Eine Methode bei unkontrollierbaren Blutungen im Thorax

**Doctorate theses 2016**

**Almási-Sperling, Veronika**, Dr. med.: Langzeitergebnisse der arterio-venösen Fistel als Gefäßzugang zur Hämodialyse bei Kindern

**Gündel, Michael**, Dr. med.: Lebertransplantation als eine Behandlungsmethode bei Patienten mit hepatozellulären Karzinom -Langzeitergebnisse

**Haep, Lisa**, Dr. rer. nat.: Neue Funktionen von IFN-gamma bei CED-assoziierten vaskulären Veränderungen

**Heidrich, Freya**, Dr. med.: Ergebnisse und Komplikationen bei der Implantation von Portkathetern

**Hieber, Sabrina**, Dr. med.: Ergebnisse der Portimplantation über einen transfemorale Zugang bei Patientinnen mit gynäkologischen Tumoren

**Kapust, Johannes**, Dr. med.: Mikrozirkulation der Haut in pAVK-Patienten im Stadium IV nach Revaskularisation – eine Angiosomkonzept basierte Auswertung mittels O2C

**Lohmüller, Clemens**, Dr. med.: Eine prospektive Intent-to-Treat Analyse der ersten 30 Single-Port-Cholezystektomien an einem Haus der Grund- und Regelversorgung

**Meisgeier, Axel**, Dr. med.: Etablierung von Laser-Mikrodissektion und hochsensitiver, zweidimensionaler, differentieller Gelelektrophorese zur Identifizierung metastasierungsassoziierter Proteine des kolorektalen Karzinoms

**Schlegel, Jörg**, Dr. med.: Diagnostik und Therapie von Aneurysmen der Arteria poplitea  
**Seidler, Michael**, Dr. med.: Bewertung der kralen perkutanen transluminalen Angioplastie als Behandlungsmethode bei dialysepflichtigen Patienten mit kritischer Extremitätenischämie

**Habilitation 2016**

**Vassos, Nikolaos**, PD Dr. med.: Multimodale Diagnose und Therapie von gastrointestinalen Stromatumoren und Weichteilsarkomen

**Department of Surgery**

Division of Pediatric Surgery

**Board qualification 2016**

Besendörfer, Manuel, Dr. med.

**Department of Surgery**

Division of Transfusion Medicine and Hemostaseology

**Doctorate theses 2015**

**Dankerl, Helen**, Dr. med.: Untersuchung der Thrombozytenfunktion in der Vollblut-Impedanz-Aggregometrie und unter hohen Scherkräften am PFA-100® bei Erstspendern

**Eckstein, Fabian**, Dr. med.: Der Einfluss von präanalytischen Bedingungen auf Plättchenmikropartikel

**Göhrling, Jasmin**, Dr. med. dent.: Studie über den Einfluss von Zentrifugation auf die Hämolyserate bestrahlter Erythrozyten

**Hofer, Martin**, Dr. med. dent.: Untersuchung der Spenderimmunität bei nicht-Zytokin-stimulierten Leukozytenspendern

**Hupke, Carolin**, Dr. med.: Untersuchung von zellulärem und frei zirkulierendem S100A4 in Relation zu den Wachstumsfaktoren VEGF, PDGF-AB und TGF-β sowie den CD62-positiven Thrombozyten bei Patienten mit kolorektalem Karzinom

**Möller, Ina**, Dr. med.: Analyse von T-Zell-Subpopulationen bei autologen und allogenen Stammzellapheresen

**Pfeffer, Sina**, Dr. med.: Anwendung der Rotating-Field-Elektrophorese zur Auftrennung der Multimere des von-Willebrand-Faktors

**Philipp, Anja**, Dr. med. dent.: Ausprägung der HNA-Merkmale 1, 3, 4 und 5 bei türkischen und deutschen Blutspendern

**Raczat, Tatjana**, Dr. med.: Der Einfluss verschiedener Antikoagulantien auf die Qualitätstestung von Thrombozyten mittels dynamischer Lichtstreuung

**Renner, Ilona**, Dr. med.: Die Bedeutung der standardisierten Gerinnungsanamnese in der Geburtshilfe

**Steininger, Philipp**, Dr. med.: Erste vergleichende Untersuchung einer neuen Leukozytapheresetechnologie bei nicht-zytokinstimulierten Spendern

**Stürhof, Anna**, Dr. med.: Veränderung der Spiegel der freigesetzten und intrazellulären thrombozytären Zytokine PDGF-AB und VEGF in Thrombozytapheresekonzentraten während der Lagerung

**Teufel, Miriam**, Dr. med.: Vergleichsuntersuchung zum Screening auf erythrozytäre Alloantikörper mit Hilfe zweier Festphasensysteme sowie zusätzlich parallele Untersuchung von Testseren mit Röhrchenmethoden

**Tran, Lan Phuong**, Dr. med.: Vergleich des Gehalts antikoagulierter Blutproben an VEGF, löslichem VEGF-Rezeptor 1, löslichem CD40 Ligand und TGF-β1 bei verschiedenen Lagerungstemperaturen und Lagerungszeiten

**Tully, Susanne**, Dr. med.: Effekt der sofortigen vs. verzögerten Zugabe einer Plättchenadditivlösung zu hochkonzentrierten Plättchenapheresekonzentraten

**Vajko, Melinda**, Dr. med.: Während der Lagerung freigesetzte und intrazellulär verbliebene Zytokine TGFβ1 und sCD40L in Thrombozytapheresekonzentraten von den Zellseparatoren Trima und Amicus

**Ziehe, Bettina**, Dr. med.: Vergleichende Untersuchung der Zellapoptose mononukleärer Zellen aus Leukozytapheresen und Leukozyten-Reduktions-System-Kammern

**Doctorate theses 2016**

**Eckstein, Markus**, Dr. med.: Die Auswirkungen einer Übernacht-Lagerung von Vollblut bei Raumtemperatur auf Hämoglobin-Modifikationen und In-vitro-Marker der Alterung von Erythrozyten

**Madler, Philipp**, Dr. med. dent.: Vergleich zweier Testsysteme zur Untersuchung von Lupus-Antikoagulationen

**Martin, Alexander**, Dr. med.: Untersuchung der Thrombozytenfunktion in der Vollblut-Impedanz-Aggregometrie und der primären Hämostase unter hohen Scherkräften am PFA-100® bei Thrombozyten-Dauerspendern

**Six, Markus**, Dr. med.: Die Einflüsse der Thrombozytenkonzentration auf die Reifung von Monozyten zu dendritischen Zellen

**Habilitation 2016**

**Hauck-Dlimi, Barbara**, PD Dr. med.: Experimente zur Lagerung von Blut und Blutstammzellen und zur HPA- und HNA-Genotypenverteilung zu Transfusionszwecken

**Board qualification 2015**

Arnold, Sabine, Dr. med.

**Board qualification 2016**

**Dullinger, Katharina**, Dr. med.  
**Kuta, Piotr**, Dr. med.

**Additional qualification 2015**

Arnold, Sabine, Dr. med.: Hemostaseology

**Department of Surgery**

Division of Trauma Surgery

**Doctorate theses 2015**

**Deschler, Gloria**, Dr. med.: Die histomorphometrische Auswertung des Knochenneubildung im Großtier-Modell des Schafes

**Konrad, Julia**, Dr. med. dent.: Vergleich verschiedener Techniken zur Mamillen-Areola-



Komplex-Rekonstruktion nach autologem Brustaufbau im Zeitraum 2005-2012

**Renner, Nina**, Dr. med.: Korrelation von Krankheitsparametern mit qualitativen Knorpelveränderungen bei Patienten mit Rheumatoider Arthritis

#### Doctorate theses 2016

**Schmidt, Thomas**, Dr. med.: Indikationen, Komplikationen und Ergebnisse der Ellenbogenarthroskopie – eine retrospektive Ergebnisbeurteilung mit Korrelationsanalyse des Patient-Rated-Elbow-Evaluation (PREE)-Scores in seiner deutschsprachigen Version

#### Habilitation 2015

**Schulz-Drost, Stefan**, PD Dr. med.: Innovative Methoden der Stabilisierung der anterioren Brustwand

#### Board qualification 2016

**Fuchs, Oliver**, Dr. med.

**Killisch Nils**, Dr. med.

**Krinner, Sebastian**, Dr. med.

**Pachowsky, Milena**, Dr. med.

**Renner, Nina**, Dr. med.

#### Additional qualification 2015

**Krause, Johannes**, Dr. med.: Special Accident Surgery

#### Additional qualification 2016

**Gelse, Kolja**, Prof. Dr. med.: Emergency Medicine

**Langenbach, Andreas**, Dr. med.: Special Accident Surgery

#### Department of Urology

Chair of Urology

#### Doctorate theses 2015

**Filin, Svitlana**, Dr. med.: Ergebnisse der Gammasonden-gesteuerten erweiterten pelvinen Lymphdissektion im Rahmen der retropubischen radikalen Prostatektomie bei 403 eigenen Prostatakarzinompatienten

**Muck, Alexander**, Dr. med. dent.: Klinisches Outcome von Patienten mit Lymphknoten-positivem Prostatakarzinom nach Prostatektomie und erweiterter pelviner Sentinel-Lymphknoten Dissektion

**Rosenbaum, Clemens**, Dr. med.: Dynamic Tissue Perfusion Measurement: A New Tool for Characterizing Renal Perfusion in Renal Cell Carcinoma Patients

#### Doctorate theses 2016

**Ellmann, Christina**, Dr. med.: Genomische Charakterisierung plazmazytoider Urothelkarzinome als seltene Variante aggressiver Harnblasenkarzinome mittels komparativer genomischer Hybridisierung und Copy Number Variation Analyse

**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

**Krieger, Stefan**, Dr. med.: Einfluss einer präoperativen Anämie auf die Sterblichkeit nach radikaler Zystektomie – Eine monozentrische Studie an 182 Patienten mit muskelinvasivem Harnblasenkarzinom

**Kühn, Charlotte**, Dr. med. dent.: Testosteron-Ersatztherapie bei hypogonadalen Männern nach Prostatakarzinom-Therapie: Eine Fragebogenbasierte retrospektive Analyse unter Urologen in Bayern, Deutschland

**Schwaiger, Brigitte**, Dr. med.: Strategien bei der Diagnostik und Therapie der kindlichen und jugendlichen Harninkontinenz

#### Habilitation 2015

**Keck, Bastian**, PD Dr. med.: Klinische, histologische und molekulare Prognosefaktoren des Urothelkarzinoms und dessen Varianten

**Walter, Bernhard**, PD Dr. med.: Über die Heterogenität urologischer Tumore am Beispiel des Nierenkarzinoms

#### Habilitation 2016

**Kunath, Frank**, PD Dr. med.: Evaluierung von wissenschaftlichen Methoden zur Etablierung des Wissenstransfers in der Urologie

#### Board qualification 2016

**Freier, Verena**, Dr. med.

**Lieb, Verena**, Dr. med.

**Schwaiger, Brigitte**, Dr. med.

**Sikic, Danijel**, Dr. med.

#### Additional qualification 2015

**Landsmann, Susanne**, Dr. med.: Master of Health Business Administration (MHBA)

#### Department of Operative Dentistry and Periodontology

Chair of Dental, Oral, and Maxillofacial Medicine – especially Operative Dentistry, Periodontology, and Pediatric Dentistry

#### Doctorate theses 2015

**Belli, Renan**, Dr. med. dent.: Fatigue Behavior of Dental Restoratives

**Bigdali, Puria**, Dr. med. dent.: Einfluss von Eugenol und Silikonöl auf die Dentinhaftung von adhäsiven Befestigungsmaterialien

**Bohn, Anna Maria**, Dr. med. dent.: Verschiedene Spülmethode zur Entfernung von Kalziumhydroxid aus dem Wurzelkanal

**Dippold, Christoph**, Dr. med. dent.: Approximale Kastenelevationstechnik – Einfluss auf die marginale Adaptation von Kompositinlays

**Günther, Oliver**, Dr. med. dent.: Analyse des Haftverbunds acht verschiedener Befestigungszemente zum Wurzelkanaladent

**Herzog, Johanna Lucia**, Dr. med. dent.: Revision von GuttaFlow: Einfluss von GuttaFlow Primer und verschiedenen Entfernungstechniken

**Kraus, Florian**, Dr. med. dent.: Apikale Reinigung von Wurzelkanälen mit drei verschiedenen Versionen der ROEKO CanalBrush

**Kuliev, Batyr**, Dr. med. dent.: Über die retrograde Obturation mit MTA-Zement und Super-EBA-Zement bei der Wurzelspitzenresektion – eine vergleichende Fallstudie in Vivo

**Maier, Eva**, Dr. med. dent.: Polymerisationseigenschaften von Bulk-Fill Kompositen

**Oefler, Frank**, Dr. med. dent.: Effizienz vier verschiedener Reinigungsprotokolle zur Entfernung artifizell platzierter Dentinspäne in lateralen Wurzelkanalextensionen

**Ostendorf, Dirk**, Dr. med. dent.: Untersuchungen des Randschlussverhaltens eines selbstadhäsiven Kompositbefestigungszementes in approximal dentinbegrenzten Klasse-II-Kavitäten bei unterschiedlichen Füllungstechniken

**Panzer, Reinhard**, Dr. med. dent.: Über die Reparaturfähigkeit polymerisierter Kompositoberflächen

**Peter, Kathrin**, Dr. med. dent.: Einfluss des Tapers bei der Entfernung von Kalziumhydroxid aus dem Wurzelkanal

**Sauter, Eva-Maria**, Dr. med. dent.: Zur Eignung von dentalen Kompositen für den direkten Höckerersatz im Seitenzahnbereich – eine Randspaltanalyse

**Schmidt, Heidi**, Dr. med. dent.: In-vivo-Abrasion und quantitative Randspaltanalyse von IPS-Empress® Inlays nach 8 Jahren

**Schmidt, Sarah**, Dr. med. dent.: Untersuchung zur Haftung von Befestigungsmaterialien an verschiedenen faserverstärkten Wurzelkanalstiften vor und nach Alterung

**Schneider, Simone**, Dr. med. dent.: Ein Modell zur Längenmessung im Wurzelkanal mit Hilfe von Hall-Sensoren

**Skibbe, Daniel**, Dr. med. dent.: Über die Haftung an polymerisierten Kompositoberflächen

**Unbehaun, Sebastian**, Dr. med. dent.: Einfluss der Probendicke auf die Haftkraft konventionell und adhäsiv befestigter Wurzelkanalstifte

**Wagner, Anna**, Dr. med. dent.: Messung der Polymerisationsschrumpfung und Sauerstoffinhibitionsschicht verschiedener K&B-Materialien

#### Doctorate theses 2016

**Adam, Max**, Dr. med. dent.: Einfluss unterschiedlicher Spülvolumina und Aktivierungen auf die Entfernung von Dentinspänen aus simulierten Wurzelkanalextensionen

**Brader, Jan**, Dr. med. dent.: Untersuchungen zur Verbesserung der Frakturresistenz endodontisch behandelte Zähne mit nicht abgeschlossenen Wurzelwachstum

**Gunkel, Maria**, Dr. med. dent.: Effekt der Doppelapplikation von verschiedenen selbststätzenden Einfläschenadhäsiven auf die Mikrozugfestigkeit im Dentin

**Lazaridou, Dimitra**, Dr. med. dent.: Two-body wear resistance of twenty modern dental materials for direct restorations

**Neuß, Michael**, Dr. med. dent.: Ermüdung des Dentin-Komposit-Komplexes im Biegeversuch

**Schütz, Esther**, Dr. med. dent.: Einfluss der Stiftlänge und des Stiftdesigns auf die Abzugs- und Haftkraft konventionell und adhäsiv befestigter Wurzelkanalstifte

**Thalheim, Günter**, Dr. med. dent.: Lehrevaluation in der Endodontie: Qualität von Wurzelkanalfüllungen mit dem MTwo-System



**Habilitation 2016**

**Ebert, Johannes**, PD Dr. med. dent.: Minimale invasive und nachhaltige Zahnerhaltung

**Department of Oral and  
Cranio-Maxillofacial Surgery**

Chair of Dental, Oral, and Maxillofacial Medicine – especially Oral and Maxillofacial Surgery

**Doctorate theses 2015**

**Abu-Nasir, Mohammed**, Dr. med. dent.: Biofunktionalisierung von Implantatoberflächen mit einem synthetisch hergestellten Peptid (P15) bei diabetischen Versuchstieren gegenüber gesunden Versuchstieren

**Bechtold, Moritz**, Dr. med.: EGFR-Überexpression als möglicher Parameter zur Einschätzung des malignen Potentials von Leukoplakien der Mundhöhle

**Bergauer, Bastian**, Dr. med. dent.: Optische Gewebedifferenzierung mittels diffuser Reflexion und Autofluoreszenz während der Ablation durch einen Er:YAG-Laser: Grundlagenstudie für eine berührungsfreie und gewebespezifische Laserschirurgie im Kopf-Hals-Bereich

**Brehm, Jasmin**, Dr. med. dent.: Speicheldiagnostik bei Patienten mit Bisphosphonat-assoziiierter Kieferknochennekrose – eine vergleichende Studie

**Buchbender, Mayte**, Dr. med. dent.: Vergleichende immunhistochemische Analyse von BMP-2, DLX-5, Osteocalcin und Runx-2 bei diabetisch induzierter Osteoporose im Kieferknochen und Femur am Tiermodell des diabetischen Hausschweins

**Gahbauer, Peter**, Dr. med.: Evaluation des Wissensstandes der Lehrkörper in Situationen des Frontzahntraumas an Grundschulen, Kindertagesstätten und Kindergärten vor- und nach Weiterbildung – eine Pilotstudie

**Hessling, Sarah**, Dr. med. dent.: Die kaufunktionelle Rehabilitation von onkologischen Patienten mit dentalen Implantaten kann mit einer hohen Erfolgsquote durchgeführt werden

**Hessner, Sascha**, Dr. med. dent.: Experimentelle Studie zur ossären Regeneration eines Critical-Size-Defektes an der Schweine-Kalotte unter Beteiligung eines PEG-Membran-Knochenersatzmaterial-Systems

**Hoffmann, Bettina**, Dr. med. dent.: Komplikationen der transantralen Oberkieferdistraktion bei Patienten mit Lippen-Kiefer-Gaumenspaltfehlbildungen

**Immig, Lisa-Kristina**, Dr. med. dent.: Vergleichende immunhistochemische Analyse von Msx-1, Msx-2, RankL, Sox-9 bei diabetisch induzierter Osteoporose im Kieferknochen und Femur am Tiermodell des diabetischen Hausschweins

**Kaiser, Eva**, Dr. med. dent.: Rekonstruktion eines Unterkieferdefektes unter Verwendung eines dreidimensionalen Hydroxylapatit-Scaffolds – eine vergleichende tierexperimentelle Studie

**Kranich, Lena**, Dr. med. dent.: Knochenneubildung und -remodelling bei der Verwendung von biofunktionalisierten Implantatoberflächen

**Kreißel, Sebastian**, Dr. med.: Vergleichende Pilotstudie zwischen PET-CT und PET-MRT in der Diagnostik oraler Plattenepithelkarzinome

**Kretz, Julia**, Dr. med. dent.: Knochenneubildung und -remodelling bei der Verwendung von biofunktionalisierten Implantatoberflächen

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**Pecher, Daniela**, Dr. med. dent.: Vergleichende experimentelle Untersuchung zur knöchernen Regeneration ossärer Defekte unter Anwendung eines Knochenersatzmaterials auf Hydroxylapatitbasis

**Redinger, Helmut Josef**, Dr. med. dent.: Untersuchungen zur Knochenregeneration nach Sinusbodenelevation unter Verwendung des Knochenersatzmaterials Aligipore® in Kombination mit Plasma Rich in Growth Factors

**Rusche, Birgit**, Dr. med. dent.: Klinische Vergleichsstudie zur Evaluation des Nachblutungsrisikos bei antikoagulierten und nicht antikoagulierten Patienten nach dentoalveolären oralchirurgischen Eingriffen

**Sendlbeck, Christina**, Dr. med. dent.: Knochenaugmentation mittels periimplantärer Elevation des ortsständigen Periosts

**Stanuch, Victoria**, Dr. med. dent.: Vergleichende immunhistochemische Analyse der M2-Makrophagenmarker CD163 und CD206 in oralen Plattenepithelkarzinomen

**Doctorate theses 2016**

**Bergt, Philipp**, Dr. med. dent.: Die pathologische Fraktur des Unterkiefers – Eine retrospektive Analyse des Patientengutes der Mund-, Kiefer-, Gesichtschirurgischen Klinik am Universitätsklinikum Erlangen

**Göllner, Luisa**, Dr. med. dent.: Der prätherapeutische Einfluss oraler Plattenepithelkarzinome auf die Sprachverständlichkeit der Patienten – eine automatisierte, objektive Funktionsanalyse

**Iliopoulos, Christos**, Dr. med.: Untersuchung des Zusammenspiels zwischen Serumlipiden und der Makrophagen Polarisation bei Patienten mit kleinen oralen Plattenepithelkarzinomen und unterschiedlichem Verlauf. Eine Pilotstudie

**Loika-Prell, Katharina**, Dr. med. dent.: Vergleichende immunhistochemische Analyse der Makrophagenpolarisation im oralen Plattenepithelkarzinom mit der Enzymexpression von Indolamin-2,3-dioxygenase (IDO) in den Tumorzellen sowie Vergleich der IDO Expression im Primärtumor zur korrespondierenden Lymphknotenmetastase

**Motel, Constantin**, Dr. med. dent.: Expressionsanalyse von microRNAs in primärem Tumorgewebe von Patienten mit Plattenepithelkarzinom der Mundhöhle

**Müller, Ricarda**, Dr. med. dent.: Epidemiologische Datenerhebung von Bisphosphonat-assoziierten Kiefernekrosen im Patientengut der Mund-, Kiefer- und Gesichtschirurgischen Klinik am Universitätsklinikum Erlangen

**Riemann, Max**, Dr. med. dent.: Orales Plattenepithelkarzinom der Zunge – Eine prospektive und objektive Evaluation der Sprachverständlichkeit von chirurgisch behandelten Patienten

**Taxis, Jürgen**, Dr. med. dent.: Oberflächen aus nanoporösem anodischen Aluminiumoxid beeinflussen Fibro- und Osteoblasten in entgegengesetzter Weise

**Voll, Mirja**, Dr. med. dent.: Studie über die Osseointegration biofunktionalisierter Implantate mit dem synthetischen Peptid P-15

**Weber, Manuel**, Dr. med. dent.: Kleine, lymphogen metastasierte orale Plattenepithelkarzinome (oscc) zeigen eine verstärkte Infiltration mit M2 polarisierten Makrophagen

**Weltzer, Wolf Philipp Adrian**, Dr. med. dent.: Tierexperimentelle Studie zur Osseointegration biofunktionalisierter Implantatoberflächen im Kiefer des diabetischen Schweins

**Wilkerling, André**, Dr. med.: Retrospektive Untersuchungen zum Einfluss des Wetters auf die Häufigkeit odontogener Logenabszesse

**Board qualification 2016**

**Iliopoulos, Christos**, Dr. med.

**Additional qualification 2016**

**Schlittenbauer, Tilo**, Dr. med. Dr. med. dent.: Plastic surgeries

**Department of Orthodontics  
and Orofacial Orthopedics**

Chair of Dental, Oral, and Maxillofacial Medicine – especially Orofacial Orthopedics

**Doctorate theses 2016**

**Kamm, Robert Alexander**, Dr. med. dent.: Die Frankfurter Horizontale in der räumlichen Cephalometrie: Eine Methode zur Steigerung der Reliabilität ihrer Referenzpunkte, analysiert mittels Kovarianzmatrizen

**Klinker, Theodor**, Dr. med. dent.: Untersuchung der Lebensqualität von Müttern innerhalb des ersten Jahres nach der Geburt eines Kindes mit Lippen-Kiefer-Gaumenspalten

**Board qualification 2015**

**Elsner, Laura**, Dr. med. dent.

**Hanke, Sebastian**, Dr. med. dent.

**Board qualification 2016**

**Detterbeck, Andreas**, Dr. med. dent.

**Dumtzlaff, Stefanie**

**Szczepanski, Agata**, Dr. med. dent.

**Department of Prosthodontics**

Chair of Dental, Oral, and Maxillofacial Medicine – especially Prosthetic Dentistry

**Doctorate theses 2015**

**Bein, Christian**, Dr. med. dent.: Klinische Studie zur Evaluation von Zusammenhängen zwischen soziodemographischen Parametern (Alter), psychosozialen Einflüssen (psychischer Gesundheitszustand) sowie der Mobilität der Patienten (physischer Gesundheitszustand) zum Mundhygienestatus bei Patienten über 70 Jahren

**Mörtlbauer, Barbara**, Dr. med. dent.: Analyse des faziellen Alveolarfortsatzes nach Implantation und Augmentation

**Scherg, Stefan**, Dr. med. dent.: Stabilität der Schraubenverbindung bei konventionellen und abutmentfreien Implantatbrücken

**Witte, Carolin**, Dr. med. dent.: Klinische Studie zur Evaluation von Zusammenhängen zwischen soziodemographischen Parametern (Alter), psychosozialen Einflüssen (psychischer Gesundheitszustand) sowie der Mobilität der Patienten (physischer Gesundheitszustand) zum Mundhygienestatus bei Patienten über 70 Jahren

#### Doctorate theses 2016

**Christian, Mirko**, Dr. med. dent.: Vergleichende klinische Studie zur Erfassung der stereognostischen Fähigkeiten sowie der Mundgesundheit bei Patienten mit einem gaumenbedeckenden Zahnersatz

**Jung, Annelina**, Dr. med. dent.: Retrospektive Studie zur Erfassung des prothetischen Versorgungstatus bei Patienten mit einer intravenösen Bisphosphonattherapie unter besonderer Berücksichtigung der Versorgung von Patienten mit einer Bisphosphonat-assoziierten Kiefernekrose

**Rieder, Dominik**, Dr. med. dent.: Der Einfluss von Implantations- und Versorgungszeitpunkt auf das ästhetische Ergebnis

#### Institute of General Practice

Chair of General Practice

#### Doctorate theses 2015

**Männer, Moritz**, Dr. med.: Welche Argumente motivieren für eine Landarztstätigkeit?

#### Board qualification 2016

**Roos, Marco**, Dr. med.

#### Institute of Radiology

Chair of Diagnostic Radiology

#### Doctorate theses 2015

**Knoch, Caira**, Dr. med.: Überprüfung der klinischen Umsetzung der Dosisreferenzwerte 2004 des Bundesamtes für Strahlenschutz an drei Kliniken

**Nothelfer, Andrea**, Dr. med.: Diffusionsgewichtete Bildgebung in der Magnetresonanztomographie der Brust – Vergleich von vier Pulssequenzen

**Schlude, Benedikt**, Dr. med.: Der Einfluss von Kopf-Hals-Pathologien auf die CT-Morphologie des distalen Ductus Thoracicus und des Ductus Lymphaticus Dexter

**Seidenfuß, Anna**, Dr. med.: Reduktion der Strahlendosis auf die weibliche Brust im Thorax CT

**Stauber, Robert**, Dr. med.: Erstellung und Evaluation eines Lernprogramms zur allgemeinen Röntgenanatomie und zur Morphologie ausgewählter Pathologien in der Computertomographie

**Voss, Lena**, Dr. med.: Erfolgs- und Komplikationsraten bei CT-gesteuerten Stanzbiopsien

#### Doctorate theses 2016

**Giese, David**, Dr. med.: Durchführbarkeit und Effizienz einer elektronischen Tablet Computer-Aufklärung im Vergleich mit der Standard-Pa-

pieraufklärung vor magnetresonanztomografischen Untersuchungen

**Großmann, Susan**, Dr. med.: 23Natrium-MRT im Verlauf der kardialen Rekompensationstherapie bei akuter Herzinsuffizienz

**Kämmerer, Nadine**, Dr. med.: Dual -Energy CT-Angiographie der Kopf- und Halsregion mit einem Single-Source CT – Ein neuer

**Schaller, Frank**, Dr. med.: Rauschreduktion in der abdominalen Computertomografie mithilfe eines iterativen Rekonstruktionsverfahrens (ADMIRE)

**Stöhr, Katharina**, Dr. med.: Dual-energy Computertomographie in der Diagnostik und im Behandlungsverlauf von Gicht

**Vogt, Sabine**, Dr. med. dent.: Die Wirkung antioxidativer Substanzen auf strahleninduzierte DNA-Doppelstrangbrüche

**Ziegler, Thomas**, Dr. med.: Perfusionsmessung der Niere mittels flow sensitive alternating inversion recovery true fast imaging with steady-state precession (FAIR true-FISP) – Quantitative Messungen im Vergleich mit dem renalen Blutfluss und im Verlauf unter Applikation von N-Monomethyl-L-Arginin, L-Arginin und dem Renininhibitor Aliskiren

#### Habilitation 2015

**Kramer, Manuel**, PD Dr. med.: Moderne CT- und MRT-Techniken in der OP-Planung kieferchirurgischer Eingriffe

#### Habilitation 2016

**Hammon, Matthias**, PD Dr. med.: Computerbasierte Unterstützungssysteme für die diagnostische Radiologie

**May, Matthias Stefan**, PD Dr. med.: Verfahren zur Optimierung der Bildqualität und Strahlenbelastung in der Computertomographie

**Schlechtweg, Philipp**, PD Dr. med.: Anwendungsmöglichkeiten neuer elektronischer Medien in der Radiologie

**Saake, Marc**, PD Dr. med.: Verfahren zur Darstellung von Blutgefäßen und der Durchblutung von Organen

#### Board qualification 2015

**Hammon, Matthias**, Dr. med.

**May, Matthias**, Dr. med.

**Ott, Sabine**, Dr. med.

#### Board qualification 2016

**Brehm, Barbara**, Dr. med.

**Dankerl, Peter**, Dr. med.

**Zeilinger, Martin**, Dr. med.

#### Institute of Radiology

Division of Neuroradiology

#### Doctorate theses 2015

**Pitann, Patrick**, Dr. med.: Multimodale Bildgebungsstrategien zur optimierten Tumorabgrenzung am experimentellen Gliommodell

#### Doctorate theses 2016

**Lang, Stefan**, Dr. med.: Matched pairs analysis in the use of 3D coils in comparison with single use of 2D coils only

**Stock, Annika**, Dr. med.: Evaluation von Patienten nach Cochlear-Implant Versorgung: klinische und bildgebende Befunde mittels innovativer Flachdetektor-Computertomographie

#### Board qualification 2015

**Rösch, Julie**, Dr. med.: Radiologist

#### Board qualification 2016

**Kästle, Nicola**, Dr. med.: Radiologist

# In Memoriam

## 2015

**Prof. Dr. Norbert Lang**

Professor emeritus and former director of the Department of Obstetrics and Gynecology

**Prof. Dr. Dr. Helmut Schwilden**

Associate professor for experimental anesthesiology

**Prof. Dr. Bernd Rautenstrauß**

Institute of Human Genetics

## 2016

**Prof. Dr. Dr. Emil Walther Steinhäuser**

Professor emeritus and former director of the Department of Oral and Cranio-Maxillofacial Surgery

**Prof. Dr. Siegfried Kallert**

Institute of Physiology and Pathophysiology





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The cover shows the Kussmaulcampus  
(©FAU/ Erich Malter) as well as figures of  
research projects within the Faculty of Medicine.





