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We are looking back on another two eventful years:

Together with the university, the Faculty of Medicine celebrated its 275<sup>th</sup> anniversary, the "Faculty's" lecture hall now bears the name of a nobel laureate originating from Erlangen, and the practice-oriented education of medical students was enhanced by an innovative component, a simulated hospital with simulated patients (SIMPATIK).

I could go on listing news for quite a while, but this is not necessary as the institutes, departments, and divisions as well as the research institutions and projects belonging to the Faculty of Medicine document and present in detail their research achievements for the years 2017 and 2018 on the following pages. As Dean, I have the pleasure to point out briefly some highlights that are not or only marginally presented in this research report.

Our Alma Mater, the Friedrich-Alexander-University Erlangen-Nürnberg, celebrated its 275<sup>th</sup> anniversary in 2018. The Faculty of Medicine has been belonging to FAU right from the beginning. On the occasion of this anniversary, the Chair of the History of Medicine was so kind to compile a Fest-schrift that portrays the political moves, technical innovations, and the social changes in the field of medicine in Erlangen. Focus of this very informative and fascinating book is on the last 100 years of the Faculty's history.

We are both, proud and thankful, that we could inaugurate the former small lecture hall "Internal Medicine" after complex and time-consuming renovation works in 2018 as the new Faculty's lecture hall. It is a great honor for the Faculty of Medicine of FAU that Professor Harald zur Hausen, founding director of FAU's Institute of Virology, has accepted being honored by naming the lecture hall after him and that he showed up in person for the inauguration. Since its inauguration, all meetings of the faculty council and all colloquia in the context of appointments of new professors take place in the Harald zur Hausen-lecture hall. It also offers room for academic ceremonies and, needless to say, for the daily student teaching, too.



The Dean and Prof. Harald zur Hausen on the occassion of the inauguration of the Harald zur Hausen-lecture hall (photo: FAU/E. Malter)

Speaking of student teaching: Since the start of the winter term 2017/18, prospective physicians can train teamwork and the examination of patients in the above-mentioned simulated hospital SIMPATIK. These trainings take place within curricular or extracurricular courses with simulated patients and help to test treatment methods only learned theoretically so far and to exercise coping with critical emergencies. In addition, the students belonging to the Faculty of Medicine dispose of study rooms on the fifth floor of the old university hospital for group- or seatwork.



Medical students in the simulation center (photo: FAU/E. Malter)

The speech therapists could celebrate, too, in 2018: For 50 years, Erlangen has been offering logopedic education – since 2011 even within the frame of a bachelor model degree program. We aim at transforming this model degree program, which has been evaluated very well, into a regular bachelor degree program.

The Faculty of Medicine has awarded for the fifth time the Jakob-Herz-Prize that was inaugurated in 2009. The awardee in 2018 was Professor Laurence Zitvogel, the scientific directress at the Gustave Roussy Cancer Center in Villejuif and since 2013 Professor of Immunobiology at the medical school of the University of Paris. Prof. Zitvogel's outstanding scientific achievements include new basic insights concerning the influence of the tumor microbiome as well as of the gut microbiome on immunotherapy. Her research approach is very promising and has led to her being awarded many important prizes within the last years.



From left to right: Prof. Dr. A. Mackensen (Director Department of Medicine 5), Prof. Dr. Dr. h.c. J. Schüttler (Dean), Prof. Dr. L. Zitvogel (Awardee), Prof. Dr. J. Hornegger (President FAU), Dr. F. Janik (Mayor of Erlangen) (oboto: G. Jannicelli)

I want to briefly point out new research projects and institutions of the reference period that enrich the research and performance spectrum of our Faculty:

 In 2018, the German Center Immunotherapy (DZI) was established. It aims at treating successfully chronic inflammatory and cancer diseases in an interdisciplinary team by targeted immunotherapies. DZI unites institutions from four out of Faculty's five core research areas.

• Since 2018, two institutions were granted new SFB/TRR (Transregios) by the DFG – both TRR reinforce the Faculty's core research area *Infection and Immunology*:

At the Department of Medicine 1, the new TRR 241 "Immune-epithelial communication in inflammatory bowel diseases" has started. In conjunction with external institutions, the TRR aims at better understanding the interaction between cells in mucous membranes and immune cells in the bowel and at developing more effective therapy methods for chronic inflammation.

At the Department of Medicine 5, scientists collaborating in the SFB/TRR 221 "Modulation of graft-versus-host- and graft-versus-leukemia-immune responses after allogeneic stem cell transplantation" look at the central problems and deficits in the field of allogeneic hematopoietic stem-cell transplantation (allo-HSCT), aiming at reducing in the long run morbidity and mortality in allo-HSCT by an highly effective graft-versus-leukemia/lymphoma (GvL) immune response.

 PRO PRICARE has been funded by the BMBF since 2017. This cooperation network, coordinated by the Institute of General Practice, focuses on the patient and investigates the patient's treatment and the costs connected with it and compares both factors with the treatment results. In the long run, the scientists aim at developing strategies that reduce or completely avoid overtreatment.

In the reference period, many changes in academic staff ensured a fresh breeze within our Faculty. Six chairs were newly staffed, and the Division of Trauma Surgery could be converted into the Department of Trauma Surgery – Orthopedic Surgery with the inauguration of Prof. Dr. M. Perl.

In the near future, we are heading a major challenge in the degree program Medicine. Starting in the winter term 2019/20, there will be 110 additional places to study medicine per year. The students' education will take place in an innovative and permanent cooperation model between our Faculty and Klinikum Bayreuth, UK Erlangen, and the University of Bayreuth, the so-called "Medizincampus Oberfranken" (medical campus of Upper Franconia). Educating from then on yearly about 500 medical students, our Faculty will become one of the biggest faculties in Germany regarding medical education.

As always, I would like to thank all friends and sponsors of our Faculty and – needless to say – the taxpayers. Without the generous financial support, cutting-edge research were not possible anymore nowadays. I would further like to thank the numerous experts who evaluate our project proposals and publications, thus helping to grant the high quality of our research and to use the results gained as early as possible for patient care.

Since 2009, this is the sixth and last research report under my term as Dean. Looking back, it is with great pleasure that I notice progress regarding research in Erlangen within these last ten years. I want to exemplify this by two aspects:

 Medical engineering has – thanks to Siemens and other companies in this sector – a long tradition in Erlangen. Referring to the example Silicon Valley, there were intensive efforts in the mid-1990s to create a Medical Valley in the Nuremberg Metropolitan Region. With the foundation of Medical Valley EMN e.V. (European Metropolitan Region of Nuremberg; registered society) in 2007, Medical Valley got a solid basis for a powerful organizational structure. This allowed to bundle and connect forces of university and non-university research institutions, of many companies and further players in the region and optimized the environment for further innovations. The bundling of all forces and the development of a cluster in the fields of medical engineering, medicine, and pharmaceutics within Nuremberg Metropolitan Region led in 2010 to a successful application in BMBF's Leading Edge Cluster competition. As "Leading Edge Cluster: Center of Excellence for Medical Engineering", the vision of a Medical Valley ultimately developed its own life and has been gathering innovative momentum since then. As one consequence, our Faculty established *Medical Engineering* as fifth core research area, besides *Infection and Immunology, Kidney and Vascular Research, Neurosciences,* and *Tumor Research.* A current example for a research project belonging to the core research area *Medical Engineering* is the MIRACUM consortium, fully funded by the BMBF (2018 - 2022) after a conceptual phase.

• In the last ten years, we succeeded in improving considerably the research infrastructure. New clinical buildings (2<sup>nd</sup> phase internal center, ward block of the surgery center) now offer optimized conditions for clinical research. Kussmaul-Campus is a medical research center that was since then built on the area of the former dermatology clinic. SEON, a nanomedical research center, was created in the vicinity of the Department of Otorhinolaryngology. A giant leap forwards for our Faculty was the inauguration of the first part of the Translational Research Center (TRC) in October 2014. The TRC reinforces considerably the interface between basic and clinical research, thus enabling a quick transfer from research results into the diagnosis and treatment of patients. Medical research is thus not an end unto itself in the famous ivory tower of science. It can be taken for granted that medical research serves to find the academic truth, but our research always also cares for the patient's benefit who comes to UK Erlangen in the hope of help and cure. The next expansion level of the TRC research building includes besides TRC 4 the Center for Medicine and Physics (ZMP), a joint project of our Faculty and the Faculty of Sciences with FAU and the Max-Planck-Society in conjunction with the Max-Planck Institute for the Science of Light. Erlangen's ZMP is drawn up transdisciplinary and pools in a synergetic way the subject-specific expertise of all participants. At the same time, ZMP's orientation is a translational one, as basic physical and mathematical research is applied to patient-relevant questions in medicine.

Let me conclude by uttering my deep gratitude for the very productive and successful collaboration in all those years. Only this reliable basis within the Faculty, Dean's office, UK Erlangen, and FAU enabled us to reach all these goals. Let us continue working together that our Faculty keeps enhancing and remains successful in the international competition for the most qualified heads and ideas.

Erlangen, July 2019

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 and Cell Biology

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#### **Research focus**

- The role of B cells in the immunopathogenesis of MS
- Development of neuroprotective treatment options for patients with MS
- The ENS as autoimmune target in MS
- Extrinsic and intrinsic innervation of the esophagus as targets of the autoimmune response in MS
- The human ENS
- Cell biology of the NF2 tumorsuppressor protein
- Vagal innervation studies
- Intrinsic choroidal neurons (ICN)
- Innervation of brown adipose tissue (BAT)

#### **Structure of the Chair**

Professorships: 3

Personnel: 24

- Scientists: 4 (thereof funded externally: 0)
- Graduate students: 11

#### **Special structural feature**

Both chairs collegially lead the Institute of Anatomy.

#### Research

The main research focus evolves around the immunopathology of multiple sclerosis (MS), which also comprises the development of new diagnostic tools and innovative therapeutic strategies. An additional major research interest is the enteric nervous system (ENS), in particular its morphology, function, and involvement in neurodegenerative diseases.

# The role of B cells in the immunopathogenesis of MS

PI: Prof. Dr. S. Kürten, Dr. R. Chunder MS is a chronic autoimmune disease of the central nervous system (CNS). The role of B cells in the immunopathogenesis of MS has increasingly attracted attention over the last years. Next to the production of autoantibodies and the presentation of autoantigens, B cells can also be involved in the formation of tertiary lymphoid organs in the CNS. Our aim is to decipher the mechanisms of B cell contribution to MS immunopathology by using animal models. In particular we are employing experimental autoimmune encephalomyelitis (EAE) as a B celldependent mouse model, which relies on the active immunization with a fusion protein of myelin basic protein and proteolipid protein. Using this model we aim to identify key molecules, which are involved in tertiary Imyphoid organ formation. These molecules are also analyzed in patients with MS and set in relation to the course and severity of the disease. In addition, we focus on the development of novel therapeutic strategies and biomakers that can be used towards individual and patientbased treatment decisions

#### **Development of neuroprotective treatment options for patients with MS** Pl: Prof. Dr. S. Kürten

All of the currently available drugs for the treatment of MS target the inflammatory component of the disease. Yet, already with the onset of the disease, neurodegeneration is evident, which progresses over time and is responsible for the irreversible loss of nerve fibers. Studying mouse models of MS we were able to show that treatment with the L-type calcium channel antagonist nimodipine leads to a decrease in axonal damage and demyelination, accompanied by an increase in remyelation. Here, we would like to study the underlying mechanisms in detail.

#### The ENS as autoimmune target in MS

PI: Prof. Dr. S. Kürten, Dr. R. Chunder

We have previously shown the degeneration of the ENS in a mouse model of MS. Here we aim to provide an in-depth analysis of the morphological and functional alterations of the ENS as a result of MS immunopathology. We also strive to identify potential target antigens and to determine the kinetics of ENS degeneration to understand whether the process is causative or rather an epiphenomenon of the disease. The results will be of major clinical importance for both, the diagnostics and therapy of MS, and may provide a completely new view on the etiology of the disease.

# Extrinsic and intrinsic innervation of the esophagus as targets of the autoimmune response in MS

Pl: Prof. Dr. J. Wörl, Prof. Dr. S. Kürten, Prof. Dr. W. L. Neuhuber Based on detailed knowledge of the innervation of the esophagus, in particular of the so-called enteric co-innervation, we are using a mouse model of MS to investigate whether glial or neuronal structures in the esophagus are damaged by autoimmune processes in MS. The aim of the project is to figure out whether swallowing disorders in patients suffering from MS are caused by morphological alterations in the esophagus. Dysphagia is frequently observed in patients with MS, while its pathogenesis is still unkown.

#### The human ENS

PI: Prof. Dr. A. Brehmer, PD Dr. S. Jabari Our current knowledge on human neuroenteric structures and functions is fragmentary, and a neuropathology of the ENS underdeveloped. Our main task is the morphological-immunohistochemical classification of enteric neurons in both, health and disease (e.g. in megasyndromes of Chagas and Hirschsprung diseases). Besides, interactions between the ENS and the intestinal epithelium (including its enteroendocrine cells) and the development of a digital pathology are in the focus.

#### Cell biology of the NF2 tumorsuppressor protein

#### PI: PD Dr. M. Kressel

The neurofibromatosis type 2 (NF2) protein merlin is a classical tumor suppressor protein. Loss of function, e.g. through inherited NF2 gene mutations, characteristically leads to tumors of Schwann cell origin of the eighth cranial nerve. Merlin is a constituent of a protein complex at the plasma membrane, which inhibits cell proliferation cell-density dependent inducing effects of the Hippo signal transduction pathway. Protein isoforms created by alternative splicing of a NF2 binding partner were identified and the effects on the subcellular localization studied. As a prerequisite for further studies, the extent to which these isoforms can be expressed in bacterial hosts was investigated.

#### Vagal innervation studies

PI: PD Dr. M. Kressel

Because of their eminent functional significance for the entire organism, intense research efforts are directed towards the course of terminal fibers of the vagus nerve and their microscopic architecture. By neuronal tract-tracing methods, the course of not yet known vagal terminal endings in the abdomen was mapped and their connection to the surrounding tissues studied.

#### Intrinsic choroidal neurons (ICN)

PI: Prof. Dr. W. Neuhuber

The choroid of higher primates, in particular humans, and of birds harbors several thousands of intrinsic neurons, the so-called ICN. They form an intrinsic network similar to the ENS and innervate choroidal blood vessels and non-vascular smooth muscle. On the other hand, ICN are contacted by postganglionic sympathetic and parasympathetic as well as trigeminal peptidergic afferent neurons. The functional significance of ICN is still enigmatic, however, they likely play a role in ocular homeostasis. This is suggested by circadian changes of vasoactive intestinal polypeptide (VIP), one of the vasodilatative transmitters of ICN. The project is a collaboration with the Department of Ophthalmology and PMU Salzburg.

### Innervation of brown adipose tissue (BAT)

PI: Prof. Dr. W. Neuhuber

Brown adipose tissue is important not only for thermogenesis in newborns, but occurs also in adults in supraclavicular and paravertebral regions. It plays a still poorly investigated metabolic role. Using immunohistochemical and molecular biological techniques, BAT and sympathetic ganglia are studied in mouse and human. The project is a collaboration with Baton Rouge, USA.

#### Teaching

The Chair of Anatomy and Cell Biology contributes to the curriculum of Medicine and Dentistry with obligatory courses and electives. In particular, the Chair is responsible for all lectures and seminars in neuroanatomy and is instrumental in organizing and conducting the dissection course, which is of central importance for the preclinical teaching curriculum and attended by approximately 230 students of medicine and dentistry each semester. In addition, the Chair offers the elective "Applied Anatomy (EMPTY course)" and "Palpatory Surface Anatomy". Interdisciplinary preclinical and clinical lectures as well as seminars are provided in collaboration with the departments of Neurology, of Obstretics and Gynecology, (Neuro)Surgery, the Institute of Radiology and the Division of Neuroradiology.

In addition, MD, PhD, Bachelor's and Master's theses are supervised.

#### **Selected publications**

Wunsch M et al. The enteric nervous system is a potential autoimmune target in multiple sclerosis. Acta Neuropathol. 2017 Aug;134(2):281-295

Schampel A, Volovitch O, Koeniger T, Scholz CJ, Jörg S, Linker RA, Wischmeyer E, Wunsch M, Hell JW, Ergün S, Kuerten S. Nimodipine fosters remyelination in a mouse model of multiple sclerosis and induces microglia-specific apoptosis. Proc Natl Acad Sci U S A. 2017 Apr 18;114(16): E3295-E3304 Zetzmann K, Strehl J, Geppert C, Kuerten S, Jabari S, Brehmer A. Calbindin D28k-Immunoreactivity in Human Enteric Neurons. Int J Mol Sci. 2018 Jan 8;19(1)

Simon M, Ipek R, Homola GA, Rovituso DM, Schampel A, Kleinschnitz C, Kuerten S. Anti-CD52 antibody treatment depletes B cell aggregates in the central nervous system in a mouse model of multiple sclerosis. J Neuroinflammation. 2018 Aug 11;15(1):225

Hohberger B, Jessberger C, Hermann F, Zenkel M, Kaser-Eichberger A, Bergua A, Jünemann AG, Schrödl F, Neuhuber W. VIP changes during daytime in chicken intrinsic choroidal neurons. Exp Eye Res. 2018 May;170:8-12

#### International cooperations

Prof. P. V. Lehmann, MD, PhD, Cellular Technology Limited, Shaker Heights: USA

Prof. C. Linington, PhD, University of Glasgow, Glasgow:  $\mathsf{UK}$ 

Prof. ABM da Silveira, PhD, Federal University of Uberlandia, Uberlandia: Brazil

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#### **Research focus**

- Temperature sensitive Transient Receptor Potential channels at the ocular surface
- Pathomechanisms of the Meibom Gland Dysfunction
- Influence of Osteopontin (OPN) to neurodegenerative changes in the eye
- HistoDigital<sup>®</sup> and cinematic rendering
- The role of effector T-cells during experimental autoimmune encephalomyelitis
- Surfactant proteins
- Test anxiety among medical and dental students
- Urea transporters at the ocular surface and within the lacrimal system
- 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: 25

#### Special structural features

- Lecture room for lessons in histology with 160 microscopes
- Electron microscopy unit

Both chairs collegially lead the Institute of Anatomy.

#### Research

For many years, the Chair of Functional and Clinical Anatomy 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 the Chair.

#### Temperature sensitive Transient Receptor Potential channels at the ocular surface

PI: PD Dr. F. Garreis, Prof. Dr. F. Paulsen The Transient Receptor Potential (TRP) proteins belong to the group of membrane-bound, ligand-gated cation channels. They serve as multiple sensors. A functional subgroup of the TRP family is the temperature-sensitive TRP channels (thermo TRP). 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 PD Dr. S. Mergler (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

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

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

PI: Prof. Dr. M. Scholz, Prof. Dr. F. Paulsen, PD Dr. F. Garreis

In close cooperation with the Department of Ophthalmology, we performed morphological, molecular, and electrophysiological studies on the structure and function of the retina of the osteopontin knockout (OPN-/-) mouse. Retinal ganglion cells (RGCs) are the only neuronal cell type of the retina, which are able to express OPN under physiological conditions. In different experimental approaches, the morphological and physiological characterization of OPN-/ mouse was performed. The results of validated analyses will give evidence about the effects due to the absence (OPN-/-) or pathological overexpression of OPN (DBA/2J) with regard to neurodegenerative changes within the eye.

#### HistoDigital<sup>®</sup> and cinematic rendering

PI: Prof. Dr. M. Scholz, Prof. Dr. F. Paulsen In close cooperation with Chimaera GmbH (Erlangen), HiD, a digital application is being developed that enables the user to create a digital volumetric reconstruction of the anatomical tissue structures from the data sets of histological section series. The goal is the future use of this application in research and teaching.

The cinematic rendering (CR) technology was originally developed by Dr. K. Engel (Siemens Healthineers) as a medical image visualization technology. It enables the generation of 3D photorealistic images of the human body. Existing imaging methods (CT, MRT etc.) provide the raw data for the volumetric representations. In direct cooperation with Siemens, this technology is to be made applicable in order to produce amazing images for teaching and learning the human anatomy.

# The role of effector T-cells during experimental autoimmune encephalomyelitis

PI: Prof. Dr. C. Flügel-Koch, Prof. Dr. F. Paulsen The central nervous system (CNS) that includes brain, spinal cord and eye has an exceptional and privileged immunological position due to the fact that cells and factors of the immune system are incapable of easily penetrating into the nervous tissue from the blood.

In autoimmune diseases like multiple sclerosis (MS), this immunological privilege is suspended, leading to structural and functional pathological alterations.

In collaboration with Prof. A. Flügel from the Institute for Neuroimmunology and Multiple Sclerosis Research of the University of Göttingen, we study the behavior of pathogenic effector T cells in various rodent models of MS, in particular of experimental autoimmune encephalomyelitis (EAE). Our focus is on how these pathogenic T cells can enter the CNS and on the morphological pathological changes they bring about.

#### **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.

### Test anxiety among medical and dental students

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

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

### Urea transporters at the ocular surface and within the lacrimal system

PI: PD Dr. C.M. Hammer, Prof. Dr. F. Paulsen Urea is an integral component of the tear film. Patients suffering from dry eye disease (keratoconjunctivitis sicca) show reduced urea levels within their tear fluid. The urea transporters UT-A and UT-B may be of significance in this respect, because they have not only been detected in kidney, but also in a variety of other tissues. The present study demonstrated the expression of UT-A and UT-B in the glands of the lacrimal system (lacrimal gland, Meibomian glands, Moll glands, Zeiss glands) and in the corneal epithelium of humans, pigs, and mice. Future research is aimed at the question whether changes in the expression of urea transporters are linked to the pathomechanism of dry eye disease.

# Ocular tissue interactions of a refractive UV femtosecond laser

PI: Dr. C.M. Hammer, Prof. Dr. F. Paulsen The already established cooperation with the De-

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

### Teaching

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

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

#### Selected publications

Asano N, Hampel U, Garreis F, Schröder A, Schicht M, Hammer C, Paulsen F. Differentiation patterns of immortalized human meibomian gland epithelial cells in threedimensional culture. Invest Ophthalmol Vis Sci 2018, 59:1343-1353

Hampel U, Garreis F, Burgermeister F, Eßel N, Paulsen F. Effect of intermittent shear stress on corneal epihelial cells using a in vitro flow culture model. Ocular Surf 2018, 16:341-351

Binder J, Krautz C, Engel K, Grützmann R, Fellner FA, Burger PHM, Scholz M. Leveraging medical imaging for medical education - A cinematic rendering-featured lecture. Ann Anat. 2018, Dec 23;222:159-165

Yu D, Yogesh Y, Chen G, Ghio A, Dang H, Burns K, Wang Y, Davis R, Randell S, Esther C, Paulsen F, Boucher RC. Loss of ßENaC function in Meibomian glands produces prseudohypoaldosteronism 1-like sex-biased ocular disease in mice. Am J Pathol 2018, 188:95-110

Schicht M, Garreis F, Hartjen N, Beileke S, Jacobi C, Sahin A, Holland D, Schröder H, Hammer CM Paulsen F, Bräuer L. SFTA3 – a novel surfactant protein of the ocular surface and its role in corneal wound healing and tear film surface tension. Sci Rep 2018, 8:9791

Scholz M, Burger P, Paulsen F. Sollen, können – und aushalten. Auswahl von Medizinstudierenden. Deutsch Ärztebl 2018, 115:A1799-1800

#### International cooperations

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

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

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

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

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

Prof. R.C. Boucher, MD, Marsico Lung Institute/UNC Fibrosis Center, Chapel Hill NC: USA

# 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
- Molecular mechanisms of development and progression of hepatocellular carcinoma
- Chondrocytic differentiation and pathophysiological processes in cartilage
- Molecular basis of regeneration and fibrosis in liver and skin
- Molecular mechanisms of hepatic metastasis
- 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: 17

#### **Special structural feature**

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

#### Research

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

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

PI: Prof. Dr. A.K. Bosserhoff, Prof. Dr. C. Hellerbrand, PD Dr. S. Kuphal, Dr. Dr. P. Dietrich, Dr. M. Kappelmann-Fenzl

Malignant melanoma, also called black skin cancer, shows a drastic increase in incidence and an unchanged high mortality in recent decades. Melanoma is a clinically relevant tumor, characterized by gradual progression, metastatic dissemination, rapid and pronounced resistance to therapy. For the analysis of melanoma formation, our analysis also deals with melanocytes and their embryonic precursors, the melanoblasts.

As metastatic melanoma curative therapy approaches are still lacking, the 10-year survival rate is below 5%. The pathogenesis of the disease is probably due to an accumulation of specific genetic and epigenetic alterations leading to deregulation of transcriptional regulation and signaling pathways in melanocytes or their precursors. The particular malignancy of melanoma is based on a specific combination of cell cycle autonomy, differentiation defects, apoptosis resistance, deregulated interaction with stromal and immune cells as well as distinctive invasiveness and metastatic ability. We are working in this field performing fundamental studies of pathophysiological changes and covering many areas. In addition to proteins in the cell-matrix association, growth factors, metabolites, and signaling pathways, transcriptional regulators and microRNAs are investigated. Next to the analysis of the function of mature microRNA as key posttranscriptional regulatory elements, their processing in melanoma is in the center of our current research.

#### Molecular mechanisms of development and progression of hepatocellular carcinoma

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

Hepatocellular carcinoma (HCC) is one of the most frequent types of cancer worldwide. Currently, there are only few therapeutic options that have only a minimal impact on the survival of patients. HCC is frequently resistant against pharmacological therapy or most patients rapidly develop resistance, respectively. We are investigating the molecular mechanisms of the development, progression, and therapy resistance of HCC. We discovered important functions of defined microRNAs and their interactions with therapeutically influenced main signaling pathways of cancer cells, such as the RAS-RAF-ERK signaling pathway.

Furthermore, we are analyzing the interaction of cancer cells with their environment (e.g. immune cells, inflammation mediators, connective tissue cells and factors) mediated by neuropeptides. Such neuroimmunological interactions could decisively influence the tumor microenvironment and thus the progression and therapy resistance of malignant diseases.

#### Chondrocytic differentiation and pathophysiological processes in cartilage

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

Cartilage is a tissue comprising only a single cell type, namely chondrocytes. In the development of the skeleton, cartilage precedes the bony skeleton and is replaced by the latter in the process of enchondral ossification. In the adult organism, cartilage covers the articular surfaces of our bones and is characterized, among other properties, by high pressure elasticity. Damage to the cartilage is so far not curable until today. 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 pathways. We study transcriptional regulators, such as AP2Epsilon and YB1. A further focus is on the molecule MIA/CD-RAP, which plays an important role in cartilage differentiation and homeostasis.

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

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

The liver is the central organ of the metabolism. Nutrients get to the liver from the digestive tract via the portal vein for subsequent degradation and/or metabolization. Thus, the liver supplies the body with vital components such as proteins, carbohydrates, and lipids. Another important function of the liver is detoxification. Alcohol abuse, obesity, metabolic disorders (e.g. hemochromatosis), viral infections (hepatitis B and C), or intoxication with chemicals and environmental toxins are common causes of liver damage. Hepatocellular injury can result in liver inflammation (hepatitis). Hepatitis can progress with hepatic fibrosis which can lead to liver cirrhosis. Cirrhosis is causing organ dysfunction and is the most important risk factor for the development of hepatocellular carcinoma (HCC). Thus,

hepatic fibrosis is the central step in the progression of chronic liver injury. Pathological fibrosis resembles impaired wound healing in which the strictly regulated repair processes are impaired after cellular injury. Since the components that are involved in wound healing or fibrosis (connective tissue cells, extracellular matrix, growth factors) are very similar, findings from the physiological wound healing can help to better understand the processes of formation and progression of liver fibrosis/cirrhosis. In this area of our research we focus on the analysis of the newly discovered molecule MIA2 and growth factors of the FGF and BMP families. Furthermore, we could characterize BMP6 as an essential regulator of iron metabolism in recent years.

# 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 a Syn on neurons. Our data show that oxidative stress promotes  $\alpha$ Syn aggregation though 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

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. 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 (fragile X mental retardation protein) 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, Dr. Dr. P. Dietrich

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

# Pathobiology of non-alcoholic fatty liver diseases

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

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

Application of some chemotherapeutic drugs can cause steatohepatitis, too, which can significantly affect morbidity and mortality of cancer patients. We were able to identify the molecular mechanisms by which irinotecan und fluorouracil (5-FU) cause hepatic steatosis and inflammation. Currently, we are investigating strategies to interfere with these pathomechanisms to improve the tolerability of chemotherapeutic drugs.

#### Teaching

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

#### **Selected publications**

Bosserhoff AK, Schneider N, Ellmann L, Heinzerling L, Kuphal S. The neurotrophin Neuritin1 (cpg15) is involved in melanoma migration, attachment independent growth, and vascular mimicry. Oncotarget. 2017;8(1):1117-1131

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Linck L, Liebig J, Völler D, Eichner N, Lehmann G, Meister G, Bosserhoff A. MicroRNA-sequencing data analyzing melanoma development and progression. Exp Mol Pathol. 2018 Dec;105(3):371-379

#### International cooperations

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

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

M. Herlyn, Wistar Institute, Philadelphia: USA

C. Jobin, Department of Medicine, University of Florida, Gainesville, Florida: USA

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

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

# **Institute of Biochemistry – Emil-Fischer-Center**

Chair of Biochemistry and Pathobiochemistry

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### **Research focus**

- SoxC proteins
- SoxE proteins
- Chromatin-modifying complexes in glial development
- MicroRNAs in glial development
- Physiological and pathophysiological signal transduction pathways in myogenesis and at the neuromuscular synapse

#### **Structure of the Chair**

Professorships: 2

Personnel: 26

- 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 the professorships of Bioinformatics and of Molecular Medicine with focus on Molecular Imaging.

#### Research

The groups belonging to the Chair of Biochemistry and Pathobiochemistry work in the field of neuroscience and attempt to unravel regulatory mechanisms of physiological and pathophysiological 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. An additional group studies neuromuscular signal transduction pathways in skeletal muscle.

### 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 of neuronal precurosor cells. Overexpression studies in the mouse have also pointed to an influence of SoxC proteins on neural maturation. An important target gene of SoxC proteins in neuronal precursor cells is the homeodomain transcription factor Prox1.

#### **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 Sox10deficient mice, glial cells are missing from the peripheral nervous system. The enteric nervous system is completely absent. Schwann cells as the myelinating cells of the peripheral nervous system depend on Sox10 at all times during their development and differentiation. In the central nervous system, Sox9 and Sox10 together regulate gliogenesis. Sox9 is responsible for the specification of neural stem cells into oligodendrocytes, whereas Sox10 guides terminal differentiation and myelination in oligodendrocytes. In the absence of Sox10 und Sox10induced Nfat proteins, oligodendrocytes would

neither express Nkx2.2 nor Myrf. The myelination program could not be induced by the interplay of these transcription factors with Sox10. 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 gains importance in mature oligodendrocytes during myelin maintenance. SoxE proteins act through recruitment of the basal transcription machinery in a mediator dependent manner as well as through interactions with chromatin-remodeling complexes. Functions of group E Sox proteins were not only obvious in transgenic mouse models, but are equally reflected in human disease. Heterozygous haploin-sufficient 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.



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

# Chromatin-modifying complexes in glial development

PI: Prof. Dr. M. Wegner

Development and differentiation of myelin-forming glial cells goes along with substantial alterations in chromatin structure that are brought about by chromatin-modifying complexes. Function and importance of single complexes varies considerably between Schwann cells and oligodendrocytes. In oligodendrocytes, the Brg1-containing BAF complex participates already in the process of specification, whereas it becomes essential in Schwann cells only during maturation by inducing transcriptional regulators of differentiation in cooperation with Sox10. In contrast, the Ep400-containing Tip60 complex supports the timely downregulation of early regulators during Schwann cell development, whereas it secures differentiation and survival in maturing oligodendrocytes.

#### **MicroRNAs in glial development**

#### PI: Dr. S. Reiprich

Control of proliferation and differentiation of oligodendrocytes depends on a complex regulatory network. Several studies have shown over the last years that microRNAs are important components of this network in addition to transcription factors. A number of functional interactions between Sox transcription factors and microRNAs were detected. Sox10, for instance, activates expression of miR-335, miR-338, and miR-155. In turn, miR-335 und miR-338 inhibit Sox9 as a regulator expressed in immature oligodendrocytes. MiR-338 and miR-155 inhibit the transcription factor Tcf7l2. By doing so, these microRNAs play a decisive role during oligodendrocyte differentiation.

#### Physiological and pathophysiological signal transduction pathways in myogenesis and at the neuromuscular synapse

PI: Prof. Dr. S. Hashemolhosseini

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

#### Teaching

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

#### Selected publications

Reiprich S, Cantone M, Weider M, Baroti T, Wittstatt J, Schmitt C, Küspert M, Vera J, Wegner M. Transcription factor Sox10 regulates oligodendroglial Sox9 levels via microRNAs. Glia 2017, 65: 1089-1102

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Truch K, Arter J, Turnescu T, Weider M, Hartwig AC, Tamm ER, Sock E, Wegner M. Analysis of the human SOX10 mutation Q377X in mice and its implications for genotypephenotype correlation in SOX10-related human disease. Hum. Mol. Genet. 2018, 27: 1078–1092

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Jacob A, Wüst HM, Thalhammer JM, Fröb F, Küspert M, Reiprich S, Balta EA, Lie DC, Wegner M, Sock E. The transcription factor prospero homeobox protein 1 is a direct target of SoxC proteins during developmental vertebrate neurogenesis. J Neurochem. 2018 Aug;146(3):251-268

Kravic B et al. In mammalian skeletal muscle, phosphorylation of TOMM22 by protein kinase CSNK2/CK2 controls mitophagy. Autophagy 2018, 14: 311-335

#### International cooperations

Prof. M. Sandri, University of Padova, Padova: Italy

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

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

Prof. W. Tetzlaff, University of British Columbia, Vancouver, BC: Canada

Prof. A. Schedl, Université Nice Sophia Antipolis, Nice: France

# **Institute of Biochemistry – Emil-Fischer-Center**

### **Professorship of Bioinformatics**

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#### **Head of Division**

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#### **Research focus**

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

#### **Structure of the Professorship**

Professorship: 1 Personnel: 8

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

#### **Special structural feature**

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

#### Research

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

### Computational analysis of host-pathogen interactions

Specific interactions with host proteins are pivotal for a successful infection by a pathogen. This project focuses on the prediction and structural characterization of host-pathogen protein interactions using computational tools. The recognition processes either occur between short sequence motifs and complementary adapter modules or between pairs of globular protein domains. These types of interactions do not only differ from a structural point of view, but also with respect to the computational tools required for their prediction and analysis.

One particular challenge for the prediction of functional interaction motifs is the short length of the respective sequence patterns resulting in a large number of false-positive hits in conventional predictions, which prove to be non-functional in subsequent experiments. Therefore, we aim at improving the specificity of the predictions by assessing the importance of motif-specific flanking sequence regions.

For the analysis of host-pathogen interactions formed between globular protein domains, a combination of molecular modeling, docking, and molecular dynamics simulations is used. The latter technique provides information about the conformational stability and energetics of an interaction that can hardly be deduced from static structures alone. These methods are for example applied to study the structure of herpesviral glycoproteins that are pivotal for binding to the host cell and following fusion with the cell membrane. Furthermore, we investigate the molecular dynamics of viral regulator proteins and their interaction with cellular targets.



Model of the antigen-binding fragment of a neutralizing antibody bound to Domain-II (green) of the HCMV gB homotrimer

One protomer is colored according to its five domains.

#### Investigation of the aggregation behavior of the Aβ-peptide of Alzheimer's disease

Protein conformational diseases are unique since they result from a drastic change in protein three-dimensional structure. Most often, the change in conformation involves a structural conversion from primarily  $\alpha$ -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 hallmark of many neurodegenerative diseases.

The most prevalent neurodegenerative disease is Alzheimer's disease, which is characterized by extracellular protein deposition of the peptide fragment Aß 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 can prevent aggregation or of solubilizing aggregates by targeting those residues that represent the hot spots of binding affinity in the fibrillar structure. We address this point by molecular dynamics simulations of  $A\beta$  oligomers and thermodynamic analyses of the aggregation interfaces. In addition, we investigate the effect of different solvent environments on the conformational stability of such Aβ oligomers.



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.

### Structure-based evaluation of protein variants

High-throughput DNA sequencing studies revealed a large number of genetic variants between individuals. Many of these sequence variants lead to amino acid exchanges, some of which are linked to disease. Due to their large number (> 10,000 per genome), it is impossible to characterize all sequence variants by experi-

ment, rendering computational prediction tools of utmost importance for the identification of pathogenic variants. Most of the current methods use evolutionary conservation and other sequence-based features to identify damaging variants, but they cannot predict the effects these variants have on protein function. Despite its innate linkage to function, structural information is yet only considered to a very limited extent in the predictions. In addition, the few existing structure-based prediction methods mainly focus on one distinct aspect of protein structure (e.g. protein stability or protein interactions) and do therefore not allow a comprehensive structural and functional annotation. The aim of the present project is to develop a robust computational framework for a comprehensive structure-based analysis and interpretation of high-throughput sequencing data.



Structure of the protein-protein complex between CYFIP (purple) and WAVE1 (green) Mutations of some CYFIP residues, which are located close to the interface, are related to intellectual disability

These residues are shown in space-filled presentation and colored by atom-types.

# Structure of receptor-ligand complexes

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

which should support the long-term development of better adjuvants for vaccines.



Structure of the Histamine-H1-Receptor (blue ribbon) with the modelled binding site of histamine (space-filled presentation)

The lipids of the cellular membrane are depicted as grey/orange lines.

### Teaching

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

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

#### **Selected publications**

Söldner CA, Sticht H, Horn AHC. Role of the N-terminus for the stability of an amyloid- $\beta$  fibril with three-fold symmetry. PLoS One. 2017, 12:e0186347

Reuter MS et al. Diagnostic Yield and Novel Candidate Genes by Exome Sequencing in 152 Consanguineous Families With Neurodevelopmental Disorders. JAMA Psychiatry. 2017, 74:293-299

Hauer NN et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. Genet Med. 2018, 20:630-638

Söldner CA, Horn AHC, Sticht H. Binding of histamine to the H1 receptor-a molecular dynamics study. J Mol Model. 2018, 24:346

Diewald B, Socher E, Söldner CA, Sticht H. Conformational Dynamics of Herpesviral NEC Proteins in Different Oligomerization States. Int J Mol Sci. 2018, 19:E2908

Söldner CA, Horn AHC, Sticht H. Interaction of Glycolipids with the Macrophage Surface Receptor Mincle - a Systematic Molecular Dynamics Study. Sci Rep. 2018, 8:5374

#### International cooperations

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

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

Prof. Dr. C. Chipot, Université de Lorraine, Nancy: France

Prof. Dr. Y. Miao, University of Kansas, Lawrence: USA

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

# **Institute of Biochemistry – Emil-Fischer-Center**

Professorship of Molecular Medicine with focus on Molecular Imaging

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**Head of Division** Prof. Dr. med. Dieter Chichung Lie

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#### **Research focus**

- Transcriptional programs in the regulation of adult neurogenesis
- Metabolic control of stem cell development and adult neurogenesis
- Role of autophagy in stem cell function and adult neurogenesis
- Functional characterization of intellectual disability factors

#### **Structure of the Professorship**

Professorship: 1

Personnel: 7

- Scientists: 3 (there of funded externally: 1)
- Graduate students: 4

#### Special structural feature

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

#### Research

Neurons and glia cells form functional networks that are the structural basis for learning, cognition, and behavior. Perturbation of the formation, maturation, and plasticity of neural circuits contributes to the pathogenesis of neurodevelopmental disorders, such as intellectual disability and neuropsychiatric diseases, like schizophrenia. Our research aims to better understand the genetic and cell biological mechanisms that regulate development and homeostasis of 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 as well as to the pathophysiology of cognitive and affective symptoms during aging and in neurodegenerative and neuropsychiatric diseases. Thus, understanding of the mechanisms regulating adult neurogenesis is of major basic neuroscientific and clinical interest. The generation of new functional neurons from stem cells is a complex multistep process. Current data indicate that each developmental step is controlled by stage-specific transcription factors. 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 fulfill additional critical functions in the synaptic integration of adult-born neurons. Moreover, we recently demonstrated that posttranslational modification by phosphorylation controls the neurodevelopmental function of SOX11. Collectively our data uncover SOXC factors as pleiotropic regulators of adult hippocampal neurogenesis. Funding: DFG

### 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 now found that specific mitochondrial metabolic pathways control distinct steps in neuronal development. 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 aging 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.

# Role of autophagy in stem cell function and adult neurogenesis

Degradation and recycling of dysfunctional cellular components are critical pathways for cellular homeostasis. In particular, somatic stem cells are highly dependent on degradation and recycling pathways to maintain their lifelong capacity for regeneration. We now demonstrated that the longevity associated transcription factors of the FoxO family are critical to regulate autophagy, i.e., a central pathway for proteins and organelles, in adult neural stem cells. Loss of FoxOs does not only impair activity of the autophagic pathway, but is associated with stem cell dysfunction and impaired integration of adult-born neurons. In ongoing projects we are now investigating if and how FoxO dysfunction may contribute to neural stem cell and neurogenesis dysfunction during aging. This project is conducted in close collaboration with Prof. J. Klucken (Division of Molecular Neurology). Funding: IZKF Erlangen



Analysis of autophagolysosomal flux using a genetic reporter system indicates impaired autophagolysomal flux in adult neural stem cells upon deletion of FoxO transcription factors.

Control cells contain both autophagosomes (red and green, yellow in the merge) and autophagolysosomes (red only). Note the almost complete absence of autophagolysosomes in FoxO-deficient cells. Treatment with Rapamycin or Trehalose enhances autophagolysomal flux in FoxO-deficient cells.

# 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. Using human pluripotent stem cells to model human neurodevelopment, we

are now investigating how SOX11 drives CNS development in conjunction with intellectual disability-related transcription 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. B. Winner (Division of Stem Cell Biology) and Prof. Dr. A. Reis (Institute of Human Genetics).

Funding: DFG

#### Teaching

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

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

#### **Selected publications**

Beckervordersandforth R et al. Role of Mitochondrial Metabolism in the Control of Early Lineage Progression and Aging Phenotypes in Adult Hippocampal Neurogenesis. Neuron, 2017, 93: 560-576

Schaffner I, Minakaki G, Khan MA, Balta EA, Schlotzer-Schrehardt U, Schwarz TJ, Beckervordersandforth R, Winner B, Webb AE, DePinho RA, Paik J, Wurst W, Klucken J, Lie DC. FoxO Function Is Essential for Maintenance of Autophagic Flux and Neuronal Morphogenesis in Adult Neurogenesis. Neuron, 2018, 99: 1188-1203

Minakaki G et al. Autophagy inhibition promotes SNCA/ alpha-synuclein release and transfer via extracellular vesicles with a hybrid autophagosome-exosome-like phenotype. Autophagy, 2018, 14: 98-119

Jung M, Haberle BM, Tschaikowsky T, Wittmann MT, Balta EA, Stadler VC, Zweier C, Dorfler A, Gloeckner CJ, Lie DC. Analysis of the expression pattern of the schizophrenia-risk and intellectual disability gene TCF4 in the developing and adult brain suggests a role in development and plasticity of cortical and hippocampal neurons. Molecular Autism, 2018, 9:20

Balta EA, Schaffner I, Wittmann MT, Sock E, von Zweydorf F, von Wittgenstein J, Steib K, Heim B, Kremmer E, Haberle BM, Ueffing M, Lie DC, Gloeckner CJ. Phosphorylation of the neurogenic transcription factor SOX11 on serine 133 modulates neuronal morphogenesis. Scientific Reports, 2018, 8 (1):16196

Balta EA, Wittmann MT, Jung M, Sock E, Haeberle BM, Heim B, von Zweydorf F, Heppt J, von Wittgenstein J, Gloeckner CJ, Lie DC. Phosphorylation Modulates the Subcellular Localization of SOX11. Frontiers in Molecular Neuroscience, 2018, 11:211

#### International cooperations

Prof. S. Jessberger, University of Zurich, Zurich: Switzerland Prof. H. Song, Perelman School of Medicine, University of Pennsylvania, Pittsburgh: USA

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

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

Prof R. DePinho, The University of Texas MD Anderson Cancer Center, Houston, Texas: USA

# Institute of Cellular and Molecular Physiology

Chair of Physiology (Systems Physiology)

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Director

Prof. Dr. med. Christoph Korbmacher

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#### **Research focus**

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

#### **Structure of the Chair**

Professorship: 1

Personnel: 19

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

#### Special structural feature

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

#### Research

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

# Renal sodium and potassium homeostasis

Sodium homeostasis and potassium homeostasis are intimately linked and critically important for

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

#### Epithelial sodium channel (ENaC)

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



Molecular mechanisms involved in the regulation of the epithelial sodium channel (ENaC) consisting of three subunits  $(\alpha, \beta, \gamma)$ 

# Regulation of ENaC by hormonal and local factors

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

#### **Activation of ENaC by proteases**

A specific feature of ENaC is its complex proteolytic processing which is critical for channel activation. Proteolytic channel activation can be nicely demonstrated in heterologous expression systems. ENaC activation by locally released proteases may be pathophysiologically relevant in the context of inflammatory kidney disease and may contribute to sodium retention for example in nephrotic syndrome. However, molecular mechanisms contributing to proteolytic ENaC activation are still incompletely understood and (patho-)physiologically relevant proteases remain to be identified. In addition to proteases activating ENaC directly by proteolytic channel cleavage at specific sites, interstitial proteases may indirectly modulate ENaC mediated transepithelial sodium transport by activating a basolateral protease-activated receptor type 2 (PAR2).



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

### Functional characterization of epithelial ion channels

Above all, electrophysiological methods are used to study the function and regulation of renal and epithelial ion channels. These include transepihelial short circuit current measurements in Ussing chambers, whole-cell current recordings using the two-electrode voltage clamp (TEVC) technique, and patch-clamp experiments which in addition to whole-cell recordings also allow single-channel recordings. To elucidate the molecular mechanisms involved in channel regulation, a range of additional molecular biological and cell physiological methods are employed including the use of Xenopus laevis oocytes, cultured cells, native tissue, and animal models (e.g. genetically modified mouse lines). Moreover, the now available structural information in combination with computer simulations and site-directed mutagenesis allows the investigation of functionally relevant channel regions. This integrated approach provides fascinating opportunities to gain novel insights into physiological and pathophysiological mechanisms and a better understanding of molecular disease processes.



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



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



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



Differential interference contrast image of a microdissected distal mouse nephron

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



Homology model of human  $\alpha\beta\gamma$ ENaC with associated taurodeoxycholic acid (t-DCA) in the pore region of the channel as predicted by molecular docking simulation.

#### Teaching

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

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

#### **Selected publications**

Rauh R, Hoerner C, Korbmacher C.  $\delta\beta\gamma\text{-ENaC}$  is inhibited by CFTR but stimulated by cAMP in Xenopus laevis oocytes. Am J Physiol Lung Cell Mol Physiol 2017, 312:L277-L287

Ilyaskin AV, Diakov A, Korbmacher C, Haerteis S. Bile acids potentiate proton-activated currents in Xenopus laevis oocytes expressing human acid-sensing ion channel (ASIC1a). Physiol Rep 2017, Feb;5(3). pii: e13132

Mansley MK, Korbmacher C, Bertog M. Inhibitors of the proteasome stimulate the epithelial sodium channel

(ENaC) through SGK1 and mimic the effect of aldosterone. Pflügers Arch 2018, 470:295-304

Bohnert BN, Menacher M, Janessa A, Wörn M, Schork A, Daiminger S, Kalbacher H, Häring HU, Daniel C, Amann K, Sure F, Bertog M, Haerteis S, Korbmacher C, Artunc F. Aprotinin prevents proteolytic epithelial sodium channel (ENaC) activation and volume retention in nephrotic syndrome. Kidney Int 2018, 93:159-172

Krueger B, Yang L, Korbmacher C, Rauh R. The phosphorylation site T613 in the  $\beta$ -subunit of rat epithelial Na+ channel (ENaC) modulates channel inhibition by Nedd4-2. Pflügers Arch 2018, 470:649-660

Ilyaskin AV, Kirsch SA, Böckmann RA, Sticht H, Korbmacher C, Haerteis S, Diakov A. The degenerin region of the human bile acid-sensitive ion channel (BASIC) is involved in channel inhibition by calcium and activation by bile acids. Pflügers Arch 2018, 470:1087-1102

#### International cooperations

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

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

 $\ensuremath{\mathsf{Prof.}}$  Dr. J. Loffing, University of Zurich, Zurich: Switzerland

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

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

# Institute of Cellular and Molecular Physiology

Professorship of Cardiovascular Physiology

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**Head of Division** 

Prof. Dr. med. Tilmann Volk

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#### **Research focus**

- Cardiac ion channels
- Electromechanical coupling

#### **Structure of the Professorship**

Professorship: 1

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

#### Special structural feature

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

#### Research

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

Our primary goal is to further understand the molecular mechanisms that underlie remodeling of the heart. This might lead to new diagnostic, therapeutic, or preventive strategies.

#### **Cardiac ion channels**

To investigate function and regulation of ion channels, a broad range of sophisticated electrophysiological, molecular biological, and cell physiological methods is applied on cultured cells, native tissues, animal models (e.g. transgenic mouse lines), and human cells. For example, the patch-clamp technique allows for a detailed analysis of membrane potential and ion channel function by electrically controlling individual cardiac myocytes. Ion channels are particularly important in shaping the action potential and in initiating the contraction. It is well established that regional differences in action potential duration (APD) in different areas of the heart are of great importance for a normal course of repolarization. For example, within the left ventricular free wall, APD is much longer in endocardial than in epicardial myocytes with the consequence that endocardial myocytes repolarize last, although they become depolarized first. Hence, the wave of excitation travels from endocardial to epicardial regions, while the wave of repolarization travels in the opposite direction. Under pathological conditions, such as cardiac hypertrophy or failure, this well-organized sequence of events is altered which is thought to contribute to the increased risk of cardiac arrhythmia and sudden cardiac death of patients with cardiac hypertrophy or failure. In order to further understand the underlying mechanisms, our research group investigates the regulation and pharmacology of ion channels (Na+, K+ and Ca2+ channels) that are responsible for cardiac excitation and repolarization by using animal models as well as tissue or cell culture. At present, the primary focus lies in the identification of signaling cascades that participate in the regulation of those ion channels under pathophysiological conditions. A promising target is the cardiac mineralocorticoid receptor that participates in the regulation of cardiac Ca<sup>2+</sup> and K<sup>+</sup> channels.

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



Isolated human ventricular cardiomyocyte during patchclamp recording

#### **Electromechanical coupling**

Electromechanical coupling is the process that links electrical signals from the cell membrane, i.e. action potentials, to the mechanical action of the cell, i.e. the contraction. In the heart, a Ca<sup>2+</sup>-influx into the cell via L-type Ca<sup>2+</sup> channels activates ryanodine receptors located intracellularly in the sarcoplasmic reticulum (SR) which in turn release much more Ca2+ from the SR. This process, called Ca2+-induced Ca2+-release, activates contraction and controls its magnitude. For example, when not enough Ca2+ is released from the SR or the release is too slow, the resulting contraction is inefficient and weak. Multiple mechanisms can cause alterations in electromechanical coupling. In heart failure, alterations in the microarchitecture of cardiac myocytes particularly contribute to a decrease in Ca<sup>2+</sup> release from the SR.

The transverse tubular system (t-system) in ventricular cardiomyocytes consists of many tubelike membrane invaginations that originate from the cell surface and reach deeply into the cell. L-type Ca<sup>2+</sup> channels are primarily localized in the t-tubular membrane in close vicinity to the ryanodine receptors. An important task of t-tubules is therefore to facilitate a close contact of L-type Ca<sup>2+</sup> channels to ryanodine receptors in order to provide the condition for an efficient and quick release of Ca2+ from the SR. Three dimensional high resolution microscopy (confocal or STED microscopy) reveals that in heart failure, t-system structure and expression of Ca2+ channels is substantially altered. These alterations lead to delayed, reduced, and disorganized Ca2+ release from the SR which can also be identified using high resolution microscopy together with Ca2+ indicators and computer assisted image analysis.

Using cell- and tissue culture models derived from human heart samples, we investigate the cellular and molecular mechanisms underlying t-system alterations with the aim to stop or even reverse these processes. Furthermore, we link structural and functional alterations at the cellular and molecular level to the clinical picture of patients in order to identify prognostic or diagnostic markers or even new therapeutic strategies.



A 3D confocal microscopic image of the t-system in a cardiomyocyte.

B Cardiomyocyte with loss of t-system, e.g. in heart failure



Immunofluorescence analysis of Ca<sup>2+</sup> channel expression using confocal and STED microscopy in a cardiomyocyte

#### Teaching

The Professorship of Cardiovascular Physiology is involved in the curricular teaching (lectures, seminars, and practical classes) for medical and dental students and for students following the degree programs Molecular Medicine (Bachelor and Master).

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

#### **Selected publications**

Seidel T, Sankarankutty AC, Sachse FB. Remodeling of the transverse tubular system after myocardial infarction in rabbit correlates with local fibrosis: A potential role of biomechanics. Prog Biophys Mol Biol. 2017. 130: 302–314

Greiner J, Sankarankutty AC, Seemann G, Seidel T, Sachse FB. Confocal Microscopy-Based Estimation of Parameters for Computational Modeling of Electrical Conduction in the Normal and Infarcted Heart. Front Physiol. 2018;9:239

#### International cooperations

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

Prof. JP Benitah, INSERM, Université Paris-Saclay, Châtenay-Malabry: France

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

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

# Institute of Physiology and Pathophysiology

### Chair of Physiology

#### Address

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#### Director

Prof. Dr. med. Christian Alzheimer

#### Contact

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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: 48

- Scientists: 22 (thereof funded externally: 7)
- Graduate students: 7

#### **Special structural features**

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

The Institute of Cellular and Molecular Physiology comprises the Chair of Physiology (Systems Physiology) and the Professoship of Cardiovascular Physiology. The chair of physiologyand the professor of cardiovascular physiology serve as director and deputy director of the Institute, respectively.

#### Research

The overarching research objective at our Institute is to understand the bioelectrical and neurochemical processes that constitute the basic language of the nervous systems and enable communication between nerve cells.

What factors elicit an electric impulse in a neuron, if, for instance, pain or temperature stimuli influence the body?

What mechanisms mediate signal transmission between nerve cells and how is information processed in neuronal networks?

Answers to questions like these will also help to elucidate the underpinnings of cognition and emotion and of disorders thereof. We explore such issues with a broad spectrum of methods, ranging from modern electrophysiological, optical, cell and molecular biological techniques to microneurography and fMRI in healthy volunteers and patients.

# Neurophysiologic substrates of higher brain functions

PI: Prof. Dr. C. Alzheimer, Dr. F. Zheng, PD Dr. Dr. T. Huth

Our research focuses on the electric behavior of neurons and neuronal networks under normal and pathological conditions. Using high-resolution neurophysiological and optical techniques, we investigate functions and regulation of ion channels and synapses. Our aim is to understand fundamental neural processes that are essential for cognitive functions as well as for affective behavior and whose dysfunctions might give rise to neuropsychiatric disorders. In particular, we are studying the following topics:

1) Role of activin, a member of the Transforming Growth Factor- $\beta$  family, as a "master molecule" tuning glutamatergic and GABAergic neurotransmission, and its impact on cognition, emotions, and neuroprotection

 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

3) Neuropsychiatric disease models and mechanisms of drug action (in collaboration with the Department of Psychiatry and Psychotherapy)

### 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, HCN, CaV3.2) came in focus because only few subtypes decide on excitability, i.e. on generation, frequency, and propagation of action potentials to the central nervous system. Neuroimmunology is a rapidly growing field that, for example, studies the interaction of substance P with the immune system that 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 that are probably involved in the generation of headaches in humans. In a similar preparation, we examine by which mechanisms the neuropeptide CGRP is released from the cranial dura mater as an indicator for trigeminovascular activation. Using immunohistochemical and molecular biological methods, we aim at detecting the intracellular signal pathways that are induced by these substances. To study the central processes of headache generation, we examine the response properties of neurons in the spinal trigeminal nucleus, record the peripheral and central blood flow, and assess the effects of potential headache therapeutics.

# 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 noninvasive 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 Medicine 1 analyze the central changes induced by chronic itch in patients suffering from cholestatic pruritus.

#### **Teaching**

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

#### **Selected publications**

Babes A, Ciotu CI, Hoffmann T, Kichko TI, Selescu T, Neacsu C, Sauer SK, Reeh PW, Fischer MJM. Photosensitization of TRPA1 and TRPV1 by 7-dehydrocholesterol: implications for the Smith-Lemli-Opitz syndrome. Pain 2017, 158: 2475-2486

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 2017, 21: 843-854

Hartmann S, Zheng F, Kyncl M, Karch S, Voelkl K, Zott B, D'Avanzo C, Lomoio S, Tesco G, Kim DY, Alzheimer C, Huth T.  $\beta$ -Secretase BACE1 promotes surface expression and function of Kv3.4 at hippocampal mossy fiber synapses. J Neurosci 2018, 38: 3480-3494

Karch S, Broichhagen J, Schneider J, Böning D, Hartmann S, Schmid B, Tripal P, Palmisano R, Alzheimer C, Johnsson K, Huth T. A new fluorogenic small molecule labeling tool for surface diffusion analysis and advanced fluorescence imaging of  $\beta$ -site amyloid precursor protein (APP)-cleaving enzyme 1 based on silicone rhodamine: SiR-BACE1. J Med Chem 2018, Jul 10. doi: 10.1021/acs.jmedchem.8b00387

Hoffmann T, Sharon O, Wittmann J, Carr RW, Vyshnevska A, De Col R, Nassar MA, Reeh PW, Weidner C. NaV1.7 and pain: contribution of peripheral nerves. Pain 2018, 159: 496-506

Obreja O, Rukwied R, Nagler L, Schmidt M, Schmelz M, Namer B. Nerve growth factor locally sensitizes nociceptors in human skin. Pain. 2018 Mar;159(3):416-426

#### International cooperations

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

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

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

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

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

#### Address

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#### Director

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#### Contact

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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: 52

• Doctors (of Medicine): 6

• Scientists: 14 (thereof funded externally: 12) Graduate students: 29

#### **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 that aim at detecting physiological and pathophysiological changes long before manifest diseases appear. Questions always arise when new technologies or working materials are introduced. New welding techniques used in the aluminum processing industry or the replacement of classical solvents by alternative solvents can be listed as examples. Furthermore, allergically mediated diseases at the workplace are still a problem although hygienic conditions have clearly been improved. Therefore, an important focus for IPASUM is on the assessment of exposure and on the effect of toxic, mutagenous, and sensitizing working materials. Many qualified field studies analyze not only the exposure, but also the data of ambient monitoring (inhalative and dermal exposure).

Funding: German employer's liability insurance association, German State Ministries, German Federal Ministry of Labor and Social Affairs

#### **Population related health studies**

Environmental medicine relates to occupational medical questions by critically proving exposure and its possible effects. IPASUM has, amongst others, the task to offer fast and adequate help if the public is postulated with high exposure to chemical agents, like PCB in public facilities, phthalates in pharmaceuticals/toys, or aluminum in deodorants.

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

#### **Biomarker in Occupational Medicine**

PI: Prof. Dr. S. Schmitz-Spanke

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

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

### Molecular markers of exposure to hazardous substances

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

### 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  $62^{nd}$  round robin test of G-EQUAS was finished within the report period. Now G-EQUAS comprises 182 analyses parameters; more than 200 laboratories worldwide (two-thirds of them international) take part in G-EQUAS every six months.

### Quality assurance of health promoting actions

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

#### **Healthcare research**

In the area of the healthcare research the project "Healthcare in Bavarian schools" was conducted. The project aims at developing the need for occupational care in Bavarian schools and at establishing a model for a decentralized support system in German schools. The project is run in cooperation with the Institute and Outpatient Clinic of Occupational-, Social- and Environmental Medicine of the LMU Munich.

#### Teaching

IPASUM shares in 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.

From 2006 until 2019, Prof. Dr. H. Drexler was Dean of Students.

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

#### **Selected publications**

Clarner A, Uter W, Ruhmann L, Wrenger N, Martin A, Drexler H. Sickness absence among peer-supported drivers after occupational trauma. Occup Med (Lond) 2017; 67(2): 143-150

Weistenhöfer W, Uter W, Drexler H. Protection during production: Problems due to prevention? Nail and skin condition after prolonged wearing of occlusive gloves. J Toxicol Environ Health A 2017; 80(7-8): 396-404 Klotz K, Weistenhöfer W, Neff F, Hartwig A, van Thriel C, Drexler H. The Health Effects of Aluminum Exposure. Dtsch Arztebl Int 2017; 114(39): 653-659

Seitz M, Kilo S, Eckert E, Müller J, Drexler H, Göen T. Validity of different biomonitoring parameters for the assessment of occupational exposure to N,N-dimethylformamide (DMF). Arch Toxicol 2018; 92(7): 2183-2193

Pink M, Verma N, Kersch C, Schmitz-Spanke S. Identification and characterization of small organic compounds within the corona formed around engineered nanoparticles. Environ.-Sci. Nano 2018; 5(6): 1420-1427

Greiner A, Göen T, Hildebrand J, Feltes R, Drexler H. Low internal exposure and absence of adverse effects in workers exposed to high air levels of inorganic selenium. Toxicol Lett 2018; 298: 141-149

#### 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)

#### Address

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#### Director

Prof. Dr. med. Cornel C. Sieber

#### Contact

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#### **Research focus**

• Clinical nutrition in older persons

- Mobility and function
- Clinical care for geriatric patients

#### **Structure of the Institute**

Professorships: 2 Personnel: 30

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

#### **Special structural feature**

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

#### Research

The demographic change poses a challenge for the public health care systems. In the future, the approach of diagnose-specific action in older persons will not be enough for the main goal of preservation of independence, mobility, and quality of life in the older population, and for prevention and treatment of age-related diseases. The two lifestyle factors, physical activity and nutrition, play a major role – next to medical intervention – to conquer the above-mentioned challenge.

Hence, research at the Institute for Biomedicine of Aging (IBA) is focusing on the areas nutrition and physical activity in older persons and the improvement of medical care for geriatric patients in a highly interdisciplinary manner. The research of is conducted in Nuremberg as well as at the St. John of God Hospital in Regensburg.

#### **Clinical nutrition in older persons**

PI: Prof. Dr. D. Volkert

The section clinical nutrition in older persons at IBA examines aspects of nutrition in relation to the maintenance of health and physical performance throughout old age and is involved in several national and international research projects in this field.

Together with Prof Dr. M. Visser (University of Amsterdam), IBA coordinated the MaNUEL (Malnutrition in the Elderly) Knowledge Hub within the European Joint Programming Initiative (JPI) "A healthy diet for a healthy life". In five work packages, systematic reviews were performed about etiology, screening, prevention, and therapy of malnutrition in old age. Determinants of malnutrition were examined in an international harmonized multicohort metaanalysis. Overarching aims of the project to build a sustainable international expert network and to harmonize research methodology and clinical practice.

Additionally, in cooperation with the European Society for Clinical Nutrition and Metabolism (ESPEN), evidence-based guidelines on clinical nutrition and hydration in geriatrics were developed and published.

Analyses of the worldwide "nutritionDay" project werefocused on the topic of dysphagia in nursing homes and the nutritional situation of affected residents. On behalf of the German Nutrition Society (DGE) and in cooperation with the German Society for Clinical Nutrition (DGEM) a nationwide "nutritionDay" initiative was launched in 2018 to assess and evaluate the nutritional situation of hospital patients and nursing home residents in Germany.

At the national level, IBA is involved in the Bavarian competence cluster of nutrition research "enable healthy food choices in all stages of life", funded by the BMBF, and represents one of the two "enable" human study centers. It is the aim of this interdisciplinary joint project to characterize nutrition during the whole life span and to develop innovative strategies and nutritional products to support a healthy diet in cooperation of the participating research institutions and food companies. Besides recruitment and comprehensive phenotyping of a cohort of healthy older persons, IBA developed and tested an age-specific protein-rich drink to prevent sarcopenia in cooperation with Fraunhofer Institute for Process Engineering and Packaging (IVV) (Freising). Further, the effects of a newly developed visually appealing, fortified and texture modified diet on energy and nutrient intake of nursing home residents with chewing and swallowing disorders were examined together with Hochschule Weihenstephan-Triesdorf and a nursing home in Nürnberg. Another sub-project to improve drinking behavior of nursing home residents by using technical aids specifically developed for this target group by computer scientists at Technical University of Munich.

#### **Mobility and function**

PI: PD Dr. E. Freiberger

The mobility and function section of IBA is active in the fields of physical activity/exercise promotion and maintenance of function and independence in older persons by participating in several national as well as international projects. At the international level, IBA is partner in the European project SPRINTT (Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies, a randomized controlled intervention trial in older persons with sarcopenia. After an extensive recruitment and screening process in the years 2017/18, a total of 123 participants were included into this study and followed in two intervention arms with and without physical activity. Related to the SPRINTT project, two sub-studies are dedicated to the analysis of risk factors of falls and gait changes in functionally impaired older persons.

Another international activity is active involvement in the steering committee of the European Network for Action on Ageing and Physical Activity (EUNAAPA) that intends to improve networking between organizations in the field of physical activity, health, and social welfare. Through its engagement in EUNAAPA, IBA is also taking part in the EU horizon 2020 research project "PROMISS" ("Prevention of Malnutrition in Senior Subjects in the EU"), supporting its dissemination.

At national level, the mobility and function section is taking part in two BMBF projects. The first one, POWER ("Prevention by Outdoorwalking in the Elderly at Risk") is investigating if regular outdoor walking with the help of volunteers can restore function in older persons at risk in the nursing home or residential care setting. In the project PRO PRICARE ("PReventing Overtreatment in PRImary CARE"; compare own report) IBA is contributing to a systematic review and expert interviews to develop an International Classification of Functioning, Disability and Health (ICF) core set for the description of functional health in the general practitioner setting.

In a collaboration the Institute for Psychogerontology at FAU, the effect of aging images on physical activities in older persons was investigated.

### Clinical care for geriatric patients

PI: Prof. Dr. C.C. Sieber

The improvement of the clinical care for geriatric patients is investigated in collaboration with the Hospital of St. John of God in Regensburg.

The project SCOPE (Screening for Chronic Kidney Disease among Older People across Europe) is financed by the Horizon 2020 program of the EU and includes eight European centers. Older persons were recruited and examined in Regensburg as well as Nuremberg to improve screening and care of chronic renal diseases in older persons.

The group of the oldest old persons are the one with the highest comorbidity rates and hospitalizations. This will increase the burden on the health care systems. On individual level, research has shown that hospitalization fuel a negative downhill spiral with further loss of function, quality of life, and independent status in the older person. Despite the disproportionate prevalence of hospitalized patients who are in the older age range, hospitalist programs often do not emphasize the need for geriatric skills. Especially, the transfer from hospital to home is a process often marked with loss of information between hospital and ambulatory health service and followed by unwanted rehospitalization. The national project TIGER (Transsektorales Interventionsprogramm zur Verbesserung der Geriatrischen Versorgung in Regensburg) is funded under the Innofond by the Federal Joint Committee (G-BA) and investigates the effectiveness of the transitional care between the stationary and the ambulant setting in a hospital in Regensburg with the aim to reduce readmission rate in persons 70 years and older.

#### 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 program 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**

Gingrich A, Spiegel A, Kob R, Schoene D, Skurk T, Hauner H, Sieber CC, Volkert D, Kiesswetter E. Amount, Distribution, and Quality of Protein Intake Are Not Associated with Muscle Mass, Strength, and Power in Healthy Older Adults without Functional Limitations-An enable Study. Nutrients. 2017 Dec 14;9(12). pii: E1358

Streicher M et al. Determinants of Incident Malnutrition in Community-Dwelling Older Adults: A MaNuEL Multicohort Meta-Analysis. J Am Geriatr Soc. 2018 Dec;66(12):2335-2343

Freiberger E, Rydwik E, Chorus A, Tak E, Delecluse C, Schena F, Waaler N, Laventure B, van Meeteren N. Enhancing Physical Activity as Lifestyle Behavior in Older Persons: The Rome Statement. J Aging Phys Act. 2018 Apr 1;26(2):345-351 Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, Kiesswetter E, Maggio M, Raynaud-Simon A, Sieber CC, Sobotka L, van Asselt D, Wirth R, Bischoff SC. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clin Nutr. 2018 Jun 18. pii: S0261-5614(18)30210-3

Dent E et al. International Clinical Practice Guidelines for Sarcopenia (ICFSR): Screening, Diagnosis and Management. J Nutr Health Aging. 2018;22(10):1148-1161

Marzetti E et al. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: Case finding, screening and characteristics of eligible participants. Exp Gerontol. 2018 Nov;113:48-57

#### International cooperations

Prof. Dr. M. Visser, Stichting VU-VUMC, Amsterdam: The Netherlands

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

Prof. Dr. M. Hiesmayr, Medizinische Universität Wien, Wien: Austria

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

# Institute of Clinical and Molecular Virology

Chair of Clinical and Molecular Virology

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#### Director

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#### **Research focus**

- Retroviral infections
- Herpesviral infections
- Antiviral immunity

#### **Structure of the Chair**

Professorships: 4

- Personnel: 106 • Doctors (of Medicine): 6
- Scientists: 13 (thereof funded externally: 9)
- Graduate students: 16

#### **Clinical focus areas**

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

#### Research

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

#### **Retroviral infections**

PI: Dr. A. Thoma-Kreß<sup>1</sup>, Prof. Dr. U. Schubert<sup>2</sup>, Prof. Dr. K. Überla<sup>3</sup>, Prof. Dr. T. Gramberg<sup>4</sup> Both human pathogenic retroviruses, human Tcell leukemia virus (HTLV) and human immunodeficiency virus (HIV), are the subject of extensive research by the Institute.

The first research group investigates the molecular mechanisms of cell-to-cell transmission of HTLV-1. The group developed new assays and methods to facilitate studies on viral transmission and the transport of viral proteins during cell-to-cell transmission.

The second research group investigates the role of regulatory HIV-1 proteins in the pathogenesis of HIV-1, whereby it could be shown that the HIV-1 p6 Gag protein regulates the membrane association, ubiquitination, and thus the entry of Gag into the MHC-1 antigen presentation pathway. While the viral protein Vpr is involved in HIV-associated fat metabolism diseases, Vpu directs the polyubiquitination of certain host cell-receptors.

One of the questions addressed in the third research group is how intron-containing HIV-1 mRNAs are captured in the cell nucleus. A genome-wide screen using the CRISPR/Cas technology led to the identification of several spliceosome-associated proteins. The inactivation of the corresponding genes increased the cytoplasmic levels of the intron-containing genomic HIV-1 RNA up to 140-fold.

The fourth group focuses on the effect of the host restriction factors SAMHD1 and TRIM5a on the replication of HIV-1 and the retranspositon of LINE-1. Using knockout mice, the group was able to show that SAMHD1 has broad antiviral activity. By blocking retrotransposition of mobile genetic elements like LINE-1, SAMHD1 also seems to contribute to genome integrity. In the field of diagnostics, the focus is on the development of phenotypic drug resistance tests for HIV-1.

#### **Herpesviral infections**

PI: Prof. Dr. M. Marschall<sup>1</sup>, Prof. Dr. T. Stamminger<sup>2</sup> (until 12/2017), Prof. Dr. A. Ensser<sup>3</sup>, PD Dr. B. Biesinger<sup>4</sup>, PD Dr. F. Neipel<sup>5</sup>, Prof. Dr. W. Doerfler<sup>6</sup>

The Institute is working on various cell biological aspects of herpesvirus infections.

The first research group studies the regulatory role of protein kinases in the replication of the human cytomegalovirus (CMV) and related herpesviruses. In particular, the importance of protein kinases for the nucleo-cytoplasmic egress of viral particles has been demonstrated. A functional involvement of the CMV-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 implicated for the first time the involvement of a cellular prolyl cis/trans isomerase, Pin1, in these processes. Particular importance had the x-raybased resolution of the crystal structure of the nuclear egress core heterodimer as a docking site and functional platform for the nuclear release of cytomegaloviral capsids.

The second group investigates immunocellular mechanisms that contribute to the defense against CMV infections. During the last two years, they could identify the cellular protein SPOC1 as a novel factor that mediates intrinsic immunity against CMV. Furthermore, viral effector proteins are characterized which play essential roles during CMV replication or dissemination.

In their search for antiviral restriction factors, the third group demonstrated that the centrosomal protein TRIM43 restricts herpesvirus infection by regulating nuclear lamina integrity. In a long standing cooperation with Prof. M. Lehner and Prof. W. Holter (Vienna), novel T cell based immunotherapies for CMV infections were investigated.

The fourth group investigates how oncoproteins of gamma herpesviruses are capable to transform human lymphocytes to permanent growth in culture. The viral oncoproteins interact with TNF receptor-associated factors (TRAF) to activate NF-kappaB, but also to inhibit interferoninducing signaling pathways. Thereby, the viral oncoproteins may contribute to viral persistence.

The fifth laboratory is studying the oncogenic Kaposi sarcoma-associated herpesvirus (KSHV). The group could show for the first time that the Ephrin receptor tyrosinkinase A2 (EphA2) is an essential receptor for KSHV upon infection of endothelial and epithelial cells. In addition, integrin alpha V contributes to the infection of epithelial cells by KSHV.

The epigenetics group (6) has continued its research on the epigenetic consequences of foreign DNA or of virus particle intrusions into mammalian cells. While many questions remain, the available evidence obtained from a number of different biological systems supports the view that the genomic integration of foreign DNA or the immortalization of cells with EBV can lead to alterations in the cells' CpG methylation profiles. These findings call for a caveat towards the interpretation of data obtained from genetically manipulated cells. Herpesviruses are often the cause of severe encephalitis.

However, using unbiased Next-Generation Sequencing, a completely unexpected pathogen, Borna disease virus 1 (BoDV-1), could be detected in brain tissue of a patient with fatal encephalitis of unknown origin. This was the first evidence demonstrating that this virus, which is transmitted by shrews, is indeed pathogenic in humans.

#### **Antiviral immunity**

PI: Prof. Dr. M. Tenbusch<sup>1</sup>, Prof. Dr. M. Mach<sup>2</sup>, Prof. Dr. K. Überla<sup>3</sup>

The first research group is developing novel gene-based immunization strategies against viral respiratory tract infections. A major focus of its work is the induction of local immune responses at the mucosal entry sides of the pathogens. The group could demonstrate that adenoviral vector immunization induces very potent antigen-specific, tissue resident memory T-cells in the lung which mediate efficient protection against infections with a broad spectrum of divergent influenza A viruses as well as against the respiratory syncytial virus.

The second laboratory has continued its efforts in isolating and defining protective antibodies against CMV, using murine CMV as a model system. A number of monoclonal antibodies directed at viral envelope glycoproteins were isolated that vastly differed in their capacity to neutralize the virus *in vitro*. Interestingly, the *in vivo* capacity to protect against murine CMV infection was not directly correlated to the neutralizing activity *in vitro*. A number of non-neutralizing antibodies could be defined which had similar protective capacity as potent neutralizing antibodies.

The third research group investigates mechanisms of adaptive immunity against HIV and aims at the development of HIV vaccines. The group was able to show in a highly relevant animal model that antibodies against HIV are able to prevent the infection of the very first cells. For vaccine development, the group uses genebased immunization methods, liposomal vaccines, nanoparticles, and virus particle vaccines. One approach is to exploit T helper cell responses induced by already approved vaccines to optimize the antibody response to the HIV Env protein. Using B- and T-cell receptor transgenic mice, the influence of particulate vaccines on the activation and differentiation of antigenspecific B cells and follicular T helper cells could also be investigated. The aim of further work is to characterize the influence of HIV infection on vaccine-induced immune responses.

#### Teaching

Curricular lectures and courses on infectiology and immunology for students of Medicine, Dentistry, pharmacy, and Molecular Medicine are jointly given by the Institute of Clinical and Molecular Virology and the Institute of Clinical Microbiology, Immunology, and Hygiene. In collaboration with further colleagues from 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 the B.Sc. und M.Sc. degree programs in Molecular Medicine, integrated immunology, biology, integrated life sciences and molecular sciences.

The course offerings are completed by the supervision of Bachelor's, Master's, MD, and PhD theses.

#### Selected publications

Bootz A, Karbach A, Spindler J, Kropff B, Reuter N, Sticht H, Winkler TH, Britt WJ, Mach M. Protective capacity of neutralizing and non-neutralizing antibodies against glycoprotein B of cytomegalovirus. PLoS Pathog 2017; 13(8):e1006601

Held FE, Guryev AA, Fröhlich T, Hampel F, Kahnt A, Hutterer C, Steingruber M, Bahsi H, von Bojnicic-Kninski C, Mattes DS, Foertsch TC, Nesterov-Mueller A, Marschall M, Tsogoeva SB. Facile access to potent antiviral quinazoline heterocycles with fluorescence properties via merging metalfree domino reactions. Nat Commun 2017; 8:15071

Elsayed H, Nabi G, McKinstry WJ, Khoo KK, Mak J, Salazar AM, Tenbusch M, Temchura V, Ueberla K. Intrastructural Help: Harnessing T Helper Cells Induced by Licensed Vaccines for Improvement of HIV Env Antibody Responses to Virus-Like Particle Vaccines. J Virol 2018; 92(14): e00141-18

Grosskopf AK, Ensser A, Neipel F, Jungnickl D, Schlagowski S, Desrosiers RC, Hahn AS. A conserved Eph family receptor-binding motif on the gH/gL complex of Kaposi's sarcoma-associated herpesvirus and rhesus monkey rhadinovirus. PLoS Pathog 2018; 14(2):e1006912

Korn K, Coras R, Bobinger T, Herzog SM, Lücking H, Stöhr R, Huttner HB, Hartmann A, Ensser A. Fatal Encephalitis Associated with Borna Disease Virus 1. N Engl J Med 2018; 379(14): 1375-1377

Lapuente D, Bonsmann MSG, Maaske A, Stab V, Heinecke V, Watzstedt K, Hess R, Westendorf AM, Bayer W, Ehrhardt C, Tenbusch M. IL-1 beta as mucosal vaccine adjuvant: the specific induction of tissue-resident memory T cells improves the heterosubtypic immunity against influenza A viruses. Mucosal Immunol 2018; 11(4): 1265-1278

#### 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, Virology, University of New South Wales, Sydney: Australia

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

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

# Institute of Clinical and Molecular Virology

**Division of Experimental Therapy** 

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#### **Research focus**

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

#### **Structure of the Division**

Professorship: 1

Personnel: 7

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

#### **Special structural features**

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

#### Research

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

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

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

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

Mammalian transglutaminases (TG) catalyze calcium-dependent irreversible post-translational modifications of proteins and their enzymatic activities contribute to the pathogenesis of several human 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 (Aß) proteins inducing posttranslational modifications via transglutaminase-catalyzed intermolecular crosslinks resulting in stable, rigid, and insoluble protein complexes. Focusing on the role of TG6 in HTT and Aß aggregation in vitro and in vivo, we therefore study TG6 expression and function in HD/AD cell culture systems, transgenic mouse and rat models including novel loss-of-function mutant mice (TG6ko mice). We expect deeper insight into the role of TG6 in the CNS and particular into TG6 dependent mechanisms contributing to HTT/Aß aggregation potentially identifying targets and novel therapeutic approaches in neurodegenerative disorders.

#### Examination of behavioral abnormalities in rats after injection with gadolinium based contrast agents: Neurobehavioral findings resulting from experiments

The objective of this study was to investigate the potential effect of a signal intensity (SI) increase and the presence of Gadolinium (Gd) in the brain after repeated administration of the Gd-based contrast agents (GBCAs) Omniscan and Gadovist on general health, motor coordination, anxiety-related behaviors as well as cognition. GBCAs represent a family of aminopolyarboxylic acid ligands chelated to gadolinium and are commonly used in patients for T1weighted magnetic resonance imaging (MRI) for diagnostic purpose. Since a few years it is known that repeated administration of some, but not all GBCAs, is associated with T1weighted signal intensity increase in the deep cerebral nuclei dentate nucleus and globus pallidus of the patients. Genesis, clinical consequences, reversibility, and potential comorbidity of this Gd-accumulation is not known yet. The American Food and Drug Administration as well as the European Medicines Agency prompted all manufacturer of GBCAs to investigate potential functional consequences of this Gd-accumulation.

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

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

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

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

#### Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition

HD is an autosomal dominant neurodegenerative disorder caused by expanded CAG repeats in the huntingtin gene. Although mutant HTT is expressed during embryonic development and throughout life, clinical HD usually manifests later in adulthood. A number of studies document neurodevelopmental changes associated with mutant HIT, but whether these are reversible under therapy remains unclear. We identify very early behavioral, molecular, and cellular changes in preweaning transgenic HD rats and mice. Interventional treatment of this early phenotype with the histone deacetylase inhibitor (HDACi) LBH589 led to significant improvement in behavioral changes and markers of dopaminergic neurotransmission and complete reversal of aberrant neuronal differentiation in vitro and in vivo. Our data support the notion that neurodevelopmental changes contribute to the prodromal phase of HD and that early, presymptomatic intervention using HDACi may represent a promising novel treatment approach for HD.

#### Teaching

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

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

#### **Selected publications**

Thangaratnarajah C, Dinger K, Vohlen C, Klaudt C, Nawabi J, Lopez Garcia E, Kwapiszewska G, Dobner J, Nüsken KD, van Koningsbruggen-Rietschel S, von Hörsten S, Dötsch J, Alejandre Alcázar MA. Novel role of NPY in neuroimmune interaction and lung growth after intrauterine growth restriction. Am J Physiol Lung Cell Mol Physiol. 2017 Sep 1;313(3):L491-L506

Amato D, Canneva F, Nguyen HP, Bauer P, Riess O, von Hörsten S, Müller CP. Capturing schizophrenia-like prodromal symptoms in a spinocerebellar ataxia-17 transgenic rat. J Psychopharmacol. 2017 Apr;31(4):461-473

Uzuneser TC, Schindehütte M, Dere E, von Hörsten S, Kornhuber J, Grömer TW, Müller CP. Schizophrenia dimension-specific antipsychotic drug action and failure in amphetamine-sensitized psychotic-like rats. Eur Neuropsychopharmacol. 2018 Dec;28(12):1382-1393

Siebzehnrubl FA et al. Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition. Proc Natl Acad Sci U S A. 2018 Sep 11;115(37):E8765-E8774

Timotius IK, Canneva F, Minakaki G, Pasluosta C, Moceri S, Casadei N, Riess O, Winkler J, Klucken J, von Hörsten S, Eskofier B. Dynamic footprint based locomotion sway assessment in alpha-synucleinopathic mice using Fast Fourier Transform and Low Pass Filter. J Neurosci Methods. 2018 Feb 15;296:1-11

Plank AC, Canneva F, Raber KA, Urbach YK, Dobner J, Puchades M, Bjaalie JG, Gillmann C, Bäuerle T, Riess O, Nguyen HHP, von Hörsten S. Early Alterations in Operant Performance and Prominent Huntingtin Aggregation in a Congenic F344 Rat Line of the Classical CAGn51trunc Model of Huntington Disease. Front Neurosci. 2018 Jan 25;12:11

#### 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
- Genetic and bacterial factors in chronic inflammation
- Pathogenicity of Coxiella burnetii
- Microbial phosphatases
- Innate and adaptive lymphoid cells in leishmaniasis
- Molecular biology of malaria
- Molecular mycology

#### **Structure of the Chair**

Professorships: 4

Personnel: 92

- Doctors (of Medicine): 10
- Scientists: 9 (thereof funded externally: 1)
- Graduate students: 22

#### **Clinical focus areas**

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

#### Research

The different research groups of the Institute of Clinical Microbiology, Immunology, and Hygiene study the innate and adaptive immune response during infectious diseases, investigate mechanisms of microbial virulence, and analyze the regulation of basic inflammatory processes, using immunological, cell-biological, and molecular techniques. Various infectious disease models are studied which include infections with 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) for flow cytometry, 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)-y 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 NO-sensitive parasite Leishmania (L.) major. The group aims to elucidate the molecular mechanisms by which TNF prevents an upregulation of host cell arginase 1. Furthermore, the group investigates whether the host or parasite arginase are critical for the resolution of cutaneous leishmaniasis and for the lifelong survival of Leishmania in vivo. In another project, the group analyses the interaction between iNOS/NO and iron metabolism and the antimicrobial and immunoregulatory function of reactive chlorine intermediates. Finally, the group studies the interaction between iNOS/NO and the iron metabolism.

### 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.



HeLa229 cells, infected with Coxiella burnetii for 60 h The nucleus (N) was stained with DAPI (blue), C. burnetii with specific antibodies (red) and the lysosomal membrane protein LAMP-1 with an anti-LAMP-1 antibody. C. burnetii can replicate to high numbers in the LAMP-1 positive C. burnetii-containing vacuole (CCV), which can reach the size of the nucleus.

#### **Microbial phosphatases**

#### PI: Dr. D. Soulat

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

#### **Innate lymphoid cells in 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 regulated. The prevalence and activation of these cells by Leishmania is also studied in the human system. In another project, the group analyzes how B cells regulate the immune response in visceral leishmaniasis and affect the course of infection.

#### Molecular biology of malaria

PI: Dr. M. Petter

Malaria pathogenesis relies on various cellular processes in the life cycle of malaria parasites that each represent promising targets for therapeutic interventions and vaccine development. These include host cell invasion, the expression of virulence factors, and the differentiation of sexual stages 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 bromodomain protein PfBDP1, which contributes to epigenetic gene regulation in malaria parasites by binding to acetylated histones.

#### **Molecular mycology**

PI: Prof. Dr. S. Krappmann

Infections with the omnipresent molds of the genus Aspergillus and especially with *A. fumiga-tus* represent a life-threatening complication for

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

#### Teaching

The Institute offers lectures and teaching courses for students of Medicine, Dental Medicine, Molecular Medicine, Biology, and Pharmacy. Particularly noteworthy is the main lecture on immunology within the master degree program Molecular Medicine, the newly established teaching modules within the elite master degree program Integrated Immunology (which started in the winter term 2018/2019) and the teaching of the interdisciplinary subject "Infectious Diseases and Immunology" within the clinical part of the training of medical students. In cooperation with the Institute of Clinical and Molecular Virology, our Institute organizes continuous medical education lectures on various infectious diseases for local physicians.

We supervise Bachelor's and Master's theses as well as MD and PhD theses.

#### **Selected publications**

Mattner J, Wirtz S. Friend or Foe? The Ambiguous Role of Innate Lymphoid Cells in Cancer Development. Trends Immunol. 2017 Jan;38(1): 29-38

Friedrich A, Pechstein J, Berens C, Lührmann A. Modulation of host cell apoptotic pathways by intracellular pathogens. Curr Opin Microbiol 2017, 35: 88-99

Ostrop J, Lang R. Contact, Collaboration, and Conflict: Signal Integration of Syk-Coupled C-Type Lectin Receptors. J Immunol 2017, 198: 14035

Leitherer S, Clos J, Liebler-Tenorio EM, Schleicher U, Bogdan C, Soulat D. Characterization of the Protein Tyrosine Phosphatase LmPRL-1 Secreted by Leishmania major via the Exosome Pathway. Infect Immun. 2017, Jul 19;85(8): pii: e00084-17

Messlinger H, Sebald H, Heger L, Dudziak D, Bogdan C, Schleicher U. Monocyte-Derived Signals Activate Human Natural Killer Cells in Response to Leishmania Parasites. Front Immunol 2018, 9: 24

Yu Y, Blachowicz A, Will C, Szewczyk E, Glenn S, Gensberger-Reigl S, Nowrousian M, Wang CCC, Krappmann S. Mating-type factor-specific regulation of the fumagillin/pseurotin secondary metabolite supercluster in Aspergillus fumigatus. Mol Microbiol 2018, 10: 1045-1065

#### International cooperations

Prof. R. Ostuni, San Raffaele Telethon Institute for Gene Therapy, Milano: Italy

Prof. M. Trost, Faculty of Medical Sciences, Newcastle University, Newcastle: UK

Prof. C. C.C. Wang, Department of Pharmacology and Pharmaceutical Sciences, University of Southern California, Los Angeles, CA: USA

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

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

## Institute of Clinical Microbiology, Immunology, and Hygiene

**Division of Infection Biology** 

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#### **Research focus**

- Immune response against helminths and allergens
- Role of dendritic cells for maintenance of immunological tolerance
- Identification of STAT6-regulated genes and proteins in B cells
- Regulation of protective immunity against helminths by STAT6 in gastrointestinal epithelial cells

#### **Structure of the Division**

Professorship: 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 Biology 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 hone marrow chimeras. We observed that basophils play an important role for protective immunity against helminths especially during secondary infections. Basophils can be efficiently activated by Fc receptors to which helminths-specific antibodies bind. These helminths-specific antibodies are probably generated by long-lived plasma cells that were induced by the primary infection and constitute the immunological memory function. It further became apparent that basophils are essential for chronic allergic inflammation of the skin. This pathologic condition can be induced by passively sensitizing basophils with haptenspecific IgE, followed by antigen-mediated IgE crosslinking. As shown by others before, mast cells are not required for this inflammatory response. The mechanisms that regulate protective and pathological functions of basophils are subject of our current investigations.

### Role of 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.

### Identification of STAT6-regulated genes and proteins in B cells

We recently demonstrated that the transcription factor STAT6 in B cells plays an important role for the germinal center reaction. Following up on this result we performed comparative transcriptome and proteome analysis of wild-type and STAT6-deficient B cells. We observed that more than 200 mRNAs were up-regulated more than 3-fold in a STAT6-dependent manner, and 149 mRNAs were more than 3-fold down-regulated. In collaboration with Prof. Dr. B. Warscheid (University of Freiburg) we demonstrated that expression of most of the STAT6-dependent proteins is regulated at the transcriptional level. We currently work on the functional characterization of some of the genes identified in this screening.

In addition, we generated transgenic mice that express a constitutively active form of STAT6 in B cells. We currently characterize these CD19Cre\_STAT6vt mice to gain a better understanding of the function of STAT6 in B cells. B cells of CD19Cre\_STAT6vt mice express more CD23 (low-affinity IgE receptor) on the cell surface and a higher frequency of germinal center B cells expresses IgG1. These mice will now be analyzed after infection with Lymphocytic Choriomeningitis Virus (LCMV) to determine whether constitutively active STAT6 can promote class switch recombination to IgG1 and IgE in this viral infection model.



Histological staining from the small intestine of a N. brasiliensis-infected mouse to detect tuft cells (green), ILC2s (red), and CD4 T cells (blue)

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

The role of intestinal epithelial cells for expulsion of helminths is poorly understood. Infection of mice with the gastrointestinal helminth Nippostrongylus brasiliensis results in a STAT6-dependent increase of goblet cells, tuft cells, and Paneth cells in the small intestine. To investigate whether expression of activated STAT6 in intestinal epithelial cells is sufficient for protective immunity against helminths, we generated Villini-Cre\_STAT6vt mice that express constitutively active STAT6 in intestinal epithelial cells. These mice show a very efficient immune response even in the absence of T cells. Based on these results we will identify and characterize STAT6regulated genes in intestinal epithelial cells.



Detection of STAT6 in the nucleus of B cells from CD19Cre\_STAT6vt mice

B cells from the spleen of wild-type (WT) and CD19Cre\_STAT6vt mice were stained with anti-STAT6 antibodies (red) and DAPI (blue). The pictures demonstrate that STAT6 is more abundant in the nucleus (blue) of CD19Cre\_STAT6vt as compared to control mice.

#### Teaching

The Division of Infection Biology offers lectures, seminars, and teaching courses for students of Medicine and Molecular Medicine as well as various teaching modules of the Faculty of Sciences.

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

#### **Selected publications**

Lehmann B, Biburger M, Brückner C, Ipsen-Escobedo A, Gordan A, Lehmann C, Voehringer D, Winkler T, Schaft N, Dudziak D, Sirbu H, Weber GF, Nimmerjahn F. Tumor location determines tissue-specific recruitment of tumor-associated macrophages and antibody-dependent immunotherapy response. Sci Immunol 2017, Jan 6;2(7). pii: eaah6413

Symowski C, Voehringer D. Interactions between Innate Lymphoid Cells and Cells of the Innate and Adaptive Immune System. Front. Immunol. 2017, 8:1422

Mokada-Gopal L, Boeser A, Lehmann CHK, Drepper F, Dudziak D, Warscheid B, Voehringer D. Identification of novel STAT6-regulated proteins in mouse B cells by comparative transcriptome and proteome analysis. J Immunol 2017, 198:3737-3745 Uderhardt S et al. Enzymatic lipid oxidation by eosinophils propagates coagulation, hemostasis and thrombotic disease. J Exp Med. 2017, 214:2121-2138

Reitz M, Brunn ML, Rodewald HR, Feyerabend TB, Roers A, Dudeck A, Voehringer D, Jönsson F, Kühl AA, Breloer M. Mucosal mast cells are indispensable for the timely termination of Strongyloides ratti infection. Mucosal Immunol. 2017 Mar;10(2):481-492

Willebrand R, Dietschmann A, Nitschke L, Krappmann S, Voehringer D. Murine eosinophil development and allergic lung eosinophilia are largely dependent on the signaling adaptor GRB2. Eur J Immunol. 2018, 48:1786-1795

#### International cooperations

Dr. J.S. Silvestre, Paris Cardiovascular Research Center, IN-SERM UMR-S 970, Paris: France

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

Dr. J. Kitaura, The University of Tokyo, Tokyo: Japan

Dr. S. Bedoui, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne: Australia

### Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Pharmacology and Toxicology

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#### Director

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#### **Research focus**

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

#### **Structure of the Chair**

Professorships: 2

Personnel: 24

- Scientists: 9 (thereof funded externally: 3)
- Graduate students: 5

#### Special structural feature

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

#### Research

Various aspects of the cardiovascular system as well as of the central and peripheral nervous system in mammals are studied. Research foci are the mechanisms underlying the generation of the cardiac rhythm and signal transduction mechanisms in cardiac hypertrophy. Another research area is the pathogenesis of acute kidney injury under septic conditions. The role of HCN channels in the nervous system and in particular in nociception and in the thalamus is analyzed. Finally, brain function under various conditions (drugs, behavioral paradigms, diseases) is studied by non-invasive brain imaging using functional magnetic resonance imaging (fMRI).

### Signal transduction of cardiac rhythmogenesis and hypertrophy

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

We found that ventricular RyR2 and CaV1.2-calcium channel mouse mutants develop a cardiac phenotype closely resembling human dilative cardiomyopathy. Pathophysiological mechanism and new treatment strategies for this disease are studied in both mouse models. In another project, the role of protein kinase A (PKA) for cardiac function was examined by using a cardiac-specific inducible PKA-mutant. Mutant animals developed ventricular dysfunction, upregulation of cardiac stress markers and delayed sarcomere shortening and calcium-decay kinetics most likely due to an impaired phosphorylation of contractile proteins and phospholamban. We could show that under pathological conditions PKA activity plays a pivotal role in the beta1 adrenergicsignaling pathway and the cardiotoxic effects after its chronic activation. Furthermore, PKA activity is important for maintaining cardiac function under chronic pressure overload.



Echocardiograms depicting the left ventricular function of control (top) and PKA-mutant (bottom) animals PKA mutants display a reduced ejection fraction and increased left ventricular volumes.

#### HCN channels in the nervous system

PI: PD Dr. S. Herrmann, Prof. Dr. A. Ludwig Downstream targets of the cAMP-dependent signaling pathway in nociception are not well understood. We disabled the function of either HCN2 or PKA selectively in a subset of peripheral nociceptive neurons. A near-complete lack of sensitization was observed in both mutant strains during cAMP-dependent inflammation. The lack of HCN2 as well as the inhibition of PKA eliminated the cAMP-mediated increase of calcium transients in isolated dorsal root ganglion neurons. Facilitation of the Ih current via cAMP was abolished in neurons without PKA activity. These results show a significant contribution of HCN2 and PKA to inflammatory pain and 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 show that HCN4 channels in different thalamic projection neurons are important for the production of rhythmic intrathalamic oscillations. In addition, thalamic HCN4 channels determine the regular thalamocortical oscillatory activity during alert states.

#### **Renal function and sepsis**

PI: Prof. Dr. K. Höcherl

Decreased renal perfusion due to renal vasoconstriction seems to be a central factor in the pathogenesis of septic acute kidney injury. An increased production of vasodilator prostaglandins including prostaglandin E2 (PGE2) and prostacyclin (PGI2) may play an important role in maintaining renal function. By using an animal model of endotoxemia, we showed that the expression of EP2-, EP4-, and IP-receptors, which mediate the PGE2 and PGI2-induced vasodilation, was increased. In contrast, expression of EP1- and EP3receptors, which transmit the vasoconstrictive effect of PGE2, was reduced. By using the isolatedperfused kidney model we found that the vasodilator effect of the above prostaglandins was much stronger in kidneys from lipopolysaccharide-treated animals as compared to controls. These results demonstrate an increased vasodilating effect of PGE2 and PGI2 during endotoxemia suggesting that these prostaglandins contribute to the maintenance of kidney function under endotoxemic conditions. Recently, the fibroblast growth factor-23 (FGF23) has been identified as an important regulator of calcium and phosphate homeostasis and the metabolism of vitamin D. FGF23 binds to the FGF-receptor-klotho-complex. Abnormal regulation of the FGF23-klothovitamin D signal transduction pathway and an altered expression of renal calcium and phosphate transporters may underlie the frequently observed hypocalcemia and changes in phosphate and vitamin D homeostasis during septic conditions. We showed that lipopolysaccharide induces hypocalcemia and hyperphosphatemia in an in vivo model. The plasma concentrations of FGF23, parathyroid hormone, and vitamin D3 were increased, whereas renal expression of klotho was reduced. In addition, we detected a change in the expression of various calcium and phosphate transporters. The renal expression of TRPV5, TRPV6, and Pit1 was stronger and the expression of calbindin-D28K, NCX1, NaPi-2a, und NaPi-2c was lower as compared to controls. Our results demonstrate that during endotoxemia a dysregulation in the FGF23-Klotho-vitamin D axis and alterations in various renal phosphate and calcium transporters take place.

#### Pharmacological fMRI imaging PI: Prof. Dr. A. Hess

This working group uses non-invasive functional magnetic resonance imaging (fMRI) to investigate dynamic-plastic processes in the central nervous system of rodents and humans. In the last two years, the group worked among other studies on two BMBF joint research projects (NeuroImpa and NeuroRad). In the NeuroImpa project, plastic brain processes were examined in var-

ious arthritis models (Prof. H.-G. Schaible and Prof. T. Kamradt, Universitätsklinikum Jena) as well as in bone healing (Prof. Dr. S. Grässel, Universität Regensburg). In the NeuroRad project, effects of different dosages of gamma-radiation on brain function of embryonic and postnatal mice were investigated in collaboration with Prof. Dr. M. Löbrich (TU Darmstadt) by using behavioral tests and fMRI. Further dynamic brain processes were investigated in rodent studies dealing with learning behavior (together with Prof. Dr. J. Braun, Otto-von-Guericke-Universität Magdeburg), depression (cooperation with Prof. D. Pollak, Medizinische Universität Wien) and anxietyassociated brain structures (cooperation with Dr. W. Haubensak, Research Institute of Molecular Pathology, Vienna). In all these projects, the graph-theoretical network analyses that we have established over several years proved to be a very potent method for selectively analyzing dynamic processes in the brain. These techniques, which had been developed in preclinical studies, were also successfully applied to the analysis of fMRI data from patients. In cooperation with the departments of Medicine 1 and 3, Department of Neurology, and the Division of Neuroradiology), we used our methods for therapy validation in various diseases (Crohn's disease, rheumatoid arthritis, epilepsy). As part of the PreCePra study at the Department of Medicine 3, which examines an fMRT-based prediction of the therapeutic response to a TNF alpha-inhibitor in rheumatoid arthritis, we could include additional patient data from the participating international centers. Therefore, we soon will have reached the number of patients envisaged for the full analysis.



The picture shows the excellent overlap of the standard ICA components (big coloured areas) of the resting state activity in the rat brain with the much finer resolved structural analysis from our newly developed graph-theoretical methods (coloured balls). The surface of the rat brain is depicted in translucent grey.

#### Teaching

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

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

#### Selected publications

Herrmann S, Rajab H, Christ I, Schirdewahn C, Höfler D, Fischer MJM, Bruno A, Fenske S, Gruner C, Kramer F, Wachsmann T, Wahl-Schott C, Stieber J, Biel M, Ludwig A. Protein kinase A regulates inflammatory pain sensitization by modulating HCN2 channel activity in nociceptive sensory neurons. Pain 2017, 158:2012-2024

Aziz Q, Finlay M, Montaigne D, Ojake L, Li Y, Anderson N, Ludwig A, Tinker A. ATP-sensitive potassium channels in the sinoatrial node contribute to heart rate control and adaptation to hypoxia. J Biol Chem. 2018, 293: 8921

Griessner J, Pasieka M, Böhm V, Grössl F, Kaczanowska J, Pliota P, Kargl D, Werner B, Kaouane N, Strobelt S, Kreitz S, Hess A, Haubensak W. Central amygdala circuit dynamics underlying the benzodiazepine anxiolytic effect. Mol Psychiatry. 2018 Nov 30

Kreitz S, de Celis Alonso B, Uder M, Hess A. A new analysis of resting state connectivity and graph theory reveals distinctive short-term modulations due to whisker stimulation in rats. Front Neurosci 2018, 12: 334

Mendez-Torrijos A, Kreitz S, Ivan C, Konerth L, Rösch J, Pischetsrieder M, Moll G, Kratz O, Dörfler A, Horndasch S, Hess A. Snack food as a modulator of human resting-state functional connectivity. CNS Spectr. 2018 Oct;23(5):321-332

Meurer M, Ebert K, Schweda F, Höcherl K. The renal vasodilatory effect of prostaglandins is ameliorated in isolatedperfused kidneys of endotoxemic mice. Pflugers Arch. 2018, 470: 1691

#### International cooperations

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

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

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

Dr. W. Haubensak, Research Institute of Molecular Pathology, Vienna: Austria

Prof. I. Vetter, The University of Queensland, Brisbane: Australia

### 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
- Quantification of drugs and endogenous substances including metabolomics
- Medication safety

#### **Structure of the Chair**

Professorships: 2

- Personnel: 25
- Doctors (of Medicine): 3
- Scientists: 7 (thereof funded externally: 3)
- Graduate students: 8

#### **Special structural feature**

The position of the executive director of the Institute rotates between the Chair of Pharmacology and Toxicology and the Chair of Clinical Pharmacology and Clinical Toxicology on a twoyear 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 and the German Federal Ministry of Health (BMG), are in the focus of our studies: Uptake and efflux transporters for drugs and endogenous compounds, mechanisms underlying drug-drug interactions, genetic determinants of drug effects (pharmacogenomics), cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism, and medication safety.

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

Pl: 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. For example, we identified using in vitro models the importance of the export transporter MATE1, which is localized in the luminal membrane of renal proximal tubular cells, for the renal secretion of drugs (e.g. memantine, metformin) and endogenous biomarkers (trimethylamine-Noxide). Moreover, we investigated the functional relevance of transporters for endogenous substances. For example, functional consequences of mutations in the SLC13A5 gene, which encodes for the uptake transporter NaCT (sodium-coupled citrate transporter), were investigated. This transporter plays an essential role in cellular energy metabolism and in brain development. Alterations in function of NaCT are associated with epileptic encephalopathy.



Influence of the T227M (C, D) and the G219R (E, F) mutations on structure of the NaCT transporter, which is important for cellular energy metabolism and in brain development (Reproduced with permission from Selch S et al, Sci Rep. 2018)

#### 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,  $\beta$ -aminoisobutyrate, nitrate and the methylarginines ADMA and SDMA. The investigations were conducted in long standing cooperations with the Department of Medicine 4, the Universities of Dresden and Kiel and the Framingham Heart Study (USA). In the reporting period we identified an independent association of the risk markers ADMA, SDMA, and homoarginine with the intake of several drugs. Furthermore, we could provide direct evidence that the protective risk marker homoarginine is a substrate of the cationic amino acid transporters CAT1, CAT2A, and CAT2B.



Kaplan-Meier plot for the relationship between tertile of plasma nitrate and survival (tertile 1=low, tertile 2=intermediate, and tertile 3=high plasma nitrate; reproduced with permission of Maas R et al, J Am Heart Assoc. 2017)

#### Analysis of drugs and endogenous substances including metabolomics

#### PI: Dr. A. Gessner, Dr. V. Taudte

The mass spectrometry unit uses samples from both, cell culture experiments and clinical and large epidemiological trials (GCKD study, popgen). 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, N1-methylnicotinamide, trimethylamine-N-oxide (TMAO), and  $\beta$ -aminoisobutyric acid. In 2018, the methodological spectrum was broadened to targeted and untargeted metabolomics due to a new mass spectrometer (Q Exactive Focus with U-HPLC) funded by the DFG. The available technologies can be used for cooperations within the Faculty and FAU as well as for external cooperations.

#### **Medication safety**

PI: Prof. Dr. R. Maas, Prof. Dr. M.F. Fromm A project funded by the German Cancer Aid was conducted with a focus on dose adjustment in oncological patients with renal insufficiency (cooperation with Prof. Dr. F. Dörje, pharmacy of UK Erlangen). Moreover, an innovative, three year clinical study is conducted in patients treated with new oral antitumor therapeutics in collaboration with the pharmacy of UK Erlangen, the Comprehensive Cancer Center Erlangen-EMN (CCC), and collaborating private practices, which is also funded by the German Cancer Aid. This prospective, randomized trial is currently testing the hypothesis whether clinical pharmacological/clinical pharmaceutical support improves patient safety, convenience and knowledge in patients newly treated with new oral antitumor therapeutics (AMBORA study).

In addition, problems of medication safety in elderly patients (e.g. anticholinergic burden and cognitive function in elderly patients) are in the focus of collaborative projects with the Geriatrie in Bayern-Database (GiB-DAT). Moreover, in a BMG-funded collaborative project, we evaluated the new nationwide medication plan in clinical praxis (MMP16).

The Chair coordinates the community of practice "Medication Safety" of the Medical Valley EMN e.V. In addition, the Chair participates in a continuing medical education program in Good Clinical Practice for physicians, as required for clinical trials of medicines, and medicinal products.



Distribution of the anticholinergic burden in 76,934 patients of the GiB-DAT Database (left) and association of anticholinergic burden and cognitive function in elderly patients (right); reproduced with permission from Pfistermeier B et al, PLoS One. 2017

#### Teaching

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

The Chair of Clinical Pharmacology and Clinical Toxicology offers supervision of Bachelor's and Master's theses as well as of MD and PhD theses.

#### Selected publications

von Loeffelholz C et al. The human longevity gene homolog INDY and interleukin-6 interact in hepatic lipid metabolism. Hepatology, 2017, 66: 616-630

Pfistermeister B, Tümena T, Gaßmann K-G, Maas R, Fromm MF. Anticholinergic burden and cognitive function in a large German cohort of hospitalized geriatric patients. PLOS ONE, 2017, 12: e0171353

Maas R, Xanthakis V, Göen T, Müller J, Schwedhelm E, Böger RH, Vasan RS. Plasma nitrate and incidence of cardiovascular disease and all-cause mortality in the community: The Framingham Offspring Study. J Am Heart Assoc. 2017 Nov 18;6(11). pii: e006224

Müller F, Sharma A, König J, Fromm MF. Biomarkers for in vivo assessment of transporter function. Pharmacol Rev, 2018, 70: 246-277

Selch S, Chafai A, Sticht H, Birkenfeld AL, Fromm MF, König J. Analysis of naturally occurring mutations in the human uptake transporter NaCT important for bone and brain development and energy metabolism. Sci Rep, 2018, 8: 11330

Maas R, Mieth M, Titze SI, Hübner S, Fromm MF, Kielstein JT, Schmidt M, Köttgen A, Kronenberg F, Krane V, Hausknecht B, Eckard KU, Schneider MP. Drugs linked to plasma homoarginine in CKD patients – A cross-sectional analysis of the German Chronic Kidney Disease Cohort (GCKD). Nephrol Dial Transplant, 2018 Nov 23. doi: 10.1093/ndt/gfy342

#### 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. R. Masereeuw, Utrecht University, Utrecht: The

Netherlands

Prof. A. Sparreboom, Ohio State University, Columbus, OH: USA

### **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**

Professorship: 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 mercuryarc 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 publication

Moeller S, Lücke C, Struffert T, Schwarze B, Gerner ST, Schwab S, Köhrmann M, Machold K, Philipsen A, Müller HH. Ischemic stroke associated with the use of a synthetic cannabinoid (spice). Asian J Psychiatr. 2017 Feb;25:127-130

## **Institute of Human Genetics**

### **Chair of Human Genetics**

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#### **Research focus**

- Neurodevelopmental disorders
- Growth disorders
- Psoriasis
- Ophthalmogenetics
- Familial cancer
- Developmental genetics

#### **Structure of the Chair**

Professorships: 2 Personnel: 49

- Doctors (of Medicine): 9
- Scientists: 9 (thereof funded externally: 3)
- Graduate students: 10

#### **Clinical focus areas**

- Genetic outpatient clinic for all aspects of genetic diseases
- Participation in different B-centers for rare diseases within the Erlangen Center for Rare 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 genome sequencing technologies are used. For various projects large groups of patients have been recruited and clinically characterized in detail. In addition, cellular models including induced pluripotent stem cells and genome editing are used.

The Institute cooperates with numerous departments and institutes within the Faculty and operates the core unit "Next Generation Sequencing".

#### Neurodevelopmental disorders

PI: Prof. Dr. C. Zweier, Prof. Dr. A. Reis Intellectual disability can occur independently, but also in a syndromic presentation with additional symptoms and malformations. These are summarized as neurodevelopmental disorders (NDDs) and genetic factors are the main cause. Over the years the working groups at the Institute identified numerous single gene defects causing NDDs. Genetic defects of members of the BAF complex, including ARID1B, are particularly frequent in patients with intellectual disability and Coffin-Siris syndrome. In the latter, mutations in DPF2, another subunit of the BAF complex, were newly identified. Furthermore, de novo variants in the F-box protein FBXO11 were implicated in variable NDDs, and a clustering of missense variants in RHOBTB2 was identified as causative for a severe developmental and epileptic encephalopathy. Drosophila was used as a model to further characterize the role of RhoBTB.



Computer-based modelling of mutations in PHD2 domain of DPF2 found in patients with Coffin-Siris syndrome

#### **Growth disorders**

PI: PD Dr. C. Thiel

The elucidation of genetic causes of growth disturbances allows insights into the regulation of fundamental cellular processes. The group focuses on the identification and functional characterization of genes involved in idiopathic short stature and ciliary growth disorders. In a genome-wide approach using exome sequencing in large study groups, the group could both expand the molecular and clinical spectrum of known entities as well as identify novel causes of idiopathic short stature.

#### Psoriasis

PI: PD Dr. U. Hüffmeier, Prof. Dr. A. Reis Complex or multifactorial diseases are caused by a combination of mostly unknown environmental and genetic factors. Numerous genetic variants, each with a small effect size, act as susceptibility factors. At the Institute, both, the more frequent forms of plaque and psoriatic arthritis as well as the rarer manifestations of pustular psoriasis, are studied. Using large patient groups, recruited genetic and functional analysis of candidate genes were continued. In generalized pustular psoriasis evidence was found for a rather oligogenic inheritance while no association of the palmoplantar form with variants in the genes IL36RN and CARD14 could be identified.

#### Ophthalmogenetics

#### PI: PD Dr. F. Pasutto, Prof. Dr. A. Reis

Glaucoma represents a heterogeneous group of eye disorders characterized by irreversible damage of the optic nerve and usually elevated intraocular pressure, leading to vision loss and ultimately, if untreated, to blindness. Genetic factors are considered to play a key role in all major forms of glaucoma. In recent years, the working group in collaboration with the Department of Ophthalmology and international consortia has made important contributions to elucidate the genetic causes of pseudoexfoliation syndrome, the most common form of secondary glaucoma. Current work focuses on the mechanisms of disease development at the main predisposition locus LOXL1.



Results of the international meta-analysis of several genome-wide association studies (GWAS) for exfoliation syndrome (modified from Aung T et al. Nat Genet 2017)

#### **Familial cancer**

#### PI: Dr. A. Ekici, Prof. Dr. A. Reis

Some 5 -10% of cancer patients are affected by a familiar cancer syndrome. These are often caused by mutations in cancer susceptibility genes, either inherited or occurring de novo. The Institute closely collaborates with several oncology departments on campus to identify mutations in both, highly penetrant and lowpenetrant genes, and to correlate genetic findings with patients' symptoms. In particular, in cooperation with working groups at the Department of Obstetrics and Gynecology, we carried out several such systematic mutation screens in large patient groups with familial breast and ovarian cancer.

#### **Developmental genetics**

PI: Prof. Dr. A. Winterpacht

This group is interested in the molecular basis of developmental processes and their individual variability, including epigenetic mechanisms and regulatory networks of organogenesis and cell differentiation. 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. Using novel single-cell transcriptomic analyses the group investigates its role in mitosis and in epigenetic regulation of meiosis as well as spermatogonial stem cell maintenance and differentiation. Hauer NN et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. Genet Med 2018, 20: 630-638

Gregor A et al. De Novo Variants in the F-Box Protein FBXO11 in 20 Individuals with a Variable Neurodevelopmental Disorder. Am J Hum Genet 2018, 103: 305-316

#### 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



Pseudotime analysis of single-cell RNA-seq data of testis cells shows continuous cell development of spermatogenesis (labeled for cell types; adapted from Lukassen et al. Sci Data 2018)

#### Teaching

The Institute of Human Genetics is involved in curricular teaching activities in Medicine and in the B.Sc. and M.Sc. degree programs Molecular Medicine as well as Cellular and Molecular Biology (M.Sc.), respectively.

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

#### **Selected publications**

Aung T et al. Genetic association study of exfoliation syndrome identifies a protective rare variant at LOXL1 and five new susceptibility loci. Nat Genet 2017, 49: 993-1004

Pasutto F et al. Pseudoexfoliation syndrome-associated genetic variants affect transcription factor binding and alternative splicing of LOXL1. Nat Commun 2017, 8: 15466

Kraus C, Hoyer J, Vasileiou G, Wunderle M, Lux MP, Fasching PA, Krumbiegel M, Uebe S, Reuter M, Beckmann MW, Reis A. Gene panel sequencing in familial breast/ovarian cancer patients identifies multiple novel mutations also in genes others than BRCA1/2. Int J Cancer 2017, 140: 95-102

Vasileiou G et al. Mutations in the BAF-Complex Subunit DPF2 Are Associated with Coffin-Siris Syndrome. Am J Hum Genet 2018, 102: 468-479

### **Institute of Human Genetics**

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Prof. Dr. med. Beate Winner

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#### **Research focus**

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

#### **Structure of the Division**

Professorship: 1

- Personnel: • Doctor (of Medicine): 1
- Scientists: 2 (thereof funded externally: 1)
- Graduate students: 12

#### **Clinical focus area**

Speaker of the Center for Rare Diseases (ZSEER)

#### Research

Research at the Division of Stem Cell Biology focuses on modeling CNS diseases using genome editing and human stem cell-based models. The physiological and pathological functions of the human brain are puzzling. Post-mortem tissue allows a structural analysis of the brain. In order to better understand the development and function of the brain, dynamic and/or functional investigations between different human brain cells are necessary. The generation of brain cells from human pluripotent stem cells in multidimensional cultures gives novel insights into structural and dynamic interactions. Specifically, we investigate neurodegeneration and regeneration in neurodegenerative and other neurologic diseases.

### Stem cell modeling of Parkinson's disease

PI: Dr. I. Prots, Prof. Dr. B. Winner Parkinson s disease (PD) is a progressive neurodegenerative disorder characterized by the loss of midbrain neurons. The accumulation of alpha-synuclein ( $\alpha$ Syn) and inflammation are suggested to play a crucial role for neurodegeneration in PD. We investigate the mechanisms of their contribution to neuronal loss and their possible interplay during PD pathology.

To model PD pathology in human system, we differentiate neurons from patient-derived induced pluripotent stem cells (iPSC) in collaboration with the Division of Molecular Neurology. We demonstrated that the formation of small oligomeric  $\alpha$ Syn aggregates reduces mitochondrial axonal transport and impairs axonal and synaptic integrity in human neurons, including PD patient iPSC-derived neurons. Axonal transport defects could be rescued by using a compound inhibiting  $\alpha$ Syn oligomer formation.

To uncover neuroinflammatory pathways in human PD pathology, we developed a human autologous co-culture of peripheral T cells and iPSC-derived midbrain neurons from PD patients and controls. We showed that T cells induce cell death of midbrain neurons in sporadic PD by IL-17, upregulation of IL-17 receptor, and NFKB activation. In the blood of PD patients, higher frequencies of IL-17-producing T cells were evident and increased numbers of T cells were detected in postmortem PD midbrain tissues. Blockage of IL-17 or IL-17R rescued the neuronal death. Possible involvement of IL-17producing T cells in PD might revise our understanding of how PD neurodegeneration can be promoted by systemic inflammation. Since inflammation can affect axonal transport, a challenging possibility of a Syn oligomer-induced axonopathy as underlying mechanism of Th17induced neuronal death in human PD pathology will be further investigated.

### Stem cell models of motor neuron disease

PI: Dr. M. Regensburger, Prof. Dr. B. Winner Motor neuron diseases are characterized by the degeneration of the upper and/or lower motor neurons. Using different paradigms, embryonic stem cell lines or patient-derived iPSC are differentiated into upper and lower motor neurons. This enables us to analyze gene expression, proteins, neuronal integrity, formation of networks, and electrophysiological firing properties. In the most frequent type of hereditary spastic paraplegia (HSP), caused by mutations in the gene SPG4, we investigate alterations of the endoplasmic reticulum which cause length dependent upper motor neuron degeneration. Mutations in SPG11 are the most frequent cause of autosomal-recessive complicated HSP, which is characterized by multisystem neuronal degeneration. We analyze the effect of SPG11 mutations in different neuronal models including 3dimensional brain organoids. We showed that GSK3 is hyperactivated in SPG11 and we are trying to reverse these specific signaling pathway abnormalities by therapeutic compounds and to establish patient-specific phenotype analyses. In neurons, differentiated from sporadic amyotrophic lateral sclerosis patients' cells, we identify disease-specific transcriptional signatures, which may cause individual susceptibility for motor neuron degeneration.

Thus, our overall goal is to better understand disease mechanisms in motor neuron diseases and to identify therapeutic targets for future translation into the clinic.

#### **Genetic pain disorders**

#### PI: Dr. E. Eberhardt

Chronic pain is a common health problem for which therapy often remains unsatisfactory. In recent years, studies of rare monogenic pain disorders have led to the identification of candidate genes and helped our understanding of the pathophysiology of pain. Among these are variants in peripheral voltage-gated sodium channels (Navs) that cause inherited pain syndromes, like primary erythromelalgia (IEM) and small-fiber neuropathy (SFN). Since rodent models lack the patient's individual genetic background, we obtained fibroblasts from two patients with chronic pain due to Nav1.9 linked SFN. Using a fibroblast reprogramming approach, we generated human induced pluripotent stem cells (hiPSCs) which we differentiate into patient-derived pain sensing peripheral neurons (nociceptors).

These nociceptors from pain patients in the dish show signs of neuronal hyperexcitability in patch-clamp recordings. Moreover, when grown on multi electrode array (MEA) plates, a pathological firing behavior was observed, mimicking the patient's C-fibers assessed in microneurography recordings. In MEA recordings, the FDA approved antiepileptic drug lacosamide strongly reduced electrical activity of hiPSC-derived nociceptors of SFN patients as compared to age matched control groups. Based on this preclinical prediction, one patient started offlabel treatment with lacosamide. Within five days, pain ratings on numeric rating scale (0 no pain, 10 worst imaginable pain) decreased from 7.5 to 1.5. Simultaneously, spontaneous activity of the patient's C-fibers objectively assessed in microneurography recordings was significantly diminished. In summary, our findings led to an individualized translational therapeutic approach based upon patient-derived sensory neurons.

### CRISPR/Cas9 gene editing of human pluripotent stem cells

PI: Dr. S. Turan

Gene editing is becoming increasingly important to generate human specific disease models with human embryonic stem cells or corrected patient derived induced pluripotent stem cells. Meanwhile, inefficient and labor-intensive gene editing techniques, such as Zinc finger nucleases or TALENs, were replaced by the CRISPR/ Cas9 technique, which allows efficient gene editing in stem cells. Hence, mastery of this method is critical to generate and study loss or gain of function stem cell models.

Our laboratory uses the CRISPR method to generate knockout or knockin models of several genes, which play a critical role in neurodevelopment and intellectual disability (SOX11, ARID1B, TCF4), motor neuron diseases (SPG4, SPG11), and PD (SNCA). We successfully generated haploinsufficiency models of intellectually disability genes of SOX11 or ARID1B.

For proteins, where antibodies are not specific enough, we are currently in the process to use CRISPR to create endogenously FLAG or fluorescent reporter tagged reporter lines to validate novel protein-protein or protein-DNA interactions.

#### Teaching

The Division of Stem Cell Biology is involved in curricular teaching activities in Medicine and in the B.Sc. and M.Sc. degree programs Molecular Medicine as well as Cellular and Molecular Biology (M.Sc.), respectively.

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

#### **Selected publications**

Sommer A, Maxreiter F, Krach F, Fadler T, Grosch J, Maroni M, Graef D, Eberhardt E, Riemenschneider MJ, Yeo GW, Kohl Z, Xiang W, Gage FH, Winkler J, Prots I, Winner B. Th17 Lymphocytes Induce Neuronal Cell Death in a Human IPSC-Based Model of Parkinson's Disease. Cell Stem Cell; 2018, 23(1):123-131

Prots I, Grosch J, Brazdis RM, Simmnacher K, Veber V, Havlicek S, Hannappel C, Krach F, Krumbiegel M, Schutz O, Reis A, Wrasidlo W, Galasko DR, Groemer TW, Masliah E, Schlotzer-Schrehardt U, Xiang W, Winkler J, Winner B. Alpha-Synuclein oligomers induce early axonal dysfunction in human iPSC-based models of synucleinopathies. PNAS; 2018, 115:7813-7818

Krach F, Batra R, Wheeler EC, Vu AQ, Wang R, Hutt K, Rabin SJ, Baughn MW, Libby RT, Diaz-Garcia S, Stauffer J, Pirie E, Saberi S, Rodriguez M, Madrigal AA, Kohl Z, Winner B, Yeo GW, Ravits J. Transcriptome-pathology correlation identifies interplay between TDP-43 and the expression of its kinase CK1E in sporadic ALS. Acta neuropathologica; 2018, 136(3):405-423

Pérez-Brangulí F, Buchsbaum IY, Pozner T, Regensburger M, Fan W, Schray A, Börstler T, Mishra H, Gräf D, Kohl Z,

Winkler J, Berninger B, Cappello S, Winner B. Human SPG11 cerebral organoids reveal cortical neurogenesis impairment. Hum Mol Genet. 2018 Nov 22. doi: 10.1093/hmg/ddy397

Popp B, Krumbiegel M, Grosch J, Sommer A, Uebe S, Kohl Z, Plötz S, Farrell M, Trautmann U, Kraus C, Ekici AB, Asadollahi R, Regensburger M, Günther K, Rauch A, Edenhofer F, Winkler J, Winner B, Reis A. Need for high-resolution Genetic Analysis in iPSC: Results and Lessons from the ForIPS Consortium. Sci Rep. 2018 Nov 21;8(1):17201

Regensburger M, Prots I, Reimer D, Brachs S, Loskarn S, Lie DC, Mielenz D, Winner B. Impact of Swiprosin-1/Efhd2 on adult hippocampal neurogenesis. Stem cell reports; 2018, 10:347-355

#### International cooperations

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

Prof. E. Jorum, Oslo University Hospital: Norway

- Prof. E. Masliah, National Institute of Aging, Bethesda: USA
- Prof. E. Reid, Cambridge Institute for Medical Research: UK
- Prof. G. Yeo, University of California San Diego: USA

### Institute of Medical Informatics, Biometry, and Epidemiology

Chair of Medical Biometry and Epidemiology

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#### **Research focus**

- Computational biostatistics
- Statistical analysis of infectious disease spread
- Dermatoepidemiology
- Cooperative epidemiological and clinical studies

#### **Structure of the Chair**

Professorships: 2

Personnel: 17

- Scientists: 10 (thereof funded externally: 5)
- Graduate students: 5

#### Research

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

#### **Computational biostatistics**

PI: 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, 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 highdimensional data setups and require heuristic (or potentially biased) feature selection methods. The new algorithm allows for simultaneous estimation of predictor effects and feature selection in GAMLSS. In the course of the project, boosting methods were further analyzed with regard to their general performance as optimization method for AUC-based performance criteria in classification and survival analysis. Furthermore, boosting methods are developed and evaluated which target the analysis of so-called joint models, addressing modeling of two related outcome variables, one a time-to-eventcomponent, the other a longitudinally observed outcome, related by a parameter of association.

## Statistical analysis of infectious disease spread

#### PI: Dr. S. Meyer

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



00 0.16 0.36 0.49 0.64 0.81 1.00 1.21 1.44 1.6 average yearly incidence (per 100'000 inhabitants)

Spatial distribution of 336 cases of invasive meningococcal disease caused by the most common bacterial finetype (B:P1.7-2,4:F1-5) in Germany, 2002 - 2008 (Adapted from: Meyer S et al. J Stat Soft. 2017)

#### Dermatoepidemiology

PI: Prof. Dr. A. Pfahlberg, Prof. Dr. W. Uter In clinical contact allergy research, a close cooperation with the German contact dermatitis group (DKG) e.V. and the multi-centric project information network of departments of dermatology (IVDK), maintained by an institute at the University of Göttingen, has been established. Pooled data collected in the participating allergy departments are analyzed in terms of contact allergy surveillance, i.e. early detection of trends in contact allergy (increase, possibly in particular subgroups) and for quality control purposes. Additionally, research projects prompt special analyses, for instance sensitization to common biocides and fragrances. Moreover, the network European Surveillance System on Contact Allergies – Data Centre (ESSCA-DC) has been collecting and analyzing such data on a European level since 2002, with the data center located at the Chair of Medical Biometry and Epidemiology.

The epidemiology of malignant melanoma and acquired melanocytic nevi is a further research

interest: Acquired melanocytic nevi, surrogate or potential precursor of malignant melanoma, are addressed by the current MONA-study which includes standardized assessment of student cohorts. Currently, results of two surveys ("Erlking Sun 2015", "Francis" from 2016) addressing knowledge on prevention of UV exposure in kindergarten staff and actual protective measures (shading etc.) in the institutions are being analyzed with the aim of identifying targets of improvement of primary prevention.

### Cooperative epidemiological and clinical studies

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

- Studies in cooperation with the Chair of Psychiatry and Psychotherapy concerning nonpharmacological interventions for dementia (DeTa-MAKS, Senior-Go)
- A multi-centric European studying on "Accelerated Partial Breast Irradiation" and a controlled clinical trial on radiochemotherapy in patients with locally advanced head/neck tumors stage III and IVA-B (PACCIS) and radiochemotherapy after induction chemotherapy with gencitabine and FOLFIRINOX, resp. (CONKO-007 study), all chaired by the Department of Radiation Oncology
- The research network PRO PRICARE (compare own report) targeting the identification of unnecessary diagnostic and therapeutic interventions, their causes, and possible strategies for a future reduction of such measures. The Chair is involved in a sub-project addressing so-called cascade effects and their causes in thyroid disease
- A European multicenter study "SCOPE" ("Screening for Chronic Kidney Disease among Older People across Europe") in cooperation with the Institute for Biomedicine of Aging
- The transsectoral TIGER Study assessing daily home support of elderly patients by "pathfinders" to reduce re-admission rates after discharge from inpatient treatment
- The ANFOLKI-36 study, which examines the effects of general anesthesia in children on their cognitive function, in cooperation with the Department of Anesthesiology and the Chair of Medical Informatics

#### Teaching

The Chair of Medical Biometry and Epidemiology contributes to curricular teaching in terms of mandatory and optional courses in Medicine, Molecular Medicine, medical technology 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

Fiessler C, Pfahlberg AB, Keller AK, Radespiel-Tröger M, Uter W, Gefeller O. Association between month of birth and melanoma risk: fact or fiction? Int J Epidemiol. 2017, Apr 1;46(2):686-693

Meyer S, Held L, Höhle M. Spatio-Temporal Analysis of Epidemic Phenomena Using the R Package surveillance. J Stat Soft. 2017; 77: 11

Uter W et al. European Surveillance System on Contact Allergies (ESSCA): results with the European baseline series, 2013/14. J Eur Acad Dermatol Venereol. 2017 Sep;31(9): 1516-1525

Mayr A, Weinhold L, Hofner B, Titze S, Gefeller O, Schmid M. The betaboost package-a software tool for modelling bounded outcome variables in potentially high-dimensional epidemiological data. Int J Epidemiol. 2018, Oct 1;47(5):1383-1388

Schäfer R et al. Quality-of-life results for accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breastconserving surgery (GEC-ESTRO): 5-year results of a randomized, phase 3 trial. Lancet Oncol. 2018 Jun;19(6):834-844

Uter W, Wolter J. Nickel and cobalt release from earrings and piercing jewellery - analytical results of a German survey in 2014. Contact Dermatitis. 2018 May;78(5):321-328

#### International cooperations

Multicentric:

Prof. C. Lidén, Prof. J.D. Johansen, Prof. C. M. Bonefeld, Dr. I. 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**

Professorship: 1

- Personnel: 19
- Doctor (of Medicine): 1
- Scientists: 14 (thereof funded externally: 11)
- Graduate students: 8

#### 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. The integration of clinical and research data within hospitals and data sharing within large networks, e.g. in the context of the German Medical Informatics Initiative and the German Biobank Alliance, are a particular focus of our research activities. Prof. Dr. H.-U. Prokosch is as Chief Information

Officer also responsible for the strategic development of information processing at UK Erlangen.

### Process support through health information systems

One of the major challenges in the design, establishment, and management of health information systems (HIS) is the intersectoral interoperability which is important to optimize the cooperation of the various health service providers across institutional boundaries in outpatient and inpatient care in order to deliver the best patient care. For an additional reduction of patient risks, we integrate clinical decision support functionalities into HIS. Clinical information flow and communication functionalities should ultimately involve and benefit patients, e.g. by the application of medication plans or by the use of a personal electronic health record. In addition to grant funded projects, the Chair also pursues and supports several innovative pilot projects embedded in the SOARIAN® 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). 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. In a second project we have initiated a user centered design process for the development of a computer-based guideline to support intraoperative emergency situations. 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 cooperation with the Department of Anesthesiology, as well as further German anesthesiologists and the foundation German anesthesiology ("Stiftung Deutsche Anästhesiologie") we perform usability analysis of different levels of prototypes and mockups for a computerized emergency checklist. Further, we cooperate with the Department of Pediatrics and Adolescent Medicine in the stepwise development and usability analysis of a web-based medication information system to support drug therapy for children. 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 the MIRACUM consortium (Medical Informatics in Research and Care in University Medicine; compare own report), we evaluate and enhance the translational platform cBioPortal (originally developed at the Memorial Sloan Kettering Cancer Center, New York, USA), which aims at integrating and visualizing clinical findings and genomic analysis data. The final goal is to thus provide an optimized information presentation for enhanced IT supported therapy decisions in molecular tumor boards.

### IT-infrastructure applications for medical research

Today, medical research is often pursued within networked multi center structures, which require efficient and safe IT-infrastructures. 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, German Biobank Alliance) and international (BBMRI Common Service IT/ADOPT) linkage of biobanking. A further focus was laid on the single-source reuse of patient data for clinical and translational research. The Chair is member and active partner in many projects and working groups of the TMF (German technology and methods platform for networked medical research) and leads the GMDS working group "Reusing electronic patient records for clinical research". We lead the MIRACUM consortium, in which we currently design, develop, and implement an ecosystem of open source software tools (MIRACOLIX: e.g. ID-management, consent-management, federated authentification, several research data repositories, long term archiving for research data), which form the building blocks for the establishment of data integration centers at each of the university hospitals.

#### **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; compare own report) 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 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**

Hinderer M, Boeker M, Wagner SA, Binder H, Ückert F, Newe S, Hülsemann JL, Neumaier M, Schade-Brittinger C, Acker T, Prokosch HU, SedImayr B. The experience of physicians in pharmacogenomic clinical decision support within eight German university hospitals. Pharmacogenomics 2017, 18.,8: 773-785

Christoph J, Knell C, Bosserhoff A, Naschberger E, Stürzl M, Rübner M, Seuss H, Ruh M, Prokosch HU, Sedlmayr M. Usability and suitability of the Omics-integrating analysis platform tranSMART for translational research and education. Appl Clin Inform. 2017, 8,4: 1173-1183

Prokosch HU et al. MIRACUM: Medical Informatics in Research and Care in University Medicine. Methods Inf Med. 2018 Jul;57(S 01):e82-e91 Maier C, Lang H, Storf H, Vormstein P, Bieber R, Bernarding J, Herrmann T, Haverkamp C, Horki P, Laufer J, Berger F, Höning G, Fritsch HW, Schüttler J, Ganslandt T, Prokosch HU, Sedlmayr M. Towards implementation of OMOP in a German university hospital consortium. Appl Clin Inform. 2018 Jan;9(1):54-61

Kraus S, Toddenroth D, Prokosch HU, Bürkle T. Using Arden Syntax Medical Logic Modules to reduce overutilization of laboratory tests for detection of bacterial infections – success or failure? Artif Intell Med. 2018 Nov;92:43-50

SedImayr B, Schöffler J, Prokosch HU, SedImayr M. Usercentered design of a mobile medication management. Informatics for health and social care. Inform Health Soc Care. 2018 Mar 5:1-12

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

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

### Institute of Medical Informatics, Biometry, and Epidemiology

### Chair of Digital Health

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#### **Research focus**

- Wearable health systems
- Context recognition
- Health marker estimation
- System modeling

#### **Structure of the Chair**

Professorship: 1 Personnel: 11

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

#### Research

The Chair of Digital Health is pursuing top-level research on foundational and applied topics of digital health and sensor-based context recognition. In the eHealth area, members of the Chair investigate data integration techniques and machine learning algorithms for patient behavior and exposure analysis. Context awareness and knowledge extraction from clinical, wearable, and ambient/in-home data are investigated to create and estimate health markers. The algorithm bandwidth stretches from time series analysis to dynamically adaptive pattern modeling. On mobile health (mHealth) and ubiquitous health (uHealth), members of the Chair are investigating novel design methods and procedures to implement wearable and implantable sensor and actuator systems, employing additive manufacturing methods, e.g. 3D printing. Through collaborative projects with various medical and business partners, the Chair validates novel technology and algorithms.

#### Wearable health systems

Mobile and wearable systems can provide access to key health-related patient behavior and exposure information, thus critically supporting medical professionals and patients in diagnosis and treatment. While smartphones could assess individual lifestyle and health information, for many medical applications the data is not sufficiently detailed or accurate. The Chair investigates the potential of new wearable and implantable systems for providing specific and reliable health, behavior, and exposure data. Our current investigations focus on 3D-printed regular-look smart eyeglasses with frame-integrated electronics and sensors to continuously acquire physiological data (e.g. heart beat via in-frame optical sensors), behavior (e.g. meal timing via in-frame electromyographic measurement), and exposure (e.g. light exposure via optical sensors). Studies showed that smart eyeglasses can provide unprecedented insight into everyday behavior (e.g. studied for dietary monitoring), while remaining inconspicuous and comfortable to wear. Research on personalized fitting optimization to achieve optimal sensor performance has been conducted.



Smart eyeglasses frames with embedded sensors for monitoring physiology, behavior, and environmental exposure

#### **Context recognition**

The Chair develops and evaluates new algorithms to analyze large, multi-modal continuous time series from mobile and wearable sensor systems. Research activities are including the spotting of rare known patterns and the mining of relationship/rules among events in unknown data patterns. For example, we could demonstrate for the first time that spotting arm gestures patterns corresponding to fluid intake is feasible in natural, free-living conditions using a wrist-worn motion monitoring device, e.g. a smart watch. The pattern spotting method is based on a novel network of hidden Markov models (HMM), where at least one HMM describes the target pattern and a multitude of further HMMs capture main concepts in the arbitrary data to be rejected. The explicit modeling of reject patterns is feasible based on the large amount of free-living data available. In addition, the HMM network can include non-target models for specific, known patterns that should be excluded from the retrieval and thus support search queries with exclude patterns.

Another arm of the Chair's research focuses on dynamically optimizing the system resources, e.g. energy, required. We investigated dynamic control strategies that adjust the system's duty cycle depending on expected information need. To verify energy savings, complete system simulations, including sensors, processing electronics, algorithms, and the dynamic control, were performed revealing savings of 30-50% at constant retrieval performance.

The Chair is furthermore actively involved in the EU-funded Marie Curie ITN project ACROSS-ING, coordinating training activities, and contributing sensor technology and context awareness algorithms.

#### Health marker estimation

Health markers (or digital biomarkers) often combine different algorithms to estimate parameters in unsupervised, free-living conditions that can support decision making by patients and/or medical professionals. The Chair is developing methods for estimating new health markers and procedures to derive known ones from using mobile and/or wearable data sources, all in collaboration with medical partners. By utilizing body-worn motion sensor data, we developed a novel marker to analyze the discrepancy and convergence prognosis between affected and less-affected body sides in hemiparesis patients, called Convergence Point (CP). CPs were investigated for walking motion parameters, e.g. stride duration, in out-patient study recordings. In addition, a range-of-motion marker was developed in collaboration with therapists, based on quantifying upper extremity postures assumed over measurement days, called Cubic Quantizer. Investigations on sleep timing estimation based on smartphone use data were performed and a novel fusion approach to combine data and expert models was introduced. The expert model is implemented based on the twoprocess circadian and homeostasis model introduced by S. Daan in 1984. We could demonstrate that our data-expert model approach outperforms data-based machine learning, in particular for artifact-rich and missing sample data, as well as under varying sleep schedules.

#### System modeling

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

#### Teaching

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

Bachelor's and Master's theses topics as well as PhD theses are offered, crossing disciplines of engineering and computer science with medicine.

#### **Selected publications**

Amft O. How Wearable Computing Is Shaping Digital Health. IEEE Pervasive Computing. 2018, 17(1), 92–98

Derungs A, Schuster-Amft C, Amft O. Longitudinal Walking Analysis in Hemiparetic Patients Using Wearable Motion Sensors: Is There Convergence Between Body Sides? Front Bioeng Biotechnol. 2018, 6: 57

Schiboni G, Amft O. (2018a). Saving energy on wristmounted inertial sensors by motion-adaptive duty-cycling in free-living. In Proceedings of the 2018 IEEE 15th International Conference on Wearable and Implantable Body Sensor Networks (BSN '18) (pp. 197–200). Las Vegas, NV, USA: IEEE

Schiboni G, Amft O. (2018b). Sparse Natural Gesture Spotting in Free Living to Monitor Drinking with Wrist-worn Inertial Sensors. In Proceedings of the 2018 ACM International Symposium on Wearable Computers (pp. 140–147). New York, NY, USA: ACM

Wahl F, Amft O. Data and Expert Models for Sleep Timing and Chronotype Estimation from Smartphone Context Data and Simulations. Proc. ACM Interact. Mob. Wearable Ubiquitous Technol. 2018, 2(3), 139:1–139:28

Zhang R, Amft O. Monitoring chewing and eating in freeliving using smart eyeglasses. IEEE J Biomed Health Inform. 2018, 22(1), 23–32

#### International cooperations

Prof. GZ Yang, Imperial College London: UK
Prof. D. Kotz, Dartmouth College, Hannover, NH: USA
Prof. K. de Graf, Wageningen University: The Netherlands
Prof. M.A. Spruit, Maastricht University: The Netherlands
Prof. L. Chen, De Montfort University, Leicester: UK
Prof. Dr. I. Korhonen, TU Tampere: Finland

### **Institute of Medical Physics**

### **Chair of Medical Physics**

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#### Director

Prof. Dr. rer. nat. Armin Nagel (acting director)

#### Contact

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#### **Research focus**

- Effects of whole-body electromyostimulation (WB-EMS) on unspecified chronic back pain in patients with unspecified chronic dorsal pain
- 3D imaging and image processing for musculoskeletal applications
- High-resolution computed tomography of the breast
- Functional and metabolic MR imaging

#### **Structure of the Institute**

Professorships: 2

Personnel: 25

- Scientists: 12 (there of funded externally: 9)
- Graduate students: 6

#### 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 are on dose reduction and the development of a special CT scanner for early detection of breast cancer. In the field of magnetic resonance imaging (MRI), new functional and metabolic imaging techniques are being developed in close collaboration with the Institute of Radiology. With new measurement methods and ultra-high field MRI (7 Tesla), the concentrations of the two most common ions (sodium and potassium) in tissue can now be determined for the first time. The main topic of the medical imaging processing group are musculoskeletal problems in the area of osteoporosis, inflammatory diseases, osteoarthrosis, 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) on unspecified chronic back pain in patients with unspecified chronic dorsal pain

PI: Prof. Dr. W. Kemmler

In this clinical study, conducted in parallel group design, a total of 155 men and women suffering of unspecified chronic back pain were assigned by computer generated block randomization (1-1-1) to three different groups: (a) whole-body electromyostimulation (WB-EMS), (b) whole body vibration (WBV) and (c) conventional training to improve back strength. The WB-EMS was carried out 1x20 min/week (85 Hz, 350 µs, intermittently 4s-4s), the WBV took place 2x15min/week and the strength training 1x45min/week. After 12 weeks, at the end of the study, all groups showed a similar high and significant improvement of the mean pain intensity, the back strength and the ADLs (Activities of Daily Living). This study was realized in cooperation with the company miha-bodytec (Gersthofen, Germany) and the German Sport University Cologne. The study results showed that all three training options have a significant and clinically high impact on chronic unspecified back pain. Therefore, patients may choose the kind of therapy according to their preferences (time efficiency, high degree of mentoring etc.).



Whole-body electromyostimulation (WB-EMS)



Whole body vibration (WBV)

to the spine column.

#### **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 combination of imaging of the bone and imaging of the muscle showed interestingly that the fat distribution in the thigh, especially in the thigh musculature, is besides bone density an important risk factor for hip fractures. In the meantime, this research has been extended

At the IMP, validated MRI as well as CT based evaluation methods are available to determine the muscle-fat distribution for the femur, the paraspinal musculature, and the hand. These tools are used to some extent in exercise studies of the OFZ (Center of Osteoporosis Research). Another research topic is the imaging of the subchondral bone for the diagnosis and progression of the osteoarthritis of the knee 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. The spatially resolved analysis of the subchondral bone density in vivo indicated the protective character of the meniscus. Further results show that the subchondral bone structure can be determined by an analysis of the texture. This is of high relevance because in vivo the single trabeculae cannot be segmented exactly due to the limited spatial resolution. An according analysis module was implemented in the analysis toolkit MIAF (Medical Image Analysis Framework) which has been developed at the IMP. This tool is now used, for the first time, for the evaluation of an international multi-center clinical study to determine the subchondral bone structure and

density of the tibial plateau and the femoral condyle in patients with osteoarthrosis.



CT image of the thigh

Top: Elderly subject age 62; bottom: Younger healthy female age 44 for comparison; Left: Segmented fascia shown as yellow contour; Center: Subcutaneous adipose tissue (yellow), muscle (purple), femoral bone (green), perimuscular adipose tissue (uncolored); Right: Muscle tissue

### High-resolution computed tomography of the breast

PI: Prof. Dr. W.A. Kalender, PhD

Since 2008, the early detection of breast cancer using CT has been a main topic. Very good results have been achieved in different respects. Especially the feasibility of the proposed concepts and the target performance parameters were verified.

In autumn 2018, the scanner received the CE label and clinical trials are currently performed at the University Hospital Zurich (USZ). Funding: EU, BMBF, DFG

#### Functional and metabolic MR imaging PI: Prof. Dr. A.M. Nagel

New image acquisition and processing techniques for MRI are being developed. The focus is on ultrahigh field (UHF) MRI (7 Tesla) and in particular X-nuclei MRI. "X" stands for any atomic nucleus with nuclear spin, except for 1H. In this area, the distribution of tissue sodium and potassium concentrations could be determined for the first time in patients. X-nuclei MRI particularly benefits from UHF MRI. UK Erlangen is one of the few sites where a clinically approved UHF 7 Tesla MRI system is installed. The increased magnetic field strength compared to conventional systems allows for a significantly improved signal-to-noise ratio (SNR), so that image resolutions of a few hundred micrometers can be achieved. In close cooperation with Siemens Healthineers, a time-of-flight angiography sequence was developed that enables highresolution (0.3 mm isotropic) resolutions of blood vessels in clinically acceptable measuring

times (about 5 minutes) without administration of contrast agents. Similarly, new functional techniques, such as Chemical Exchange Saturation Transfer (CEST) MRI, particularly benefit from the increased SNR and higher spectral resolution. On the other hand, there are also some challenges with UHF MRI, which require the development of new data acquisition techniques. For example, a parallel transmission technology (pTx) could be implemented for CEST-MRT, which enables a significant improvement for quantitative CEST-MRI measurements. With the CEST-MRI, conclusions can be drawn about metabolite concentrations and pH levels.

#### Teaching

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

#### Selected publications

Engelke K. Quantitative Computed Tomography-Current Status and New Developments. J Clin Densitom. 2017 Jul – Sep;20(3):309-321

Kalender WA, Kolditz D, Steiding C, Ruth V, Luck F, Rossler AC, Wenkel E. Technical feasibility proof for high-resolution low-dose photon-counting CT of the breast. Eur Radiol 2017; 27(3): 1081-1086

Kemmler W, von Stengel S. Bone: High-intensity exercise to prevent fractures - risk or gain? Nat Rev Endocrinol 2018, 14:6-8

Kemmler W, Weissenfels A, Willert S, Shojaa M, von Stengel S, Filipovic A, Kleinöder H, Berger J, Fröhlich M. Efficacy and safety of low frequency Whole-Body Electromyostimulation (WB-EMS) to improve health-related outcomes in non-athletic adults. A systematic review. Frontiers of Physiology. 2018, May 23;9:573

Engelke K, Museyko O, Wang L, Laredo JD. Quantitative analysis of skeletal muscle by computed tomography imaging-State of the art. J Orthop Translat. 2018 Oct 28;15:91-103

Gast LV, Gerhalter T, Hensel B, Uder M, Nagel AM. Double quantum filtered 23Na MRI with magic angle excitation of human skeletal muscle in the presence of B0 and B1 inhomogeneities. NMR Biomed 2018; 31(12): e4010

#### International cooperations

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

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

Prof. X. Cheng, Department of Radiology, Bejing Jishuitan Hospital, Peking: China

Dr. A. Ghasem Zadeh, Department of Medicine, University of Melbourne, Melbourne: Australia

Prof. Dr. L. Bragazoni, Department for Life Quality Studies, University of Bologna, Bologna: Italy

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

## Institute of Neuropathology

### Chair of Neuropathology

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#### **Research focus**

- Neuropathological classification of focal epilepsies in humans
- Epigenetic mechanisms of epileptogenesis
- Molecular myopathology

#### **Structure of the Institute**

Professorships: 2

Personnel: 17

- Doctors (of Medicine): 3
- Scientists: 5 (thereof funded externally: 4)
- Graduate students: 2

#### **Clinical focus areas**

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

#### Research

The Institute of Neuropathology scientifically addresses diseases of the central nervous system and the skeletal musculature. Our internationally highly visible research expertise is in the area of human epilepsy and neuro-muscular disorders.

Our Institute welcomes visiting scientists to train them in studying human tissue samples for research purpose, but also for clinical diagnostics, e.g. from Australia (2018), Brazil (2017, 2018), Mexico (2018), and the Netherlands (2018).

### Neuropathological classification of focal epilepsies in humans

PI: Prof. Dr. I. Blümcke

This research project is focused on drug-resistant focal epilepsies in humans to decipher pathomechanisms and clinically define brain lesions associated with chronic seizures, e.g. hippocampal sclerosis, glio-neuronal tumors, and focal cortical dysplasia. We perform systematic analysis in surgically resected human brain specimens in correlation with clinical histories and postsurgical follow-up data, and our work contributed in establishing new international standards for clinico-pathological diagnosis of focal cortical dysplasia (ILAE classification 2011) and hippocampal sclerosis (ILAE classification 2013). Extensive collaboration with our clinical and neuropathology colleagues from Germany and many other European countries were helpful to establish the European Epilepsy Brain Bank, a reference and consultation center for neurosurgical epilepsy tissue specimen. The collection of more than 10.000 specimen and collaboration with 35 European centers will help us to target the integration of genetics and histopathology for a better understanding of etiology and pathogenesis of epilepsy-associated brain lesions and also a better disease classification in the near future (see the following research focus).

We are also in charge to develop a digital microscopy platform for the European Reference Network "EpiCare" (WP6), which will be based on whole slide imaging technology for microscopic review and semi-automated analysis with machine learning algorhythms. Funding: EU

### Epigenetic mechanisms of epileptogenesis

#### PI: Dr. K. Kobow

Our work specifically addresses methylation profiles and the epigenetic signaling machinery, i.e. histone code modifications, DNA methylation, or miRNA, in relation to epileptic neuronal activity using human surgical specimens and an experimental cell culture model. We also seek for new therapeutic strategies addressing the epigenetic signaling machinery, such as ketogenic diet. The integration of our data with histomorphological studies obtained from the European Epilepsy Brain Bank and the ERN "Epi-Care" (see above) will help to develop new biomarker for disease mechanisms and successful new therapies.

Funding: EU

#### Molecular myopathology

PI: Prof. Dr. R. Schröder

The central research topic of this group is the pathogenesis of myofibrillar myopathies, which are morphologically characterized by the presence of pathological protein aggregation in cross-striated muscle cells. This group of often heritable myopathies and cardiomyopathies is clinically marked by a progressive course and premature death. To date, no specific treatment is available for these disorders. The main focus of our group is the generation and characterization of transgenic mouse and cell models for desmin-, VCP-, and filamin C-related myopathies and cardiomyopathies. The clinical, morphological, biochemical, and molecular analysis of these models provides deeper insights into the molecular "sequence" that leads to pathological protein aggregation and progressive muscle damage in these disorders. This work is the basis for the evaluation of novel targeted treatment strategies.

Funding: DFG, Deutsche Gesellschaft für Muskelkranke e.V.



Transfection of desmin into fibroblasts

The picture shows a 3T3 mouse fibroblast cell line transiently transfected with a cardiomyopathy causing human desmin mutant (desmin-R406W) 18 hours after transfection. The cell is stained with vimentin-specific (green) and desmin-specific (red) antibodies. Vimentin is building a filament network whereas desmin-R406W is only present as small dot-like aggregates.

#### Teaching

The Institute of Neuropathology offers lectures and teaching courses in histopathology for students in Medicine, Dentistry and Molecular Medicine. Comprehensive lectures (clinicopathology conferences) are organized together with the Departments of Neurology and Neurosurgery.

In addition, we annually organize the International Summer School for Neuropathology and Epilepsy Surgery. The 6<sup>th</sup> Summer School took place from the 27 - 30 April 2017 at the Cleveland Clinic (USA), the 7<sup>th</sup> Summer School from 22 – 25 July 2017 in Campinas (Brazil), the 8<sup>th</sup> Summer School from 26 – 29 July 2018 in Erlangen and the 9<sup>th</sup> Summer School from 17 – 20 September 2018 in Beijing (China). In total, we have trained more than 300 participants from over 40 countries in our summer schools on the subject of epilepsy-associated brain lesions in hands-on workshops at the microscope and through innovative digital pathology platforms.

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

#### **Selected publications**

Blümcke I et al. Histopathological findings in brain tissue obtained from epilepsy surgery. New England Journal of Medicine 2017 Oct 26;377(17):1648-1656

Capper D et al. DNA methylation-based classification of central nervous system tumours. Nature. 2018 Mar 22;555(7697):469-474

D'Gama AM, Woodworth MB, Hossain AA, Bizzotto S, Hatem NE, LaCoursiere CM, Najm I, Ying Z, Yang E, Barkovich AJ, Kwiatkowski DJ, Vinters HV, Madsen JR, Mathern GW, Blümcke I, Poduri A, Walsh CA. Somatic Mutations Activating the mTOR Pathway in Dorsal Telencephalic Progenitors Cause a Continuum of Cortical Dysplasias. Cell Rep. 2017 Dec 26;21(13):3754-3766

Kiese K, Jablonski J, Hackenbracht J, Wrosch JK, Groemer TW, Kornhuber J, Blümcke I, Kobow K. Epigenetic control of epilepsy target genes contributes to a cellular memory of epileptogenesis in cultured rat hippocampal neurons. Acta Neuropathol Commun. 2017 Oct 31;5(1):79

Di Liberto G et al. Neurons under T Cell Attack Coordinate Phagocyte-Mediated Synaptic Stripping. Cell. 2018 Oct 4;175(2):458-471.e19

Winter L, Unger A, Berwanger C, Spörrer M, Türk M, Chevessier F, Strucksberg KH, Schlötzer-Schrehardt U, Wittig I, Goldmann WH, Marcus K, Linke WA, Clemen CS, Schröder R. Imbalances in protein homeostasis caused by mutant desmin. Neuropathology Appl Neurobiol 2018 Sep 4

#### International cooperations

International League against Epilepsy

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

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

Dra. I. Wang and L. Jehi; Epilepsy Center, Cleveland Clinic Foundation, Cleveland, Ohio: USA

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

### **Institute of Pathology**

### Chair of General Pathology and Pathological Anatomy

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#### **Research focus**

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

#### **Structure of the Chair**

Professorships: 6

Personnel: 80

- Doctors (of Medicine): 14
- Scientists: 4 (thereof funded externally: 4)
- Graduate students: 35

#### **Clinical focus areas**

- Histopathology with specific expertise in
- Breast pathology
- Gynecological pathology
- Urogenital pathology
- Head and neck pathology
- Soft tissue pathologyMolecular pathology
- · Molecular patriology

#### Research

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

#### **Diagnostic molecular pathology**

PI: Prof. Dr. F. Haller, Dr. E.A. Moskalev, Dr. L. Tögel, Prof. Dr. R. Stöhr

The aim of the group is the development and functional validation of novel genetic and epigenetic markers with diagnostic, prognostic, or predictive impact in solid tumors. The successful establishment of next-generation sequencing technology enabled the group to identify novel key molecular events in different salivary gland tumors and soft tissue neoplasms. Whole genome sequencing in collaboration with the German Cancer Research Center identified recurrent translocations in acinic cell carcinomas of the salivary glands. Another focus of the group is the massive parallel sequencing of multi-gene panels in lung cancer, soft tissue tumors, cancer of the urogenital tract, and head and neck cancer to correlate the presence of mutations among distinct genetic pathways with specific histomorphological subtypes, clinical behavior, and therapy response. The functional characterization of novel genetic or epigenetic aberrations in cell culture systems is another aim to develop the basis for future therapeutical options. Since 2016 the 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. Since 2018, patient samples presented in the molecular tumor board are analyzed in collaboration with the routine diagnostic molecular pathology group. Also since 2018, the Institute participates in the national network genomic medicine (nNGM) with a focus on providing state-of-the-art molecular diagnostic work-up of lung cancer samples.

### 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. For translation we are equipped with diverse tissue

mircroarrays of CRC patients and immunostainings can be already digitally analyzed. A broad spectrum of 2D and 3D models, patient-derived 3D organoids, co-culture models of tumor cells and immune cells, and CRISPR-ko cell lines is established. The chorioallantoic membrane assay is used as an alternative *in vivo* test model. Novel experimental conditional ko mice were generated. Since many years we have been studying successfully the anti-cancer effects of novel plant-derived compounds for colorectal tumor cells especially in combination treatment with clinically used drugs.

#### Breast and gynecological tumors

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

#### Tumors of the head and neck region

PI: Prof. Dr. A. Agaimy, Prof. Dr. F. Haller We investigate the molecular changes in tumors of the head and neck region in cooperation with the Departments of Otorhinolaryngology – Head and Neck Surgery and of Oral and Cranio-Maxillofacial Surgery. This research project has two objectives: One is to compile a molecularpathological 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, Prof. Dr. Dr. R. Stöhr, PD Dr. Dr. C. Stöhr, PD Dr. S. Bertz, Dr. M. Eckstein, I. Polifka, V. Weyerer, Dr. E. Erlmeier The group investigates the basic molecular principles of the development, progression, and sub-

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

Selected main topics of the group are:

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

 Identification of molecular risk factors and prognostic relevant alterations of squamous cell carcinoma of the penis

### Pathology of immune and inflammatory reactions

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

This group focusses on the characterization of immunological interactions of different tumors (in particular: colon carcinoma, Barrett's carcinoma of the esophagus, muscle invasive urothelial carcinoma, squamous cell carcinoma of the head and neck) with their immunological microenvironment. There are numerous national and international cooperations.

In particular, the characterization of antitumorally active immune cell populations and their immunosuppressive antagonists are the focus. Based on differentially expressed immune cell populations and their activity status, which is largely controlled by immune-checkpoints, different immunophenotypes should be identified which potentially harbor both, prognostic and a predictive significance (for example with regard to a response to chemotherapies and/or immunotherapies). Another key topic is the establishment and harmonization of predictive diagnostic tools to predict immunotherapy response such as immuno-checkpoint protein expression (especially PD-L1) and other next generation immuno-oncological biomarkers (e.g. digital pathological assessment of cytotoxic immuncell-infiltrates). In connection with this, the group carries out biomarker programs in different retrospective and prospective clinical trials (e.g. CheckRad-study in the setting of HNSCC).

#### Teaching

The Institute of Pathology is involved in the compulsory and elective curricular teaching of Medicine and Dentistry and of the degree programs Molecular Medicine and Medical Process Management. Particularly noteworthy is the interdisciplinary teaching in the context of 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**

Sikic D, Keck B, Wach S, Taubert H, Wullich B, Goebell PJ, Kahlmeyer A, Olbert P, Isfort P, Nimphius W, Hartmann A, Giedl J; Bridge Consortium. Immunohistochemical subtyping using CK20 and CK5 can identify urothelial carcinomas of the upper urinary tract with a poor prognosis. PLoS One. 2017 Jun 20;12(6):e0179602 Weyerer V et al. Immunohistochemical and molecular characterizations in urothelial carcinoma of bladder in patients less than 45 years. | Cancer. 2017 Feb 5;8(3):323-331

Bure I, Geer S, Knopf J, Roas M, Henze S, Ströbel P, Agaimy A, Wiemann S, Hoheisel JD, Hartmann A, Haller F, Moskalev EA. Long noncoding RNA HOTAIR is upregulated in an aggressive subgroup of gastrointestinal stromal tumors (GIST) and mediates the establishment of gene-specific DNA methylation patterns. Genes Chromosomes Cancer. 2018 Nov;57(11):584-597

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Maiuthed A, Ninsontia C, Erlenbach-Wuensch K, Ndreshkjana B, Muenzner JK, Caliskan A, Husayn AP, Chaotham C, Hartmann A, Vial Roehe A, Mahadevan V, Chanvorachote P, Schneider-Stock R. Cytoplasmic p21 Mediates 5-Fluorouracil Resistance by Inhibiting Pro-Apoptotic Chk2. Cancers (Basel). 2018 Oct 9;10(10). pii: E373

#### International cooperations

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

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

Prof. I. Nagtegaal, Radboud University Medical Centre Nijmegen, Nijmegen: The Netherlands

Dr. S. Castellví-Bel, IDIBAPS / CIBERehd / Hospital Clínic Centre Esther Koplowitz (CEK), Barcelona: 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 therapeutic target in kidney diseases
- Pathomechanisms and modulation of impaired angiogenesis and angioadaption in chronic renal failure
- The role of DPP4 in crescentic glomerulonephritis
- Chronic kidney disease of unknown etiology (CKDu)
- SriKid H<sub>2</sub>O Investigation of correlations between localized chronic kidney diseases and water quality in Sri Lanka
- Pathology work-up of GvL and GvHD in mice and man
- Mechanisms of cardiac injury and regeneration
- Terminal differentiation of heart muscle cells
- Role of the receptor GPR126 in heart and kidney development
- Cardiac tissue engineering

#### **Structure of the Division**

Professorships: 2 Personnel: 32

- Doctors (of Medicine): 5
- Scientists: 3 (thereof funded externally: 0)
- Graduate students: 19

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

Funding: IZKF

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

PI: Prof. 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 reenter into the cell cycle despite its terminal differentiation, but are unable to divide and die. In this project, we try to inhibit cell cycle progression in podocytes to prevent loss of these cells and progression of kidney disease.

Funding: Emerging Fields Initiative: CYDER (compare own report)

#### Pathomechanisms and modulation of impaired angiogenesis and angioadaption 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 characteristical cardiovascular structural alterations, like left ventricular hypertrophy with reduced myocardial capillary density, increased intercapillary distance, and reduced myocardial ischemia tolerance. Our own data as well as data from the literature indicate that impaired angiogenesis in particular in response to hypertrophy or ischemia plays an important pathophysiological role. Using a well-established animal model of CKD (subtotally nephrectomised rat, SNX), we will investigate mechanisms of CKD-induced impaired angiogenesis. Funding: DFG

## The role of DPP4 in crescentic glomerulonephritis

PI: Prof. Dr. C. Daniel

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

Funding: Boehringer Ingelheim GmbH

#### SriKid H<sub>2</sub>O – Investigation of correlations between localized chronic kidney diseases and water quality in Sri Lanka Pl: Prof. Dr. K. Amann

Together with nephrologists (Dr. N. Nanayakkara, Prof. Dr. K.-U. Eckardt), hydrogeologists (Prof. J. Barth, Prof. R. Chandrajith) and toxicologists (Prof. C. Zwiener) from Germany and Sri Lanka, we investigate in this interdisciplinary project causes and pathogenesis of chronic kidney disease of unknown etiology (CKDu) that is restricted to dry areas in tropical regions. Beside histopathological characterization of renal biopsies using immunohistology and electron microscopy, comprehensive analysis of drinking water will be done. The aim of this project is to uncover the causes and pathogenesis of this lifethreatening disease.

Funding: BMBF

#### Pathology work-up of GvL and GvHD in mice and man

PI: Prof. Dr. M. Büttner-Herold

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

### 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. Recently, we could demonstrate that the nuclear receptor PPAR delta is required for zebrafish heart regeneration and that its genetic as well as pharmacologic activation improves cardiac function in mice after an experimental myocardial infarct.

Funding: EFI-CYDER

### 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 proliferation 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. In addition, based on live cell imaging we have revealed the cellular mechanism that underlies the loss of proliferation resulting in binucleation and identified new marker proteins, which will help in the future to evaluate the efficiency of regenerative cardiac therapies.

Funding: EFI-CYDER, ELAN Fonds, DFG

### Role of the receptor GPR126 in heart and kidney 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 NTFGpr126 to an unknown receptor on heart muscle cells. In addition, the analysis of several Gpr126 zebrafish mutants indicates that Gpr126 plays also a role during kidney development.

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) and Prof. T. Scheibel (Bayreuth Materialzentrum, University of Bayreuth), we currently focus on the analysis of electroconductive materials and recombinantly produced silk. Our work benefits strongly from our membership in the newly funded SFB-TRR 225, which explores the fundamentals of biofabrication and its systematic exploitation with the aim and vision to generate functional human tissue models. Funding: DFG

#### 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**

Roeder SS, Barnes TJ, Lee JS, Kato I, Eng DG, Kaverina NV, Sunseri MW, Daniel C, Amann K, Pippin JW, Shankland SJ. Activated ERK1/2 increases CD44 in glomerular parietal epithelial cells leading to matrix expansion. Kidney Int. 2017 Apr;91(4):896-913

Magadum A, Ding Y, He L, Kim T, Vasudevarao MD, Long Q, Yang K, Wickramasinghe N, Renikunta HV, Dubois N, Weidinger G, Yang Q, Engel FB. Live cell screening platform identifies PPAR? as a regulator of cardiomyocyte proliferation and cardiac repair. Cell Res. 2017; 27(8):1002-1019

Roshanbinfar K, Vogt L, Greber B, Diecke S, Boccaccini AR, Scheibel T, Engel FB. Electroconductive Biohybrid Hydrogel for Enhanced Maturation and Beating Properties of Engineered Cardiac Tissues. Adv Funct Mater. 2018; 28(42): 1803951 Leone M, Musa G, Engel FB. Cardiomyocyte binucleation is associated with aberrant mitotic microtubule distribution, mislocalization of RhoA and IQGAP3, as well as defective actomyosin ring anchorage and cleavage furrow ingression. Cardiovasc Res. 2018; 114(8):1115-1131

Pfister F, Amann K, Daniel C, Klewer M, Buttner A, Buttner-Herold M. Characteristic morphological changes in anti-VEGF therapy induced glomerular microangiopathy. Histopathology. 2018 Dec;73(6):990-1001

Prochnicki A, Amann K, Wegner M, Sock E, Pfister E, Shankland S, Pippin J, Daniel C. Characterization of Glomerular Sox9(+) Cells in Anti-Glomerular Basement Membrane Nephritis in the Rat. Am J Pathol. 2018 Nov;188(11):2529-2541

#### International cooperations

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

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

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

Prof. 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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#### **Research focus**

- 275 years Faculty of Medicine at FAU
- Constitutional medicine and medical theory, 1910–1930
- 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"
- Galen Compendium and catalogue of Galenic writings
- Receptions of ancient psychopathology
- The German Society for Gynecology and Obstetrics under nazism
- Health and society in early modern Europe
- Polish-German cooperation in the history of medicine
- History of hospitals
- Medical history in objects objects in the web
- The world-wide correspondence of Johann Lukas Schönlein

#### **Structure of the Chair**

Professorship: 1 Personnel: 8

- Doctor (of Medicine): 1
- Scientists: 7 (thereof funded externally: 5)
- Graduate students: 8

#### **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 region up to the early 21<sup>st</sup> century. This includes medicine in National Socialism which is studied both from a prosopographical and thematic perspective. Constitutional medicine before, during, and after World War I and the emergence of statistical methods in medical research is studied in a habilitation project. Other research is concerned with ancient medicine, medicine in pre-modern times and medical historian museology.

#### 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

The project studied 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 rested on the 20<sup>th</sup> and beginning 21<sup>st</sup> centuries. Contemporary history was approached by comprehensive use of oral history during which faculty members underwent structured interviews.



Cover of the Festschrift, published in 2018

#### **Constitutional medicine and medical theory, 1910–1930** Pl: Dr. N. Metzger

This habilitation project studies the modern constitutional medicine emerging since 1911 in German-speaking countries and dominating medical research of various disciplines during the 1920s. This interdisciplinary research program broached the issue of individual factors in emergence and development of diseases in patients' bodies, thus promoting the wider introduction of medical statistics into medical research. Additionally, constitutional medicine furthered discussion on medical theory with medical professionals, especially regarding the definition of the normal and the pathological and during the 1920s - the limits of metrical methodologies.

#### 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 (2013–2019)

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 The project examined a certain amount of cases of forced euthanasia ("T 4-Aktion") and systematic starvation to death ("B-Kost") in Erlangen Heil- und Pflegeanstalt (Erlangen mental hospital) during the Nazi regime from multiple perspectives, both within its clinical context and the town of Erlangen. Until now unstudied source material provided the basis for reconstructing both, the (criminal) acts of individuals or institutions and the life stories of their victims.

#### Galen – Compendium and catalogue of Galenic writings

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

The Greek physician Galenus of Pergamum (129–approximately 210 AD) figures as the most influential medical author of the Roman imperial period. This research project aims at a comprehensive depiction of Galenism both, in its time of emergence and its impact on medicine in the historical 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 Paulos 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.

### The German Society for Gynecology and Obstetrics under Nazism

PI: Prof. Dr. F. Dross, PD Dr. W. Frobenius, A. Thum (2016–2019)

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 also in lobbying gynecological interests. After publishing the findings in one monograph (2016) and a series of articles intended for the professional gynecologist reader (2017), the project is currently focusing on a commemorating book acting as a memorial to persecuted, exiled, and murdered members of the society during the Nazi years.

### Health and society in early modern Europe

#### PI: Prof. 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 transindividual value, arbitrated between medical expertise, professional practice by diverse health care professions, municipal administration and personal plight. The project focuses on the segregation of leprose persons as practiced by early modern urban societies.

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

#### PI: Prof. Dr. F. Dross

Since 2005, the imately 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: Prof. 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. The PI is president of the German Society for the History of Hospitals and editor of its annual research journal "Historia Hospitalium".

#### Medical history in objects – Objects in the web

PI: Prof. Dr. F. Dross

Funding: BMBF (2017–2020)

Funded by the BMBF, the academic collections of FAU and the Germanische Nationalmuseum Nuremberg joined to develop a shared strategy for making the objects in their collections digitally accessible. The Medical Collection Erlangen preserves instruments and devices no longer needed in clinical practice, medical research, and education and is one of six university collections

### The world-wide correspondence of Johann Lukas Schönlein

PI: Prof. Dr. F. Dross, Prof. Dr. R. Wittern-Sterzel, Prof. Dr. B. Manger

In late summer 2017, a large number of letters to Johann Lukas Schönlein (1793—1864) in private Erlangen ownership was discovered. Originally from Bamberg, Schönlein held chairs at the medical faculties of Würzburg, Zurich, and Berlin, being the major historical figure in the transitional phase between a natural philosophy à la Schelling and science-oriented modern medicine. The approximately 1,200 formerly unknown letters are currently undergoing inventory in preparation to making them accessible to scholarship. In late 2018, the corpus was introduced into scholarly discourse by holding a conference and presented to the wider public via an exhibition.

#### Teaching

Curricular teaching by the Chair for History of Medicine includes both, compulsatory and elective courses for students of Medicine, Dentistry and Molecular Medicine. Each semester and in collaboration with the Chair of Anatomy and Cell Biology, 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 MD theses.

#### Selected publications

Frobenius W, Thum A, Dross F. Die Deutsche Gesellschaft für Gynäkologie im Nationalsozialismus. Teile 1-4. in: Der Frauenarzt 58 (2017), Nr. 2-4

Metzger N. Es sind noch große Forschungserträge zu erhoffen. Entwicklungen der Konstitutionslehre in den 1920er Jahren. in: Medizinhistorisches Journal 52 (2017): 270-307

Dross F. Wallensteins Zipperlein. in: B. Emich, D. Niefanger, D. Sauerer, G. Seiderer (Hg.), Wallenstein: Mensch - Mythos – Memoria. Berlin: Duncker & Humblot 2018: 253-269

Leven KH. Ethics and Deontology. In: Pormann PE (Hg.): The Cambridge Companion to Hippocrates. Cambridge 2018: 152-179

Leven KH, Rauh P, Thum A, Ude-Koeller S. Die Medizinische Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg. Kontexte, Köpfe, Kontroversen (1743-2018). Wien, Köln, Weimar: Böhlau 2018

Metzger N. Not a Daimon, but a Severe Illness. Oribasius, Posidonius and Later Ancient perspectives on superhuman agents causing disease. in: Mental Illness in Ancient Medicine. From Celsus to Caelius Aurelianus. Singer P, Thumiger C (Hg.). Leiden: Brill 2018 (Studies in Ancient Medicine 50): 79-106

#### International cooperations

S. Hildebrandt, MD, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts: USA

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

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

Prof. Dr. P.E. Pormann, 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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#### **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 Professorship**

Professorship: 1

Personnel: 14

- Doctors (of Medicine): 3
- Scientists: 8 (thereof funded externally: 5)
- Graduate students: 24

#### **Special structural features**

The Professorship for Medical Ethics is responsible for 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 for the History of Medicine and Medical Ethics.

#### Research

The main areas of research are clinical ethics and ethics consultation, medicine and human rights, and global health ethics and philosophy of medicine. The field of clinical ethics deals with foundational ethical questions concerning the adequate care for patients, motivation of the acts of physicians during the daily routine, and conflict situations in hospital and other medical facilities. Central questions 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 "Opti-Dem" (on Dementia Care), runs the "Forum Medicine and Human Rights" and edits twelve book series.

#### **Clinical Ethics and Ethics Consultation**

PI: Prof. Dr. A. Frewer, PD Dr. L. Bergemann, Dr. C. Eibauer, Dr. C. Hack, Dr. D. Rottke 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, PD Dr. L. Bergemann, Dr. M. Mylius, PD 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, PD Dr. M. Schmidhuber, S. Klotz

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 decisions taken in clinical practice and to develop normative criteria based on human rights and medical ethics. Practical examples are studied intensively with issues of dialysis, transplantation, new conflicts arising from international patient mobility, "health literacy" education, contributions to "health-empowerment" of vulnerable groups and end-oflife-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. R. Erices, Dr. C. Herrler, PD Dr. A. Reis, PD 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. The seminars on "Ethical Communicative Competencies" (with role plays for students and simulated patients, some inter-professional) deserve to be mentioned particularly.

This broad offer on the complex ethical questions (modules: Breaking bad news, Speaking about death and dying, Intercultural communication, Acting at borders – Coping with dementia, Communicative Competencies for errors in medicine) is unique at medical faculties in Germany.

Prof. Dr. A. Frewer is Senior Advisory Consultant of the World Health Organization (WHO).

Bachelor's and Master's theses and medical or philosophical dissertations as well as "Habilita-tions"/PhD studies are supervised.

#### **Selected publications**

Frewer A, Bergemann L, Hack C, Ulrich HG. (Hrsg.) Die kosmopolitische Klinik. Globalisierung und kultursensible Medizin. Jahrbuch Ethik in der Klinik (JEK), Band 10. Würzburg, 2017

Klotz S, Bielefeldt H, Schmidhuber M, Frewer A. (Eds.) Healthcare as a Human Rights Issue. Normative Profile, Conflicts and Implementation. Bielefeld, 2017 Schmidhuber M, Bergemann L, Frewer A. (Eds.) Ethical Dimensions of International Dementia Plans. New Strategies for Human Rights. Global Health, Ethics and Human Rights, Vol. 3. Würzburg, 2017

Bergemann L, Frewer A. (Hrsg.) Vulnerabilität und Autonomie in der Medizin. Menschenrechte – Ethik – Empowerment. Bielefeld, 2018

Erices R, Frewer A, Gumz A. The role of the State Security Service (Stasi) in the context of international clinical trials conducted by western pharmaceutical companies in Eastern Germany (1961-1990). PLoS One. 2018 Apr 2;13(4):e0195017

Frewer A, Bergemann L, Hack C. (Hrsg.) Kliniken unter Geschwindigkeitsdruck versus "Slow Care"? Zur Ethik von Zeit und Achtsamkeit in der Medizin. In: Jahrbuch Ethik in der Klinik (JEK), Band 11. Würzburg, 2018: 9-18

#### International cooperations

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

PD Dr. A. Reis, Department of Global Health Ethics, World Health Organization, Geneva: Switzerland

Prof. U. Schmidt, PhD., 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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#### Contact

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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 EMTactivator 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**

Professorship: 1

- Personnel: 17
- Doctor (of Medicine): 1
- Scientists: 5
- (thereof funded externally: 3)
- Graduate students: 6

#### Special structural feature

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

#### Research

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

### Cellular plasticity as driving force of metastasis

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

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

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

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

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

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

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

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

#### Role of the EMT-activator ZEB1 in pancreas development und homeostasis PI: Dr. M. Stemmler

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

#### Role of the EMT-activator ZEB1 in

skeletal development and osteosarcoma PI: Dr. S. Brabletz, Dr. M. Ruh, Prof. Dr. T. Brabletz

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

#### 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, Medicine, and biology. Bachelor's and Master's theses are supervised.

#### **Selected publications**

Krebs AM, Mitschke J, Losada ML, Schmalhofer O, Boerries B, Busch H, Boettcher M, Mougiakakos D, Reichardt W, Bronsert P, Brunton VG, Winkler TH, Brabletz S, Stemmler MP, Brabletz T. The EMT activator ZEB1 is a key factor for cellular plasticity and promotes metastasis in pancreatic cancer. Nat Cell Biol, 2017, 19: 518-29

Ye X, Brabletz T, Kang Y, Longmore GD, Nieto MA, Stanger BZ, Yang J, Weinberg RA. Upholding a role for EMT in breast cancer metastasis. Nature 2017, 547: E1-E3

Aiello NM, Brabletz T, Kang Y, Nieto MA, Weinberg RA, Stanger BZ. Upholding a role for EMT in pancreatic cancer metastasis. Nature 2017, 547: E7-E8

Schwab A et al. Polyol Pathway Links Glucose Metabolism to the Aggressiveness of Cancer Cells. Cancer Res 2018, 78: 1604-18

Lafita-Navarro MC, Kim M, Borenstein-Auerbach N, Venkateswaran N, Hao YH, Ray R, Brabletz T, Scaglioni PP, Shay JW, Conacci-Sorrell M. The aryl hydrocarbon receptor regulates nucleolar activity and protein synthesis in MYCexpressing cells. Genes Dev 2018, 32: 1303-1308

Brabletz T, Kalluri R, Nieto MA, Weinberg RA. EMT in cancer. Nat Rev Cancer 2018, 18: 128-34

#### International cooperations

Dallas: USA

Prof. Dr. G. Berx, University of Ghent VIB, Gent: Belgium Dr. M. Conacci-Sorrell, UT Southwestern Medical Center,

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

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

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

## Nikolaus-Fiebiger-Center of Molecular Medicine

Chair of Experimental Medicine II (Molecular Oncology)

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#### Director

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#### **Research focus**

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

#### **Structure of the Chair**

Professorship: 1

- Personnel: 12
- Scientists: 3 (thereof funded externally: 0)
- Graduate students: 4

#### Special structural feature

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

#### Research

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

#### Molecular oncology of Wnt signaling

The Wnt signaling pathway controls the stability of  $\beta$ -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 consisting of the scaffold components axin or conductin, the serine/threonine kinase GSK3<sup>β</sup>, and the tumor suppressor APC (Adenomatous Polyposis Coli). The Wnt signal inhibits phosphorylation of βcatenin 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 β-catenin mutations are also found in a multitude of other tumor types suggesting that aberrant activation of Wnt signaling is a key mechanism of oncogenic transformation. We are analyzing the molecular roles of central components of the pathway, which are mostly involved in β-catenin degradation. Among these are Amer1, Axin, Conductin as well as the phosphatase PGAM5 that all modulate  $\beta$ -catenin phosphorylation.

#### Amer proteins

PI: Dr. I. Behrens Amer1 (APC membrane recruitment1) is the best characterized member of the Amer protein family which also includes Amer2 and Amer3. Amer1 interacts with APC and can recruit it to the plasma membrane, thereby acting as a negative regulator of Wnt signaling. The Amer1 gene is mutated in up to 30% of Wilms tumors, but also in 7 – 12% of colorectal carcinomas. Moreover, Amer1 mutations underlie the inherited disease OSCS, which is characterized by bone malformations and defects in other organs. In order to determine the consequences of Amer1 mutation for tumorigenesis in vivo, we conditionally knocked-out the Amer1 gene specifically in gut epithelium by crossing floxed Amer1 mice with villin-Cre mice. Efficient depletion of Amer1 in intestinal epithelial cells was verified by genetic means and RT-PCR analysis. Detailed analysis of histological sections revealed no alterations of epithelial cell proliferation and differentiation after Amer1 loss. There was also no signs of tumorigeneis following Amer1 depletion even after more than nine months of inspection. This indicates that Amer1 does not act as a tumor suppressor in mice in the absence of other oncogenic mutations. Since Amer1 mutations cooccur with APC mutations in most of the colorectal cancer cases, and APC is the central tumor suppressor and gatekeeper of these tumors, we crossed conditional Amer1 k.o. mice with APCmin mice in which the APC gene is mutated. APCmin develop tumors (polyps) mainly in the small intestine, but also at a lower rate in the colon a few months after birth. An initial analysis after three months did not show an impact of Amer1 depletion on polyp number and size in the APCmin mice. Results after longer time periods are pending.

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

PI: Dr. D. Bernkopf

Axin and conductin (also known as axin2) are structurally related inhibitors of Wnt/β-catenin signaling that promote degradation of βcatenin. Whereas axin is constitutively expressed, conductin is a Wnt target gene implicated in Wnt negative-feedback regulation. By proteome analysis we could demonstrate an interaction of axin with the mitochondrial phosphatase PGAM5. We found that knockdown of PGAM5 activates the Wnt pathway. However, we also found that PGAM5 gets cleaved and released to the cytoplasm after damage of the mitochondrial membrane potential. Cytoplasmic PGAM5 interacts with axin, and the resulting complex induces dephosphorylation of  $\beta$ catenin leading to its stabilization and activation of β-catenin-defendant transcription. It was previously shown by others that Wnt stimulation leads to mitochondrial biogenesis, pointing to a role of the PGAM5-Axin-β-catenin axis in mitochondrial homeostasis. Indeed, overexpression of cytoplasmic PGAM5 sufficed to increase mitochondrial numbers by a factor of approximately 1.5. On the basis of our results we propose the following model: mitochondrial damage associated with a loss of membrane potential leads to the release of cytoplasmic PGAM5 which stimulates Wnt signaling resulting in formation of new mitochondria that compensate for the initial loss of mitochondria.



Staining of endogeneous  $\beta$ -catenin (red) after transfection of PGAM5 or a phosphatase-inactive mutant of PGAM5, H105A (green) Nuclei are in blue (DAPI).



Scheme showing role of PGAM5 in mitochondrial homeostasis
# Teaching

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

#### **Selected publications**

Rauschenberger V, Bernkopf DB, Krenn S, Jalal K, Heller J, Behrens J, Gentzel M, Schambony A. The phosphatase Pgam5 antagonizes Wht/beta-Catenin signaling in embryonic anterior-posterior axis patterning. Development 2017, 144, 2234-2247

Unterer B, Wiesmann V, Gunasekaran M, Sticht H, Tenkerian C, Behrens J, Leone M, Engel FB, Britzen-Laurent N, Naschberger E, Wittenberg T, Stürzl M. IFN-gamma-response mediator GBP-1 represses human cell proliferation by inhibiting the Hippo signaling transcription factor TEAD. Biochem J 2018, 475, 2955-2967

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

Bernkopf DB, Daum G, Bruckner M, Behrens J. Sulforaphane inhibits growth and blocks Wnt/beta-catenin signaling of colorectal cancer cells. Oncotarget 2018, 9, 33982-33994

Bernkopf DB, Behrens J. Cell intrinsic Wnt/beta-catenin signaling activation. Aging (Albany NY) 2018, 10, 855-856

Bernkopf DB, Behrens J. Feedback regulation of mitochondrial homeostasis via Wnt/beta-catenin signaling. Mol Cell Oncol 2018, 5, e1458015

#### International cooperation

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

# Department of Orthopedics in the Malteser Waldkrankenhaus St. Marien gGmbH

# Chair of Orthopedics and Orthopedic Surgery

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### **Research focus**

- Roentgen-Stereophotogrammetric-Analysis (RSA) for quality control in total hip and knee arthroplasty
- Neuromuscular disorders
- Preoperative planning of total joint arthroplasty

# **Structure of the Department**

Professorship: 1 Personnel: 8 • Doctors (of Medicine): 3

• Graduate students: 41

### **Clinical focus areas**

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

### Research

The Department of Orthopedics deals with innovative research questions concerning *in vivo* diagnostics and therapy within the field of total hip and knee arthroplasty. Main topics represent the assessment of *in vivo* implant migration, the preoperative planning of total hip and knee arthroplasty and spinal intervertebral fusions as well as gait and posture analysis. Additionally clinical studies within the field of neuromuscular diseases were performed.

Research staff is organized within the "Research Network Musculoskeletal Biomechanics (MSB-NET)" of the German Society for Orthopedics and Traumatology (DGOU) and have exchange opportunities with similar national research institutions. Currently, the Department of Orthopedics provides the speaker of MSB-nets cluster "Implant fixation and Implant safety".

### Roentgen-Stereophotogrammetric-Analysis (RSA) for quality control in total hip and knee arthroplasty

PI: Prof. Dr. R. Forst, Dr. F. Seehaus Implantation and revision statistics for total hip and knee arthroplasty have shown a continuous increase within the recent years. Aseptic implant loosening is a clinical challenge and still one of the most common causes of total joint arthroplasty revision surgery. By Roentgen-Stereophotogrammetric-Analysis (RSA) method, it is possible to assess clinically the in vivo implant fixation of a new implant designs or coatings within the first two postoperative years. The RSA method allows an accurate in vivo measurement of the relative implant-to-bone movement, the so-called implant migration. It has been shown scientifically that the continuously increasing early implant migration correlates very well with a later aseptic loosening within the first two postoperative years, which predicts RSA as a reliable surrogate marker for later aseptic loosening of the implant. The current focus of RSA research at the Department of Orthopedics is on the experimental validation of new RSA approaches as well as the clinical assessment of in vivo migration of total hip arthroplasty.

The Department of Orthopedics collaborates with the Laboratory for Biomechanics and Biomaterials of Hannover Medical School, Laboratory for Biomechanics and Implant Research of the Orthopedic University Hospital Heidelberg and the Institute of Medical Technology of Ostbayerische Technische Hochschule Amberg-Weiden.

#### **Neuromuscular disorders**

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

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

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

# Preoperative planning of total joint arthroplasty

PI: Prof. Dr. R. Forst, Dr. F. Seehaus

Preoperative planning of total hip or knee arthroplasty is carried out within clinical practice two-dimensionally with the aid of planning software using conventional X-ray images (a.p. pelvis overview or whole-leg image in combination with a m.l. knee x-ray). In the case of severe anatomical deformities within the region of the hip or knee joint, two-dimensional planning is often difficult. Currently, three-dimensional preoperative planning of total joint arthroplasty is propagate and suggested by the medical industry. For a three-dimensional planning approach, a CT data set of the joint is required for, which is accompanied by an additional radiation exposure for the patient.

Aim of the project is the clinical validation (retrospective) of the three-dimensional planning environment in the field of total hip and knee arthroplasty or spinal intervertebral fusion.

## Teaching

The Department of Orthopedics participates within the curricular teaching of Medicine. To increase interdisciplinary teaching at FAU, interdisciplinary courses for students of Medicine and medical technology are held in cooperation with the Faculty of Engineering. Lecture and seminar are open to students of medical technology, as well as materials scientists, industrial engineers, mechanical engineers, or mechatronics. The existing curriculum for medical students (internship at Department of Orthopedics) is continuously expanded by practical exercises/ laboratories. Currently the concept of a so called "Saw-Bone-Lab" is validated for the medical students. Within this course, students should be trained skills in the field of plate osteotomy and or the implantation of total knee and hip arthroplasty using Saw-Bones.

In addition Bachelor's and Master's theses from students of the Faculty of Engineering as well as medical dissertations are supervised. Currently, six Chinese guest physicians (PhD Fellowships), 41 doctoral students, and 3 post-doctoral qualification applicants are supervised by the Department of Orthopedics.

Results of current projects were presented by research staff and PhD students at national and international conferences.

#### **Selected publications**

Mauerer A, Stenglein S, Schulz-Drost S, Schörner C, Taylor D, Krinner S, Heidenau F, Adler W, Forst R. Antibacterial Effect of a 4x Cu-TiO2 Coating Simulating Acute Periprosthetic Infection-An Animal Model. Molecules. 2017, 22(7). pii: E1042

Dussa CU, Döderlein L, Forst R, Böhm H, Fujak A. Management of Severe Equinovalgus in Patients With Cerebral Palsy by Naviculectomy in Combination With Midfoot Arthrodesis. Foot Ankle Int. 2017, 38(9):1011-1019

Jacobsen A, Seehaus F, Hong Y, Cao H, Schuh A, Forst R, Sesselmann S. Model-based roentgen stereophotogrammetric analysis using elementary geometrical shape models: 10 years results of an uncemented acetabular cup component. BMC Musculoskelet Disord. 2018, 19(1):335

Sommer C, Geber C, Young P, Forst R, Birklein F, Schoser B. Polyneuropathies. Dtsch Arztebl Int. 2018, 115(6):83-90

Sesselmann S, Hong Y, Schlemmer F, Hussnaetter I, Mueller LA, Forst R, Tschunko F. Radiostereometric migration measurement of an uncemented Cerafit® femoral stem: 26 patients followed for 10 years. Biomed Tech (Berl). 2018, 63(6):657-663

Hotfiel T, Heiss R, Janka R, Forst R, Raithel M, Lutter C, Gelse K, Pachowsky M, Golditz T. Acoustic radiation force impulse tissue characterization of the anterior talofibular ligament: a promising noninvasive approach in ankle imaging. Phys Sportsmed. 2018, 46(4):435-440

#### International cooperation

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

# Department of Orthopedics in the Malteser 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

### **Structure of the Division**

Professorship: 1

- Personnel: 3
- 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)
- Audited center for arthritis surgery
- Treatment of patients with rare diseases of the synovia (synovial joint chondromatosis, pigmented villonodular synovitis, etc.)

#### Research

Clinical research still focuses on the outcome of arthroscopic synovectomies as well as joint replacements of hip and knee. Basic osteoarthritis research (in cooperation with Prof. Dr. K. Gelse, Department of Trauma Surgery – Orthopedic Surgery; compare own report) has its focus on chondrocyte differentiation in human osteoarthritis. Dynamic pedographic measurements that started on rheumatoid patients investigate meanwhile also pathologies in soccer players.

#### Arthroscopic synovectomy

PI: Prof. Dr. B. Swoboda

Clinical studies investigated the effect of arthroscopic synovectomies in patients with rheuma-

toid 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 preoperative findings, surgical requirements, postoperative 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.

### 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**

Klinger P, Lukassen S, Ferrazzi F, Ekici AB, Hotfiel T, Swoboda B, Aigner T, Gelse K. PEDF Is Associated with the Termination of Chondrocyte Phenotype and Catabolism of Cartilage Tissue. Biomed Res Int. 2017:7183516 Hotfiel T, Carl HD, Eibenberger T, Gelse K, Weiß J, Jendrissek A, Swoboda B. Cementless femoral components in bicondylar hybrid knee arthroplasty in patients with rheumatoid arthritis: A 10-year survivorship analysis. J Orthop Surg (Hong Kong). 2017 May-Aug;25(2):2309499017716252

Hotfiel T, Carl HD, Wendler F, Jendrissek A, Heiß R, Swoboda B. Plantar pressures increase with raising body weight: A standardised approach with paired sample using neutral shoes. J Back Musculoskelet Rehabil. 2017; 30(3):583-589

Heiss R, Kellermann M, Swoboda B, Grim C, Lutter C, May MS, Wuest W, Uder M, Nagel AM, Hotfiel T. Effect of Compression Garments on the Development of Delayed-Onset Muscle Soreness: A Multimodal Approach Using Contrast-Enhanced Ultrasound and Acoustic Radiation Force. Impulse Elastography. J Orthop Sports Phys Ther. 2018; 48(11): 887-894

Hotfiel T, Heiss R, Swoboda B, Kellermann M, Gelse K, Grim C, Strobel D, Wildner D. Contrast-Enhanced Ultrasound as a New Investigative Tool in Diagnostic Imaging of Muscle Injuries-A Pilot Study Evaluating Conventional Ultrasound, CEUS, and Findings in MRI. Clin J Sport Med. 2018; 28(4): 332-338

Kellermann M, Heiss R, Swoboda B, Gelse K, Freiwald J, Grim C, Nagel A, Uder M, Wildner D, Hotfiel T. Intramuscular Perfusion Response in Delayed Onset Muscle Soreness (DOMS): A Quantitative Analysis with Contrast-Enhanced Ultrasound (CEUS). Int J Sports Med. 2017; 38(11): 833-841

#### International cooperation

Prof. Dr. T. Kirsch, PhD, Department of Orthopedic Surgery, 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 Chair**

Professorships: 2

- Personnel: 450 • Doctors (of Medicine): 141
- Scientists: 8 (thereof funded externally: 3)
- Graduate students: 8

#### **Clinical focus areas**

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

#### Special structural features

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

#### Research

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

# Clinical and experimental pharmacology of anesthesia

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.

During the reporting period, the pharmacokinetics of the opioid hydromorphone was investigated during postoperative pain therapy in cardiac surgery patients. The main focus of these investigations was the external validation of a pharmacokinetic model of hydromorphone that has been developed in previous studies. Further, a new pharmacokinetic model for dexmedetomidine in Chinese children, aged between 1 and 9 years, was developed within the framework of a research cooperation with the Department of Anesthesiology, Wenzhou Medical University, China.

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

In the area of experimental pain research, the Heisenberg professorship, which has been existing since May 2014, was extended by the DFG for additional two years. The research topics of this program are the pathomechanisms of cold hyperalgesia and cold allodynia, which are investigated in the somatic and trigeminal system.

To improve the study of trigeminal sensory neurons that innervate teeth, a new method has been developed that allows to identify this particular subpopulation of cells in the trigeminal ganglion. This method made it possible to identify, to quantify the expression, and to study the function of ion channels and receptors characteristic for tooth innervation by immunohistochemistry and in live cell cultures.

Another translational project, in cooperation with the Department of Medicine 1, deals with heritable polymorphisms that lead to a heightened susceptibility for acute and chronic pruritus. Here, differences between a large body of inbred strains are quantified and analyzed for the respective differences in genetic haplotypes. Another research area deals with the analysis of rare hereditary pain syndromes using human induced pluripotent stem cells (hiPSC) generated from skin biopsies. In cooperation with the Division of Stem Cell Biology, we differentiate hiPSC-derived pain sensing neurons (nociceptors) from affected pain patients, which otherwise are not available for analysis. This disease model improves our understanding of the pathophysiology of hereditary pain syndromes and enables us to develop individual therapeutic approaches, which we can then transfer to the patient. Pain sensing neurons (C-fibers) of the patients in vivo display pathological activity that can only be assessed with non-routine special examinations (microneurography). In our disease model we could show that also patientderived nociceptors show pathological hyperactivity in vitro and therefore mimick the disease of the patient.

Further, new therapeutic concepts for chronic pain syndrome after traumatic brain injury have been developed and tested in preclinical studies in cooperation with the Department of Anesthesia, Pain, and Perioperative Medicine of the Stanford University, USA. The promising results achieved with these studies build the platform for further confirmatory investigations.

#### **Clinical research in perioperative pain**

The molecular basis for the interindividual variability of pain sensation in healthy volunteers was the main focus of the investigations. The genome-wide methylation analysis results support the hypothesis that epigenetic regulation of TRPA1 seems to regulate thermal and mechanical pain sensitivities.

An ongoing further project investigates 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. These parameters will be applied to automatically identify risk profiles for clinical outcome parameters like mortality and cardiac morbidity.

# Medical technology of diagnostic and therapeutic procedures

The development of innovative dosing algorithms for intravenous drug therapy and the biosignal analysis for anesthesia control are the main research tasks.

During the reporting period, we investigated the impact of the cardiovascular function on the pharmacokinetics of anesthetic drugs drugs with high hepatic metabolism. The implementation of the monitoring variable cardiac output as a covariate of the pharmacokinetic model may lead to a relevant improvement of anesthesia control through a more precise prediction of the dose-concentration relationship, as demonstrated in a preclinical study for the opioid sufentanil as an example.

On the basis of the gathered experience from earlier investigations, a new software solution for an individual effect related dosing of anesthetic drugs was implemented and *in silico* tests successfully validated.

In addition, the software interfaces for the import of cardiorespiratory variables as anesthesia control parameters were also implemented and successfully tested.

# Research projects furthering the medical education

An emphasis of the scientific work during the reporting period is the development of curricula. Using a six steps' 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 and Maxillofacial Surgery. The elective course "rescue medicine" bridges into multiprofessional teaching.

Furthermore the Department of Anesthesiology is one of the hosts for the written and oral examination for the European Diploma of Anesthesiology and Intensive Care (EDAIC).

For the training in education new teaching concepts could be implemented, including virtual situative learning in the simulation and training center.

The Department of Anesthesiology supervises MD and PhD theses.

#### **Selected publications**

St Pierre M, Breuer G, Strembski D, Schmitt C, Luetcke B. Does an electronic cognitive aid have an effect on the management of severe gynaecological TURP syndrome? A prospective, randomised simulation study. BMC Anesthesiol 2017; 17(1): 17-72

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Eisenried A, Meidahl ACN, Klukinov M, Tzabazis AZ, Sabbadini RA, Clark JD, Yeomans DC. Nervous system delivery of antilysophosphatidic acid antibody by nasal application attenuates mechanical allodynia after traumatic brain injury in rats. Pain 2017 158(11): 2181-2188

Gombert S, Rhein M, Eberhardt M, Münster T, Bleich S, Leffler A, Frieling H. Epigenetic divergence in the TRPA1 promoter correlates with pressure pain thresholds in healthy individuals. Pain 2017 158(4): 698-704

Touska F, Turnquist B, Vlachova V, Reeh PW, Leffler A, Zimmermann K. Heat-resistant action potentials require TTXresistant sodium channels NaV1.8 and NaV1.9. J Gen Physiol. 2018 Aug 6;150(8):1125-1144

Birkholz T, Leuthold C, Schmidt J, Ihmsen H, Schüttler J, Jeleazcov C. Influence of Cardiac Output on the Pharmacokinetics of Sufentanil in Anesthetized Pigs. Anesthesiology 2018; 128(5): 912-920

#### International cooperations

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

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

Prof. V. Vlachová, Czech Academy of Sciences, Prag: Czech Republic

Prof. D.C. Yeomans, Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, Stanford: USA

Prof. M. Kurrek, Department of Anesthesiology, University of Toronto, Toronto: Canada

# **Department of Anesthesiology**

# **Division of Molecular Pneumology**

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#### **Head of Division**

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### **Research focus**

- Immunopathogenesis of lung tumor
- Immunopathogenesis of allergic asthma

# **Structure of the Division**

Professorship: 1

Personnel: 13

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

### Research

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

#### Immunopathogenesis of lung tumor

Lung cancer belongs to the cancer types with the highest mortality rate causing over a million deaths per year worldwide. Besides cigarette smoking, different other risk factors comprising gender and specific genetic traits are thought to contribute to lung cancer development. Treatment options include surgery, chemo- and radiotherapy which yield modest response and a 5-year survival rate of only 15 %. Present studies concentrate on immunotherapy as a new breakthrough treatment in oncology. Here, effector and cytotoxic T cells play an indispensable role for successful anti-tumoral immune responses. Over the past years our group has been focusing on the analysis of T cells present in the tumor microenvironment, including tumor infiltrating lymphocytes (TIL) as well as 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 like programmed cell death protein 1 (PD-1). These inhibitory receptors contribute to the functional impairment of T cell activation promoting T cell exhaustion and cancer immune evasion. Cancer immunotherapies have been developed that reactivate exhausted TILs by blocking inhibitory checkpoint receptors or other immunoregulatory cells.

In collaboration with the Division of Thoracic Surgery we analyzed lung samples from over 100 patients who were suffering from non-small cell lung cancer (NSCLC), underwent surgery, and gave their approval to be enrolled in our study. The diagnosis of lung cancer is based on pathological confirmation at the Institute of Pathology. The histological types of lung cancer are classified according to the classification of the World Health Organization (WHO) formulated in 2004. The staging of lung cancer is based on the Cancer TNM Staging Manual formulated by the International Association for the Study of Lung Cancer (IASLC) in 2010. Lung tissue samples were taken from the tumor area, representing the solid tumor tissue, the peri-tumoral area surrounding the tumor in a range of 2 cm, and the tumor-free control area. From these tissues, histological tissue arrays were generated, RNA and proteins were extracted, and we are able to isolate TILs. This whole procedure is substantial to identify specific biomarkers present in each patient which is a very important task to set up new therapeutical approaches. In fact, immunotherapy against immunosuppressive markers on TILs is a promising approach in the clinic and has been shown to partially reverse T cell exhaustion and to enhance anti-tumoral immunity in several cancer types including lung cancer. It should be noted, however, that clinical responses vary considerably and many patients do not or not completely respond to these antibody therapies. Thus we aim at identifying new TIL markers to be targeted in conjunction with common immunotherapeutica setting.

By using single gene-deficient mice in a murine model of lung carcinoma, we identified several not yet reported markers that might play a regulatory role in the immune responses to lung cancer and seem to be implicated in the reactivation of exhausted TILs. At the moment our studies focus on the following research topics:

- Role of NFATc1 in T cell-specific immune responses during the development of NSCLC
- Role of STAT1 in innate and adaptive immune responses during the development of NSCLC
- Role of Foxp3 and Tbet co-expressing Treg cells during the development of NSCLC



Co-localization of NFATc1 (brown) and CD3 (blue) in the tumoral lung region of early stage NSCLC patients

# 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 Pre-Dicta (Post-infectious immune reprogramming and its association with persistence and chronicity of respiratory allergic diseases; since 2011) with healthy and asthmatic pre-school children aged between 4 to 6 years, we have gained insight into important immunological processes during asthma development in general and in context to viral infections in particular. Since 2016, a local follow-up study (AGENDAS: Genetic, age, gender, and environmental factors that modify immuno-responses and the development of allergic asthma during the school age in childhood) has been recruiting healthy and asthmatic school children (6 to 10 years) during symptomatic or convalescent visit with the aim to substantiate and extend the results obtained in PreDicta. Especially the connection between rhinovirus infections and interferon type I and type III responses are a major research focus in our Division, but also T and B cell responses as well as innate lymphoid cells (ILC) are of interest to our group. Here we concentrate on cytokine patterns released by the different cell populations, e. g. IL-4 release from Th2 cells, and the expression of key transcription factors, such as T-bet in Th1 cells or Foxp3 in Treqs. 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, NIP45, NFATc1, contribute to determine the role of these factors/mediators in allergic 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 the following research topics:

- Role of the transcription factor NFATc1 and BATF in allergic asthma
- Role of Nip45 in allergic asthma
- Interferon type I and III immune responses to rhinovirus infections in asthma
- Role of ILC2s (innate lymphoid cells type 2) in experimental allergic asthma
- Role of vitamine D3 in asthma

#### Teaching

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

#### **Selected publications**

Vahl JM, Friedrich J, Mittler S, Trump S, Heim L, Kachler K, Balabko L, Fuhrich N, Geppert Cl, Trufa DI, Sopel N, Rieker R, Sirbu H, Finotto S. Interleukin-10-regulated tumour tolerance in non-small cell lung cancer. Br J Cancer. 2017 Nov 21;117(11):1644-1655

Kachler K, Bailer M, Heim L, Schumacher F, Reichel M, Holzinger CD, Trump S, Mittler S, Monti J, Trufa DI, Rieker RJ, Hartmann A, Sirbu H, Kleuser B, Kornhuber J, Finotto S. Enhanced Acid Sphingomyelinase Activity Drives Immune Evasion and Tumor Growth in Non-Small Cell Lung Carcinoma. Cancer Res. 2017 Nov 1;77(21):5963-5976

Bergauer A et al. IFN- $\alpha$ /IFN- $\gamma$  responses to respiratory viruses in paediatric asthma. Eur Respir J. 2017 Mar 29;49(3). pii: 1700006

Hentschke I, Graser A, Melichar VO, Kiefer A, Zimmermann T, Kroß B, Haag P, Xepapadaki P, Papadopoulos NG, Bogdan C, Finotto S. IL-33/ST2 immune responses to respiratory bacteria in pediatric asthma. Sci Rep. 2017 Mar 6;7:43426

Bielor C et al. Role of TGF- $\beta$  in anti-rhinovirus immune responses in asthmatic patients. J Allergy Clin Immunol. 2017 Jul;140(1):283-286

Heim L, Friedrich J, Engelhardt M, Trufa DI, Geppert CI, Rieker RJ, Sirbu H, Finotto S.NFATc1 Promotes Antitumoral Effector Functions and Memory CD8+ T-cell Differentiation during Non-Small Cell Lung Cancer Development. Cancer Res. 2018 Jul 1;78(13):3619-3633

#### International cooperations

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

Prof. S.T. Weiss, Translational Genomics Core, Partners HealthCare, Cambridge, MA: USA Prof. Dr. M.L. Kowalski, Department of Immunology, Rheumatology and Allergy, Medical University of Łódz, Łódz: Poland

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

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

# **Department of Anesthesiology**

# **Division of Palliative Medicine**

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#### **Head of Division**

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#### **Research focus**

- Ethical aspects in palliative care
- Family caregivers in palliative care and quality of care in the end of life
- Clincial-experimental research
- Research projects furthering the curriculum and medical education

## **Structure of the Division**

Professorship: 1

Personnel: 50

- Doctors (of Medicine): 8
- Scientists: 6 (thereof funded externally: 5)
- Graduate students: 23

#### **Clinical focus areas**

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

# Research

Health services research in palliative care examines the "reality" of palliative care. It provides information about healthcare concepts under everyday conditions. In this way, health services research in palliative care answers questions that neither biomedical basic research nor classical clinical research can answer.

Clinical-experimental research at the Division of Palliative Medicine deals with innovative approaches to optimize the treatment of patients with severe diseases, e. g. technical applications in palliative medicine.

#### Ethical aspects in palliative care

PI: Prof. Dr. C. Ostgathe, Dr. C. Klein One possible option for patients with symptoms refractory to treatment is palliative sedation (PS) that can be offered and performed after careful consideration of the clinical situation. Despite ethical implications, PS is seen as integral part of palliative care (inter-)nationally.

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

# Family Caregivers in palliative care and quality of care in the end of life

Pl: Prof. Dr. C. Ostgathe, PD Dr. S. Stiel (until 2017), Dr. M. Heckel (since 2018), PD Dr. S. Gahr

• Validation of the "Care of the Dying Evaluation (CODE)" for deceased patients' informal

caregivers in the German-speaking area In 2018, the validation study on the "Care of the Dying Evaluation" (CODE) assessing the quality of care by relatives of deceased patients in palliative medicine and other departments was completed. The study was conducted in collaboration with the university hospital Mainz. The questionnaire was answered in writing by relatives who had accompanied the patient during the last three days of his life. The validation study and the results on the quality of care during the last three days of life in two German hospitals will be published in 2019. The questionnaire fulfils the statistical quality criteria of validity and reliability for survey instruments. It can be used for research and in practice and allows for international comparability. An international project (iCODE) incorporates the results of the present validation study.

- Funding: DFG
- Hospice and Palliative Care in Bavaria: well connected – optimally cared for! (PallBayNet) Several inpatient and community palliative care providers established regional hospice and palliative care networks in Bavaria aiming at connecting different services. General patterns of work and collaboration, the organization and communication within networks and between partners were investigated. A best practice recommendation on the collaboration in networks was developed and published by the work group.

Funding: Bavarian State Ministry of Public Health and Care Services

 Predictors of anxiety and depression in patients with progressive, life-limiting disease an exploratory analysis of hospice and palliative assessment 2007 – 2011

The retrospective analysis of data from the treatment and documentation routines of palliative wards, hospices, and other treatment providers of patients with progressive, life-limiting diseases explored the characteristics in which psychologically burdened patients differ from those without. The data on "depression", "anxiety", "tension" and "disorientation, confusion" from the validated symptom problem checklist of the Hospice and Palliative Survey (HOPE) served as markers for psychological stress.

• Coordination Office Palliative Care in the network of German Comprehensive Cancer Centers

In the first project phase from 2014 – 2017, a "best practice strategy" for a structured integration of specialized palliative care in a Comprehensive Cancer Center (CCC) was developed using scientific methods. This includes both the integration of palliative medicine into the course of treatment and into the research and teaching activities of the individual CCCs. Since 2017, the implementation of best practice recommendations, the implementation and evaluation of the jointly developed standard operation procedures (SOP), joint documentation for the identification and evaluation of quality indicators, and the development of a needs-oriented medical education and training program have been started.

Funding: German Cancer Aid

### **Clinical-experimental research**

PI: Prof. Dr. C. Ostgathe, Dr. T. Steigleder Clinical-experimental research at the Division of Palliative Medicine deals with innovative approaches to optimize the treatment of patients with severe diseases.

One research focus is medical applications in palliative medicine. This focus is represented by the working group PallMeT.

 GUarded by Advanced Radar technologybased Dlagnostics Applied in palliative and intensive care Nursing (GUARDIAN)

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

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

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



Project GUARDIAN: Preparation for the clinical study with healthy volunteers (Image: I. Gheith)

#### Research projects furthering the curriculum and medical education PI: Dr. T. Steigleder

Research focuses on studies of content as well as formal aspects of teaching palliative medicine with the aim of researching and developing better courses. Furthermore, psychological and physiological factors, such as the psychological phenomena endowment effect and loss aversion, as well as physiological factors, such as prenatal testosterone exposure, are research topics.

### Teaching

The Division of Palliative Medicine is an integral part of the teaching force for Medicine, psychogerontology, and Medical Process Management. In addition to the comprehensive curricular teaching, it offers workshops for medical students as part of the clinical team on treating palliative care patients with simulated patients under constant supervision and with structured feedback. Furthermore, we established a multiprofessional seminar in 2013 that takes place once each term. Tutors and participants both comprise many different health professions.

The Division of Palliative Medicine offers the chance to accomplish a MD thesis or a dissertation in human biology as well as Bachelor's and Master's theses of many degree programs. A research workshop is also held for students writing their final thesis in the division.

#### **Selected publications**

Heckel M, Geissdörfer W, Herbst F, Stiel S, Ostgathe C, Bogdan C. Nasal carriage of Methicillin-resistant Staphylococcus aureus (MRSA) at a palliative care unit: A prospective single service analysis. PLoS ONE 2017, 12(12):e0188940 Hofmann S, Hess S, Klein C, Lindena G, Radbruch L, Ostgathe C. Patients in Palliative Care – Development of a Predictive Model for Anxiety using Routine Data. PLoS ONE 2017, 12(8):e0179415

Herbst FA, Heckel M, Stiel S, Ostgathe C. [Development of empirical recommendations for regional hospice and palliative care networks in Germany: A qualitative study.] Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen 2018, pii: S1865-9217(18)30198-3

Will C, Shi K, Schellenberger S, Steigleder T, Michler F, Fuchs J, Weigel R, Ostgathe C, Koelpin A. Radar-Based Heart Sound Detection. Scientific Reports 2018, 8(1):11551

Stiel S, Nurnus M, Ostgathe C, Klein C. Palliative Sedation in Germany: Factors and Treatment Practices Associated with different Sedation Rate Estimates in Palliative and Hospice Care Services. BMC Palliative Care 2018, 17(1):48

Stiel S, Heckel M, Wendt KM, Weber M, Ostgathe C. Palliative care patients' quality of dying and circumstances of death - Comparison of informal caregivers' and healthcare professionals' estimates. American Journal of Hospice and Palliative Medicine 2018, 35(7):1023-1029

# **Department of Cardiac Surgery**

# Chair of Cardiac Surgery

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#### Director

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#### **Research focus**

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

# **Structure of the Chair**

Professorship: 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
- Minimally invasive valve surgery
- Mechanical circulatory support
- Wound management
- Heart insufficiency therapy
- Rhythm surgery
- Surgery in grown-up with congenital heart disease
- Interventional heart valve surgery
- Interventional aortic surgery

### Research

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

### **Chronic rejection of allografts**

PI: PD Dr. C. Heim

Transplant vasculopathy is the main reason for late graft failure after heart transplantation. In order to develop effective therapeutic strategies and translate them into clinical success, a detailed understanding of the mechanisms responsible for the development of transplant vasculopathy is essential. We have recently established and characterized the abdominal aortic allograft model as a suitable tool to study the development of transplant vasculopathy. Ongoing projects involve the role and importance of platelets and their inhibition in the development of transplant vasculopathy. Immunmodulatory effects of Clopidogrel could be shown in small animal models. The results of these preclinical studies could be translated into a multi-center study (CEDRIC). Additionally, microvascular integrity of pulmonary grafts was shown to be essential for the long-term success of animal transplant models. In cooperation with the Department of Medicine 4, another major aim of this working group is the use of antiproliferative substances to explore potential strategies to avoid the development of transplant vasculopathy in experimental transplant models.



Mechanisms in CAV

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

### Therapy of end-stage heart failure: Heart transplantation or support with a left or right ventricular assist device PI: Dr. R. Tandler

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

# Electromechanical coupling in heart failure

# PI: PD Dr. C. Heim

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

# Development of a non-blood contacting heart actor

PI: Prof. Dr. M. Weyand

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

#### High speed camera investigations on heart valves in a pulse duplicator PI: Dr. M. Kondruweit

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

### Teaching

The Department of Cardiac Surgery takes part in compulsory and elective subjects for the curricular teaching of the Medicine and Dentristy. Bachelor's and Master s theses are supervised as well as MD and PhD theses.

#### **Selected publications**

Heim C, Tandler R, Kondruweit M, Weyand M. Chirurgische Therapiemöglichkeiten bei Herzinsuffizienz. CHAZ. 2018; 4:209-215

Gocht A, Spriewald B, Distler JHW, Ramsperger-Gleixner M, Ensminger SM, Weyand M, Heim C. Small Molecule Tyrosine Kinase Inhibitor Nintedanib Reduces Development of Cardiac Allograft Vasculopathy in Murine Aortic Allografts. Transplantation Direct. 2018 Jun 18;4(7):e367

Gocht A, Distler JHW, Spriewald B, Ramsperger-Gleixner M, Weyand M, Ensminger SM, Heim C. Effects of different serotonin receptor subtype antagonists on the development of cardiac allograft vasculopathy in murine aortic allografts. Transpl Immunol. 2018; 49:43-53

Ghaderi S, Alidadiani N, SoleimaniRad J, Heidari HR, Dilaver N, Heim C, Ramsperger-Gleixner M, Baradaran B, Weyand M. DJ1 and microRNA-214 act synergistically to rescue myoblast cells after ischemia/reperfusion injury. J Cell Biochem. 2018;119(9):7192-7203

Heim C, Tandler R, Weyand M. ESC-leitlinienbasierte Therapieempfehlungen für herzinsuffiziente Patienten in der Herzchirurgie. 2018; 32(5), 391-401

Heim C, Gocht A, Weyand M, Ensminger SM. New Targets for the Prevention of Chronic Rejection after Thoracic Organ Transplantation. Thorac Cardiovasc Surg. 2018; 66(01):31-41

#### International cooperation

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

# **Department of Cardiac Surgery**

**Division of Pediatric Cardiac Surgery** 

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#### **Head of Division**

Prof. Dr. med. Robert Cesnjevar

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#### **Research focus**

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

# **Structure of the Division**

- Professorship: 1
- Personnel: 9
- Doctors (of Medicine): 4
- 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
- Surgical reconstruction of cardiac valves and "physiological" cardiac valve replacement

#### Research

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

#### Organ protection: cerebral perfusion / beating-heart-surgery / distal thoracic aorta perfusion (descendens perfusion)

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.

Selective perfusion of the distal thoracic aorta during aortic arch reconstruction (descending aortic perfusion) represents a further strategy improvement. This method serves to continuously and optimally care for all subdiaphragmal organs during surgical therapy of congenital heart defects with aortic arch hypoplasia - or interruption. Based on our primary clinical data, this technique seems to improve outcomes of newborns and infants. This critical patient group is particularly sensitive for insufficient perfusion during cardiopulmonary bypass. Continuous perfusion of the descending aorta, via a separate arterial pump on cardiopulmonary bypass, together with selective cerebral perfusion and/or selective myocardial perfusion represents an essential and consistent advancement towards a functional total body perfusion during complex aortic arch operations.

### 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 "Goldstandard", 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 largesized 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.

Decellularized aortic homografts (cell-free aortic full roots from human donors) for aortic valve replacement have been used clinically in children and young adults since 2002. The 10-year clinical study data had proven very good midterm results without calcification as compared to conventional homografts. Since 2018, we have been implanting decellularized aortic homografts as a valid alternative to Ross procedures in young children and adults who required aortic valve replacement. A relevant advantage of decellularized aortic homografts as compared to mechanical heart valves is that patients do not need any long-term anticoagulation therapy. The valves also seem to have the potential to grow. Meanwhile, decellularized pulmonary valve homografts are available for our patients as well.

#### **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 pumpspecific characteristics. It was demonstrated that overall improvement in the management results in more safety and improved outcomes for patients on support.

### **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 (Di-Ethyl-Hexyl-Phthalate) 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 could be followed on additional screens in the operating room. We supervise Bachelor's and Master's theses as

well as MD and PhD theses.

#### **Selected publications**

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

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

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

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

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

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

#### International cooperations

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

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

# **Department of Dermatology**

Chair of Skin and Venereal Diseases

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#### **Director / Directress**

Prof. Dr. med. univ. Gerold Schuler (until 30.9.2019) Prof. Dr. med. Carola Berking (as of 1.10.2019)

#### Contact

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#### **Research focus**

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

## **Structure of the Chair**

Professorships: 4

Personnel: 216

- Doctors (of Medicine): 43
- Scientists: 24 (thereof funded externally: 17)
- Graduate students: 12

#### **Clinical focus areas**

- Immunotherapy of melanoma and uveal melanoma (checkpoint blockade, DC 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 melanoma. In this research area, several directions developed, including studies to understand the pathogenesis of melanoma, the immunological response, the cellular immune therapy, and the identification of melanoma biomarkers. In detail, the Department of Dermatology is analyzing the biology and function of dendritic cells (DC), optimizing antigen-specific tumor vaccines using DC, developing a GMP compliant protocol for the use of CAR-T cells, analyzing the function of extracellular vesicles from plasma, and characterizing tissue sections with an improved automated immunofluorescence technology called MELC technology. Additional projects focus on the pathogenesis of HIV infection and autoimmune diseases. 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 aim of this working group, consisting of the GMP laboratory (manufacture of cellular therapeutics) and a clinical unit (patient application), is the production and clinical application of advanced therapy medicinal products (ATMPs). After seven phase I and II trials using DC vaccines, a multicenter phase III trial using tumor mRNA as vaccine antigen was started in July 2014. 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 German university eye hospitals). Since the start of the trial, 163 patients have been screened and 77 have been included.

Current improvements are the use of Next Generation Exon and RNA sequencing in conjunction with HLA-epitope prediction in order to improve the vaccination strategy as well as an optimized maturation of DC with the help of mRNA coding for NFkB. Such an optimized vaccine will be used within a Phase I clinical trial in metastatic uveal melanoma.

Based on preclinical work, also the adoptive transfer of T cells reprogrammed by RNA (CSPG4-CAR T cells) will start in late 2019 within a small Phase I trial. The GMP-quality team has successfully developed the implementation of all cellular therapies. Immunomonitoring is performed by the core unit FACS.

In 2019, a clinical trial (in cooperation with the Department of Medicine 1) will start to treat patients with colitis ulcerosa by the adoptive transfer of regulatory T cells produced in the GMP laboratory.

### RNA electroporation to improve DC vaccines and to generate antigenspecific T cells

PI: PD Dr. N. Schaft, PD Dr. J. Dörrie

This team examines the electroporation of mRNA for clinical application. With this technology, the DC-vaccine can be optimized and loaded with antigen and on the other hand, tumor-specific T cells can be generated. An activator of the NFkB pathway was mutated in such a way that it became constitutively active and generates DC, which induce long-living and more efficient tumor antigen-specific T cells and additionally activate NK cells. A clinical trial with these cells is in preparation. Using mRNA transfection, T cells can be reprogrammed to directly recognize tumor (or virus-infected) cells. For classical T cells, this technique was established previously and recently  $\gamma/\delta$ T cells were added (in collaboration with the Children's Cancer Research Institute, Vienna).

Additionally, the transfection of patient T cells with a CSPG4-specific CAR was established under GMP conditions to treat cutaneous and uveal melanoma patients. This also is currently transferred to clinical application.

In view of future combination therapies, it was examined how modern targeted kinase inhibitors influence the functionality of T cells.

# Functional role of DC subpopulations and antigen presentation

PI: Prof. Dr. D. Dudziak

This research 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 of a specific DC subpopulation. Besides, in close collaboration with various clinical institutions, DC subpopulations and other antigen presenting cells from human tissues are characterized by multicolor confocal immunofluorescence analysis and 18-color flow cytometry and human antigen targeting antibodies are generated. Prof. Dr. D. Dudziak is the coordinator of the Emerging Fields Initiative 'BIG-THERA', which correlates tumor immune cell infiltration in breast cancer via big-data radiogenomic approaches depending on checkpoint therapy (compare own report).

# Role of miRNA in cancer and immune-related diseases

PI: Prof. Dr. J. Vera-González MicroRNAs 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 immunerelated diseases. In collaboration with Prof. 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. In 2018, the project was selected and further funded by the BMBF in preparation for a potential follow-up grant aiming at the founding of a startup company. Initial discussions with industrial partners were very promising.

### Characterization of the toponome of tissue and cells by multi-epitope ligand cartography (MELC)

PI: Prof. Dr. A. Baur, Dr. C. Ostalecki 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 via antibodies 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 nevi. Through cooperation with industrial partners, we currently establish a new software for the analysis of our multi-antigen stained tissue slides. The project is funded by Bayern Innovativ and is meant to foster the interaction between a recently established start-up out of the Department of Dermatology (Tissomatic GmbH).

# 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 Bcells is addressed ex vivo and in vitro by molecular biological and immune-histochemical 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 optimize selection of therapeutic options. With a semi-automated mRNA extraction from formalin fixed paraffin-embedded (FFPE) sections of primary melanomas and melanoma metastases, a set of 20 indicator genes, previously identified by array analyses, was evaluated. The comparison of responders and non-responders for different immunotherapy options (DC-vaccination, checkpoint blockade antibodies) 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 (IBD)

#### PI: Dr. C. Bosch-Voskens

The focus of this project, funded by KFO 257 and since July 2018 via SFB/Trans Regio 241 (compare own reports), is on regulatory T cells (Treg). In IBD, it is postulated that insufficient numbers of regulatory T cells (Treg) that attenuate local proliferation of effector T cells in the gut can be corrected by infusion of autologous Tregs. An authority-approved Treg cell 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 the Department of Medicine 1).

# Teaching

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

#### **Selected publications**

Gross S, Erdmann M, Haendle I, Voland S, Berger T, Schultz E, Strasser E, Dankerl P, Janka R, Schliep S, Heinzerling L, Sotlar K, Coulie P, Schuler G, Schuler-Thurner B. Twelveyear survival and immune correlates in dendritic cell-vaccinated melanoma patients. JCI Insight. 2017 Apr 20;2(8). pii: 91438

Khan FM, Marquardt S, Gupta SK, Knoll S, Schmitz U, Spitschak A, Engelmann D, Vera J, Wolkenhauer O, Pützer BM. Unraveling a tumor type-specific regulatory core underlying E2F1-mediated epithelial-mesenchymal transition to predict receptor protein signatures. Nat Commun. 2017 Aug 4;8(1):198

Lehmann CHK, Baranska A, Heidkamp GF, Heger L, Neubert K, Lühr JJ, Hoffmann A, Reimer KC, Brückner C, Beck S, Seeling M, Kießling M, Soulat D, Krug AB, Ravetch JV, Leusen JHW, Nimmerjahn F, Dudziak D. DC subset-specific induction of T cell responses upon antigen uptake via Fc $\gamma$  receptors in vivo. J Exp Med. 2017 May 1;214(5):1509-1528

Ostalecki C, Lee JH, Dindorf J, Collenburg L, Schierer S, Simon B, Schliep S, Kremmer E, Schuler G, Baur AS. Multiepitope tissue analysis reveals SPPL3-mediated ADAM10 activation as a key step in the transformation of melanocytes. Sci Signal, 2017;10 (470): pii: eaai8288

Voskens CJ, Fischer A, Roessner S, Lorenz C, Hirschmann S, Atreya R, Neufert C, Atreya I, Neurath MF, Schuler G. Characterization and Expansion of Autologous GMP-ready Regulatory T Cells for TREG-based Cell Therapy in Patients with Ulcerative Colitis. Inflammatory Bowel Disease 2017 Aug;23(8):1348-1359

Hecht M et al. Clinical outcome of concomitant vs interrupted BRAF inhibitor therapy during radiotherapy in melanoma patients. Br J Cancer, 2018,118(6):785-92

#### International cooperations

Prof. K. Saksela, Department of Virology, University of Helsinki, Helsinki: Finland

Prof. Dr. P. Coulie, de Duve Institute and the Université catholique de Louvain, Brussels: Belgium

Prof. Dr. J. Ravetch, Rockefeller University, New York: USA

Prof. Dr. H. Schmidt, Department of Pharmacology and Personalized Medicine, Maastricht University, Maastricht: The Netherlands

# **Department of Dermatology**

# **Division of Immune Modulation**

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Head of Division

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#### **Research focus**

- Immune-modulation in autoimmunity and transplantation
- Transcriptional *in vivo* targeting of Dendritic cells (DC)
- Signal transduction of CD83 in DC and regulatory T cells
- Immune-modulation by TSLP and CD83
- Interaction of DC and viruses

## **Structure of the Division**

Professorship: 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

#### PI: PD Dr. E. Zinser

The project group focuses on the immuno-suppressive properties of soluble CD83 (sCD83). Using a recombinantly expressed sCD83 molecule, it was possible to inhibit the paralyses associated with EAE, an animal model for the early, inflammatory phase of Multiple Sclerosis in a prophylactic as well as in a therapeutic setting. Furthermore, 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, B cells as well as microglia cells. This allows the elucidation of the biological function of CD83 expression in these specific cell populations. In addition, the group is currently investigating the precise function of sCD83-mediated immune-regulatory and tolerogenic mechanisms using a murine model of cornel allograft transplantation. By detailed functional examinations, we aim to elucidate how sCD83 induced corneal allograft tolerance is maintained directly by immune cells of the donor graft and to use this knowledge to develop future therapeutic strategies

# Transcriptional *in vivo* targeting of Dendritic cells (DC)

# 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 Treq.

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.

# Signal transduction of CD83 in DC and regulatory T cells

PI: Prof. Dr. A. Steinkasserer

This group concentrates on structural analyses and characterization of CD83 related signal transduction pathways. Specific interaction partners have been identified using a Ligand-Based Receptor Capture assay and will now be further evaluated. In addition, the three-dimensional structure of the extracellular CD83 domain has been established up to a resolution of 1.7Å, using X-ray crystallography. To identify possible binding motifs in silico, a bioinformatic modeling study has been performed. Using our recently generated DC specific CD83 conditional KO animals, we discovered that CD83 modulates proinflammatory TLR2/4 signaling pathways, thereby potently regulating immune responses in a DC dependent manner. Regarding regulatory T cells, we reported for the first time that CD83 is essential for the resolution of inflammation, since deletion of CD83 on these cells causes a massive over activation of the immune system with exacerbated autoimmune reactions, as observed in animal models for arthritis and inflammatory bowel disease (IBD). In follow up studies we will now elucidate the precise underlying mechanisms and use this knowledge for the development of future therapeutic intervention strategies for patients suffering from autoimmune disorders.

#### **Immune-modulation by TSLP and CD83** PI: PD Dr. M. Lechmann

TSLP (Thymic Stromal Lymphopoietin) 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 IBD, is capable to directly stimulate intestinal epithelial cells and promotes the regeneration of the epithelial barrier. In the second project, the CD83specific 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 KOmouse, the influence of CD83 on differentiation and function of regulatory T cells. With regard to the therapeutic application of sCD83, a study in an animal model of IBD, 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. L. Grosche

DC play a pivotal role in the induction of protective antiviral immune responses. The focus of this project group is the identification of virusspecific immune evasion mechanisms during herpesviral infections of DCs, by herpes simplex virus type-1 (HSV-1) and human cytomegalovirus (HCMV). Regarding this, we have shown that HSV-1 as well as HCMV downmodulate the expression of the surface molecule CD83 on infected mature DCs via a proteasome-dependent mechanism, which subseguently leads to hampered antiviral immune responses. A second HSV-1- and HCMV-mediated immune evasion mechanism is the inhibition of mDC migration. This was shown to be caused, among others, by rapid induction of mDC adhesion. The precise molecular mechanism is currently under investigation. Furthermore, this group is interested in the characterization of HSV-1 replication in immature versus mature DCs. Contrary to previous hypotheses, we showed that HSV-1 indeed establishes its complete gene expression cascade in mature DCs. However, supernatants of mature DCs, in contrast to immature DCs, barely contain any infectious progeny virions, and almost exclusively contain non-infectious L-particles. We have proven that HSV-1 capsids are trapped inside the nucleus of mature DCs, while immature DCs facilitate an autophagy dependent complete viral replication cycle. An additional project deals with the analysis of non-infectious L-particles, due to their ability to transfer functional viral proteins to un-infected bystander cells. Thus, L-particles constitute an additional immune evasion strategy of HSV-1, since they can also modulate bystander cells for viral benefit.

## 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.

#### **Selected publications**

Heilingloh CS, Klingl S, Egerer-Sieber C, Schmid B, Weiler S, Mühl-Zürbes P, Hofmann J, Stump JD, Sticht H, Kummer M, Steinkasserer A, Muller YA. Crystal structure of the extracellular domain of the human dendritic cell surface marker CD83. J Mol Biol. 2017 Apr 21;429(8):1227-1243

Horvatinovich JM, Grogan EW, Norris M, Steinkasserer A, Lemos H, Mellor AL, Tcherepanova IY, Nicolette CA, DeBenedette MA. Soluble CD83 Inhibits T Cell Activation by Binding to the TLR4/MD-2 Complex on CD14+ Monocytes. J Immunol. 2017, 198(6):2286-2301

Hammer A, Waschbisch A, Knippertz I, Zinser E, Berg J, Jörg S, Kristina Kuhbandner K, David C, Pi J, Bayas A, De-Hyung Lee, Haghikia A, Gold R, Steinkasserer A, Linker RA. Role of Nrf2 Signaling for Effects of Fumaric Acid Esters on Dendritic Cells. Front. Immunol. 2017 Dec 22;8:1922

Grosche L, Draßner C, Mühl-Zürbes P, Kamm L, Le-Trilling V, Trilling M, Steinkasserer A, Heilingloh CS. Human Cytomegalovirus-Induced Degradation of CYTIP Modulates Dendritic Cell Adhesion and Migration. Front Immunol., 2017 Apr 21;8:461

Grosche L, Kummer M, Steinkasserer A. What Goes Around, Comes Around - HSV-1 Replication in Monocyte-Derived Dendritic Cells. Front Microbiol. 2017 Nov 7;8:2149

Döbbeler M et al. CD83 expression is essential for Treg cell differentiation and stability. JCI insight, 2018, 3(11). pii: 99712

#### International cooperations

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

Dr. C. Nicolette, Argos Therapeutics, Durham: USA

# Department of Medicine 1 – Gastroenterology, Pneumology, and Endocrinology

Chair of Internal Medicine I

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### **Research focus**

- Intestinal diseases
- Experimental hepatology
- Therapeutic targets for treatment of IBD
- Division of clinical and experimental pulmonology
- Molecular gastroenterology
- Molecular hepatology and GI-oncology
- Molecular neuro-gastroenterology
- Patient-oriented research and innovative therapeutic strategies in IBD
- Cell trafficking and T cells in IBD
- Cytokines and transcription factors in IBD and carcinoma

### **Structure of the Department**

Professorships: 9

Personnel: 329

- Doctors (of Medicine): 66
- Scientists: 19 (thereof funded externally: 13)
- Graduate students: 61

#### **Clinical focus areas**

- Gastroenterology
- Pneumology
- Endocrinology and diabetology
- Hepatology
- Nutritional medicine
- Intensive careEmergency reception

### Research

The Department of Medicine 1 focuses on studying the functions and interactions of genes and proteins that are associated with the pathogenesis of gut, lung, and liver diseases. Beside the well established immunological, molecular biological and cell biological techniques, also innovative and interdisciplinary detection methods are developed. In July 2018 the DFG funded SFB/Transregio 241 (TRR 241) "Immune-Epithelial Communication in Inflammatory Bowel Diseases" started (compare own report).

### Intestinal diseases

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

#### **Experimental hepatology**

PI: PD Dr. S. Wirtz, PD Dr. C. Günther, PD Dr. A. Kremer

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

# Therapeutic targets for treatment of IBD

PI: Dr. I. Atreya, Dr. R. Lopez-Posadas

We try to achieve improved insights into the immunopathogenesis of chronic inflammatory diseases of the intestine (IBD) or lung. In this context, we in particular focus on T lymphocytes and innate lymphoid cells and their capacity to accumulate in inflammatory tissue sites and interact locally with epithelial cells or other tissueresident cell types. Supported by innovative experimental settings, we are able to perform detailed functional analyses and advanced imaging of primary human immune cells derived from the peripheral blood or tissue biopsies of affected patients. Overall, our investigations intend to identify new therapeutic target structures for an improved treatment of inflammatory diseases.

# 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. Our experimental research attempts focus on the role and function of immune cell subpopulations in the pathogenesis of pulmonary diseases. The lung biobank established and located at our Department allows us to study the immunological micromilieu of the lung in great detail. For example, the presence and functionality of innate immune cell subpopulations in the broncho-alveolar lavage is assessed in current research projects.

### **Molecular gastroenterology**

PI: Prof. Dr. C. Becker

This group focuses on the immunological and molecular mechanisms that lead to the development of infection, IBD, 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 and resolution of inflammation and colon cancer. The researchers were able to show that necroptosis can play an important role for the therapy of colorectal cancer. 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.

#### Molecular hepatology and GI-oncology PI: Dr. Dr. P. Dietrich

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

# Molecular neuro-gastroenterology

PI: PD Dr. M. Engel

The main focus of this group is the elucidation of novel neuro-immunological mechanisms in the pathogenesis of IBD. Several studies about the role of neuropeptides and TRP-channels in colonic inflammation were conducted during the reporting period. We could show that ongoing activation and consecutive desensitization of nociceptive and peptidergic neurons expressing TRP channels led to anti-inflammatory and hypolagesic effects not only in the intestine, but rather in the whole organism of the mouse. In addition to their ability to release immuno-regulatory neuropeptides from peptidergic neurons, TRP channels are also functionally expressed in non-neuronal cells. For the first time we discovered the functional role of TRPM8 in several populations of murine macrophages. TRPM8 in macrophages was essential for anti-inflammatory action in the context of DSS colitis, which was mediated through a balance shift of pro- and anti-inflammatory cytokine expression.

# Patient-oriented research and innovative therapeutic strategies in IBD

PI: Prof. Dr. R. Atreya

This group aims at characterizing the molecular mechanism of action of anti-inflammatory therapies in IBD and the identification of biomarkers for the prediction of therapeutic response. The translational identification and characterization of immunological resistance mechanisms against biologics is another research focus of the group. The clinical application of molecular endoscopy for the individual prediction of therapeutic response in IBD represents another field of our group.

# Cell trafficking and T cells in IBD

### PI: Dr. S. Zundler

The main interest of this group is to understand processes of cell trafficking in intestinal immunology with special focus to IBD and related translational applications. During the reporting period, the researchers characterized the role of so-called tissue-resident memory T cells in chronic colitis. They were able to demonstrate a key role of these cells in the orchestration of intestinal inflammation in pre-clinical models and human patient samples. Moreover, the group explored the importance of different gut homing pathways for several immune cell populations. The superordinate objective of these investigations was to generate new insights for the optimization of existent and the development of novel therapeutic approaches in IBD.

# Cytokines and transcription factors in IBD and carcinoma

## PI: PD Dr. B. Weigmann

The research focus of the work group are specific proteins, so-called transcription factors and immunologically important cytokines, which are produced by T cells. The NFAT transcription factors are important for the activation of Th2 cells and have been previously associated with ulcerative colitis (UC). Another focus of the work group is interleukin-9, which was identified in association with UC and is produced by a specific T-cell population, Th9 cells. The regulation of GATA-3 by the use of blocking antisense Oligonukteotide, so-called DNAzyme, could serve as a basis for a new effective therapy concept for UC. Furthermore, the effect of cyclosporin A (CsA), which is used in UC, is the subject of current studies. Here, the mechanism of action should be elucidated because CsA cannot be used in Crohn's disease and is only effective in acute UC.

# 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 and 5 as well as the Institutes of Clinical Microbiology, Immunology, and Hygiene and of Clinical and Molecular Virology, respectively. The Department of Medicine 1 offers a student ultrasound training with exclusive devices for this propose.

MD and PhD doctorates are supervised.

#### **Selected publications**

He GW, Günther C, Kremer AE, Thonn V, Amann K, Poremba C, Neurath MF, Wirtz S, Becker C. PGAM5-mediated programmed necrosis of hepatocytes drives acute liver injury. Gut. 2017 Apr;66(4):716-723

Zundler S, Schillinger D, Fischer A, Atreya R, López-Posadas R, Watson A, Neufert C, Atreya I, Neurath MF. Blockade of  $\alpha$ E $\beta$ 7 integrin suppresses accumulation of CD8+ and Th9 lymphocytes from patients with IBD in the inflamed gut in vivo. Gut. 2017 Nov;66(11):1936-1948

Pavel ME et al. Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 18.10 (2017): 1411-1422

Knieling F, Gonzales Menezes J, Claussen J, Schwarz M, Neufert C, Fahlbusch FB, Rath T, Thoma OM, Kramer V, Menchicchi B, Kersten C, Scheibe K, Schürmann S, Carlé B, Rascher W, Neurath MF, Ntziachristos V, Waldner MJ. Raster-Scanning Optoacoustic Mesoscopy for Gastrointestinal Imaging at High Resolution. Gastroenterology 154.4 (2018): 807-809

Dietrich P, Koch A, Fritz V, Hartmann A, Bosserhoff AK, Hellerbrand C. Wild type Kirsten rat sarcoma is a novel microRNA-622-regulated therapeutic target for hepatocellular carcinoma and contributes to sorafenib resistance. Gut 67.7 (2018): 1328-1341

Atreya R, Neurath MF. Mechanisms of molecular resistance and predictors of response to biological therapy in inflammatory bowel disease. Lancet Gastroenterol Hepatol. 2018 Nov;3(11):790-802

#### 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 (CMR)
- Cardiac computed tomography

## **Structure of the Department**

Professorship: 1

Personnel: 215

- Doctors (of Medicine): 46
- Scientists: 3 (thereof funded externally: 2)
- Graduate students: 24

### Clinical focus areas

- Interventional cardiology
- Electrophysiology
- Intensive care medicine
- Cardiac imaging

### Research

The Department of Medicine 2 - Cardiology and Angiology conducts clinically oriented research in the field of cardiovascular diseases with three special areas of focus. One area of focus consists of fundamental scientific research on the development and progression of atherosclerosis conducted by the working group for molecular cardiology, which is located in the "Translational Research Center". Other areas of research focus are related to everyday clinical practice in the field of interventional cardiology and in the field of cardiac imaging. In addition, the Department of Medicine 2 is involved in a large number of national and international multicenter trials, primarily in the fields of interventional cardiology, invasive electrophysiology, as well as pacemaker and ICD therapy.

# Molecular and experimental cardiology

PI: Dr. B. Dietel, Dr. M. Tauchi-Brück

The Department of Medicine 2 operates two large-scale laboratories in the 'Translational Research Center' (TRC; compare own report). The focus of the scientific work of this working group is the investigation of basic mechanisms, which contribute to the development and progression of atherosclerotic vascular deposits. In addition to genotyping studies, cell culturebased analytical methods as well as experimental animal studies are conducted by the working group. Based on the molecular biological findings, therapeutic approaches are developed and tested for their suitability for prevention and treatment of atherosclerosis.

#### Interventional cardiology

#### PI: Dr. L. Gaede

In addition to single and multi-center studies on the analysis of coronary physiology by means of pressure wire measurement (FFR), the integration of non-invasive imaging (echocardiography and CT) for guidance of interventional therapy in the cardiac catheterization laboratory is a special focus of the scientific activity. This includes complex coronary interventions such as the recanalization of chronic vascular occlusions, transcatheter treatment of different valvular pathologies, the closure of paravalvular leaks as well as structural defects ASD and VSD, and the implantation of atrial appendage occluders.

Another intensive research focus is the simulation of FFR data from anatomical models based on invasive coronary angiography.



Simulation of Fractional Flow Reserve (FFR), based on coronary anatomy obtained from invasive coronary angiography

#### Interventional valve treatment PI: PD Dr. M. Arnold

In addition to analysis of procedural parameters and outcome after transcatheter aortic valve implantation (TAVI), the treatment of mitral and tricuspid valve regurgitation with transcatheter techniques is a particularly intensive field of research. Furthermore, the Department of Medicine 2 participates in several national and international registries, including a registry concerning treatment of tricuspid valve regurgitation with the use of the "Cardioband".

#### Electrophysiology

PI: PD Dr. M. Arnold

The focus of the scientific activity is the development and evaluation of procedures for cardiac resynchronization therapy. A recent area of research is the evaluation of an intracardiac left ventricular stimulation system for cardiac resynchronization therapy without the need for placing a lead in coronary veins.

Another focus is the evaluation of laser ablation in patients with atrial fibrillation within the context of international multicenter studies.

Likewise, the utility of esophageal cooling techniques to avoid complications in cases of complex left atrial ablation treatments is being systematically investigated.

#### **Cardiac magnetic resonance (CMR)** PI: PD Dr. M. Marwan

This working group within the Department of Medicine 2 works in close cooperation with the Institute of Radiology.

One focus of the working group is the optimization of image acquisition protocols in patients with cardiac arrhythmias and on late gadolinium enhancement (LGE) for the prediction of tissue viability in patients with chronically occluded coronary arteries.

In addition, the use and applicability of T1-mapping techniques for tissue characterization is an important area of research that allows contrastfree scar and fibrosis imaging in patients with a history of infarction, hypertrophic or dilated cardiomyopathy, peri-myocarditis, or cardiac amyloidosis.

#### **Cardiac computed tomography**

PI: PD Dr. M. Marwan

The working group pursues several projects in the field of non-invasive coronary imaging using CT, for example the non-invasive determination of the fractional flow reserve from CT coronary angiography data sets.

A new area of interest is the analysis of myocardial "strain" from CT, i.e. deformation of the myocardium during contraction and relaxation using dynamic CT data sets.

In collaboration with international partners, the group is involved in research projects regarding the role of epicardial adipose tissue as a marker of the extent and activity of coronary atherosclerosis with the aim of predicting future cardiac events. Innovative, complex software algorithms are used for the analysis of fatty tissue. A further key focus is the planning and optimization of cardiac interventions using computed tomography in the sense of "therapeutic imaging" (complex coronary interventions, transcatheter aortic valve replacement, left atrial appendage occlusion, and other interventions in structural heart disease).

### Teaching

The Department of Medicine 2 participates with compulsory and elective subjects in the curricular teaching of Medicine, with a special emphasis on bedside and interactive teaching. We supervise MD theses.

#### **Selected publications**

Achenbach S, Paul JF, Laurent F, Becker HC, Rengo M, Caudron J, Leschka S, Vignaux O, Knobloch G, Benea G, Schlosser T, Andreu J, Cabeza B, Jacquier A, Souto M, Revel D, Qanadli SD, Cademartiri F; X-ACT Study Group. Comparative assessment of image quality for coronary CT angiography with iobitridol and two contrast agents with higher iodine concentrations: iopromide and iomeprol. A multicentre randomized double-blind trial. Eur Radiol. 2017;27(2):821-830

Gaede L, Liebetrau C, Dörr O, Blumenstein J, Elsässer A, Hamm CW, Möllmann H, Schlundt C, Nef HM, Achenbach S. Long-term clinical outcome after implantation of the self-expandable STENTYS stent in a large, multicenter cohort. Coron Artery Dis. 2017;28(7):588-596

Hell MM, Achenbach S, Yoo IS, Franke J, Blachutzik F, Roether J, Graf V, Raaz-Schrauder D, Marwan M, Schlundt C. 3D printing for sizing left atrial appendage closure device: Head-to-head comparison with computed tomography and transesophageal echocardiography. EuroIntervention. 2017;13(10):1234-1241

Bittner DO, Mayrhofer T, Puchner SB, Lu MT, Maurovich-Horvat P, Ghemigian K, Kitslaar PH, Broersen A, Bamberg F, Truong QA, Schlett CL, Hoffmann U, Ferencik M. Coronary Computed Tomography Angiography-Specific Definitions of High-Risk Plaque Features Improve Detection of Acute Coronary Syndrome. Circ Cardiovasc Imaging. 2018 Aug;11(8):e007657

Goeller M, Achenbach S, Cadet S, Kwan AC, Commandeur F, Slomka PJ, Gransar H, Albrecht MH, Tamarappoo BK, Berman DS, Marwan M, Dey D. Pericoronary Adipose Tissue Computed Tomography Attenuation and High-Risk Plaque Characteristics in Acute Coronary Syndrome Compared With Stable Coronary Artery Disease. JAMA Cardiol. 2018 Sep 1;3(9):858-863

Marwan M, Ammon F, Bittner D, Röther J, Mekkhala N, Hell M, Schuhbaeck A, Gitsioudis G, Feyrer R, Schlundt C, Achenbach S, Arnold M. CT-derived left ventricular global strain in aortic valve stenosis patients: A comparative analysis pre and post transcatheter aortic valve implantation. J Cardiovasc Comput Tomogr. 2018 May - Jun;12(3):240-244

#### 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

 $\mathsf{Prof.}$  Dr. P. Smits, Maasstad Hospital, Rotterdam: The Netherlands

# Department of Medicine 3 – Rheumatology and Immunology

Chair of Internal Medicine III

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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 neutrophile 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)
- Immunbiology and molecular mechanisms of inflammation
- Analysis of inflammatory mechanisms in adult onset Still's disease
- Molecular and cellular immunology in metabolism
- Epidemiology and experimental imaging

# **Structure of the Chair**

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 Medicine 3 focuses on translational and clinical inflammation research to decipher the mechanisms that are responsible for pathogenesis and perpetuation of rheumatic inflammatory and autoimmune diseases. The emphasis of the experimental research is on the interaction between immune cells and cells of affected organs. The main focus of the clinical research is 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 neutrophile 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

Various national and international phase lb-IV studies are conducted to investigate new treatment approaches in rheumatic diseases. The major focus are on treatments with "biologicals and small molecules", e.g. blockade of the proinflammatory cytokine TNF $\alpha$ , IL-6, IL-17, IL12/23, 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) Pl: Prof. Dr. |. 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. A. Bozec

Arthritis, adipose, and diabetes appear to form an alliance that has a 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 adipozytes.

# Pathomechanisms of bone destruction in RA

PI: Prof. Dr. G. Schett, Dr. U. Steffen

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.

# Immunbiology and molecular mechanisms of inflammation

PI: Prof. Dr. G. Krönke

Insights into basic principles of immunity are a key for the better understanding of autoimmunity and inflammation. Simultaneously, they allow the development of new therapeutic strategies for autoimmune and chronic inflammatory diseases. We investigate molecular mechanisms that link innate and adaptive immunity and thus influence inflammation, tolerance, and autoimmune responses. Our aim is to understand key decisions points that trigger a physiological immune response or cause autoimmunity (e.g. RA and systemic lupus).

# 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 immunomedulators (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.

# Epidemiology and experimental imaging

PI: Dr. A. Kleyer, Dr. D. Simon

Epidemiological research with well-defined patient cohorts is an essential element to understand the course of rheumatic diseases and to provide optimal targeted treatment. Our group is particularly interested in the early stages of RA and psoriatic arthritis (PsA). We are developing and establishing new outcome measures by using experimental imaging to study the transition from silent disease to clinical evident inflammation.

## Teaching

The Department of Medicine 3 is embedded into the curriculum-based teaching of the Medicine and Dentistry. 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**

Kienhöfer D et al. Experimental lupus is aggravated in mouse strains with impaired induction of neutrophil extracellular traps. JCI Insight. 2017 May 18;2(10): pii: 92920

Pfeifle R et al. Regulation of autoantibody activity by the IL-23-TH17 axis determines the onset of autoimmune disease. Nat Immunol. 2017, 18(1):104–113

Rauber S et al. Resolution of inflammation by interleukin-9-producing type 2 innate lymphoid cells. Nat Med. 2017, 23(8):938-944

Meng X, Grötsch B, Luo Y, Knaup KX, Wiesener MS, Chen XX, Jantsch J, Fillatreau S, Schett G, Bozec A. Hypoxia-inducible factor-1 $\alpha$  is a critical transcription factor for IL-10producing B cells in autoimmune disease. Nat Commun. 2018 Jan 17;9(1):251

Lucas S, Omata Y, Hofmann J, Böttcher M, Iljazovic A, Sarter K, Albrecht O, Schulz O, Krishnacoumar B, Krönke G, Herrmann M, Mougiakakos D, Strowig T, Schett G, Zaiss MM. Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. Nat Commun. 2018 Jan 4;9(1):55

Zehender A, Huang J, Györfi AH, Matei AE, Trinh-Minh T, Xu X, Li YN, Chen CW, Lin J, Dees C, Beyer C, Gelse K, Zhang ZY, Bergmann C, Ramming A, Birchmeier W, Distler O, Schett G, Distler JHW. The tyrosine phosphatase SHP2 controls TGF $\beta$ -induced STAT3 signaling to regulate fibroblast activation and fibrosis. Nat Commun. 2018 Aug 14;9(1):3259

#### 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: UK

# Department of Medicine 3 – Rheumatology and Immunology

**Division of Molecular Immunology** 

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### Head of Division

Prof. Dr. rer. nat. Hans-Martin Jäck

#### Contact

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### **Research focus**

- The role of miRNA in B cell maturation and pathogenesis of multiple myeloma
- Nonsense-codon mediated decay of nonfunctional mRNA
- Molecular control of early B cell differentiation
- Molecular control of peripheral B cell and plasma cell differentiation
- Selection of B cells
- Metabolic control of B cells

### **Structure of the Division**

Professorship: 1

Personnel: 17

- 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 nonfunctional mRNA (mRNA surveillance). Nonsense Ig mRNA is encoded from non-productively rearranged Ig genes during B cell development because of a defective VDJ recombination. As faulty mRNA can be translated into potentially toxic proteins, the elucidation of control mechanisms and factors involved in mRNA decay is of interest for B and T cell maturation. The role of NMD in central B cell maturation is analyzed in a mouse line in which a specific NMD factor which was discovered in our laboratory can be conditionally deleted in developing B cell progenitors. In parallel, immunoprecipitation analyses followed by mass spectrometry analyses are carried out to identify novel interaction partners and their role in the degradation of faulty mRNAs and early B cell maturation.

# Molecular control of 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 miRNAs. In future studies, we will analyze further potential target genes of KLF2 and their role in pre-B cell differentiation.

### 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. We are currently dissecting the underlying mechanisms by identifying new target genes of KLF2 using comparative transcriptome and single cell sequencing 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.

#### Selection of B cells

#### PI: Prof. Dr. D. Mielenz

The hallmark of every B cell is the B cell receptor (BCR), which specifically recognizes a foreign antigen and thus mediates on the one hand the effective and specific immune response, but at the same time prevents potentially dangerous interactions of B cells with endogenous substances. Newly formed B cells must therefore be selected positively for the presence of BCR. At the same time, a negative selection is required in which self-reactive B cells are sorted out. In addition, the BCR must be able to recognize foreign substances (= antigens) of any structure without the humoral immune system reacting with hypersensitivity reactions, such as IgE-mediated type I allergy. In specialized structures, so-called germinal centers, the B cell memory is generated, which is needed to establish a longlasting, highly specific immunity. The various demands imposed on the BCR in the course of development and selection therefore require a finely tuned intracellular signal transmission machinery and a flexible adaptation of the metabolism. Many of these elements are not fully characterized yet. The main goal of this project is to understand BCR selection during B cell development and germinal center reaction. Particular attention is paid to the B cell cytoskeleton, metabolism, and intracellular transport structures.

#### **Metabolic control of B cells**

PI: Prof. Dr. Dr. D. Mielenz

B cells reprogram their metabolism after BCR activation, but also after activation via TLR4, CD40, and the interleukin-4 receptor in the course of plasma cell differentiation. The reprogramming of the metabolism also plays an important role in particular in the case of the pre-BCR checkpoint. In this project we investigate how the mitochondrial respiratory chain and the mitochondrial Ca2+ concentration influence the pre-BCR control point and plasma cell differentiation. We also work on a mitochondrial, Ca2+ binding protein, Swiprosin-2/EFhd1, which influences the mitochondrial Ca2+ concentration after ROS Induction and Cxcr4 activation in pro-B cells and thereby possibly requlates the mitochondrial respiratory chain. Our results to date suggest that the mitochondrial respiratory chain is essential for the development of B cells in the bone marrow at the pre-BCR checkpoint as well as for the development of plasma cells. The focus is now on the mitochondrial control of transcription factors such as Bach-2 and Blimp-1. Based on this work, indepth analyses could lead to targeted manipulation of B cell metabolism during plasma cell differentiation and selective depletion of unwanted plasma cells.



Establishment of a four-color fluorescence-based flow cytometry protocol that distinguishes viable dividing plasmablasts from nondividing plasma cells and, based on CD19 surface abundance, identifies two mature plasma cell populations in the spleen and the bone marrow of mice

(according to Pracht K et al., Eur. J. Immunol. 2017)

# 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**

Stein M, Dütting S, Mougiakakos D, Bösl M, Fritsch K, Reimer D, Urbanczyk S, Steinmetz T, Schuh W, Bozec A, Winkler TH, Jäck HM, Mielenz D. A defined metabolic state in pre B cells governs B-cell development and is counterbalanced by Swiprosin-2/EFhd1, Cell Death Differ. 2017, 24(7): 1239-1252

Pracht K, Meinzinger J, Daum P, Schulz SR, Reimer D, Hauke M, Roth E, Mielenz D, Berek C, Côrte-Real J, Jäck HM, Schuh W. A new staining protocol for detection of murine antibody-secreting plasma cell subsets by flow cytometry, Eur J Immunol. 2017, 47(8): 1389-1392

Lang SC, Harre U, Purohit P, Dietel K, Kienhöfer D, Hahn J, Baum W, Herrmann M, Schett G, Mielenz D. Neurodegeneration Enhances the Development of Arthritis. J. Immunol. 2017, 198, 2394–2402

Urbanczyk S, Stein M, Schuh W, Jäck HM, Mougiakakos D, Mielenz D. Regulation of energy metabolism during early B lymphocyte development. Int J Mol Sci. 2018 Jul 27;19(8). pii: E2192

Haberland K, Ackermann JA, Ipseiz N, Culemann S, Pracht K, Englbrecht M, Jäck HM, Schett G, Schuh W, Krönke G. Eosinophils are not essential for maintenance of murine plasma cells in the bone marrow, Eur J Immunol. 2018, 48(5): 822-828

Meinzinger J, Jäck HM, Pracht K. miRNA meets plasma cells "How tiny RNAs control antibody responses", Clin Immunol. 2018 Jan;186:3-8

#### International cooperations

Prof. A. Cunningham, University of Birmingham: UK

Dr. O. Baris, CNRS Angers: France

Dr. E. Greotti, University of Padova: Italy

# Department of Medicine 4 – Nephrology and Hypertension

Chair of Internal Medicine IV

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#### Director

Prof. Dr. med. Mario Schiffer

#### Contact

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#### **Research focus**

- Identification and modification of hereditary kidney disease
- Pathophysiological relevance of hypoxiainducible gene expression
- Pathogenesis of arterial hypertension and hypertensive target organ damage
- Systemic consequences of chronic kidney disease
- Acute and chronic renal allograft failure

### **Structure of the Department**

Professorships: 5

Personnel: 231

- Doctors (of Medicine): 51
- Scientists: 13 (thereof funded externally: 11)
- Graduate students: 16

### **Clinical focus areas**

- Diagnosis and treatment of all acute and chronic kidney diseases
- Kidney transplantation including living donor transplantation
- Sepsis and multiorgan failure
- Extracorporeal blood purification
- Refractory arterial hypertension

### Research

Research at the Department of Nephrology and Hypertension has a strong translational focus. Accordingly, projects encompass experimental and patient-orientated research. Our research aims at better understanding the initiation and course of acute and chronic kidney diseases and the development and complications of arterial hypertension.

The appointment of Prof. Dr. Mario Schiffer as new director of our Department has especially strengthened our research fields "Identification and modification of hereditary kidney disease" and "Acute and chronic renal allograft failure". Furthermore, a new research focus "Proteinuric kidney diseases" will be established.

# Identification and modification of hereditary kidney disease

PI: Prof. Dr. M. Schiffer, Prof. Dr. M. Wiesener, PD Dr. B. Buchholz

Recent advances in sequencing technologies permit comprehensive searches for possible genetic causes of kidney diseases, particularly in cases with a family history of the disease. Meticulous assessment of family history, pathological changes, and comorbidities is required. Experimental approaches including cell culture and zebrafish models are used to test for the functional relevance of identified genetic mutations. The ultimate aims are the improvement of diagnostic and therapeutic approaches in these kidney diseases. We developed a specific immunohistological test for one form of hereditary tubulointerstitial kidney disease.

Further work focused on one relatively frequent genetic disease, autosomal dominant polycystic kidney disease (ADPKD). Pharmacological interventions to alleviate cyst growth were tested in cell culture and mouse models. In addition, patients with ADPKD are offered participation in observational or therapeutic multicenter studies in our outpatient clinic.



Distinct biallelic expression of mucin 1 and MUC1-fs: (A) Immunohistochemical staining and (B) immunofluorescent detection of mucin 1 (C-term) and MUC1-fs in renal tubules of a patient with ADTKD-MUC1 (green, MUC1fs; red, wild-type mucin 1)

# Pathophysiological relevance of hypoxia-inducible gene expression

PI: Prof. Dr. C. Willam, PD Dr. Dr. J. Schödel, PD Dr. C. Warnecke

One pathomechanism, which is highly relevant in acute kidney failure as well as in the development of renal cell carcinoma, concerns hypoxia in kidney tissue. Focus of these studies is the regulation and functional role of the hypoxia inducible transcription factors HIF-1 and HIF-2. Based on studies of the physiological expression of these factors and their regulating enzymes, the activity of the HIF system is being investigated in different types of kidney disease. In addition, experiments are performed to test if kidney disease can be influenced by modulation of the HIF system. In addition, the epigenetic regulation of HIF transcription is being investigated in renal cell carcinoma. In parallel, the potential long term consequences of hypoxia on renal structure are being analyzed, in particular fibrogenesis, epithelial mesenchymal transition, and the growth of renal cysts.

# Pathogenesis of arterial hypertension and hypertensive target organ damage

PI: Prof. Dr. R. Schmieder, Prof. Dr. J. Titze, Prof. Dr. R. Veelken, Dr. C. Kopp

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 nonosmotically active sodium exist in the body and that their capacity has an important impact on blood pressure regulation. 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 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.

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.

# Systemic consequences of chronic kidney disease

PI: Prof. Dr. K.U. Eckardt, Prof. Dr. K.F. Hilgers 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 in this context deal with epidemiological questions, aspects of public health care, and the causes of an increased cardiovascular risk. 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 collaborate with the coordinating center in Erlangen to study 5,000 patients with chronic kidney disease and to follow them for up to ten years. These patient-centered studies are complemented by experimental investigations of mechanisms of vascular disease in rodent models of chronic kidney failure. We could show that post-ischemic angiogenesis following arterial occlusion is impaired in rats with chronic kidney disease, and that stimulation of HIF improved post-ischemic angiogenesis under these circumstances.

# Acute and chronic renal allograft failure

PI: Prof. Dr. M. Schiffer, Prof. Dr. M. Wiesener, Dr. K. Heller

In cooperation with the departments of Urology and of Surgery, around 70 kidney and combined kidney-pancreas transplantations are performed per year, including living donor transplantations. Blood group incompatible living donation is a particular focus. The research program in this field aims at optimizing long term graft function. Therefore, our transplant center was included in the innovative NTX 360° project, which aims to improve long-term care of kidney transplant recipients.

In addition, multicenter trials and observational studies are being conducted to evaluate novel immunosuppressive drugs or their combination.

## Teaching

The Department of Medicine 4 contributes in many ways to the teaching schedule in internal medicine, including lectures, seminars, bedside teaching in small groups, and internships. We offer electives featuring interdisciplinary teaching, focusing on vascular medicine (together with the Department of Pediatrics and Adolescent Medicine) or intensive care medicine (together with the Department of Anesthesiology). Our faculty members supervises Bachelor's and Master's theses as well as MD and PhD theses.

### **Selected publications**

Grampp S, Schmid V, Salama R, Lauer V, Kranz F, Platt JL, Smythies J, Choudhry H, Goppelt-Struebe M, Ratcliffe PJ, Mole DR, Schödel J. Multiple renal cancer susceptibility polymorphisms modulate the HIF pathway. PLoS Genet. 2017 Jul 17; 13(7):e1006872 Schneider MP, Raff U, Kopp C, Scheppach JB, Toncar S, Wanner C, Schlieper G, Saritas T, Floege J, Schmid M, Birukov A, Dahlmann A, Linz P, Janka R, Uder M, Schmieder RE, Titze JM, Eckardt KU. Skin Sodium Concentration Correlates with Left Ventricular Hypertrophy in CKD. J Am Soc Nephrol. 2017 Jun;28(6):1867-1876

Schellinger IN, Cordasic N, Panesar J, Buchholz B, Jacobi J, Hartner A, Klanke B, Jakubiczka-Smorag J, Burzlaff N, Heinze E, Warnecke C, Raaz U, Willam C, Tsao PS, Eckardt KU, Amann K, Hilgers KF. Hypoxia inducible factor stabilization improves defective ischemia-induced angiogenesis in a rodent model of chronic kidney disease. Kidney Int. 2017 Mar;91(3):616-627

Kraus A, Peters DJM, Klanke B, Weidemann A, Willam C, Schley G, Kunzelmann K, Eckardt KU, Buchholz B. HIF-1 $\alpha$  promotes cyst progression in a mouse model of autosomal dominant polycystic kidney disease. Kidney Int. 2018 Nov;94(5):887-899

Knaup KX, Hackenbeck T, Popp B, Stoeckert J, Wenzel A, Büttner-Herold M, Pfister F, Schueler M, Seven D, May AM, Halbritter J, Gröne HJ, Reis A, Beck BB, Amann K, Ekici AB, Wiesener MS. Biallelic Expression of Mucin-1 in Autosomal Dominant Tubulointerstitial Kidney Disease: Implications for Nongenetic Disease Recognition. J Am Soc Nephrol. 2018 Sep;29(9):2298-2309

Ott C, Kopp C, Dahlmann A, Schmid A, Linz P, Cavallaro A, Hammon M, Ditting T, Veelken R, Uder M, Titze J, Schmieder RE. Impact of renal denervation on tissue Na(+) content in treatment-resistant hypertension. Clin Res Cardiol. 2018 Jan;107(1):42-48

#### International cooperations

Prof. R. Kleta, University College, London: UK

Prof. P.J. Ratcliffe, University of Oxford, Oxford: UK

Prof. M.D. Feldman, University of Philadelphia, Philadelphia: USA

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

Prof. D. Peters, University of Leiden, Leiden: The Netherlands

# Department of Medicine 5 – Hematology and Oncology

Chair of Hematology and Oncology

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Director

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#### **Research focus**

- Immune regulation by DN T cells
- Adoptive cell therapy with memory B-lymphocytes for patients after allogeneic stem cell transplantation (alloSCT)
- T cells between immunotherapy and autoimmunity
- Immunometabolism
- Tumor associated macrophages and posttranscriptional regulation by Hoxa9
- Communication of tumor cells and microenvironment
- Molecular immunotherapy
- T cell-based immunotherapy of ocular melanoma
- Tumor microenvironment
- Tumor immune escape
- Cellular immunotherapy
- HLA-laboratory

# **Structure of the Department**

Professorships: 2

- Personnel: 131
- Doctors (of Medicine): 38
- Scientists: 9 (thereof funded externally: 7)
- Graduate students: 13

### **Clinical focus areas**

- In-patient and out-patient care of patients with leukemia, lymphoma, and non-malignant hematologic diseases
- Allogeneic and autologous stem cell transplantation
- Out-patient stem cell transplant unit
- In-patient and out-patient care of patients with urological tumors, bone and soft tissue sarcoma, head and neck tumors, lung tumors and other solid tumors
- Out-patient unit for urologicial tumors (AURONTE)
- Hematological diagnostics

#### Research

The main research focus of the Department of Medicine 5 concentrates on tumor immunology. Several research groups examine basic immunological mechanisms of tumor formation, tumor defense, and tumors escape. We have a special research focus on the characterization and blockade of graft-versus-host reactions after allogeneic stem cell transplantation and the improvement of graft-versus-leukemia responses. The long-term goal is to translate these concepts into innovative cell-based therapies.

#### 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: DFG, 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: DFG

# T cells between immunotherapy and autoimmunity

### PI: PD Dr. Dr. A.N. Kremer

The main focus of this group is the separation of beneficial graft-versus-leukemia (GvL) effect after alloSCT from detrimental GvHD by characterization of the intracellular processing pathways of HLA class II restricted antigens as well as the identification of tumor-specific T-cell targets in breast cancer.

Further we analyze the role of these antigens in the pathogenesis of autoimmune diseases and the CD4+ T cell mediated eradication of HLA class II negative tumors via indirect antigen presentation.

Funding: DFG, Else Kröner Fresenius Foundation, Ernst Jung-Foundation, IZKF

#### Immunometabolism

PI: Prof. Dr. D. Mougiakakos

We focus on alterations of the metabolism and the immune system in cancer and after stem cell transplantation. An understanding regarding tumor-associated (metabolic) strategies contributing to an immunosuppression will support development of therapeutic strategies. Furthermore, we aim at "learning" how tumors weaken immune responses in order to translate these findings into potential experimental approaches for the treatment of GvHD following SCT.

Funding: 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: PD 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 protumorigenic because they promote angiogenesis and metastasis. The underlying mechanisms responsible for this observation remain unclear. Our research is focused on the functional and molecular analysis of the tumor microenvironment and aims at identifying and modulating potential therapeutic target structures. 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 posttranscriptional 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: DFG, 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 approach for lymphoma patients.

Funding: ELAN, Trunk Foundation, industry, DFG

#### Molecular immunotherapy

#### PI: Dr. F. Müller

The young research group exploits antibodytargeted 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: DFG, IZKF, Research Foundation of Medicine, industry

# T cell-based immunotherapy of ocular melanoma

#### PI: Dr. J. Bosch

The main focus of our research group is to develop a T cell-based immunotherapy specifically designed for treatment of ocular melanoma. We focus on analysis of immune cell infiltration in the primary tumor originating in the immune-privileged eye. In addition, we determine if uveal melanoma vaccines or bi-specific antibodies activate different subpopulations of CD4+ T cells and which cytokines activated T cells secrete. Furthermore, we test if chimeric antigen receptor modified (CAR) T cells are reactive and cytotoxic against uveal melanoma cells. Funding: DFG

# Tumor-microenvironment and transendothelial migration

PI: Dr. Y. Resheq

Our group analyses the impact of H<sub>2</sub>O<sub>2</sub>-depletion on dendritic cells in the tumor microenvironment in order to understand the significance of this mechanism. Additionally, we focus study the transendothelial migration of immune-cells in various diseases (including GvHD and RCC due to its immunogenic properties). Herein, we use so called flow-based adhesion assays allowing a precise visualizing of the transmigrationcascade and thus the identification of innovative therapeutical targets.

Funding: ELAN, Staedtler Foundation, Roggenbuck Foundation, Research Foundation of Medicine

#### 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: DFG

#### **Cellular immunotherapy**

PI: Prof. Dr. A. Mackensen, Dr. R. Gary, Dr. M. Aigner

The focus of this group lies on adoptive T cell therapy. Within the scope of a clinical trial phase I/IIa, CMV- and EBV-specific T cells are manufactured for patients after allogeneic stem cell transplantation to mediate protection against CMV and EBV infection. The T cell reconstitution after alloSCT is analyzed by Next Generation Sequencing of T cell receptors in cooperation with Charité Berlin.

In addition, we are establishing the GMP compliant manufacturing of CARs (chimeric antigen receptor T cells) and TRUCKS (cytokine producing CARs) and their translation to the clinic. Funding: Deutsche Krebshilfe

#### **HLA-laboratory**

PI: Prof. Dr. B. Spriewald

In recent years, the laboratory has been interested in new methods for the detection of various subclasses of anti-HLA antibodies in solid organ transplantation. Our immunogenetic studies look into polymorphisms of several cytokines and T cell regulatory genes and their association with rheumatic and malignant disorders. Another focus is on experimental studies for the induction of transplantation tolerance and reduction of chronic rejection. These studies are performed in close collaboration with the working group of experimental heart surgery.

### Teaching

The Department of Medicine 5 takes part in the curricular teaching for Medicine and Dentistry. Bachelor's and Master's theses as well as MD and PhD theses are offered and supervised regularly.

#### Selected publications

Tittlbach H, Schneider A, Strobel J, Zimmermann R, Maas S, Gebhardt B, Rauser G, Mach M, Mackensen A, Winkler TH, Winkler J. GMP-production of purified human B lymphocytes for the adoptive transfer in patients after allogeneic hematopoietic stem cell transplantation. J Transl Med. 2017 Nov 7;15(1):228

Resheq YJ, Menzner AK, Bosch J, Tickle J, Li KK, Wilhelm A, Hepburn E, Murihead G, Ward ST, Curbishley SM, Zimmermann HW, Bruns T, Gilbert DF, Tripal P, Mackensen A, Adams DH, Weston CJ. Impaired Transmigration of Myeloid-Derived Suppressor Cells across Human Sinusoidal Endothelium Is Associated with Decreased Expression of CD13. J Immunol. 2017 Sep 1;199(5):1672-1681

Bruns H, Böttcher M, Qorraj M, Fabri M, Jitschin S, Dindorf J, Busch L, Jitschin R, Mackensen A, Mougiakakos D. CLLcell-mediated MDSC induction by exosomal miR-155 transfer is disrupted by vitamin D. Leukemia. 2017 Apr;31(4):985-988

Jitschin R, Saul D, Braun M, Tohumeken S, Völkl S, Kischel R, Lutteropp M, Dos Santos C, Mackensen A, Mougiakakos D. CD3J/CD3-bispecific T-cell engaging (BiTE®) antibody construct targets monocytic AML myeloid-derived suppressor cells. J Immunother Cancer. 2018 Nov 5;6(1):116

Spriewald BM, Bach C, Zingsem J, Strobel J, Winkler J, Mackensen A, Roesler W. Depletion of donor-specific anti-HLA A2 alloantibodies in a hematopoietic cell transplant recipient using directed mismatched platelet transfusions. Bone Marrow Transplant. 2018 Jun;53(6):791-794

Gary R, Aigner M, Moi S, Schaffer S, Gottmann A, Maas S, Zimmermann R, Zingsem J, Strobel J, Mackensen A, Mautner J, Moosmann A, Gerbitz A. Clinical-grade generation of peptide-stimulated CMV/EBV-specific T cells from G-CSF mobilized stem cell grafts. J Transl Med. 2018 May 9;16(1):124

#### International cooperations

M. Miano, MD, Department of Pediatric Haematology-Oncology, IRCCS Istituto Giannina Gaslini, Genoa: Italy

Prof. F. Falkenburg, Leiden University: The Netherlands

Dr. T. Graf, Centre for Genomic Regulation, University of Barcelona: Spain

Dr. I. Pastan, NCI, NIH, Bethesda: USA

Prof. R. Kiessling, Karolinska Institut, Stockholm: Sweden

# **Department of Neurology**

# Chair of Neurology

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#### Contact

Prof Dr. med. Frank Seifert, MHBA Phone: +49 9131 8544512 Fax: +49 9131 8534846 frank.seifert@uk-erlangen.de

#### **Research focus**

- Stroke research clinical and experimental
- Neurocritical care
- Telemedicine and health services
- Epilepsy
- Neuroimmunology
- Pain and functional imaging
- Autonomic nervous system
- Neuromuscular diseases
- Dystonia and botulinum toxin therapy
- Neuro-oncology

# **Structure of the Chair**

Professorships: 4

Personnel: 309

- Doctors (of Medicine): 64
- Scientists: 12 (thereof funded externally: 9)
- Graduate students: 35

#### **Clinical focus areas**

- Emergency care
- Stroke
- Neurocritical care
- Epilepsy center of epilepsy (EZE)
- Neuroimmunology
- Neuromuscular diseasesPain medicine
- Neuro-oncology
- Autonomic nervous system disorders
- Neurophysiology
- Ultrasound
- Dystonia und botulinum toxin therapyNeurocognitive disorders
- riveurocognitive di
- Telemedicine

# Research

The Department of Neurology is one of the largest neurological centers in Germany treating 4,000 in-patients and more than 19,000 outpatients each year. The research activities of our Department are shown in detail below. During the reporting period more than 200, some of them high-ranking publications, could be published.

# Stroke research – clinical and experimental

PI: Prof. Dr. H. Huttner, PD Dr. B. Kallmünzer 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, and secondary prevention of cardioembolism.



Neuronal cell culture

### 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: PD Dr. L. 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 networkwide 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, MHBA

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;
- Magnetoencephalography;
- 5) Neuropsychology/Cognition and invasive EEG;
- Quantitative EEG in epilepsy and encephalopathy;
- 7) Drug monitoring;
- 8) Historical aspects of epileptology;
- 9) Socio-economic aspects of epilepsy.

Funding: EU, DFG, Bavarian State Ministry of Health and Care

### Neuroimmunology

PI: Prof. Dr. R. Linker

- Three research groups successfully focus on
- 1) immunregulation and biomarkers in multiple sclerosis (MS) patients,
- neuroprotection and neurodegeneration in experimental models with a focus on glial cells, and
- 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 Erlangen, DFG, several industryfunded research projects

### Pain and Headache

PI: Prof. Dr. F. Seifert

This group investigates neural mechanisms of sensory, autonomic, and cognitive processing in pain disorders (neuropathic pain, headache), stroke, and MS. We use psychophysical and autonomic testing combined with functional and structural brain imaging methods (voxel-based lesion symptom mapping (VLSM), functional magnetic resonance imaging (fMRI), repetitive transcranial magnetic stimulation (rTMS).

#### Autonomic nervous system

PI: 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, MS, traumatic brain injury, and in persons who are exposed to repetitive mild head and brain injuries.



Neuronal cell culture

#### **Neuromuscular diseases**

PI: Dr. M. Türk, Dr. C. Möbius, 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:

- Immunopathogenesis of autoimmune myositis, myasthenia gravis, and immune neuropathies;
- Studies on the pathogenesis of myofibrilar 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 ultrasoundguided electromyography.

#### Neuro-oncology PI: PD Dr. M. Uhl

The goal of interdisciplinary neuro-oncology is the treatment of patients with brain tumors. Beside the daily routine patients, we have the ambition to provide attractive clinical trials for all patients. A focus here are currently translational immune therapy studies of the phases II and III.

### Teaching

Between everyday clinical 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, Köhrmann M, Crodel C, Kloska S, Dörfler A, Hösl KM, Schwab S, Hilz MJ. Lesion mapping of stroke-related erectile dysfunction. Brain. 2017 Jun 1;140(6):1706-1717

Staykov D, Kuramatsu JB, Bardutzky J, Volbers B, Gerner ST, Kloska SP, Doerfler A, Schwab S, Huttner HB. Efficacy and safety of combined intraventricular fibrinolysis with lumbar drainage for prevention of permanent shunt dependency after intracerebral hemorrhage with severe ventricular involvement: A randomized trial and individual patient data meta-analysis. Ann Neurol. 2017 Jan;81(1):93-103

Wilck N et al. Salt-responsive gut commensal modulates T(H)17 axis and disease. Nature. 2017 Nov 30;551(7682): 585-589

Kuramatsu JB et al. Management of therapeutic anticoagulation in patients with intracerebral haemorrhage and mechanical heart valves. Eur Heart J. 2018 May 14;39(19): 1709-1723

Lang JD, Kostev K, Onugoren MD, Gollwitzer S, Graf W, Müller T, Olmes DG, Hamer HM. Switching the manufacturer of antiepileptic drugs is associated with higher risk of seizures: A nationwide study of prescription data in Germany. Ann Neurol. 2018 Dec;84(6):918-925

Gerner ST et al. Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. Ann Neurol. 2018 Jan;83(1):186-196

#### International cooperations

Prof. J. Frisen, Department of Cell and Molecular Biology, Karolinska Institute, Stockholm: Sweden

Prof. D. Henshall, Royal Collage Dublin: Ireland

S. Hanslmayr, Birmingham: UK

Prof. Dr. M.-J. Hilz, Icahn School of Medicine at Mount Sinai: USA

Prof. R. Guerrini, Florence: Italy

# **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

Personnel: 20

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

## **Clinical focus areas**

- Outpatient clinical and research center for neurodegenerative movement disorders
- Center of the National Network for Parkinson's disease and European Huntington's disease Center
- Rare genetic movement disorders (Center for rare 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 workup, 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 intraand extracellular α-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 central nervous system (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, particular 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-theart 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 of 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.

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 compromising the Faculty of Engineering (Pattern Recognition Lab) and the Institute of Sport Science and Sport (Faculty of Humanities, Social Sciences, and Theology) has been funded by the Emerging Fields Initiative. 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, Portabiles Healthcare Technology, has been founded 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 (GRK 2162 "Neurodevelopment and vulnerability of the central nervous system"; compare own report) has successfully started.

#### **Selected publications**

Gassner H, Marxreiter F, Kohl Z, Schlachetzki J, Eskofier B, Winkler J, Klucken J. Gait and cognition in Parkinson's disease: cognitive impairment is inadequately reflected by gait performance during dual task. Front Neurol 2017, 8:550

Schlachetzki J, Barth J, Marxreiter F, Gossler J, Kohl Z, Reinfelder S, Gassner H, Aminian K, Eskofier B, Winkler J, Klucken J. Wearable sensors objectively measure gait parameters in Parkinson's disease. PloS One 2017, 12(10): e0183989

Regensburger M, Türk M, Pagenstecher A, Schroeder R, Winkler J. VCP-related multisystem-proteinopathy presenting as early-onset Parkinson's disease. Neurology 2017, 89(7):746-748

Marxreiter F, Gaßner H, Borozdina O, Barth J, Kohl Z, Schlachetzki JCM, Thun-Hohenstein C, Volc D, Eskofier BM, Winkler J, Klucken J. Sensor-based gait analysis of individualized improvement during apomorphine titration in Parkinson's disease. J Neurol 2018, 265(11):2656-2665

Minakaki G et al. Autophagy inhibition promotes SNCA/alpha-synuclein release and transfer via extracellular vesicles with a hybrid autophagosome-exosome-like phenotype. Autophagy 2018, 14(1): 98–119

Schlachetzki J, Prots I, Jenhan T, Chun H, Kaoru S, Gosselin D, Winner B, Glass C, Winkler J. A monocyte gene expression signature in the early clinical course of Parkinson's disease. Sci Rep 2018, 8(1):10757

#### 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
- Scull base surgery
- Epilepsy surgery
- Vascular neurosurgery
- Spine surgery
- Neurotramatology
- 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.

• 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 epilepsyassociated 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.

• 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.

#### Metabolic imaging

Major focus of this group was on studies of metabolic imaging for the characterization of the infiltration of gliomas with proton MR spectroscopy and FET-PET. Furthermore, studies of the tumor invasion into fiber tracts and its influence on their reconstruction and neurologic symptoms and studies of metabolic changes in temporal lobe lesions with 1H MR spectroscopy were investigated. Furthermore, we investigate the cortical plasticity after gliome resection adjacent to eloquent brain areas and intraoperative MR spectroscopy in gliomas.

#### Neuroendocrinology

The Department of Neurosurgery is a nationally and internationally specialized center for the whole spectrum of sellar pathologies. Clinically we investigate the influence of interventional/ operative, radiotherapeutic, and pharmacological approaches on normal and hypersecretory pituitary gland function in the course of the "Acrostudy" (treatment and MRI follow-up of the medicinal therapy with Somavert®). Also, investigations on somatostatin analoga and their clinical relevance in the treatment of growth hormone secreting pituitary adenoma represent a central part. Our clinical and laboratory chemical analyses and screening studies are supported by the companies Pfizer and Novartis. The efficacy of novel intra-operative technologies in pituitary adenoma surgery and craniopharyngiomas is evaluated. Novel procedures include endoscopic surgery, such as endoscopic assisted microsurgery and intraoperative MRI. These techniques allow controlling resections in cases of intrasellar and suprasellar tumors. Goal of these clinical long-term studies is to define the relapse frequencies of sellar tumors, including different prognostic factors.

The field of neuroendocrinology within the Department of Neurosurgery was established in 2007 in the framework of an endowed professorship for clinical and experimental neuroendocrinology (Prof. Dr. C. Schöfl, now Department of Medicine 1). In cooperation with the Institute of Radiology, body composition, liver and muscle fat content are determined by MRI in patients with various hypothalamic-pituitary diseases (e.g. pituitary deficiency, acromegaly, and M. Cushing). The results are correlated with various metabolic characteristics and with novel parameters involved in the metabolic control. The aims of these studies are to obtain novel insights in the neuroendocrine control of metabolic and energetic processes.

Another translational scientific project involves the functional characterization of mutations of the metabotropic calciumsensing 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 genotypephenotype relation. Furthermore, agonists and antagonists of the CaSR are tested in vitro whether they can rescue the molecular defect of the mutated CaSR. This potentially offers a therapeutic approach specifically tailored to patients' molecular CaSR defect (individualized medicine).

Further projects investigate various aspects of growth-hormone secreting human adenoma cells *in vitro*, like the expression of certain membrane receptors (e.g. somatostatin receptors) and the characteristics of signaling cascades (cAMP- and Ca2+-PI-signaling pathway). The *in vitro* data are related to various clinical data in order to extract potential prognostic factors concerning therapeutic outcome and to define potential new therapeutic targets.

# Neurooncology

Gliomas are the most common primary tumors of the brain and about 70% of these tumors are malignant gliomas. Currently, there is no promising therapy for the treatment of malignant tu-
mors 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.

## Teaching

The Department of Neurosurgery is involved in the curricular teaching of Medicine and Dentistry 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**

Ackermann A, Karagöz AÇ, Ghoochani A, Buchfelder M, Eyüpoglu I, Tsogoeva SB, Savaskan N. Cytotoxic profiling of artesunic and betulinic acids and their synthetic hybrid compound on neurons and gliomas. Oncotarget. 2017 Jun 7;8(37):61457-61474

Chen D, Fan Z, Rauh M, Buchfelder M, Eyupoglu IY, Savaskan N. ATF4 promotes angiogenesis and neuronal cell death and confers ferroptosis in a xCT-dependent manner. Oncogene. 2017 Oct 5;36(40):5593-5608

Buchfelder M, van der Lely AJ, Biller BMK, Webb SM, Brue T, Strasburger CJ, Ghigo E, Camacho-Hubner C, Pan K, Lavenberg J, Jönsson P, Hey-Hadavi JH. Long-term treatment with pegvisomant: observations from 2090 acromegaly patients in ACROSTUDY. Eur J Endocrinol. 2018 Dec 1;179(6): 419-427

Stadlbauer A, Zimmermann M, Doerfler A, Oberndorfer S, Buchfelder M, Coras R, Kitzwögerer M, Roessler K. Intratumoral heterogeneity of oxygen metabolism and neovascularization uncovers 2 survival-relevant subgroups of IDH1 wild-type glioblastoma. Neuro Oncol. 2018 Oct 9;20(11): 1536-1546

Stadlbauer A, Mouridsen K, Doerfler A, Bo Hansen M, Oberndorfer S, Zimmermann M, Buchfelder M, Heinz G, Roessler K. Recurrence of glioblastoma is associated with elevated microvascular transit time heterogeneity and increased hypoxia. J Cereb Blood Flow Metab. 2018 Mar;38(3):422-432

Stadlbauer A, Roessler K, Zimmermann M, Buchfelder M, Kleindienst A, Doerfler A, Heinz G, Oberndorfer S. Predicting Glioblastoma Response to Bevacizumab Through MRI Biomarkers of the Tumor Microenvironment. Mol Imaging Biol. 2018 Oct 25

#### International cooperations

Prof. DS Olsson, MSc, MD, PhD, University of Gothenburg, Göteborg: Sweden

Prof. Dr. JP Martinez-Barbera, UCL GOS Institute of Child Health, London: UK

## **Department of Nuclear Medicine**

## Chair of Clinical Nuclear Medicine

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#### Director

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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 Department of Chemistry and Pharmacy at FAU.

#### **Imaging and physics research group** PI: Dr.-Ing. P. Ritt

Advances in medical imaging have led to 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-99mand Lu177-SPECT/CT

In SPECT, image guality 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 centimeter. 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 correction of 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 dosevoxel-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 new and mild labeling techniques via F-18-fluorophenylazacarboxylate, the development of new F-18-labeled glycoconjugates and Ga-68and Lu-177-labeled ligands for the neurotensin receptor (NTS1) and for the neuropeptide-Y receptor (Y1R). We were successful to evaluate the first F-18-labeled antagonist radioligand for the in vivo detection of mammary carcinoma and to study new D3-subtype selective radioligand for the detection of D3 receptor in the brain using preclinical animal models. These projects were supported by the DFG and were performed in close cooperation with the Chair of Pharmaceutical Chemistry (Faculty of Sciences). The development of all new radiotracers has been intensively supported by small animal PET imaging studies. Moreover, the radiopharmaceutical research projects are supported by the Emerging Field Initiative of the FAU.

The GMP radiopharmacy of the clinic has the approval for the production of radiopharmaceuticals according to §13, AMG (Medicinal Products Act). Based on the translational research efforts, new radiopharmaceuticals, such as Tc-99m-MIP-1404 or Ga-68-PSMA-11 for the diagnosis of prostate cancer, have been introduced into the clinic. In the future, various new radiopharmaceuticals will be available for clinical use within the Department of Nuclear Medicine.



Evaluation of specific binding of new radiopharmaceuticals for the neurotensin receptor (NTS1): The binding of a Ga-68-labeled NTS1 ligand on tumor tissue slices (left: Control) is diminished in the presence of neurotensin (NT; middle: Competitive binding). Right: histological HE-staining of the same tumor tissue

### 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 Management. 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**

Reinfelder J, Kuwert T, Beck M, Sanders JC, Ritt P, Schmidkonz C, Hennig P, Prante O, Uder M, Wullich B, Goebell P. First Experience With SPECT/CT Using a 99mTc-Labeled Inhibitor for Prostate-Specific Membrane Antigen in Patients With Biochemical Recurrence of Prostate Cancer. Clin Nucl Med. 2017, 42(1):26-33

Maschauer S, Einsiedel J, Reich D, Hübner H, Gmeiner P, Wester HJ, Prante O, Notni J. Theranostic Value of Multimers: Lessons Learned from Trimerization of Neurotensin Receptor Ligands and Other Targeting Vectors. Pharmaceuticals 2017, 10(1):E29

Keller M, Maschauer S, Brennauer A, Tripal P, Koglin N, Dittrich R, Bernhardt G, Kuwert T, Wester HJ, Buschauer A, Prante O. Prototypic 18F-Labeled Argininamide-Type Neuropeptide Y Y1R Antagonists as Tracers for PET Imaging of Mammary Carcinoma. ACS Med Chem Lett. 2017, 8(3):304-309

Wetzl M, Sanders JC, Kuwert T, Ritt P. Effect of reduced photon count levels and choice of normal data on semiautomated image assessment in cardiac SPECT. J Nucl Cardiol. 2018, Apr 13

Schmidkonz C, Cordes M, Schmidt D, Bäuerle T, Goetz TI, Beck M, Prante O, Cavallaro A, Uder M, Wullich B, Goebell P, Kuwert T, Ritt P. 68Ga-PSMA-11 PET/CT-derived metabolic parameters for determination of whole-body tumor burden and treatment response in prostate cancer. Eur J Nucl Med Mol Imaging. 2018, 45(11):1862-1872

Schmidkonz C, Cordes M, Beck M, Goetz TI, Schmidt D, Prante O, Bäuerle T, Cavallaro A, Uder M, Wullich B, Goebell P, Kuwert T, Ritt P. Assessment of Treatment Response by 99mTc-MIP-1404 SPECT/CT: A Pilot Study in Patients With Metastatic Prostate Cancer. Clin Nucl Med. 2018, 43(8):e250-e258

## International cooperations

A.H. Vija, PhD, Siemens Molecular Imaging, Hofmann Estates: USA

A. Opanowski, Progenics Pharmaceuticals, New York: USA Dr. R. Haubner, Department of Nuclear Medicine, Medi-

zinische Universität Innsbruck, Innsbruck: Austria

Prof. Dr. M. Pomper, Johns Hopkins University, Baltimore: USA

Prof. Dr. P. Cumming, 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 f
  ür Frauengesundheit, IFG<sup>®</sup>)
- Biobanking
- Specialized obstetrics and perinatal medicine
- Laboratory for reproductive biology with gynecological endocrinology and reproductive medicine

## **Structure of the Department**

Professorships: 3

- Personnel: 364
- Doctors (of Medicine): 54
- Scientists: 8 (funded externally: 5)
- Graduate students: 17

## **Clinical focus areas**

- Laparoscopic and open surgery for gynecologic malignancies
- Conservative and operative treatment of endometriosis (rASRM IV, DIE)
- Immune therapy for gynecologic carcinomas and breast cancer
- Antenatal, intrapartum and postnatal care of high-risk patients (congenital cardiac defects, autoimmune diseases etc.)
- Intensive monitoring and care of cases with severe early preeclampsia
- Antenatal diagnostic and care of fetal malformations
- Fertility preserving therapy of malignancies including cryoconservation of ovarian tissue

## 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, Prof. Dr. P. Fasching, PD Dr. M. Rübner, PD Dr. P. Strissel 1. In collaboration with the Johns Hopkins University and the Sloan Kettering Cancer Center (USA) we demonstrated that DNA-demethylation 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 doublestranded (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. A similar interaction of endogenous retroviral genes and the interferon pathway was also detected in lung carcinoma cells, which supports a general connection of interferon induction in tumors. These interactions could therefore lead to novel treatments.

2. The establishment of primary human breast cells and breast cancer cells from tissues and tumors has advantages as 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 as 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, Prof. Dr. S. Kehl, PD Dr. F. Faschingbauer, PD Dr. M. Rübner, Dr. H. Hübner, Dr. M. Schneider, Dr. E. Schwenke

The main focus of the molecular research in obstetrics and perinatal medicine is the detection of molecular causes of gestational diseases and biomarkers for e.g. choriocarcinomas (malign transformation of trophoblast like cells), preeclampsia (PE), or intrauterine growth restriction (IUGR). In cooperation with the Department of Pediatrics and Adolescent Medicine, dysregulations within the retinoic acid signaling pathway were analyzed. The detection of a promoter hypermethylation and loss of expression of the retinoic acid dependent gene RARRES1 was awarded the science award of the Deutsche Gesellschaft für Gynäkologie und Geburtshilfe. Besides this, the impact of posttranslational tubulin modifications on the placental vascular system of placentas associated with PE or IUGR was analyzed.

## Clinical trials (Clinical Research Unit and Institut für Frauengesundheit GmbH, IFG<sup>®</sup>)

PI: Prof. Dr. M.W. Beckmann, Prof. Dr. P.A. Fasching, Dr. P. Gaß, PD Dr. L. Häberle, PD Dr. A. Hein, Dr. H. Hübner, Dr. S. Kellner, PD Dr. C.R. Löhberg, Prof. Dr. M.P. Lux, Dr. N. Nabieva, PD Dr. P.G. Oppelt, A.-K. Theuser, Dr. B. Volz Until the end of 2018, over 220 projects with clinical phase I-IV studies have been carried out. The goal is to personalize the treatment to in turn enhance the efficacy and reduce adverse events. For this purpose whole genome analyses are as used as highly modern target therapies. Trials include curative as well as palliative treatments. One of the projects that especially supports this purpose is the PRAEGNANT-registry for metastatic breast cancer patients, started in 2014. The goal is the discovery of new biomarkers that can make a statement regarding the efficacy and toxicity of therapy concepts as well as the patients' quality of life. On the basis of whole genome sequencing the intention is to find novel therapy concepts within trials or to specify treatments that already are approved for other indications. Further projects in cooperation with the Department of Medicine 5 focus on the immune monitoring of patients treated with CDK4/6 inhibitors or the identification of so-called neoepitopes and T-cells that are directed against the tumor and might enable a personalized vaccination or T-cell therapy.

In addition to the self-initiated trials the site has participated at a number of internationally significant pivotal trials.

#### Biobanking

PI: Prof. Dr. P.A. Fasching, PD Dr. M. Rübner, Dr. H. Hübner

The translational biobank is one of world's largest biobanks within the field of gynecological research. Currently, biomaterials from around 60,000 participants (115,000 blood, 13,500 tissue, 25,000 urine, 80,000 serum/plasma and fecal samples) are stored. In cooperation with the Institute of Pathology, the translational biobank was able to collect 9,500 tumor blocks from patients of various clinical studies. This allows the correlation of data from germline DNA with tumor data (expression and mutation analyses). The PRAEGNANT study network is a key element of the biomaterial collection. Thanks to this network, an infrastructure for metastatic breast cancer patients (approximately 2,900 patients from 60 German study centers) could be created, which enabled the use of precision medicine. By using the knowledge from the research program of the PRAEGNANT study, the main goal is to reveal novel, personalized therapeutic options to facilitate the inclusion into clinical studies and to enable advanced research projects. Among other things, the network allows the sequencing of germline and tumor DNA from all PRAEGNANT patients in order to reveal tumor specific mutations and personalized therapeutic options based on these findings.

## Specialized obstetrics and perinatal medicine

PI: PD Dr. F. Faschingbauer, Prof. Dr. S. Kehl For the first time worldwide, our group has been able to treat the genetic disease hypohidrotic ectodermal dysplasia prenatally in cooperation with Prof. Dr. H. Schneider (Department of Pediatrics and Adolescent Medicine). Hypohidrotic ectodermal dysplasia is an Xlinked recessive disease. Affected children suffer from, among other things, disturbed tooth development and lack of sweat ability, which can potentially cause life-threatening hyperthermia episodes. The group led by Prof. Dr. H. Schneider succeeded in producing the disease causing functionless protein ectodysplasin in a recombinant form. By application of this protein into the amniotic fluid by means of amniocentesis, three fetuses could be treated intrauterine in individual therapeutic trials. All three fetuses showed a normal or almost normal sweat capacity postpartum and over the following two years.

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. Sequential use of mechanical and pharmaceutical methods reduced caesarean section rate in obese nulliparous women by 18%. 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

PI: Prof. Dr. R. Dittrich, Dr. L. Lotz, Dr. T. Hildebrandt, Prof. Dr. S. Cupisti, PD Dr. P.G. Oppelt, Dr. S. Burghaus

Research focuses on the optimization and further development of fertility preservation (cryopreservation of germ cells, physiology of the contractions of the non-pregnant uterus, pathology of genital malformations, transsexuality). The Department of Obstetrics and Gynecology is the largest German transplantation center for ovarian tissue in the field of fertility preservation for patients with cancer. Besides studies on xenotransplantation of ovarian tissue, an in vitro culture system for the ex vivo maturation of ovarian tissue was established. Furthermore, the development of an artificial ovary is being investigated by means of electrospinning. A uterine perfusion model was established and the technique of uterine transplantation was optimized in a sheep model. On the basis of this preliminary work, the Department of Obstetrics and Gynecology was granted approval as a transplantation center for female uterus with uterine sterility.

In the endometriosis center of the highest stage, anamnestic and clinical data of patients with endometriosis are collected in a database. Blood samples are collected to expand an existing biobank. The aim of an International Endometriosis Evaluation Program (IEEP-Study) is to identify risk factors and predictive markers with regard to diagnosis and recurrence of the disease as well as the result of a therapy as a function of the main complaint of the patient – pain, sterility, or other reasons. To date, the program has collected data from more than 10,000 patients. To investigate the invasiveness of endometriosis cells, a vertical collagen assay was implemented that correlates clinical factors of the patients, such as pain and the extent of endometriosis, with the invasion of endometriosis cells.

## Teaching

The Department of Obstetrics and Gynecology is among the first departments at German university hospitals which has its own certified quality management (actual DIN EN ISO 9001:2015) for medical education. It is regularly recertified. It participates in curricular education of 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

Michailidou K et al. Association analysis identifies 65 new breast cancer risk loci. Nature, 2017. 551(7678): 92-94

Topper MJ, Vaz M, Chiappinelli KB, DeStefano Shields CE, Niknafs N, Yen RC, Wenzel A, Hicks J, Ballew M, Stone M, Tran PT, Zahnow CA, Hellmann MD, Anagnostou V, Strissel PL, Strick R, Velculescu VE, Baylin SB. Epigenetic Therapy Ties MYC Depletion to Reversing Immune Evasion and Treating Lung Cancer. Cell, 2017. 171(6): 1284-1300 e21 Dittrich R et al. Fertility Preservation for Patients with Malignant Disease. Guideline of the DGGG, DGU and DGRM (S2k-Level, AWMF Registry No. 015/082, November 2017) - Recommendations and Statements for Girls and Women. Geburtshilfe Frauenheilkd, 2018. 78(6): 567-584

Fasching PA et al. BRCA1/2 Mutations and Bevacizumab in the Neoadjuvant Treatment of Breast Cancer: Response and Prognosis Results in Patients With Triple-Negative Breast Cancer From the GeparQuinto Study. J Clin Oncol, 2018. 36(22): 2281-2287

Schneider H, Faschingbauer F, Schuepbach-Mallepell S, Körber I, Wohlfart S, Dick A, Wahlbuhl M, Kowalczyk-Quintas C, Vigolo M, Kirby N, Tannert C, Rompel O, Rascher W, Beckmann MW, Schneider P. Prenatal Correction of X-Linked Hypohidrotic Ectodermal Dysplasia. N Engl J Med, 2018. 378(17): 1604-1610

Slamon DJ et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol 2018, 36(24): 2465-2472

#### International cooperations

Prof. Dr. D. Easton, Breast Cancer Consortium, Cambridge: UK

Prof. Dr. D. Lambrechts, Katholische Universität Leuven, Leuven: Belgium

Prof. Dr. D. Slamon, University of California Los Angeles (UCLA), Los Angeles: USA

Prof. Dr. R. Weinshilboum, Mayo Clinic, Rochester, Rochester: USA

Prof. Dr. S. Baylin, Johns Hopkins Medical Center, Baltimore, Baltimore: USA

Prof. K. Chiappinelli, George Washington University, Washington DC: USA

## **Department of Ophthalmology**

## Chair of Ophthalmology

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#### Contact

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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 vitreal surgery (23-gauge-vitrectomy)
- Minimal invasive glaucoma surgery employing implants
- Refractive surgery with the femtosecond laser
- Cataract surgery with innovative intraocular lenses
- Intraocular injections of compounds to treat age related macular degeneration (AMD)
- Special consultation
- Departments of optometry, fluorescence angiography, and laser
- Outpatients' department
- Cornea bank
- Laboratories

## Research

The Department of Ophthalmology belongs to the leading centers in the areas of lamellar corneal transplantation including structural biology of the cornea as well as diagnostics and pathophysiology of glaucomas at a national and international level. An interdisciplinary team of clinician and basic scientists conducts patientoriented 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-ofthe-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 AMD.

## Functional aspects of retinal neurodegeneration

Pl: 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.

## 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

 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.

## **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 TGFB1, oxidative stress, and mechanical stress.

## Development of new methods for lamellar corneal transplantation

PI: Prof. Dr. F.E. Kruse, Prof. Dr. T. Fuchsluger, Dr. 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**

Pasutto F et al. Pseudoexfoliation syndrome-associated genetic variants affect transcription factor binding and alternative splicing of LOXL1. Nat Commun. 2017 May 23;8:15466

Tsai TI, Joachimsthaler A, Kremers J. Mesopic and photopic rod and cone photoreceptor driven visual processes in mice with long-wavelength shifted cone pigments. Invest. Ophthalmol Vis. Sci. 2017, 58:5177–5187

Schrems WA, Schrems-Hoesl LM, Mardin CY, Laemmer R, Kruse FE, Horn FK. Can Glaucomatous Visual Field Progression be Predicted by Structural and Functional Measures? J Glaucoma. 2017 Apr;26(4):373-382

Aher AJ, McKeefry DJ, Parry NRA, Maguire J, Murray IJ, Tsai TI, Huchzermeyer C, Kremers J. Rod- versus cone-driven ERGs at different stimulus sizes in normal subjects and retinitis pigmentosa patients. Doc Ophthalmol. 2018, 136: 27-43

Augustin VA, Weller JM, Kruse FE, Tourtas T. Fungal Interface Keratitis After Descemet Membrane Endothelial Keratoplasty. Cornea. 2018 Nov;37(11):1366-1369

Menzel-Severing J, Zenkel M, Polisetti N, Sock E, Wegner M, Kruse FE, Schlötzer-Schrehardt U. Transcription factor profiling identifies Sox9 as regulator of proliferation and differentiation in corneal epithelial stem/progenitor cells. Sci Rep. 2018; 8(1): 10268

#### International cooperations

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

Prof. Dr. N. Koizumi, Department of Biomedical Engineering, Faculty of Life and Medical Sciences, Doshisha University, Kyotanabe: Japan

Prof. T. Aung, Singapore Eye Research Institute, Singapore National Eye Centre: Singapore

# Department of Otorhinolaryngology – Head and Neck Surgery

## Chair of Otorhinolaryngology

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#### **Research focus**

- Ultrasound, endoscopy, and salivary glands
- Division of Phoniatrics and Pediatric Audiology
- Experimental Oncology/nanomedicine (SEON)Speech perception with hearing aids and
- Cochlear implants • Allergology/clinical immunology and rhinology
- Experimental otolaryngology
- Laboratory for sleep disorders/somnology

## **Structure of the Department**

Professorships: 5

Personnel: 342

- Doctors (of Medicine): 41
- Scientists: 35 (thereof funded externally: 20)
- Graduate students: 57

## **Clinical focus areas**

- Minimal invasive surgery of salivary glands
- Lancer surgery
- Cochlear implantat surgery
- Nose/paranasal surgery
- Clinical and surgical treatment of voice disorders
- Pediatric hearing disorders
- Diagnosis and treatment of sleep disorders

## Research

The Department of Otorhinolaryngology – Head and Neck Surgery is one of the largest hospitals in Germany and has a comprehensive research repertoire. In the clinical area, the focus is on ultrasound, the diagnosis/treatment of salivary gland diseases, tumor and voice disorders, vestibular and hearing impairments as well as somnology and allergology. These foci are reflected in the basic research area. Nanomedicine, which carries out translational projects as well as extensive basic research, is another highly interdisciplinary focus.

## Ultrasound, endoscopy, and salivary glands

In modern ultrasound systems and endoscopy units, studies on sonographic imaging of head and neck malignancies and salivary gland tumors remain a cornerstone of scientific work. The role of ultrasonography for the diagnosis of sialolithiasis was systematically examined using a large group of patients. Our results show an accuracy of approximately 95% for the diagnosis of sialolithiasis. Gland-conserving surgery for benign salivary gland diseases is one of our priorities. The main topics are currently the longterm results after limited, extracapsular resection especially of cystadenolymphomas and pleomorphic adenomas of the glandula parotis. Minimally invasive interventions of the salivary glands and their excretory ducts are not only applications in daily practice, but have been systematically reviewed and evaluated scientifically. Combined endoscopic and open surgical procedures provide a new way of treating obstructive salivary gland disorders. The application of Pneumatic Intracorporeal Lithotripsy, introduced in 2015, has been expanded in our Department, particularly in the context of the multimodal treatment of the difficult cases of sialolithiasis, which until recently required resection of the affected salivary gland under general anesthesia.

## Division of Phoniatrics and Pediatric Audiology

Our clinical research focuses on the development of new methods allowing for quantitative voice diagnostics. The major part is the objective analysis of endoscopic high speed recordings during voice production. Within our basic research we concentrate on physical interactions during voice production. We develop and analyze numerical models (lumped-mass models, finite-volume-models) and experimental models (synthetic silicon vocal folds and ex-vivo animal cadaver larynx models). We expect to gain more insight into the interaction between airflow, vocal fold dynamics and resulting acoustics for physiologic and pathologic voice production. Since 2016, we have been analyzing the vocal fold tissue from the molecular-biological point of view. All these topics have the goal to enhance diagnostics and the treatment of our patients.

## Experimental Oncology/nanomedicine (SEON)

## PI: Prof. Dr. C. Alexiou

Superparamagnetic iron oxide nanoparticles offer several possibilities for the application in medicine. For instance, they can serve as drug carrier vehicles 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 (MTE). 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. One important part in this regard is the transfer of the synthesis process from the laboratory towards the production according to GMP guidelines. This aim thrived due to our cooperation with the pharmacy of the UK Erlangen within the European FP7 Project "Nanoathero", which was successfully finished in July 2018. Because of further funding from the Manfred-Roth foundation, we are able to continue our translational efforts beyond the year 2018. To finally apply magnetic nanoparticles for imaging and diagnosis of tumors, their suitability is also evaluated using Magnetic Particle Imaging (supported by the DFG). With regard to the development of endothelialized tissue scaffolds for cardiovascular applications, we have been supported by the BMBF since 2018 to establish and apply complex, small-diameter structures using magnetic cell seeding. Concerning tissue reconstruction we aim to develop a vocal fold implant by means of MTE (supported by the EKFS Foundation). To understand the interplay of magnetic nanoparticles with biological matrices, SEON has been engaging for several years in the DFG Priority Program SPP 1681. Furthermore, SEON is involved in two interdisciplinary projects in the Emerging Fields Initiative (EFI) of the FAU. Thematically, these projects include the establishment of magnetic T cell targeting and Magnetic Nanoparticle Communication. The latter project was extended in November 2018 by the BMBFfunded project "MaMoKo".



Nanolive 3D Cell Explorer – A non-invasive and label-free holotomographic live cell imaging microscope, based on the specific refractive index (RI) of cells and cell components

## Speech perception with hearing aids and Cochlear implants

Cochlear Implants (CI) provide an efficient treatment for people with profound hearing loss and deafness. During the last decades cochlear implantation was improved and current implant systems allow for a reasonable speech perception in everyday life. Aim of the research project was to develop a model which allows a prognosis of CI performance. We developed a test battery of speech audiometric measurements in quiet and in noise in order to determine the amount of information that can be processed by the auditory system (information carrying capacity, ICC). Based on etiologic data, patient history, and audiometric findings, we developed a model for a prognosis of cochlear implant outcome.

## Allergology/clinical immunology and rhinology

Endonasal endoscopic sinus surgery and following oral desensitization with ASS come into question as a treatment for NSAID-intolerant patients. The aim of the study is to elaborate and perform a treatment scheme for a treatment with an intravenous desensitization with ASS. The collected data of the intravenous desensitization as an efficient therapy for patients with NSAID-intolerance is going to be evaluated and compared to oral desensitization with ASS.

#### **Experimental otolaryngology**

In our group we investigate among others the development of tinnitus. We developed a new model based on information-theoretical approaches in which tinnitus is a by-product of a mechanism that is able to improve hearing thresholds. Data of a collective of roughly 40,000 patients with and without tinnitus and results from animal research support this model. In both cases we investigate space-time patterns of cortical activity with a new statistical method developed by us and are therefore able to describe tinnitus-specific activity in the brain. Additionally, we were able to categorize human sleep stages from EEG data with this method and generate new insight for the sleep medicine. Furthermore, we develop new methods for the determination of sensory thresholds in humans and animals with which it is now possible to determine thresholds, e.g. of auditory brainstem responses, in a completely automatic and objective manner. For all these and other questions we additionally develop artificial neuronal network models and applications for artificial intelligence.

## Laboratory for sleep disorders/ somnology

The sleep medicine department offers a comprehensive spectrum of current diagnostics and therapy of all sleep disorders according to ICSD-3 with a focus on "sleep-related breathing disorders". In addition to the investigation of the pathophysiological role of the endonasal microbiome and so-called mucin-associated peptides in the context of obstructive sleep apnea (OSA), other main research areas are the optimization of sleep diagnostics and the individualization of therapeutic concepts in OSA. The focus here is on the validation of a serological biomarker in the context of screening diagnostics. Both, the use as a screening tool in the context of primary diagnostics and for individual cardiovascular risk stratification as well as the monitoring of the course of therapy and the therapeutic success in OSA, are examined. Another focus lies on the validation of a compact screening questionnaire (Erlanger Questionnaire) for the detection of nocturnal respiratory disorders in different patient collectives.

## Teaching

The Department of Otorhinolaryngology - Head and Neck Surgery is involved in the curricular teaching of Medicine and Dentistry 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**

Janikowska A, Matuszak J, Lyer S, Schreiber E, Unterweger H, Zaloga J, Groll J, Alexiou C, Cicha I. A novel human artery model to assess the magnetic accumulation of SPIONs under flow conditions. Sci Rep, 2017, 7: 42314-42331

Gollnast D, Tziridis K, Krauss P, Schilling A, Hoppe U, Schulze H. Analysis of audiometric differences of patients with and without tinnitus in a large clinical database. Front. Neurol, 2017, Feb 9;8:31

Unterweger H, Dézsi L, Matuszak J, Janko C, Poettler M, Jordan J, Bäuerle T, Szebeni J, Fey T, Boccaccini AR, Alexiou C, Cicha I. Dextran-coated superparamagnetic iron oxide nanoparticles for magnetic resonance imaging: Evaluation of size-dependent imaging properties, storage stability and safety. Int J Nanomed, 2018, 13: 1899-1915

Döllinger M, Kniesburges S, Berry DA, Birk V, Wendler O, Dürr S, Alexiou C, Schützenberger A. Investigation of phonatory characteristics using ex-vivo rabbit larynges. J Acoust Soc Am, 2018, 144: 142-52

Mantsopoulos K, Koch M, Goncalves M, Iro H. Investigation of the surgical strategies for unilateral multifocal cystadenolymphomas of the parotid gland. Oral Oncology, 2018, Jul;82:176-180

Krauss P, Schilling A, Bauer J, Tziridis K, Metzner C, Schulze H, Traxdorf M. Analysis of Multichannel EEG Patterns During Human Sleep: A Novel Approach. Front Hum Neurosci, 2018, 12:121

#### International cooperations

Prof. Dr. E. Tombacz, University of Szeged, Faculty of Science and Informatics, Szeged: Hungary

Prof. Dr. H. Mangge, Medizinische Universität Graz, Graz: Austria M. Kunduk, PhD, Louisiana State University, Baton Rouge: USA

L.P. Fulcher, PhD, Bowlinmg Green State University, Bowling Green: USA

Prof. Dr. P. van Dijck/D. Persic, PhD, University Medical Center Groningen, Department of Otorhinolaryngology, Groningen: The Netherlands

# **Department of Pediatrics and Adolescent Medicine**

## **Chair of Pediatrics**

#### Address

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#### Director

Prof. Dr. med. Dr. h.c. Wolfgang Rascher (until 30.6.2019) Prof. Dr. med. Joachim Wölfle (as of 1.7.2019)

#### Contact

Prof. Dr. med. Holm Schneider Phone: +49 9131 8533775 Fax: +49 9131 8533013 holm.schneider@uk-erlangen.de

### **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
- Experimental and translational imaging
- Perinatal hypoxic brain injury and neuroprotection

## **Structure of the Chair**

Professorships: 5 Personnel: 430

- Doctors (of Medicine): 75
- Scientists: 15 (thereof funded externally: 10)
- 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, preclinical, and clinical studies. Further main research interests lie in the fields of pediatric oncology 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: Prof. 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 ageappropriate formulations. We have been working for many years on methods to improve medication safety. Data on adverse drug reactions are being collected systematically; highrisk medications have been detected and particularly vulnerable groups of patients have been identified. Our contribution to the "AMTS-Aktionsplan 2013-2015" (item 16: Development of recommendations for the use of drugs in children particularly in the inpatient care) led to current BMG-funded activities of our Department to establish an evidence-based dosing information database for children in Germany. We are also in charge of the country-wide project "KiDSafe" funded by the Innovation Fonds. Within this project the aforementioned dosing database (pediatric formulary) and other measures to increase medication safety are being evaluated in detail. Moreover, we actively participate in several EU-funded projects (e.g. GAPP, EPTRI, c4c) and have coordinated a multicenter phase 3 study to investigate the use of clonidine as sedative agent in pediatric intensive care units (CloSed; compare own report). The aim of most projects is a pediatric-use marketing authorization for the studied drugs.

## Perinatal programming and early determination of renal and cardiovascular disorders

PI: Prof. Dr. A. Hartner, PD Dr. F. Fahlbusch Our research aims at elucidating the consequences of an early impairment of organ development for the pathogenesis of diseases during adolescence and adult life. To this purpose, the sequelae of a congenital reduction of nephron numbers or disruption of renal development for the kidney and the cardiovascular system are being studied. We have been focusing on the pathogenetic mechanisms of inflammatory renal disease, hypertension, and heart failure. In further studies, we are attempting to clarify which placental alterations may lead to defects in organ systems of the offspring and can expedite the onset of later disease. These studies are being performed in collaboration with the Perinatal Center of Middle Franconia and the Comprehensive Cancer Center Erlangen-EMN.

#### Genetic skin diseases of the neonate PI: Prof. Dr. H. Schneider

Our primary research goal is to identify pathogenetic mechanisms underlying genodermatoses (hereditary disorders of the skin and its

appendages) at the molecular level and to develop appropriate therapeutic approaches. Some of these diseases may be associated with life-threatening complications already in the first weeks after birth. In addition to the skin, other organs, such as eye, ear, and lung, are frequently affected by pathogenetic processes. First systematic natural history studies in patients of different age groups allowed the characterization of genotype-phenotype relationships as a prerequisite for specific therapeutic attempts. In DFG-funded projects, we have been investigating the feasibility of prenatal protein replacement or gene therapy in mouse models of epidermolysis bullosa, lamellar ichthyosis, and hypohidrotic ectodermal dysplasia. We coordinated the first clinical trial in children with hypohidrotic ectodermal dysplasia, a multicenter study to evaluate the safety and efficacy of a recombinant ectodysplasin A1 administered at the earliest stage of postnatal development. Based on promising preclinical data, the results of this clinical trial, and the success of named-patient use case studies, we are currently preparing a phase 3 trial to investigate such protein replacement therapy in utero.

## Genomic aberrations in childhood malignancies

## PI: Prof. Dr. M. Metzler

Cancer cells show characteristic genetic alterations which are important not only for tumorigenesis and disease progression, but also as molecular markers allowing the detection of specific tumor cells – for diagnostic purposes, monitoring of tumor response to therapy, and for relapse recognition. Besides investigating such molecular markers, we have been analyzing germ-line mutations of selected tumor types that predispose to malignancies early in life. As national study center for chronic myeloid leukemia in childhood and adolescence, we are continuing intense research on clinical and biological aspects of this model disease.

## Differentiation pathways during skeletal development

PI: Prof. Dr. M. Rauh, Prof. Dr. H. Schneider To clarify the role of certain signaling molecules during skeletal development, we have been using a broad spectrum of methods including gene expression assays, immunohistochemistry, models of osteogenesis *in vitro* and *in vivo*, and determination of various enzyme activities by mass spectrometry. A related research project is focused on the controlled differentiation of cord blood-derived mesenchymal stem cells into osteoblasts and chondrocytes. These cells could be used for autografts, e.g. in the treatment of cleft lip and palate (the most frequent congenital malformation) to reduce the number of surgical interventions required.

#### **Experimental and translational imaging** PI: Dr. F. Knieling

Conventional diagnostic imaging methods are often invasive, time-consuming, and harbor risks for complications. These limitations potentiate in children and adolescents, whose organisms are particularly vulnerable. Light- and sound-based imaging approaches, like multispectral optoacoustic tomography (MSOT), offer novel opportunities to perform non-invasive diagnostics. Pulsed laser light in the nearinfrared spectrum leads to the generation of ultrasonic waves, which are received by special transducers. Our current projects combine MSOT and other imaging technologies with aspects of basic research and clinical pediatrics to achieve rapid translation of the findings into routine diagnostic procedures.



The principle of multispectral optoacoustic tomography

## Neonatal neurology and neuroprotection

PI: Prof. Dr. R. Trollmann

The research of this group is focused on the early detection of perinatally acquired brain lesions and neuroprotection. In an established mouse model of perinatal hypoxia, we have been investigating molecular effector mechanisms of the immature brain after perinatal damage due to hypoxia and excitotoxicity as well as neuroprotective strategies, e.g. administration of erythropoietin and prolyl hydroxylase inhibitors. We are studying the impact of acute hypoxia on early neuronal migration, angiogenesis, astrocytic, and blood-brain barrier function and have been evaluating approaches to pharmacological stabilization of hypoxia-inducible transcription factors (HIF). Moreover, age-specific effects of excitotoxic stimuli on the regulation of excitatory neurotransmitter systems during early development are being characterized in a mouse model of neonatal seizures. The investigation of hypoxia-induced neuroinflammatory mechanisms *in vitro* and in animal models also stimulates the progress of projects on neuroprotective strategies beyond the neonatal period.

## Teaching

The Department of Pediatrics and Adolescent Medicine participates with compulsory and elective courses in the degree programs in Medicine and Dentistry. Alongside traditional teaching, special research seminars and interdisciplinary courses are offered. An "emergency care simulator", adapted to the needs of neonatology and pediatric intensive care, enables the training of emergency medical procedures and team-work analysis of the management strategies applied. This includes regular reviews of real emergency situations experienced in our clinic.

Individual researchers supervise Bachelor's and Master's theses as well as MD and PhD theses.

#### **Selected publications**

Neubert A, Baarslag MA, Dijk MV, Rosmalen JV, Standing JF, Sheng Y, Rascher W, Roberts D, Winslade J, Rawcliffe L, Hanning SM, Metsvaht T, Giannuzzi V, Larsson P, Pokorná P, Simonetti A, Tibboel D; CLOSED Consortium. The CLOSED trial; CLOnidine compared with midazolam for SE-Dation of paediatric patients in the intensive care unit: study protocol for a multicentre randomised controlled trial. BMJ Open 2017, 7:e016031

Hübner H, Strick R, Wachter DL, Kehl S, Strissel PL, Schneider-Stock R, Hartner A, Rascher W, Horn LC, Beckmann MW, Rübner M, Fahlbusch FB. Hypermethylation and loss of Retinoic Acid Receptor Responder 1 expression in human choriocarcinoma. J Exp Clin Cancer Res 2017, 36:165

Knieling F et al. Multispectral optoacoustic tomography for assessment of Crohn's disease activity. N Engl J Med 2017, 376:1292-1294

Schneider H, Faschingbauer F, Schuepbach-Mallepell S, Körber I, Wohlfart S, Dick A, Wahlbuhl M, Kowalczyk-Quintas C, Vigolo M, Kirby N, Tannert C, Rompel O, Rascher W, Beckmann MW, Schneider P. Prenatal correction of X-linked hypohidrotic ectodermal dysplasia. N Engl J Med 2018, 378:1604-1610

Anderson ND et al. Rearrangement bursts generate canonical gene fusions in bone and soft tissue tumors. Science 2018 Aug 31;361(6405)

Trollmann R, Mühlberger T, Richter M, Boie G, Feigenspan A, Brackmann F, Jung S. Differential regulation of angiogenesis in the developing mouse brain in response to exogenous activation of the hypoxia-inducible transcription factor system. Brain Res 2018, 1688:91-102

#### International cooperations

Prof. Dr. T. Grange, Department of Pediatrics, Washington University School of Medicine, St. Louis: USA Dr. P. Schneider, Department of Biochemistry, University of Lausanne, Epalinges: Switzerland

Dr. O. Delattre, INSERM U830, Institut Curie, Paris: France

Prof. Dr. D. Reinhardt, Department of Anatomy & Cell Biology, McGill University, Montreal: Canada

Prof. Dr. Catherine Tuleu, University College London, London: UK

Prof. Dr. Dick Tibboel, Erasmus Medical Center, Rotterdam: The Netherlands

# **Department of Pediatrics and Adolescent Medicine**

**Division of Pediatric Cardiology** 

## Address

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## **Head of Division**

Prof. Dr. med. Sven Dittrich

### Contact

Prof. Dr. med. Sven Dittrich Phone: +49 9131 8533750 Fax: +49 9131 8535987 kinderkardiologie@uk-erlangen.de

### **Research focus**

- Cardiopulmonary exercise testing in patients with congenital heart disease
- Perioperative risk stratification after surgery for congenital heart disease
- Comparison of peak serum level, serum-clearance, and urinary lactate excretion as a prognostic marker for outcome and major adverse events in children after cardiac surgery
- Pathophysiology of the Fontan circulation
- Quality of life in patients and families with congenital heart disease (L.I.S.A.-Studie)
- Patient Blood Management (PBM)
- Digital health at the interface of ambulatory and inhospital treatment of congenital heart disease
- Clinical application of echocardiographic deformation imaging in the field of pediatric cardiology
- Pathophysiology of congenital heart disease in a rat model
- Multimodality imaging in pediatric cardiology

## **Structure of the Division**

- Professorship: 1
- Personnel: 79
- Doctors (of Medicine): 22
- Scientists: 2 (thereof funded externally: 2)
- Graduate students: 20

#### **Clinical focus areas**

- Interventional therapy of congenital heart defects in the catheter laboratory
- Surgical therapy of congenital heart defects in close cooperation with the Division of Pediatric Cardiac Surgery
- Intensive care after cardiac surgery

## Research

In the Division of Pediatric Cardiology, patient research on treatment techniques and care structures is performed. A particular focus is on different modalities of cardiovascular imaging and pathophysiology in univentricular hearts after Fontan operations. In basic research there are two working groups on the pathophysiology of congenital heart defects in the small animal model and a material biobank on the molecular genetic causes of congenital heart defects.

#### Cardiopulmonary exercise testing in patients with congenital heart disease Pl: Dr. Dr. I. Schöffl

Our goal is to establish cardiopulmonary exercise testing (CPET) for children at a younger age and to reach a better understanding of the use of CPET in children with congenital heart disease. We want to establish an exercise regimen for children with congenital heart disease in order to improve their fitness, their quality of life and their heart function.

## Perioperative risk stratification after surgery of congenital heart disease

PI: Dr. M. Alkassar, Dr. R. Zant

The first 45 minutes after cardiac surgery in pediatric patients is crucial for the later outcome. Due to the intraoperative blood contact with artificial surfaces during cardiopulmonary bypass support, the operation itself, and intraoperative organ ischemia, there is a consecutive systemic inflammatory response commencing in the early phase post-surgery. Therefore, aim of this study is to identify patients with a high risk of profound shock by defined clinical parameters. Once identified, a structured approach is initiated to provide optimal organ-oxygenation.

### Comparison of peak serum level, serum-clearance, and urinary lactate excretion as a prognostic marker for outcome and major adverse events in children after cardiac surgery PI: Dr. R. Zant. Dr. M. Schöber

Urinary lactate measured as ratio of urinary lactate to urinary creatinine has to the best of our knowledge not been evaluated as prognostic parameter in critically ill patients so far. However, this method may provide advantages and therefore may be superior to serum lactate measurements in this patient collective: Urinary lactate summarizes a greater time period and therefore may be superior by equalizing short, but clinically irrelevant peak values.

#### Pathophysiology of the Fontan circulation Pl: Dr. J. Moosmann

Fontan patients are infants who were born with only one functional ventricle (single ventricle malformation) and were palliated by the Fontan procedure during the first years of life. Fontan circulation results in a passive pulmonary blood flow and the single ventricle supporting the systemic perfusion. 3-15% of all Fontan patients develop a protein loosing enteropathy (PLE). In this project immunologic, hemodynamic, and laboratory alterations of the Fontan circulation leading to PLE are investigated.

Our collaborators are the Institute of Human Genetics, the Department of Medicine 5, and the laboratory of the Department of Pediatrics and Adolescent Medicine.

- Current projects are:
- miRNA analysis for identifying inflammatory pathways in Fontan patients with and without PLE
- Identification of immunologic alterations of lymphocytes in Fontan patients
- Microbiome analyses of stool in Fontan patients
- Metabolomics study of Fontan patients

## Quality of life in patients and families with congenital heart disease (L.I.S.A.-Studie)

PI: Dr. W. Wällisch

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 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 und 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, or family orientated rehabilitation, with regard to the recovery process. This randomized, placebo-controlled trial includes children from 3-18 years of age. We were able to enroll 125 patients over a 30-month study period. The results will be published in the near future.

## Patient Blood Management (PBM)

PI: Dr. J. Schirrmeister, K. Rubarth

The center of attention of PBM lays upon preserving and strengthening a patient's own resources. This regards prophylaxis and therapy of preoperative anemia, operative loss of blood as well as postoperative bleeding and anemia triggered by numerous iatrogenic blood withdrawals from children undergoing heart surgery. Our aim is to show that implementing a PBM does not cause an extension of postoperative (pediatric intensive care unit) treatment by PICU. Observation will end as soon as the patient is able to leave the PICU.

The PBM-concept is partially based on the assumption that there is an acceptance of lower hemoglobin levels as well as avoiding a preoperative anemia. This can be provided by an in time identification and treatment of upcoming problems like an iron deficiency.

## Digital health at the interface of ambulatory and inhospital treatment of congenital heart disease

PI: Dr. U. Doll

Since 2007, the Division of Pediatric Cardiology is connected with surrounding clinics and pediatric cardiologists` offices in a "University competence network for congenital heart disease in Northern Bavaria". Sponsored by "Bayern Innovativ GmbH", a telemedicine platform has been established via cloud for bidirectional data transfer. Thus, it is possible to transfer relevant findings and image files to our colleagues within the network. Besides, we receive echocardiographic data for discussion and as a second opinion and to arrange for in-patient treatment, if necessary. In addition, pediatric cardiologists from our network can prospectively participate in interactive chats.

## Clinical application of echocardiographic deformation imaging in the field of pediatric cardiology

PI: Dr. M. Schöber

Deformation imaging by strain represents an echocardiographic technology for measuring myocardial deformation of the myocardium. It can give insights into cardiac pathophysiology and expands the ability to evaluate ventricular function in children with congenital or acquired heart disease. Currently, we routinely utilize strain imaging in our Echolab when assessing ventricular function in congenital heart lesions and impaired ventricular function. Another field of research is the acute effect of anthracycline therapy on myocardial function in pediatric oncology diseases. Deformation imaging is an exciting area of investigation in the field of echocardiography that is likely to significantly improve the diagnostic capabilities of cardiac ultrasound in the future.

## Pathophysiology of congenital heart disease in a rat model

PI: Dr. M. Alkassar

Due to the small amount of children with congenital heart disease, cellular and animal models play an important role. We examine changes in the development of power inside single cardiac muscle cells and tissue in diseased animals. These results are used to optimize a simulation software specifically designed to depict impending cardiac insufficiency at an early stage. The simulation illustrates the power inside the cardiac muscle in four dimensions and shows critical areas.

Funding: Klaus Tschira Foundation

## Multimodal imaging in pediatric cardiology

#### PI: Dr. M. Alkassar

Aim of our multimodal research is to further optimize the therapy by three-dimensional display of anatomical structures. We established new three-dimensional display options with echocardiography, CT, and MRI which help to develop a realistic idea of heart and vessels. The use of such a display in the field of pediatric cardiology is investigated in various studies. We were able to prove an enormous advantage of 3D-heart models in the context of catheterizations. A following study currently investigates the benefit of 3D-imaging regarding the compensation of respiration and heartbeat. Another study investigates the advantages of 3D-models in the preprocedural planning of surgical operations. Therefore we project very real-looking three-dimensional images of the heart with the help of a virtual reality glasses (VR) into the room. For a tactile perception, we also create three-dimensional life-sized pressure of the heart of silicone. The Division of Pediatric Cardiology is one of the leading international centers for the establishment and further development of multimodal methods for the treatment of children with heart disease in Germany.

## 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

Hammon M, Rompel O, Seuss H, Dittrich S, Uder M, Rüffer A, Cesnjevar R, Ehret N, Glöckler M. Accuracy and Specific Value of Cardiovascular 3D-Models in Pediatric CT-Angiography. Pediatr Cardiol. 2017 Dec;38(8):1540-1547

Maass PG, Glažar P, Memczak S, Dittmar G, Hollfinger I, Schreyer L, Sauer AV, Toka O, Aiuti A, Luft FC, Rajewsky N. A map of human circular RNAs in clinically relevant tissues. J Mol Med (Berl). 2017 Nov;95(11):1179-1189 Messroghli DR et al. Toward evidence-based diagnosis of myocarditis in children and adolescents: Rationale, design, and first baseline data of MYKKE, a multicenter registry and study platform. Am Heart J 2017;187:133-144

Stegmann H, Bauerle T, Kienle K, Dittrich S, Alkassar M. 4D cardiac magnetic resonance imaging, 4D and 2D transthoracic echocardiography: a comparison of in-vivo assessment of ventricular function in rats. Lab Anim 2018; 23677218789971

Ehret N, Alkassar M, Dittrich S, Cesnjevar R, Ruffer A, Uder M, Rompel O, Hammon M, Glöckler M. A new approach of three-dimensional guidance in paediatric cath lab: segmented and tessellated heart models for cardiovascular interventions in CHD. Cardiol Young 2018;28(5):661-667

# **Department of Plastic and Hand Surgery**

Chair of Plastic and Hand Surgery

## Address

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#### Director

Prof. Dr. med. Dr. h.c. Raymund E. Horch

## Contact

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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**

Professorship: 1

Personnel: 29

- Doctors (of Medicine): 16
- Scientists: 7 (thereof funded externally: 7)
- Graduate students: 35

#### **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. R.E. Horch<sup>1-5</sup>, Prof. Dr. J. Beier<sup>1</sup>, Prof. Dr. A. Arkudas<sup>2-9</sup>, PD Dr. A.M. Boos<sup>2,10</sup>, Dr. A. Kengelbach-Weigand<sup>2,9,10</sup>, Dr. D. Steiner<sup>3-5</sup>, Dr. A. Cai<sup>1,8</sup>, M. Hessenauer<sup>6</sup>, Dr. W. Müller-Seubert<sup>7</sup>

1) Tissue engineering of skeletal muscle The final aim of this project is the generation of axially vascularized, innervated skeletal muscle tissue. 2) Generation of axially vascularized bone 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.

3) Tissue engineering of axially vascularized bone in a small animal model

The aim of this study is to generate axially vascularized bioartifical bone tissue using bioactive matrices in combination with endothelial cells (EC) and adipose derived stem cells (ADSC).

4) Investigation of the specific cell-cell interactions between ADSC and EC concerning osteogenic differentiation

5) Biofabrication of cellularized and AV loop vascularized tissue containers for the transplantation of drug-producing cells

6) Intravital microscopy in the AV loop model To understand the mechanisms of de novo tissue formation in the AV loop model, we developed a suitable chamber model which allows intravital microscopic evaluation.

7) Ischemic tolerance of different tissues

By using the model of rat hindlimb amputation, extracorporeal perfusion, and replantation, we analyze and try to prolong the critical ischemia time of different tissues.

8) Perfusion-based de- and recellularization of a whole skeletal muscle

A skeletal muscle will be decellularized, thereafter recellularized and the construct implanted *in vivo* by vascular and nerve anastomoses to engineer a skeletal muscle.

9) Differences in functional cell properties of ADSC affected by patient factors

10) Skin tissue engineering by the use of ADSC Current treatment options for chronic wounds will be optimized using growth factors and ADSC.

## Interaction of regenerative strategies and tumor progression

PI: Prof. Dr. R.E. Horch<sup>1-7</sup>, Prof. Dr. A. Arkudas<sup>7</sup>, PD Dr. A.M. Boos<sup>1-6</sup>, Dr. A. Kengelbach-Weigand<sup>1-7</sup>, Dr. R. Götzl<sup>6</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 endothelial progenitor cells (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 EPC.

4) Paracrine and cell-cell interaction of ADSC and mammary epithelial cells in the focus of development of breast cancer

This study evaluates the influence of ADSC on the behavior of cells in the breast and breast cancer tissue.

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 by analyzing stem cells from tumor-associated adipose tissue compared to stem cells from healthy adipose tissue.

6) Characterization of ADSC from different harvesting methods

This project aims at investigating the impact of different surgical procedures during the harvesting of ADSCs on their behavior and functionalities.

7) Using biofabrication, a 3D tumor model will be developed, serving for the investigation of different aspects of tumor progression in a controlled manner both *in vitro* and in the vascularized *in vivo* AV loop model.

#### **Clinical experimental research**

PI: Prof. Dr. R.E. Horch<sup>1-8</sup>, Prof. Dr. J. Beier<sup>1</sup>, Prof. Dr. A. Arkudas<sup>2,3,8</sup>, PD Dr. Boos<sup>5</sup>, Dr. I. Ludolph<sup>1,4-7</sup>, Dr. A. Cai<sup>2</sup>, Dr. G. Bührer<sup>7</sup>, J. Grüner<sup>2</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 and free flap autonomization in the long term follow-up, intraoperative fluorescence imaging of tissue perfusion using a laser camera was performed.

2) Prospective analysis of grip force in common hand conditions

Hand conditions may be accompanied by a loss of hand function or grip force. This prospective study evaluates the effect of a surgical procedure on hand grip force.

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) Influence of different silicone surface textures to prevent capsular fibrosis of the breast

Capsular fibrosis represents a significant complication following implantation of silicone breast implants, necessitating further surgical intervention. Experimental *in vitro* studies are conducted to investigate diverse silicone surface textures and their influence on capsular fibrosis.

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) Comparison of thermography and ICG-angiography in the perfusion analysis of free flaps for autologous breast reconstruction

Intraoperative perfusion of free flaps from the abdomen for autologous breast reconstruction is assessed by using thermography and ICG-angiography.

7) Analysis of skin elasticity before and after body contouring procedures

In a prospective trial different skin elasticity parameters are assessed in patients after massive weight loss. Data are collected before and after body contouring procedures to gain more insight in the characteristics of the skin.

8) 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. R.E. Horch<sup>1-8</sup>, Dr. M. Schmitz<sup>8</sup>, Dr. I. Ludolph<sup>2-6</sup>, Dr. A. Cai<sup>4</sup>, Dr. W. Müller-Seubert<sup>1</sup>, Dr. T. Hauck<sup>7</sup>

1) Retrospective analysis of surgical therapy in cubital tunnel syndrome

In this study, outcomes and complications after partial medial epicondylectomy in cubital tunnel syndrome are analyzed.

2) Retrospective analysis of body contouring procedures after massive weight loss in patients with body mass index greater 35

In this retrospective study, complications after body contouring procedures in patients with a BMI greater 35 are analyzed.

3) Negative pressure wound therapy with instillation in chronic-infected wounds

The aim of this retrospective study is to investigate an effect of negative pressure wound therapy with instillation with regard to a reduction of the bacterial load as well as the bacterial count in chronically infected wounds.

4) Analysis of quality of life and physical activity of postbariatric patients

The impact of body contouring procedures on quality of life and physical activity of patients that have undergone massive weight loss is retrospectively analyzed.

5) Negative pressure wound therapy in the treatment of chronic ulcers of the lower leg

In this study patients with problem wounds of the lower leg are investigated with regard to the use of negative pressure wound therapy and the defect reconstruction.

6) ICG-angiography for analysis of the zonal perfusion of free flaps from the abdomen in autologous breast reconstruction

By using ICG-angiography intraoperatively, the zonal perfusion of DIEP/msTRAM flaps is analyzed to gain further insight in the vascular anatomy and the perforasome theory and to optimize the outcome of such procedures.

7) The role of the pedicled gastrocnemius flap in covering defects in the knee and proximal lower leg area

This retrospective study evaluates the outcome of pedicled gastrocnemius flaps. The results are evaluated using a self-created and a validated questionnaire (Knee Outcome Survey).

8) Dupuytren s disease

Retrospective analysis of severe, advanced and relapsing Dupuytren s disease with actual evaluation by DASH-Score. Evaluation of the Erlangen distraction device.

## Teaching

With compulsory and elective subjects, the Department of Plastic and Hand Surgery is involved in the curriculum-based teaching in medicine. In this context, besides a preclinical conjoint course together with the Institute of Anatomy, a microsurgical suture course is offered besides theoretical courses.

Furthermore, MD and PhD theses are supervised.

## Selected publications

Witt R, Weigand A, Boos AM, Cai A, Dippold D, Boccaccini AR, Schubert DW, Hardt M, Lange C, Arkudas A, Horch RE, Beier JP. Mesenchymal stem cells and myoblast differentiation under HGF and IGF-1 stimulation for 3D skeletal muscle tissue engineering. BMC Cell Biol, 2017. 18(1): p. 15

Rottensteiner-Brandl U, Distel L, Stumpf M, Fey T, Köhn K, Bertram U, Lingens LF, Greil P, Horch RE, Arkudas A. Influence of Different Irradiation Protocols on Vascularization and Bone Formation Parameters in Rat Femora. Tissue Eng Part C Methods, 2017. 23(10): p. 583-591 Cai A, Hardt M, Schneider P, Schmid R, Lange C, Dippold D, Schubert DW, Boos AM, Weigand A, Arkudas A, Horch RE, Beier JP. Myogenic differentiation of primary myoblasts and mesenchymal stromal cells under serum-free conditions on PCL-collagen I-nanoscaffolds. BMC Biotechnol, 2018. 18(1): p. 75

Steiner D, Lingens L, Fischer L, Köhn K, Detsch R, Boccaccini AR, Fey T, Greil P, Weis C, Beier JP, Horch RE, Arkudas A. Encapsulation of Mesenchymal Stem Cells Improves Vascularization of Alginate-Based Scaffolds. Tissue Eng Part A, 2018. 24(17-18): p. 1320-1331

Schmid R, Wolf K, Robering JW, Strauß S, Strissel PL, Strick R, Rübner M, Fasching PA, Horch RE, Kremer AE, Boos AM, Weigand A. ADSCs and adipocytes are the main producers in the autotaxin-lysophosphatidic acid axis of breast cancer and healthy mammary tissue in vitro. BMC Cancer, 2018. 18(1): p. 1273

An R, Schmid R, Klausing A, Robering JW, Weber M, Bäuerle T, Detsch R, Boccaccini AR, Horch RE, Boos AM, Weigand A. Proangiogenic effects of tumor cells on endothelial progenitor cells vary with tumor type in an in vitro and in vivo rat model. Faseb Journal, 2018. 32(10): p. 5587-5601

#### International cooperation

Prof. S. Jiaming, Tongji Medical College, Huazhong University of Science and Technology, Wuhan: China

# **Department of Psychiatry and Psychotherapy**

Chair of Psychiatry and Psychotherapy

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Director

Prof. Dr. med. Johannes Kornhuber

## Contact

Marita Imrich Phone: +49 9131 8534166 Fax: +49 9131 8534862 direktion-psych@uk-erlangen.de

## **Research focus**

- Depression
- Dementias
- Addictive behavior
- Clinical neurochemistry and neurochemical dementia diagnosis
- Neurophotonics
- Health Services Research
- Sensors
- Molecular psychiatry

## **Structure of the Chair**

Professorships: 3 Personnel: 225

- Doctors (of Medicine): 36
- Scientists: 25 (thereof funded externally: 11)
- Graduate students: 84

## **Clinical focus areas**

- Depression
- Memory disorders
- Dementia
- Schizophrenia
- Addiction
- Anxiety disorders

## Research

Our research is based on a broad spectrum of methods, ranging from basic clinical research to clinical research and care research.

## Depressions

Sphingolipids are essential components of the nerve cell membrane and regulate the flow of signals between neurons. We were able to show that alcohol exerts a paradoxical antidepressant effect on the influence of an important sphingolipid-metabolizing enzyme. In addition, we also described altered alternative splicing of this enzyme in patients with depressive disorders which makes it also a target for improved pharmacotherapy.

Funding: DFG, BMBF, and IZKF

Results from a multicenter randomized controlled study of the efficacy of a bouldering psychotherapeutic group intervention in people with depression showed an improvement in depressive symptoms as compared to a homebased supervised exercise program. Funding: DFG

## Dementia

A study showed that the  $A\beta$  peptide  $A\beta1-40$  is also reduced in the inflammatory central nervous system diseases Multiple Sclerosis (MS) and bacterial meningitis, but not in Alzheimer's disease. Thus, the use of the ratio  $A\beta1-42 / A\beta1-$ 40 allows a sharper diagnostic separation between these diseases (AD). The finding also speaks against the view of AD as a potentially Infect-triggered immunopathology.

In another study, the population of peripheral helper T helper (Th) was studied in various stages of AD with a significant increase in the interleukin-17-secreting Th17 cells in the stage of mild cognitive impairment, indicating that not only the innate, but also the adaptive immune system could be involved in the pathogenesis of AD.

The DeTaMAKS study is the first controlled, randomized study of the effectiveness of the nondrug MAKS-therapy<sup>®</sup> in day care in combination with a short-term telephone intercom. The results for the six months intervention period showed a significant effect of the MAKS-therapy<sup>®</sup>, stabilizing cognitive as well as everyday practice abilities of people with cognitive impairments at least at the initial level while they lessened in the control group.

The national graduate school "Optimization strategies for dementia" (OptiDem), granted by the Karl and Veronica Carstens foundation, was .successfully completed with eleven graduate students.

## Addiction disorders

International multicenter studies identified new genetic mechanisms involved in the development of alcohol addiction. In the animal model, it was possible to characterize the physiological mechanisms in the brain via which spontaneous genetic changes lead to a reduced function of the reward system.

## Funding: DFG, IZKF

We asked which role the protein EFhd2 plays in the control of alcohol addiction-associated behavior. We found that EFhd2 knock out mice drink more alcohol than controls and spontaneously escalate their consumption. This coincided with a sensation-seeking and low anxiety phenotype.

#### Funding: IZKF

We were able to provide evidence that intrauterine androgen exposure poses the risk of substance abuse, externalizing behaviors in childhood, suicides, and adult physical disorders. In addition, it can also shorten life expectancy. We also found smaller 2D:4D levels for alcohol dependence and binge drinking in clinical and non-clinical cohorts. This biomarker suggests that testosterone exposure before birth increases the subsequent risk of alcohol-related disorders.

In a series of studies, we have proven the validity and reliability of the new criteria for internet gambling disease and the pathological use of social networks.

## Clinical neurochemistry and neurochemical dementia diagnostics

The ISO 15189-accredited laboratory participated in two large-scale, EU-funded projects dealing with neurochemical dementia diagnostics (BiomarkAPD and IMI-EMIF) and coordinated two work packages. Both projects led to improvement of the understanding of the role of CSF biomarkers in the diagnostics of neurodegeneration disorders, like AD, including approaches to validate Neurofilament Light (NfL) as a blood-based biomarker.

Erlangen Score interpretation algorithm, developed in the Laboratory for Clinical Neurochemistry, was further validated and meanwhile entered routine application, also in some other European centers.

The laboratory coordinated the first international inter-center proficiency testing scheme for CSF biomarkers biobanking.

## Neurophotonics

The group developed a new method for the optical measurement of nerve cell network connectivity and published its first results in 2017. This project was funded by the Else-Kröner-Fresenius Foundation and is now exploring the mode of action in the second section of antidepressants.

An ongoing project funded by the DFG investigated the properties of antipsychotic drugs that are relevant for efficacy at the synapse.

In addition, various chemotherapeutic agents have been tested for their safety in the function of nerve cells in collaboration with the neurosurgical clinic.

#### **Health Services Research**

In cooperation with the interdisciplinary pain center, an instrument for the operationalization of successful treatment which is based on Patient Reported Outcomes (PROs) was developed in order to evaluate routines of the care. A validation with long-term data of chronic pain patients was performed and showed in an international publication that the instrument differentiates satisfactorily between long-term successfully treated patients and low-responders.

In health services research, there are few longterm studies that extend beyond a period of five years. It is therefore a special feature that the course of stroke patients up to 7.5 years after discharge from inpatient neurological rehabilitation was investigated and published in a cohort study in cooperation with the specialist hospital Herzogenaurach, division of neurorehabilitation.

#### Sensors

We investigated the influence of macronutrients on olfactory, cognitive, metabolic, and psychophysiological parameters in three human studies. In the first placebo-controlled study, nutrient solutions (protein, carbohydrate or fat, 600 kcal) or placebo were slowly administered intravenously. With regard to hunger and food craving, cognition and olfaction, the nutrient solutions did not differ. The second study investigated the effects of an isocaloric and isovolumic nutrient solution (600 kcal) as a function of different oral administration (normal intake versus slow interval intake). The third study is a placebo-controlled study in which various nutrient solutions (protein, carbohydrate or fat, 600 kcal) or placebo were administered orally at a normal rate of intake.

The newly developed odor test for food-associated odors could be further validated. The comparison of the test with the already validated identification test of the Sniffin 'Sticks test showed that both tests do not differ in terms of identification rate and intensity.

## **Molecular psychiatry**

As part of the research network GeNeRARe (German Network for RASopathy Research), the causes of cognitive impairment that occur in the rare RASopathy Noonan Syndrome (NS) were investigated in an animal model. We showed that, despite the hyperactivity of the neuronal RAS signaling pathway, gene expression following neuronal stimulation in the mutants was severely blunted, which could explain the cognitive deficits.

Funding: BMBF

In collaboration with Prof. Dr. T. Walter (university of Tübingen) and using functional MRI, we dissected regional and temporal dynamics of glutamatergic transmission upon single administration of antidepresant ketamine in healthy volunteers.

#### Funding: DFG

Using live-cell imaging in neurons we studied physiological role of amyloid beta in regulation of synaptic vesicle cycling. This peptide is associated with AD and our data indicate that dysregulation of presynaptic homeostasis might contribute to early synaptic dysfunction observed in AD long before measurable cell loss and plaque formation.

Funding: DFG

Our further publications deal with establishment of synaptic specificity and mechanism underlying regulation of neurotransmission by anxiolytic drug riluzole and upon manipulation of neuronal extracellular matrix. Funding: DFG:

## Teaching

The Department of Psychiatry and Psychotherapy participates with compulsory and elective subjects in the curricular teaching of Medicine and Logopedics. Particularly noteworthy here is the interdisciplinary teaching within the framework of the cross-sectional subjects EKM, Q9 (clinical pharmacology / pharmacotherapy) and Q10 (prevention and health promotion) and in the context of the compulsory elective subject of sexual medicine.

The Department has further expanded the simulation program of patients. Students can practice acting in difficult situations with agitated, affective, rejecting and uncooperative patients. In addition, Objective Structured Clinical Examinations (OSCE) stations were developed to validate communication and investigation skills. Bachelor's and Master's theses as well as MD and PhD theses are supervised.

#### Selected publications

Altmüller F, Pothula S, Annamneedi A, Nakhaei-Rad S, Montenegro-Venegas C, Pina-Fernández E, Marini C, Santos M, Schanze D, Montag D, Ahmadian MR, Stork O, Zenker M, Fejtova A. Aberrant neuronal activity-induced signaling and gene expression in a mouse model of RA-Sopathy. PLoS Genet. 2017 Mar 27;13(3):e1006684

Bachlechner S, Denzer-Lippmann MY, Wielopolski J, Fischer M, Buettner A, Doerfler A, Schöfl C, Münch G, Kornhuber J, Thürauf N. The Effects of Different Isocaloric Oral Nutrient Solutions on Psychophysical, Metabolic, Cognitive, and Olfactory Function in Young Male Subjects. Front Psychol. 2017 Nov 23;8:1988

Lenz B et al. Prenatal and adult androgen activities in alcohol dependence. Acta Psychiatr Scand. 2017 Jul;136(1):96-107 Straubmeier M, Behrndt E-M, Seidl H, Özbe D, Luttenberger K, Graessel E. Non-pharmacolgical treatment in people with cognitve impairment. Dtsch Arztebl Int. 2017 Dec 1;114(48):815-821

Mielenz D et al. EFhd2/ Swiprosin-1 is a common genetic determinator for sensation seeking/ low anxiety and alcohol addiction. Mol Psychiatry. 2018 May;23(5):1303-1319

Stelzer EM, Book S, Graessel E, Hofner B, Kornhuber J, Luttenberger K. Bouldering psychotherapy reduces depressive symtoms even when general physical activity is controlled for: a randomized controlled trial. Heliyon. 2018 Mar 23;4(3):e00580

#### 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

## Address

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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
- Neural processing of emotional and disorder specific stimuli in girls with eating disorders
- Parenting stress in the context of mental health treatments for children and adolescents
- Therapeutic interventions Clinical effects and underlying mechanisms
- Prenatal trauma and fetal programming in a mouse model

## **Structure of the Division**

Professorship: 1

- Personnel: 156
- Doctors (of Medicine): 27
- Scientists: 4 (thereof funded externally: 0)
- Graduate students: 14

## **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 the Division of Child and Adolescent Mental Health are to contribute to a better understanding of the developmental processes and the neurobiological 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 Pl: Dr. A. Fichler

A longitudinal study, including 250 families, conducted in cooperation with the Departments of Obstetrics and Gynecology and of Psychiatry and Psychotherapy, examines the longterm effects of prenatal risks (including alcohol consumption, depression, stress) on child adaption aged between 6-9 (data collection 2012-2015) and 11-13 years (data collection since 2019). Child developmental status is operationalized in a multi-level design (cognitive, emotional, social factors): In addition to neuropsychological (e.g. intelligence testing) and neurophysiological measures (e.g. event-related cortical potentials), neurobiological markers are of interest, too, (e.g. alcohol metabolites in the meconium of the newborn; saliva/hair cortisol concentrations; epigenetic data from buccal cells; blood immune markers). The 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 and supported by the Robert Enke Foundation, we have added a sample of children with a risk factor of early life stress, 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 develop-

ment were observed, which were moderated by positive parenting behavior. The mothers of affected children showed increased concentrations of the stress hormone cortisol in saliva.

Furthermore, again in cooperation with the Departments of Obstetrics and Gynecology and of Psychiatry and Psychotherapy and supported by the BMBF, we investigate in a randomized controlled study the effects of an app-based mind-fulness-based program during pregnancy - designed to reduce the prenatal risks of maternal stress and substance use - on self-regulation, developmental status, and mental health in one year-old children.

Funding: Robert-Enke-Foundation, BMBF

## Neural processing of emotional and disorder specific stimuli in girls with eating disorders

PI: Dr. S. Horndasch

In girls and women with eating disorders (anorexia nervosa, bulimia nervosa) versus typically developing girls and an adult control group, 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 a visual attentional bias (measured via eye-tracking) towards body shape-related information and enhanced motivated attention (measured via EEG event-related potentials) following pictures of strongly underweight women. fMRI data reflect differential neural processing of food and body stimuli in patients with anorexia nervosa versus control participants and in adolescents versus adults.

Our current study is looking at neural reaction patterns of anticipation (when looking at food pictures) and actual consumption (when eating high and low calory food) via resting state fMRI.

## Parenting stress in the context of mental health treatments for children and adolescents

PI: Dr. V. Irlbauer-Müller

Psychiatric disorders in children and adolescents are associated with a higher level of parenting stress. The affective-cognitive characteristic of parents has a negative impact on the observable parenting behavior, increasing the probability of dysfunctional parent-child-interaction and influences the child-/adolescent-reported internalized representation of the parent-childrelationship. Additional negative consequences for the child's/adolescent's psychological health and the parent-child-interaction are possible. Therefore psychiatric/psychotherapeutic support for children and adolescents has to include evidence-based interventions for both, the individual and for the family, especially for the parents. The current study compares different parent-specific interventions focusing the effects on the self-reported parenting stress and the child-/ adolescent-reported internalized representation of the parent-child-relationship.

### Therapeutic interventions – Clinical effects and underlying mechanisms PI: Dr. P. Studer

PI: Dr. P. Studer

Neurofeedback involves a brain-computer interface which enables to learn self-control over specific aspects of neural (EEG) activity. While our earlier multi-center studies were essential in demonstrating the clinical effectiveness of neurofeedback (theta/beta and slow cortical potential training) for children with ADHD, our recent meta-analysis indicated in addition that neurofeedback effects (compared to non-active control treatments) lasted longer after the end of treatment. Our recent studies ("short-term studies" with less training session) aim 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. In our recently established light laboratory, we observed positive effects of blue versus red light on attention in 'healthy' adolescents (increased performance, reduced reaction time variability) and obtained first hints for improved sleep according to actigrahy measures after red versus blue light.

Further studies are planned to evaluate the effectiveness of light therapy in adolescents with psychiatric disorders.

Funding: ELAN-Fonds

### Prenatal trauma and fetal programming in a mouse model Pl: Dr. S. Frey

We applied our mouse model of prenatal trauma to investigate molecular and epigenetic consequences for fetal brain development. Timing and their underlying mechanisms are of special interest. Prenatal trauma may cause decreased weight, increased HPA-axis activity, and behavioral symptoms of fear in the affected pups. Expression and methylation of Crhr1 changed postnatally in the dorsal hippocampus and prenatally in the hypothalamus. Our findings support the hypothesis that trauma-induced neuroendocrine and behavioral alterations are associated with stable changes of 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 Medicine.

MD theses as well as Bachelor's and Master's theses (mainly in psychology) are supervised.

### **Selected publications**

Van Doren J, Heinrich H, Bezold M, Reuter N, Kratz O, Horndasch S, Berking M, Ros T, Gevensleben H, Moll GH, Studer P. Theta/beta neurofeedback in children with ADHD: Feasibility of a short-term setting and plasticity effects. Int J Psychophysiol. 2017 Feb;112:80-88 Irlbauer-Müller V, Eichler A, Stemmler M, Moll GH, Kratz O. [Parenting stress and the reliability of parental information in the diagnostics of children and adolescents with symptoms of psychiatric and behavioral disorders]. Z Kinder Jugendpsychiatr Psychother. 2017 Jul;45(4):303-309

Heinrich H, Grunitz J, Stonawski V, Frey S, Wahl S, Albrecht B, Goecke TW, Beckmann MW, Kornhuber J, Fasching PA, Moll GH, Eichler A. Attention, cognitive control and motivation in ADHD: Linking event-related brain potentials and DNA methylation patterns in boys at early school age. Sci Rep. 2017 Jun 19;7(1):3823

Eichler A, Hudler L, Grunitz J, Grimm J, Raabe E, Goecke TW, Fasching PA, Beckmann MW, Kratz O, Moll GH, Kornhuber J, Heinrich H. Effects of prenatal alcohol consumption on cognitive development and ADHD-related behaviour in primary-school age: a multilevel study based on meconium ethyl glucuronide. J Child Psychol Psychiatry. 2018 Feb;59(2):110-118

Horndasch S, Kratz O, Van Doren J, Graap H, Kramer R, Moll GH, Heinrich H. Cue reactivity towards bodies in anorexia nervosa - common and differential effects in adolescents and adults. Psychol Med. 2018 Feb;48(3):508-518

Stonawski V, Frey S, Golub Y, Rohleder N, Kriebel J, Goecke TW, Fasching PA, Beckmann MW, Kornhuber J, Kratz O, Moll GH, Heinrich H, Eichler A. Associations of prenatal depressive symptoms with DNA methylation of HPA axis-related genes and diurnal cortisol profiles in primary schoolaged children. Dev Psychopathol. 2018 Apr 2:1-13

#### International cooperations

Prof. L. Gabel, Lafayette College, Easton, Pennsylvania: USA

Dr. M. Arns, Brainclinics, Nijmegen: The Netherlands

# **Department of Psychiatry and Psychotherapy**

Division of Psychosomatic Medicine and Psychotherapy

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**Head of Division** 

Prof. Dr. (TR) Yesim Erim

## Contact

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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 back
  - ground

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**

Pl: 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.

#### **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, placebo-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.

## 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**

Erim Y, Scheel J, Beckmann M, Klein CG, Paul A. Standardized Evaluation of Candidates Before Liver Transplantation With the Transplant Evaluation Rating Scale. Psychosomatics. 2017 Mar - Apr;58(2):141-150

Morawa E, Dragano N, Jöckel KH, Moebus S, Brand T, Erim Y. Somatization among persons with Turkish origin: Results of the pretest of the German National Cohort Study. J Psychosom Res. 2017 May;96:1-9

Paslakis G, Fauck V, Röder K, Rauh E, Rauh M, Erim Y. Virtual reality jogging as a novel exposure paradigm for the acute urge to be physically active in patients with eating disorders: Implications for treatment. Int J Eat Disord. 2017 Nov;50(11):1243-1246

Nacak Y, Morawa E, Tuffner D, Erim Y. Insecure attachment style and cumulative traumatic life events in patients with somatoform pain disorder: A cross-sectional study. J Psychosom Res. 2017 Dec;103:77-82

Scheel JF, Schieber K, Reber S, Stoessel L, Waldmann E, Jank S, Eckardt KU, Grundmann F, Vitinius F, de Zwaan M, Bertram A, Erim Y. Psychosocial Variables Associated with Immunosuppressive Medication Non-Adherence after Renal Transplantation. Front Psychiatry. 2018 Feb 15;9:23

Georgiadou E, Zbidat A, Schmitt GM, Erim Y. Prevalence of Mental Distress Among Syrian Refugees With Residence Permission in Germany: A Registry-Based Study. Front Psychiatry. 2018 Aug 28;9:393

# **Department of Radiation Oncology**

## Chair of Radiotherapy

### Address

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#### Director

Prof. Dr. med. Rainer Fietkau

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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): 21
- Scientists: 31 (thereof funded externally: 6)
- Graduate students: 65

## **Clinical focus areas**

- Percutaneous radiotherapy
- Treatment planning
- Image guided radiotherapy (IGRT)
- 3D conformal radiotherapy
- Intensity modulated radiotherapy (IMRT
- Intensity modulated arc therapy (VMAT)
- Stereotactic body radiation therapy (SBRT)
- Whole-skin- and whole-body-irradiation
- Brachytherapy
- Intensity modulated brachytherapy (IMBT)
- Image guided brachytherapy (IGBT)Deep regional hyperthermia with MR-Ther-
- mometry
- Local hyperthermia for the treatment of superficial tumors
- Radio-chemo-therapy
- Radio-immuno-therapy
- Low dose radiation therapy (LDRT)

## Research

Clinical, biological, immunological as well as physical aspects of radiation oncology are scientifically analyzed. Clinical aspects of radiation oncology are predominantly examined within phase I, II, and III trials. This takes place on the ward, in the outpatient department, the therapeutics department (including brachytherapy) as well as the treatment planning department and hyperthermia unit. Coordination of the clinical trials is carried out by the in-house clinical trials office. Translational and basic radio(immune)-biological research is carried out by two groups, the classical radiation biology group and the radiation immune biology group. The "Medical Radiation Physics" group has the main scientific focus in respiratory and general organ motion during radiation therapy. In addition, the group is responsible for all medical physics duties of clinical radiation therapy (including control of brachytherapy implants).

#### **Clinical trials**

PI: Prof. Dr. R. Fietkau, Prof. Dr. V. Strnad, Prof Dr. O. Ott, PD Dr. S. Semrau, Prof. Dr. U. Gaipl, Dr. M. Haderlein, Dr. G. Lahmer, Dr. M. Hecht, Dr. N. Goerig

Phase-III multicenter trials:

1. First-line treatment of locally advanced HNSCC with double checkpoint blockade and radiotherapy dependent on intratumoral CD8+ T cell infiltration (CheckRad-CD8) - IIT

Funding: AstraZeneca GmbH

2. Preoperative radiochemotherapy and adjuvant chemotherapy with 5-fluorouracil versus preoperative radio-chemotherapy and adjuvant chemotherapy with 5-fluorouracil combined with oxaliplatin in patients with locally advanced UICC stage II and III rectal cancer (CAO/ ARO/AIO-04) Funding: German Cancer Aid

3. Comparison of partial breast interstitial brachytherapy with external whole breast beam radiotherapy in patients with low risk invasive and in situ breast carcinomas (APBI-III)

Funding: German Cancer Aid

4. Salvage Brachytherapy and Hyperthermia for Recurrent H&N-tumors (HyBT-H&N)

5. Pancreatic carcinoma: chemoradiation compared with chemotherapy alone after induction chemotherapy (CONKO-007)

Funding: German Cancer Aid

6. Effects of deep regional hyperthermia in patients with anal carcinoma treated by standard radiochemotherapy (HYCAN)

7. Cetuximab in combination with platinumbased chemotherapy or radiotherapy in patients with recurrent and/or metastatic SSCHN in clinical routine (SOCCER)

Funding: Merck Serono GmbH

Phase-II trials:

1. Randomized phase II study of immune stimulation with Pembrolizumab and radiotherapy in second line therapy of metastatic head and neck squamous cell carcinoma (IMPORTANCE), IIT Funding: MSD

2. PDR/HDR interstitial brachytherapy alone in patients with pT1/pT2 pN0 breast carcinomas after breast conserving surgery (APBI-IV)

3. 3D conformal, external partial breast irradiation in patients with pT1/2 pN0 breast carcinomas after breast conserving surgery (APBI-V)

4. Neoadjuvant chemoradiation with 5-FU (or capecitabine) and oxaliplatin combined with deep regional hyperthermia in locally advanced or recurrent rectal cancer (HyRec)

5. Enhancement of neurocognitive functions by hippocampal sparing radiotherapy (HIPPOSPARE 01)

6. Efficacy of dose intensified radiotherapy of spinal metastases by hypofractionated radiation and IGRT hfSRT mediated boost (SPIN-MET)

7. Salvage brachytherapy and interstitial hyperthermia for locally recurrent prostate carcinoma following radiation therapy (Prostata-BT-HT)

8. De-intensification of postoperative radiotherapy in selected patients with head and neck cancer (DIREKHT)

9. Investigation of the timely-coordinated therapy of patients with metastatic cancer by radiotherapy together with immune checkpoint inhibition (ST-ICI)

10. Analysis of CMV infections in patients with brain tumors or brain metastases during and after radio(Chemo)therapy (GLIO-CMV-01)

11. Immunophenotyping from blood of patients with malignant gliomas (IMMO-GLIO-01)

12. Immunophenotyping from blood of patients suffering from chronic degenerating joint diseases and receiving LDRT (IMMOLDRT-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.

## **Clinical trials office**

PI: Dr. D. Lubgan, M. Lang-Welzenbach, S. Rutzner

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 (IIT and as participating center)

2. Organization of meetings and international training courses

3. Scientific research

## **Radiation biology**

PI: Prof. 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 (Prof. 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, 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. Geometrical and dosimetric verification for interstitial brachytherapy by an electromagnetic tracking system.

Funding: Elekta

2. Automated analysis of clinical data from record and verify (R+V) and treatment planning systems.

3. Four dimensional radiation dose calculation of motion compensated radiotherapy

4. New techniques in hyperthermia quality assurance

## **Radiation immunobiology**

PI: Prof. Dr. U. Gaipl, PD Dr.-Ing. B. Frey Connections between local and systemic, immune-mediated effects of ionizing radiation alone and in combination with immunotherapy (vaccination, immune checkpoint blockade) and the underlying immune mechanisms are examined. A further research aim is the analysis of osteoimmunlogical effects of low dose radiation (X-Ray and radon radiation). Moreover, detailed immunomonitoring of radiation-exposed patients is performed in the framework of clinical trials (IMPORTANCE, CheckRadCD8, IMMO-LDRT, IMMO-GLIO, CONKO, GLIO-CMV, DI-REKHT, ST-ICI, RAD-ONO2) and respective biomaterial is stored in the in-house biobank.

The following third-party supported projects are currently handled:

1. Modulation of inflammation and genetic risks of dense ionizing radiation

Funding: BMBF, GREWISalpha network

2. Impact and mechanisms of PD-L1, PD-L2 and EGF-R expression on glioma cells following radiochemotherapy and its consequences for combination with vaccination and PD-1 inhibition Funding: DFG

3. Multi-scale-analyses of deep regional hyperthermia as a novel and additive tumor treatment – Microthermia

Funding: Bavarian Research Foundation 4. RAD-ON02 trial: Determination of immunologic and pain relieving effects of radon spa therapy in patients with musculoskeletal disorders Funding: Bavarian State Ministry of Health and Care 5. 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)

6. 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

Radiation therapy planning at the Department of Radiation Oncology: A medical physics expert is discussing the treatment plan together with a physician The translational and interdisciplinary examination of the therapy plays a major role in the scientific actions of the Department. (Image: UK Erlangen/M. Kohler)

## 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 Comprehensive Cancer Center (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". In addition the Department offers interdisciplinary courses for students of physics, medical technology, molecular medicine, medicine, and natural sciences.

Students have the opportunity to work on the Bachelor's or Master's theses and graduates are supervised during their PhD and MD projects, all embedded in the research focus of the Department. Laboratory rotations are offered for fast-track students of GK 1660 (compare own report).

#### **Selected publications**

Frey B, Rückert M, Deloch L, Rühle PF, Derer A, Fietkau R, Gaipl US. Immunomodulation by ionizing radiation-impact for design of radio-immunotherapies and for treatment of inflammatory diseases. Immunol Rev. 2017 Nov;280(1): 231-248

Frey B, Rückert M, Weber J, Mayr X, Derer A, Lotter M, Bert C, Rödel F, Fietkau R, Gaipl US. Hypofractionated Irradiation Has Immune Stimulatory Potential and Induces a Timely Restricted Infiltration of Immune Cells in Colon Cancer Tumors. Front Immunol. 2017 Mar 8;8:231

Polgár C et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2017 Feb;18(2):259-268

Fietkau R. Which fractionation of radiotherapy is best for limited-stage small-cell lung cancer? Lancet Oncol. 2017 Aug;18(8):994-995

Deloch L, Derer A, Hueber AJ, Herrmann M, Schett GA, Wölfelschneider J, Hahn J, Rühle PF, Stillkrieg W, Fuchs J, Fietkau R, Frey B, Gaipl US. Low-Dose Radiotherapy Ameliorates Advanced Arthritis in hTNF-a tg Mice by Particularly Positively Impacting on Bone Metabolism. Front Immunol. 2018 Sep 18;9:1834

Kallis K, Kreppner S, Lotter M, Fietkau R, Strnad V, Bert C. Introduction of a hybrid treatment delivery system used for quality assurance in multi-catheter interstitial brachytherapy. Phys Med Biol. 2018 May 2;63(9):095008

#### International cooperations

Dr. K. Luminczky, Prof. G. Safrany, Frédéric Joliot-Curie National Research Institute for Radiobiology and Radiohygiene (NRIRR), Budapest: Hungary

Prof. Dr. C. Polgár, Center of Radiotherapy, National Institute of Oncology, Budapest: Hungary

Dr. S. Candéias, CEA Laboratoire de Chimie et Biologie des Métaux Biosciences and Biotechnolgy Institute of Grenoble, Grenoble: France

Dr. C. Badie, Public Health England, Centre for Radiation, Chemical & Environmental Hazards Didcot: UK

# **Department of Surgery**

## Chair of Surgery

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### Director

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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-y in gastrointestinal diseases
- Tumor-micromilieu induced plasticity of tumor endothelial cells in colorectal carcinoma
- Genome editing of pancreatic tumor models
- Organoid models in pancreatic cancer
- Immunepathophysiology of acute (sepsis) and chronic (colitis) inflammation
- Immunephenotyping and liquid biopsy analysis of gastrointestinal tumors

## **Structure of the Chair**

Professorships: 4 Personnel: 308

- Doctors (of Medicine): 38
- Scientists: 10 (thereof funded externally: 6)
- Graduate students: 44

#### **Clinical focus areas**

- Oncological surgery
- Surgery of the gastrointestinal tract
- Metabolic and bariatric surgery
- Endocrinological surgery
- Minimally invasive surgery
- Transplantation
- Outpatient surgery
- Surgical emergency

## Research

Clinical research at the Department of Surgery mainly consists of the clinical cancer registry, randomized trials of gastrointestinal tumors and evaluation of nationwide hospital discharge data. The translational research is focused on

colorectal cancers/inflammatory bowel diseases and pancreatic cancer. Groups of investigators focusing on tumor micromilieu and sepsis are connecting the main research topics.

## **Evaluation of prognosis of** gastrointestinal tumors

PI: Prof. Dr. R. Grützmann, Prof. Dr. S. Merkel Since 1978, a clinical cancer registry has been prospectively maintained for organ specific tumor documentation. At present, more than 30,000 patients are registered. Main foci are on colorectal cancer with over 13,000 and pancreatic cancer with over 2,700 documented cases. Patients are followed for life with only 1% of patients lost to follow-up. The scientific evaluation of this data focuses on health services research, quality management, the improvement of tumor classification, the identification of prognostic factors, the definition of quality indicators, and quality of life research. The documentation of specific diagnostics and multimodal treatment strategies results from an interdisciplinary cooperation of numerous departments and institutes at the Faculty of Medicine.

## **Randomized trials for gastrointestinal** tumors

PI: Prof. Dr. R. Grützmann, Dr. H. Golcher The Department of Surgery respectively the interdisciplinary Colorectal Cancer Center/ Modul Pancreas Cancer took part in different multicenter trials about gastrointestinal tumors, inter alia " Pancreatoduodenectomy with or without 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. The surgical second opinion ("panel of surgeons") for the CONKO-007-trial (patients with non resectable pancreatic carcinoma) is organized by the study team, too, and evaluation takes place in the daily tumor conference.

## **Outcomes research of complex surgery** with hospital discharge data PI: Dr. C. Krautz

A variety of surgical procedures in general surgery are associated with varying perioperative outcomes due to their complexity. Analyses of nationwide hospital discharge data provide the possibility to examine the underlying

causes. Currently, we are assessing the effects of volume-based referral on perioperative outcomes in complex surgery in order to give recommendations for the future hospital market structure in Germany.

## The interferon-y pathway in the immune escape of colorectal cancer

PI: PD Dr. N. Britzen-Laurent, Prof. Dr. Dr. M. Stürzl

The presence of an interferon-γ-dominated Th1 immune response in colorectal cancer (CRC) has been associated with improved clinical outcome. Several CRC cell lines are resistant to IFN-y action. In these cell lines, the loss of IFNγ-responsiveness correlated with the down-regulation or with the presence of a mis-glycosylated form of the IFN-y receptor alpha chain (IFN $\gamma$  R $\alpha$ ). A knock-out of the IFN- $\gamma$  receptor in intestinal epithelial cells of mice fostered tumor growth. In accord with this decreased expression of IFN  $\gamma$  R $\alpha$  in human CRC correlated with reduced cancer-related survival and increased metastasis. Our data suggest that the loss of IFN-y responsiveness is a common escape mechanism of CRC tumor cells against the antitumorigenic effects of IFN-γ.

Funding: IZKF, DFG

### Angiocrine mechanisms of tumor suppression in colorectal cancer

PI: PD Dr. E. Naschberger, Prof. Dr. Dr. M. Stürzl Investigation of cellular memory processes in human tumor endothelial cells allowed the identification of SPARCL1 as angiocrine mediator in CRC. SPARCL1 is specifically expressed and released by tumor vessel cells in tumors with a Th1 tumor microenvironment (TME). It inhibits proliferation and migration of CRC tumor vessel and tumor cells. In accord with this SPARCL1 expression in human CRC tissues and mouse models is associated with reduced angiogenic activity and improved prognosis of the patients. SPARCL1 is a vessel-derived tumor suppressor in CRC actively contributing to the favorable prognosis associated with a Th1-TME. Funding: IZKF, DFG

## Genome editing of pancreatic tumor models

### PI: Prof. Dr. C. Pilarsky

Pancreatic cancer is the fourth most frequent cause of cancer in the western world with a five year survival rate of 8%. This is caused by chemoresistance of the tumor. In this project we are trying to understand more precisely which mechanisms influence such a chemoresistance.

Based on the well-known changes in the tumor genome, we are targeting specific genes, especially gene involved in DNA repair, with CRISPR/Cas9 technology and are testing whether our tumor models become more sensitive to the application of chemotherapeutic agents. This allows an adaptation of chemotherapeutic regimens to the mutation pattern of the individual tumor within the framework of modern precision medicine.

## Organoid models in pancreatic cancer

PI: Prof. Dr. C. Pilarsky

In this project we will test the influence of the culture conditions on the chemosensitivity of pancreatic carcinomas. For this purpose, pancreas tumor cells are grown as a special tissue culture, the organoid culture, and treated with chemotherapeutic agents. This allows us to examine how the individual models can be treated in a tissue. This allows a better understanding of the necessary dosage of chemotherapeutic agents and a possible better preclinical testing of new chemotherapies.

### Immunepathophysiology of acute (sepsis) and chronic (colitis) inflammation PI: PD Dr. G. Weber

The immune system consists of innate and adaptive components that operate in close proximity to protect the host against infections. During infection the host can be at risk due to imbalanced immune responses. A major therapeutic goal, then, is to establish an equilibrium between controlling infection and controlling inflammation. One promising strategy is to harness the endogenous immune system to augment processes that are beneficial and curb processes that cause harm. Such strategies, however, require understanding of the diseases pathophysiology. Currently, we are focusing on the role of interleukin-3 as central regulator for acute and chronic inflammation.

## Immunephenotyping and liquid biopsy analysis of gastrointestinal tumors

## PI: PD Dr. G. Weber

Successful treatment of cancer disease is based on the in-depth understanding of the involved mechanisms leading to cancer development and progression. Thus, precise knowledge of the immunogenicity of the individual tumor as well as early and precise diagnosis is required. Within this project, we will develop non-invasive alternative techniques – so called liquid biopsies - to diagnose cancer disease, predict and monitor disease progression, and finally to improve patient selection for established treatment strategies. In addition, we are immunologically phenotyping the individual cancer disease to evaluate immune therapeutic strategies.

## Teaching

The Department of Surgery is offering courses for students of Medicine, Dentistry, Molecular Medicine, and biology. The Dr. House colloquium is an interdisciplinary lecture with the internal medicine. By the implementation of a surgical skills lab, surgical residents as well as medical students benefit from learning different surgical approaches and may acquire basic surgical skills using modern laparoscopic simulators. MD and PhD theses are supervised.

#### **Selected publications**

Lehmann B, Biburger M, Brückner C, Ipsen-Escobedo A, Gordan S, Lehmann C, Voehringer D, Winkler T, Schaft N, Dudziak D, Sirbu H, Weber GF, Nimmerjahn F. Tumor location determines tissue-specific recruitment of tumor-associated macrophages and antibody-dependent immunotherapy response. Sci Immunol. 2017 Jan 6;2(7). pii: eaah6413

Naschberger E, Geißdörfer W, Bogdan C, Tripal P, Kremmer E, Stürzl M, Britzen-Laurent N. Processing and secretion of guanylate binding protein-1 depend on inflammatory caspase activity. J Cell Mol Med. 2017 Sep;21(9):1954-1966

Liu B, Yang H, Taher L, Denz A, Grützmann R, Pilarsky C, Weber GF. Identification of Prognostic Biomarkers by Combined mRNA and miRNA Expression Microarray Analysis in Pancreatic Cancer. Transl Oncol. 2018 11:700-714

Krautz C, Nimptsch U, Weber GF, Mansky T, Grützmann R. Effect of Hospital Volume on In-hospital Morbidity and Mortality Following Pancreatic Surgery in Germany. Ann Surg. 2018 267:411-417

Merkel S, Schellerer VS, Wein A, Semrau S, Geppert C, Göhl J, Hohenberger W, Weber K, Grützmann R. The influence of tumour site on prognosis in metastatic colorectal carcinomas with primary tumour resection. Int J Colorectal Dis. 2018 33:1215-1223

Unterer B, Wiesmann V, Gunasekaran M, Sticht H, Tenkerian C, Behrens J, Leone M, Engel FB, Britzen-Laurent N, Naschberger E, Wittenberg T, Stürzl M. IFN-γ-response mediator GBP-1 represses human cell proliferation by inhibiting the Hippo signaling transcription factor TEAD. Biochem J. 2018 475:2955-2967

#### International cooperations

Prof. M. Gack, Department of Microbiology, The University of Chicago, Chicago: USA

Prof. R.D. Kamm, Massachusetts Institutes of Technology -MIT, Cambridge: USA

Prof. M. Kelly/Prof. D.C. Winter, Department of Surgery, St. Vincent's University Hospital Dublin, Dublin: Ireland

Prof. F.K. Swirski, Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston: USA

Prof. D. Tuveson, Cold Spring Harbor Laboratory, Cold Spring Harbor: USA

## **Department of Surgery**

## Division of Pediatric Surgery

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## **Head of Division**

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### Contact

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#### **Research focus**

- Preliminary results of enteral surface stimulation (ESS) 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**

Professorship: 0

Personnel: 12

- Doctors (of Medicine): 8
- Graduate students: 3

## **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) 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 being treated effectively. In contrast, a long-term course of constipation can frequently not be treated sufficiently. Since curative 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) 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 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 electric field (voltage between 5V and 8V at a frequency of 15 Hz) in order to improve intestinal peristalsis and relieve constipation. 18 patients, aged 3 - 13 years, were treated between 2013 and 2015. Symptomatic changes were evaluated by using questionnaires and observing changes in clinical examination. Satisfaction levels of 67% were achieved. 77% of patients experienced a persisting improvement of constipation after their ESS-treatment had finished. 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 noninvasive therapy option for chronic pediatric constipation, which shows high symptomatic improvement at a low complication rate. High efficiency seems to occur particularly in schoolchildren 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 seems to be a new auspicious therapy, completing and enriching the existing options.



Enteral Surface Stimulation (ESS): 2 self-adhesive electrodes (blue), connected to a stimulator device, generate an electric field with impact to the enteric nerve system and consecutive stimulation of the bowel

## 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 a surgical instrumental developer (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 chondrotomias 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.

## 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 (PREVENA<sup>™</sup>), 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) Pl: Prof. Dr. S. Schulz-Drost

PI: PIOI. DI. 3. SCHUIZ-DIOS

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 as 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-/postoperative 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 phantom-courses for minimally invasive pediatric surgery in skills lab and hands-on courses. The Division of Pediatric Surgery supervises PhD theses.

## **Selected publications**

Ewert F, Syed J, Kern S, Besendörfer M, Carbon RT, Schulz-Drost S. Symptoms in pectus deformities: A scoring system for subjective physical complaints. Thorac Cardiovasc Surg 2017, 65: 43-49

Ewert F, Syed J, Wagner S, Besendoerfer M, Carbon RT, Schulz-Drost S. Does an external chest wall measurement correlate with a CT-based measurement in patients with chest wall deformities? J Pediatr Surg 2017, 52: 1583-1590

Grupp S, Fürst V, Buder T, Fichte A, Krinner S, Carbon RT, Hennig FF, Langenbach A, Schulz-Drost S. Comparative studies of different types of osteosynthesis on the human corpse preparation in bilateral antero-lateral flail chest. Injury 2017, 48: 2709-2716

Schulz-Drost S, Luber AM, Simon K, Schulz-Drost M, Syed J, Carbon RT, Besendörfer M. Elastic stable chest repair and its hybrid variants in 86 patients with pectus excavatum. J Thorac Dis 2018, 10: 5736-5746

Jabari S, Carbon R, Besendörfer M, Hartmann A, Rompel O, Hoerning A, Söder S. Asymmetric Omphalopagus in a triplet after in vitro fertilization: A rare case of conjoined twinning. Case Rep Pediatr 2018, 23;2018:9349606

Horn-Hofmann C, Scheel J, Dimova V, Parthum A, Carbon R, Griessinger N, Sittl R, Lautenbacher S. Prediction of persistent post-operative pain: Pain–specific psychological variables compared with acute post-operative pain and general psychological variables. Eur J Pain 2018, 22: 191-202

#### International cooperations

Prof. Dr. A. Fisher, Biochemical Center of Research, Weizman Institue of Science, Rehovot: Israel

Prof. Dr. G. Berci, Endoscopic Research, Cedars-Sinai Medical Center, Los Angeles: USA

AO Foundation. TK Thoracic Surgery Expert Group, Davos: 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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**Head of Division** 

Prof. Dr. med. Dr. h.c. Horia Sirbu

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## **Research focus**

- Surgical therapy of hyperhidrosis a prospective quality control study
- Surgical management of pulmonary metastases from colorectal cancer
- Deep intrathoracic vacuum therapy in septic thoracic surgery
- Imunological and molecular characterization of malignant lung tumors
- Neoadjuvant therapy of locally advanced nonsmall cell lung carcinoma IIIA; simultaneous radiochemotherapy followed by surgery
- The impact of patho-histologic response following neo-adjuvant radiochemotherapy in locally advanced non-small cell lung cancer
- Prognostic effect of "Salvage"-resection in locally advanced non-small cell lung cancer
- The value of the systematic extensive lymph node dissection in the operative treatment in non-small cell lung cancer
- Pulmonary resection with parietal pleurectomy (WRPP) versus parietal pleurectomy (PP) for the treatment of primary pneumothorax
- Functional analysis of human dendritic cell subpopulations

## **Structure of the Division**

Professorship: 1 Personnel: 9

- Doctors (of Medicine): 6
- Scientists: 6 (therof funded externally: 0)
- Graduate students: 3

## **Clinical focus areas**

- Gentle surgical techniques for lung cancer, lung tumors
- Successful treatment of pathological sweating (hyperhidrosis)
- Video-assisted correction of chest deformations, e.g. pectus excavatum

## Research

The research focus of the Division of Thoracic Surgery is to research innovative therapies for operative pulmonary and thoracic diseases to develop new clinical treatment concepts. Furthermore, experimental immunological projects with samples from the lung and human lymphoid organs are carried out within the framework of the cooperation with other divisions and departments.

## Surgical therapy of hyperhidrosis – a prospective quality control study

PI: Dr. 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, PD 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 in septic thoracic surgery

PI: PD 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.

## Immunological and molecular characterization of malignant lung tumors

PI: Prof. Dr. S. Finotto (Division of Molecular Pneumology), Dr. D.I. Trufa, Prof. Dr. H. Sirbu The aim of this research project is to investigate the immunological and molecular basis. The focus within this project are the malignancies that become visible in the lung, especially nonsmall 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.

### Neoadjuvant therapy of locally advanced non-small cell lung carcinoma IIIA; simultaneous radiochemotherapy followed by surgery

PI: Prof. Dr. H. Sirbu, Prof. Dr. R. Fietkau, PD Dr. W. Schreiner

In this trial, we compare the therapy concept of neoadjuvant radiochemotherapy (45Gy/Cisplatin, Etoposide), followed by surgery, with the concept of definitive radiochemotherapy in patients with locally advanced, non-small cell lung carcinoma stadium IIIA.

### The impact of patho-histologic response following neo-adjuvant radiochemotherapy in locally advanced non-small cell lung cancer

PI: PD Dr. W. Schreiner, Prof. Dr. R. J. Rieker (Institute of Pathology)

The purpose of the study is the analysis of patho-histologic response of the primary tumor following neo-adjuvant chemoradiation therapy and the long-term impact on survival in order to identify the predisposing factors for survival improvement in patients with locally advanced non-small cell lung cancer.

#### Prognostic effect of "Salvage"resection in locally advanced non-small cell lung cancer

PI: PD Dr. W. Schreiner, Prof. Dr. H. Sirbu, Prof. R. Fietkau (Department of Radiation Oncology) The study purpose is the prognostic effect and impact on local tumor control due to the "Salvage"-surgery for local recurrence and/or persisted primary tumor despite definitive radiochemotherapy in patients with primary inoperable locally advanced non-small cell lung cancer.

#### The value of the systematic extensive lymph node dissection in the operative treatment in non-small cell lung cancer

PI: PD 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.

## Pulmonary resection with parietal pleurectomy (WRPP) versus parietal pleurectomy (PP) for the treatment of primary pneumothorax

PI: Prof. Dr. H. Sirbu, Dr. W. Dudek Prospective randomized multicenter clinical trial which compares two established surgical procedures (WOPP-study). The aim of the study is to analyze the pneumothorax recurrence rate within the first 24 months after surgical procedure: Parietal pleurectomy with apical lung resection (WRPP) or parietal pleurectomy (PP). Funding: DFG

## Functional analysis of human dendritic cell subpopulations

PI: Prof. Dr. D. Dudziak (Department of Dermatology), Prof. Dr. H. Sirbu

The main scientific focus of the research group of Prof. Dr. D. Dudziak is the characterization of Dendritic cells (DCs) and the initiation of specific T cell immune responses. These studies are being conducted both in the murine and the human setting. First detailed phenotypic and functional analyses of DC subpopulations have been performed with various human lymphoid tissues (spleen, blood, thymus, bone marrow, cord blood, tonsils) and were recently published). In a collaborative research project with Prof. Dr. H. Sirbu, comparative analyses of the development of different immune cells were extended to other human organs, such as lymph nodes, blood, lungs, and adult thymus. The latter shows residual activity of T cell development, despite a progressed thymic involution. Of note, the analysis of the phenotype and function of the DC subpopulations in various human tissues of the very same donor is of high value, in order to account for the high degree of inter-individual variance.

## Teaching

For medical students, the Division of Thoracic Surgery offers current lectures on relevant topics (malignant pulmonary disease, pneumothorax, pulmonary emphysema, pleural empyema, trauma, etc.), an interactive EKM course (introduction into clinical medicine) and offers the possibility of hospitalization on the ward, in the ambulance, and in the operation room of thoracic surgery. The applicants for the practical year in thoracic surgery are given special knowledge (participation to medical thoracic conferences/boards, conduct an interview, preparation of a treatment plan and discussion with the tutor, learning of special aspects of risk medical informing, presentation of the patient during the medical visit, active participation in the operating room).

Furthermore, in the Division of Thoracic Surgery supervises Bachelor's, Master's as well as MD theses.

### **Selected publications**

Dudek W, Schreiner W, Hohenberger W, Klein P, Sirbu H. Forty-Two Years' Experience with Pulmonary Resections of Metastases from Colorectal Cancer. Thorac Cardiovasc Surg. 2017 Oct;65(7):560-566

Dudek W, Schreiner W, Stapel P, Vassos N, Grützmann R, Sirbu H. Surgery of colorectal lung metastases: Results of a survey in Germany. Chirurg. 2017 Jun;88(6):512-517

Dudek W, Schreiner W, Horch RE, Sirbu H. Sternal resection and reconstruction for secondary malignancies. J Thorac Dis. 2018 Jul;10(7):4230-4235

Schreiner W, Dudek W, Lettmaier S, Fietkau R, Sirbu H. Long-Term Survival after Salvage Surgery for Local Failure after Definitive Chemoradiation Therapy for Locally Advanced Non-small Cell Lung Cancer. Thorac Cardiovasc Surg. 2018 Mar;66(2):135-141

Schreiner W, Gavrychenkova S, Dudek W, Rieker RJ, Lettmaier S, Fietkau R, Sirbu H. Pathologic complete response after induction therapy-the role of surgery in stage IIIA/B locally advanced non-small cell lung cancer. J Thorac Dis. 2018 May;10(5):2795-2803

Schreiner W, Gavrychenkova S, Dudek W, Lettmaier S, Rieker R, Fietkau R, Sirbu H. Lung Resection after Definitive and Neo-Adjuvant Chemoradiation for Stage IIIA/B Locally Advanced Non-Small Cell Lung Cancer: a Retrospective Analysis. Zentralbl Chir. 2018 Jun;143(3):307-315

## **Department of Surgery**

## Division of Transfusion Medicine and Hemostaseology

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### **Head of Division**

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### **Research focus**

- Development of new minimally invasive photopheresis methods
- Functional modulation of dendritic cells
- Collection of monocytes for the generation of dendritic cells (DC)
- · Clinical research related to hemostaseology
- Clinical research related to hemotherapy
- Mesenchymal stromal cells (MSC)
- Optimization of collection procedures to get regulatory T cells (Tregs)
- Legislation of transfusion

## **Structure of the Division**

Professorships: 1 Personnel: 76

- Doctors (of Medicine): 6
- Scientists: 6 (thereof funded externally: 0)
- Graduate students: 10

#### **Clinical focus areas**

- Clinical transfusion medicine
- Blood component supply
- Immunohematological and hemostaseological diagnostics
- Outpatient and inpatient coagulation counseling
- Production and storage of stem cell preparations
- Minimally invasive photopheresis methods

### Research

Research in the Division of Transfusion Medicine and Hemostaseology focuses on the characterization of specific blood components, stem cell concentrates, and new experimental cellular preparations. Clinical problems with respect to hemotherapy and coagulation management are also investigated. In the GMP laboratory of the Division, interdisciplinary experimental preparations for innovative clinical trials are produced and tested (Advanced Therapy Medicinal Products, ATMP).

## **Development of new minimally invasive photopheresis methods** PI: Prof. Dr. H. Hackstein

Current standard photopheresis methods are only able to treat small children to a limited extent. The project group has modified the clinical photopheresis methods and is developing new minimally invasive treatment methods so that critically ill infants can also be successfully treated with a graft versus host disease after bone marrow transplantation. This new miniphotopheresis procedure is characterized by the fact that only very small amounts of blood (100-200 ml whole blood) are required and thus even very small children or vital unstable, critically ill adult patients with contraindications to classical apheresis can be treated.

## Functional modulation of dendritic cells

### PI: Prof. Dr. H. Hackstein

The project group is investigating pharmacological substances that control or block key functions of dendritic cells with the aim of activating or blocking antigen-specific immune responses. The immunosuppressant rapamycin, for example, is the first clinically used drug that inhibits both, antigen uptake and mobilization of dendritic cells *in vitro* and *in vivo*. Current research projects investigate the role of RNA-editing enzymes in the hematopoietic differentiation of dendritic cells and translational protocols for the accelerated differentiation of monocytes in dendritic cells.

## Collection of monocytes for the generation of dendritic cells (DC)

### PI: Prof. Dr. E. Strasser

Circulating monocytes are precursors of DC, which play a key role in the immune system's function by presenting antigens to specific lymphocytes. The collection and cultivation of these cells enables the development of new strategies in the treatment of malignant diseases. Members of the Division of Transfusion Medicine and Hemostaseology cooperate with colleagues from the Department of Dermatology to adjust the collection procedures optimally to the specific clinical and experimental demands of procedures aimed at the cultivation, expansion, and priming of DC.

## Clinical research related to hemostaseology

PI: Prof. Dr. R. Zimmermann, Prof. Dr. E. Strasser Other research interests include thrombophilia, traveller's thrombosis, and hemostasis dysfunctions resulting in bleeding disorders. Other current study objectives are preanalytical determinants of fibrinolysis tests, hemostasis tests in systemic lupus erythematodes, and other currently relevant topics.

## Clinical research related to hemotherapy

PI: Prof. Dr. V. Weisbach, Prof. Dr. R. Zimmermann, Prof. Dr. E. Strasser

We examine antibodies against red cell antigens, characterize factors influencing the quality of stored red cell concentrates, and study the complex dysfunctions of the coagulation system.

## Mesenchymal stromal cells (MSC)

PI: Prof. Dr. V. Weisbach

Mesenchymal stromal cells (MSC) are the predecessors of osteoblasts, chondrocytes, and adipocytes. The term "MSC" especially covers cells cultivated and expanded ex vivo. These cells are a mixture of stem and progenitor cells up to mature stroma cells and are named MSC according to a definition of the International Society of Cellular Therapy. It is expected that MSC will play a major role in future applications of regenerative medicine. The main focus of the working group is the preparation, characterization, and expansion of MSC especially from placentar tissues.

## Optimization of collection procedures to get regulatory T cells (Tregs)

PI: Prof. Dr. E. Strasser, PD Dr. J. Strobel T cells play an important role in adoptive immune response in many diseases (infectious and inflammatory diseases, tumors). DC act as antigen presenting cells for specific T cells activation. The collection of circulating T cells as well as the culture and expansion of T cells, especially regulatory T cells (Tregs), enables the development of new strategies for the anti-inflammatory and immunosuppressive therapies. Members of the Division of Transfusion Medicine and Hemostaseology cooperate with colleagues from the departments of Medicine 1, Dermatology, and Medicine 5 to optimally adjust the collection procedures to the specific clinical and experimental demands of procedures aimed at the cultivation and expansion of

Tregs. In the context of cell preparation, analysis of factors responsible for cell damage (cell apoptosis and necrosis) is relevant to optimize the quality of leukocyte products. Verdú-Amorós J, Woessmann W, Maecker-Kolhoff B, Schulz A, Strauss G, Bein G, Hackstein H. Mini photopheresis for refractory chronic graft-versus-host disease in children and adolescents. Transfusion 2018; 58: 2495-2500

## Legislation of transfusion

## PI: Prof. Dr. R. Zimmermann

Under the auspices of the Legal Counsel and Managing Director of the UK Erlangen, Dr. A.W. Bender, the Division of Transfusion Medicine and Hemostaseology is involved in publications on the legislation and law of blood transfusion in Germany. In the center of attention is the book "Transfusion Law", published by the Wissenschaftliche Verlagsgesellschaft Stuttgart, that has become the benchmark in this field of law and has found its way into the jurisdiction of the German Federal High Court of Justice. Alongside, book contributions and articles on different aspects of the legislation and law of blood transfusion are published.

## Teaching

The Division of Transfusion Medicine and Hemostaseology is involved in compulsory and optional courses in the curricular teaching of Medicine and Dentistry. Particularly noteworthy is the interdisciplinary teaching of laboratory diagnostics and clinical pathology together with the Department of Medicine 5 and the Clinical Chemistry Laboratory and the participation in the block training in surgery. We supervise MD and PhD theses.

#### **Selected publications**

Dullinger K, Pamler I, Brosig A, Mohrez M, Hähnel V, Offner R, Dormann F, Becke C, Holler E, Ahrens N. Granulocytapheresis with modified fluid gelatin versus high-molecularweight hydroxyethyl starch: a matched-pair analysis. Transfusion 2017; 57: 397-403

Steininger P, Strasser E, Ziehe B, Eckstein R, Rauh M. Change of the metabolomic profile during short-term mononuclear cell storage. Vox Sang. 2017; 112: 163-172

Strobel J, Hohensee F, Kuta P, Eckstein E, Zingsem J. Comparison of six different cryoprotective agents used for deep freezing and storage of CD34+ cells derived from cord blood and peripheral blood stem cell concentrates. Clin Lab 2017; 63: 543-550

Hecker M, Sommer N, Foch S, Hecker A, Hackstein H, Witzenrath M, Weissmann N, Seeger W, Mayer K. Resolvin E1 and its precursor 18R-HEPE restore mitochondrial function in inflammation. Biochim Biophys Acta Mol Cell Biol Lipids 2018; 1863: 1016-1028

Pfeiffer H, Völkl S, Gary R, Mackensen A, Achenbach S, Strasser E, Aigner M. Impact of collection programs for the generation of monocyte-apheresis products on product quality and composition as starting material for the generation of cellular therapeutics. Transfusion 2018; 58: 2175-2183

## **Department of Trauma Surgery – Orthopedic Surgery**

Chair of Trauma Surgery and Orthopedics

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#### **Research focus**

- Development of a modular hybrid concept for the reconstruction of the joint surfaces
- Cartilage regeneration and meniscus transplantation
- Gait and motion analysis
- MRI-imaging of the skeletal system
- Lesions of the anterior chest wall in combination with fractures of the spine

## **Structure of the Department**

Professorships: 2 Personnel: 20

Doctors (of Medicine): 20

- Graduate students: 6
- 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 Department of Trauma Surgery – Orthopedic Surgery (until 1/2019: Division of Trauma Surgery) covers a broad spectrum of research activites 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 Department.

## Development of a modular hybrid concept for the reconstruction of the joint surfaces

PI: Prof. Dr. K. Gelse

The project "MoJo 3D – Modular composite Joint 3D" focuses on a complete novel technology for the reconstruction of a functional joint surface for the treatment of osteoarthritis or traumatically-induced cartilage defects (compare own report).

The purpose is the generation of a resilient and low-friction joint surface by an individualized, modular concept. The interdisciplinary work comprises research capacities of the materials science, cellular biology, stem cell research, tissue-engineering, orthopedics, trauma surgery, and rheumatology. Current work focuses on the establishment of a composite, modular structure of different materials, which is adapted to the biological and biomechanical demands of the human joint. This project brings the expertise of above mentioned research fields of the FAU together in order to establish a complete novel concept for assembling and application for regenerative therapies.

## Cartilage regeneration 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, PDGF and TFF3 proved to be very efficient chemotactic factors.

## Gait and motion analysis

PI: Dr. S. Krinner

This research group focuses on a subproject of the Emerging Fields Initiative (EFI-Moves) 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. Furthermore, two different running techniques were compared with respect to the biomechanical joint forces. We could demonstrate significant differences in ground reaction forces and loading rates for the large joints of the lower extremities between forefoot and rearfoot running.

## MRI-imaging of the skeletal system

PI: Dr. M. Pachowsky, Dr. S. Söllner

Magnetic Resonance Imaging (MRI) is able to non-invasively depict structural and ultra-structural changes in different diseases without radiation. MRI has become the gold-standard in some cerebral and joint diagnostics.

Besides morphological description of anatomy and pathology, modern MR protocols assess additionally quantitative aspects of joint tissue. This conclusive information has the unique potential to assess and quantify changes of different tissues at very early stages of the disease. Thus, by using these quantitative MR imaging methodologies (i.e. T2 mapping), pathophysiological pathways are longitudinally visualized, representing options for early diagnosis, prevention approaches, or therapy monitoring.

Current projects focus among others on the assessment of cartilage regions at risk in the knees of young athletes, on changes in intervertebral discs after kyphoplasty, and on new approaches on visualizing tissue metabolites in ultra-highfield MR sequences.

## Lesions of the anterior chest wall in combination with fractures of the spine PI: Dr. S. Krinner

Fractures of the anterolateral chest wall, especially sternal fractures are rather rare. However, in the presence of such injuries, there may be concomitant injuries directly associated with sternal fractures, such as fractures of the anterolateral bony chest wall and spine injuries. The aim of this work is to provide a systematic analysis of mechanisms, which may lead to injuries of the anterolateral chest wall in combination with spinal injuries and thus destabilization of the torso in the sagittal plane. There are particularly critical anatomic regions that must not be overlooked during initial diagnostics. After appropriate assessment, you should always keep in mind the biomechanical relationships that exist in the area of the bony thoracic wall, including the spinal column, with regard to further therapeutic steps. A corresponding sagittal instability can be addressed by various stabilization methods and the osteosynthesis of the anterolateral chest wall should definitely be included in the therapy consideration.

## Teaching

The Department of Trauma Surgery – Orthopedic Surgeryparticipates with elective and compulsory courses in the curricular teaching of students of Medicine and Dentistry, as well as medical engineering. The interdisciplinary teaching for the purposes of preparation for examinations has to be outlined.

The Department of Trauma Surgery – Orthopedic Surgerysupervises numerous MD theses.

## Selected publications

Gelse K, Körber L, Schöne M, Raum K, Koch P, Pachowsky M, Welsch G, Breiter R. Transplantation of Chemically Processed Decellularized Meniscal Allografts. Cartilage. 2017 Apr;8(2):180-190

Kluge F, Hannink J, Pasluosta C, Klucken J, Gaßner H, Gelse K, Eskofier BM, Krinner S. Pre-operative sensor-based gait parameters predict functional outcome after total knee arthroplasty. Gait Posture. 2018 Oct;66:194-200

Knorz S, Kluge F, Gelse K, Schulz-Drost S, Hotfiel T, Lochmann M, Eskofier B, Krinner S. Three-Dimensional Biomechanical Analysis of Rearfoot and Forefoot Running. Orthop J Sports Med. 2017 Jul 24;5(7):2325967117719065

Klinger P, Lukassen S, Ferrazzi F, Ekici AB, Hotfiel T, Swoboda B, Aigner T, Gelse K. PEDF Is Associated with the Termination of Chondrocyte Phenotype and Catabolism of Cartilage Tissue. Biomed Res Int. 2017;2017:7183516

Soellner ST, Goldmann A, Muelheims D, Welsch GH, Pachowsky ML. Intraoperative validation of quantitative T2 mapping in patients with articular cartilage lesions of the knee. Osteoarthritis Cartilage. 2017 Nov;25(11):1841-1849

Pachowsky ML, Kleyer A, Wagner L, Langenbach A, Simon D, Janka R, May M, Welsch GH. Quantitative T2 Mapping Shows Increased Degeneration in Adjacent Intervertebral Discs Following Kyphoplasty. Cartilage. 2018 Mar 1:1947603518758434

# **Department of Urology and Pediatric 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): 20
- Scientist: 1 (thereof funded externally: 0)
- Graduate students: 12

### **Clinical focus areas**

- Urologic policlinic and children's urology ward
- Minimal invasive urology including robotics
- Kidney transplantation unit
- Kidney transplantation unit focused on children
- Ambulant uro-oncologic therapy center (AURONTE)
- Certified center for prostate cancer with kidney- and bladder cancer
- Certified continence and pelvic floor center
- Adult's urologic ward, therapy center for private insurance patients within Malteser Waldkrankenhaus St. Marien
- Trial documentation center within Malteser Waldkrankenhaus St. Marien

## Research

The research topics in the Department of Urology and Pediatric Urology cover the areas of basic as well as translational urologic research, with a particular focus on high-quality statistical assessment. Substantial parts of our research rely on a well-maintained, high quality repository of tissue sample and other biomaterials that allows the active participation even in European multicenter, EU-funded studies in patients with urologic tumors.

## Continuous extension of an annotated tumor tissue repository containing urologic tumors

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. 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 Comprehensive Cancer Center (CCC) biobank. For the application of the required Standard Operating Procedures (SOP), we have established a close cooperation with the German Prostate Carcinoma Consortium 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 and Pediatric Urology. All incorporated procedures are consistent with the legal, ethical, technical, and organizational regulations of tissue repositories and databases (patients' informed consent, data security, SOPs, and quality management).

### **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 draw therapeutic decisions based on a common interdisciplinary conference. Thus, it can be assured that all currently activated and planned clinical trials are open to all common patients. Currently open clinical trials mainly focus on new therapeutic options for patients with bladder or prostate cancer. An overview of all currently active clinical trials can be found on the website of our Department.

# 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 primary tissue samples retrieved from the CCC biobank, we were able to identify a collection of proteins and RNAs that have the potential for being valuable clinical biomarkers. This knowledge is now being transferred to an experimental diagnostic setting. This will be combined with the advantages of non-invasive biomaterial sampling by investigating protein- and RNAbased 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 followup examinations in blood serum.

## Biomarker-supported MRI-TRUS-fusion guided biopsies for the diagnosis of prostate cancer

#### PI: PD Dr. B. Keck, Dr. A. Kahlmeyer

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 MRI-TRUS-fusion guided biopsies is able to reduce the diagnosis rate of well-differentiated, clinically insignificant prostate cancers while highly aggressive prostate cancers can be diagnosed with improved sensitivity. Nevertheless, the clinical interpretation of PIRADS class 3 lesions still poses a great challenge because these are not unanimously regarded as suspicious for a tumor. Here, the diagnostic procedure is supported by an experimental diagnostic method. Tumor-specific RNA-based biomarkers are assessed in blood serum. By combining advanced MRI-imaging and biomarker analysis, it could be possible to aid in the clinical decision if patients should undergo prostate biopsy or clinical surveillance.

## Multifactorial models in uro-tumorpathology

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, cell lineage), and molecular parameters on RNA and protein level (e.g. stem cell-associated factors, new biomarkers) and analyze them in multifactorial models for their relevance in tumorigenesis, disease progress, and survival of the urological tumor patients. We aim at supporting our physicians in identifying urological tumor patients and finding the right therapy stratification and therapy monitoring and in further expanding the basic, molecular knowledge for urological cancers.

## 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 and Pediatric Urology or one of the associated teaching hospitals.

The Department also allows additional education for achievement of the specialization in 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 and Pediatric Urology uses patient simulators. These include models for practicing sterile placement of catheters or laparoscopic methods including a simulator at the da Vinci®-operation 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

Sikic D, Keck B, Wach S, Taubert H, Wullich B, Goebell PJ, Kahlmeyer A, Olbert P, Isfort P, Nimphius W, Hartmann A, Giedl J, Bridge Consortium. Immunohistochemical subtyping using CK20 and CK5 can identify urothelial carcinomas of the upper urinary tract with a poor prognosis. PLoS One. 2017 Jun 20;12(6):e0179602

Bellut J, Bertz S, Nolte E, Stohr C, Polifka I, Lieb V, Herrmann E, Jung R, Hartmann A, Wullich B, Taubert H, Wach S. Differential prognostic value of MYC immunohistochemistry in subtypes of papillary renal cell carcinoma. Sci Rep. 2017 Nov 27;7(1):16424

Kunath F, Schmidt S, Krabbe LM, Miernik A, Dahm P, Cleves A, Walther M, Kroeger N. Partial nephrectomy versus radical nephrectomy for clinical localised renal masses. Cochrane Database Syst Rev. 2017 May 9;5:CD012045

Greither T, Fischer K, Theil G, Marcou M, Holzhausen HJ, Weigelt K, Serrero G, Hicks D, Yue BB, Fornara P, Wullich B, Taubert H, Wach S, Lieb V. Expression of GP88 (progranulin) in serum of prostate cancer patients is associated with Gleason scores and overall survival. Cancer Manag Res. 2018 Oct 5;10:4173-4180

Narayan V, Kahlmeyer A, Dahm P, Skoetz N, Risk MC, Bongiorno C, Patel N, Hwang EC, Jung JH, Gartlehner G, Kunath F. Pembrolizumab monotherapy versus chemotherapy for treatment of advanced urothelial carcinoma with disease progression during or following platinum-containing chemotherapy. A Cochrane Rapid Review. Cochrane Database Syst Rev. 2018 Jul 23;7:CD012838

Goebell PJ, Staehler M, Muller L, Nusch A, Scheffler M, Sauer A, von Verschuer U, Tech S, Kruggel L, Janicke M, Marschner N, RCC Registry Grp Tumour Registry. Changes in Treatment Reality and Survival of Patients With Advanced Clear Cell Renal Cell Carcinoma - Analyses From the German Clinical RCC-Registry. Clin Genitourin Cancer. 2018 Dec;16(6):e1101-e1115

#### International cooperations

Prof. Dr. H. Grönberg, Department of Medical Epidemiology and Biostatistics, Karolinska Institut, Stockholm: Sweden

Prof. Dr. L. Dyrskjot, Department of Molecular Medicine, Århus University Hospital, Århus: Denmark

Dr. B. 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

## Address

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#### Director

Prof. Dr. med. dent. Anselm Petschelt

## Contact

Prof. Dr.-Ing. Ulrich Lohbauer Phone: +49 9131 8543740 Fax: +49 9131 8533603 Ulrich.Lohbauer@dent.uni-erlangen.de

#### **Research focus**

- Clinical fractography on dental ceramic restorations
- Residual stresses and crystallization behavior in Lithium Disilicate glass-ceramics
- Tailoring of crystal alignment in glass-ceramic dental materials
- Measurement of mechanical properties and reliability
- Amalgam alternative restoration materials
- Material properties self-adhesive cements
- Polymerization properties of bulk-fill composites

## **Structure of the Department**

Professorship: 1

Personnel: 50

- Doctors (of Medicine): 20
- Scientists: 4 (thereof funded externally: 2)
- Graduate students: 30

## **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 laboratory 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 observed. The method of fractography is intended to clinically analyze failed dental restorations in order to assign relevant fracture mechanisms. In principle, fracture surfaces are intraorally replicated and macroscopically or microscopically investigated, using light or scanning electron microscopy. Specific fracture patterns thus provide information of involved failure mechanisms and respective reasons for failure. In a joint project with a German CAD/CAM milling center, approximately 1,000 failed restorations were fractographically examined and relevant reasons for failure were assessed. Based on the results originating from the Department of Operative Dentistry and Periodontology, a new nonprofit organization (Fracto Forum International e.V.) was founded. International workshops on dental fractography were already organized.

## Residual stresses and crystallization behavior in Lithium Disilicate glass-ceramics

PI: Prof. Dr. U. Lohbauer, Dr. R. Belli Classic ceramic materials in dentistry for inlays, partial crowns, and crowns were made out mainly of feldspathic glasses. These are highly esthetic, but deficient in mechanical properties. To provide for more mechanical durability, lithium disilicate glass-ceramics with high crystal fraction have been developed and gained wide popularity, with new materials being introduced in the market every year. However, the crystalline and the glass phases in such materials can suffer from incompatibility regarding their thermal behavior, resulting in weakening residual stresses in the glass. To overcome this problem, a deeper understanding of the crystallization behavior of lithium disilicate is necessary by tailoring the base glass composition. By performing controlled fracture tests, we gain insights on the fundamentals determining the resistance of such materials and are able to devise strategies to improve their damage tolerance.

## 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 approach has potential for application with lithium disilicate (LS2) glass-ceramics which contain needle-form Li2Si2O5 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, it is necessary to investigate specific material responses using state-of the-art mechanical testing.



Subtractive processing of a bilayered CAD/CAM dental bridge construct

## Measurement of mechanical properties and reliability

PI: Dr. R. Belli, Prof. Dr. U. Lohbauer Standardized measurements of mechanical properties help guiding materials development and serve as quality control for medical products being introduced into the market. Such mechanical tests must be controlled and conducted strictly according to international testing standards (i.e. DIN, ISO, ASTM). In the research laboratory for dental biomaterials we have worked on the constant improvement of our testing approaches to conform and validate testing standards. For that, we use standard reference materials and participate in inter-laboratory Round-Robin tests that provide means for improving the quality and sensitivity of testing procedures of dental materials.



Set-up for the fatigue testing of a polymer-infiltrated ceramic single crown over a titanium implant
# Amalgam alternative restoration materials

PI: Prof. Dr. U. Lohbauer, Dr. R. Belli

Amalgam has been used in the past for treatment of small, carious defects in a wide, permanent, and insurance-covered manner. Adhesive polymer based materials are not sufficiently economical, while glass ionomer based materials do not provide sufficient strength potential for permanent supply. In the research laboratory for dental biomaterials, new materials are being investigated that meet the requirements of mechanical strength as well as cost-effectiveness without adhesive bonding and without light polymerization.

# 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. It is therefore of importance to investigate the material properties of self-adhesive cements (adhesion, strength, swelling, expansion stress) and influencing factors (pH neutralization, hy-

# Polymerization properties of "bulk-fill" composites

drophilicity, chemical composition).

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. In the research laboratory for biomaterials, we investigate the polymerization properties of "bulk-fill" composites and make a parallel to conventional composite chemistry (degree of polymerization, hardness, shrinkage and shrinkage stress) up to how they influence the restored tooth cavity (marginal integrity and bond strength).

# Teaching

The Department of Operative Dentistry and Periodontology is involved in the curricular teaching within the frame of the dental students' degree program. Interdisciplinary lectures are held at the Department of Materials Science and Engineering (Faculty of Engineering). In 2018, the Department of Operative Dentistry and Periodontology released a comprehensive text book for dental students entitled "Werkstoffkunde in der Zahnmedizin – Moderne Materialien und Technologien".

The Department offers supervision of Bachelor's and Master's theses as well as MD and PhD theses in conjunction with the Departments of Medical Engineering and Materials Science and Engineering.

### **Selected publications**

Bitter K, Maletic A, Neumann K, Breschi L, Sterzenbach G, Taschner M. Adhesive Durability Inside the Root Canal Using Self-adhesive Resin Cements for Luting Fiber Posts. Oper Dent. 2017 Nov/Dec;42(6):E167-E176

Wendler M, Belli R, Schachtner M, Amberger G, Petschelt A, Fey T, Lohbauer U. Resistance curves of short-fiber reinforced methacrylate-based biomedical composites. Eng Fract Mech 2017;190:146-158

Lohbauer U, Scherrer SS, Della Bona A, Tholey M, van Noort R, Vichi A, Kelly JR, Cesar PF. ADM guidance-Ceramics: all-ceramic multilayer interfaces in dentistry. Dent Mater 2017;33:585-598

Belli R, Wendler M, Zorzin JI, Lohbauer U. Practical and theoretical considerations on the fracture toughness testing of dental restorative materials. Dent Mater 2018;34:97-119

Belli R, Wendler M, Cicconi MR, de Ligny D, Petschelt A, Werbach K, Peterlik H, Lohbauer U. Fracture anisotropy in texturized lithium disilicate glass-ceramics. J Non-Cryst Solids 2018;481:457-469

Belli R, Wendler M, Petschelt A, Lube T, Lohbauer U. Fracture toughness testing of biomedical ceramic-based materials using beams, plates and discs. J Eur Ceram Soc 2018;38:5533-5544

### 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

Prof. Y. Zhang, University of New York, New York: USA

# **Department of Oral and Cranio-Maxillofacial Surgery**

Chair of Dental, Oral, and Maxillofacial Medicine – especially Oral and Maxillofacial Surgery

## Adress

Glückstrasse 11 91054 Erlangen Phone: +49 9131 8533601 Fax: +49 9131 8536288 www.mkg-chirurgie.uk-erlangen.de

## Director

Prof. Dr. med. Dr. med. dent. Marco R. Kesting

## Contact

PD Dr. med. Dr. med. dent. Falk Wehrhan Phone: +49 9131 8533601 Fax: +49 9131 8536288 mkg-chirurgie@uk-erlangen.de

## **Research focus**

- Tumor research
- Regeneration processes in inflamed and weakly replaced tissue
- Oral medicine
- Biomedical technology

# **Structure of the Department**

Professorships: 2

- Personnel: 100
- Doctors (of Medicine): 18
- Scientist: 1
- Graduate students: 20

### **Clinical focus areas**

- Tumor surgery and reconstructive surgery of
- the oral cavity and the faceTraumatology of the facial skull
- Haumatology of the facial skull
- Surgery of facial skull deformities and orthognathic surgery
- TMJ surgery
- Dentoalveolar surgery

## Research

The scientific focus of the Department of Oral and Cranio-Maxillofacial Surgery relies on tumor research and the further development of reconstructive surgery. Oral manifestations as expressions of general diseases are investigated as a bridge between Dentistry and Medicine. Another research focus is dedicated to digitalization projects in research and teaching. In addition, biomedical research is an established scientific aspect of the Department.

# **Tumor research**

• Reconstruction and regeneration of weak tissues

In 3-20% of cases, postoperative thromboembolic complications and wound healing disorders occur during oral and maxillofacial reconstruction in pre-irradiated tissue using microvascular anastomosed grafts. Pathomorphologically, media fibrosis and endothelial damage as well as overexpression of proliferative cytokines are found in the transition area between graft and storage. Since current fibrosis models describe this as a misguided recourse to embryonic tissue regeneration, this research focus consists in the analysis of highly conserved transcription factors of fibrogenesis in pre-irradiated tissue.

## • Tumor immunology

Carcinogenesis and tumor progression can be understood as immunologically mediated processes in the sense of tolerance induction towards the tumor. We were able to show that there is a correlation between increased tumor malignancy and increased M2 macrophage polarization. In addition, regulatory mechanisms of macrophage polarization are currently analyzed. An additional focus lies on the investigation of the prognostic and pathophysiological significance of checkpoint expression; this is investigated within the framework of a DFGfunded project. Here, an increased expression of the immune checkpoints PD-L1 and PD-L2 in oral cavity carcinomas as well as an association between tumor progression and checkpoint mediated systemic immune tolerance could already be shown.

In a project supported by the Förderverein of the Tumorzentrum Erlangen, the expression of immune checkpoints in tissue samples and peripheral blood of patients with oral cavity carcinoma is investigated by means of NanoString analyses.

In addition, we are working on the establishment of an immunoscore for an improved prognostic assessment of oral cavity carcinomas and neoplasias of the facial skin. Within the framework of this project, a Next-Generation Tissue Microarray will be created. The aim is to supplement the TNM score with immunological parameters and to identify patient subgroups that might benefit particularly from adjuvant immunotherapy.

In the future, it will be investigated whether a "liquid-immuno-biopsy" of tumor-specific miRNA in peripheral blood is suitable as a diagnostic marker for tumor recurrences and as a predictive marker for the response to tumor therapy with checkpoint inhibitors. The longterm vision is to evaluate neoadjuvant low-dose radioimmunotherapy as induction therapy prior to definitive surgical tumor therapy in a prospective therapy study for patients with oral cavity carcinoma. We are also working on the development of a multiple marker system for early diagnosis and the malign transformation potential of oral leukoplakia. Next generation sequencing will be used to identify genes and miRNAs that are directly involved in the malignant transformation of leukoplakia. In retrospective studies, it has already been shown that the detection of MAGE-A expression in leukoplakia is a highly specific indication of a timely malignant transformation.

## Regeneration processes in inflamed and weakly replaced tissue

Since teeth and parts of the jawbone are derivatives of the neuroectoderm (cranial neural crest), osteoblast progenitors of this region have specific cellular properties, e.g. a special plasticity. Based on the model disease MRONJ, osteobiological and osteoimmunological characteristics and underlying signaling pathways are compared with extracranial tissues in order to understand the exclusivity of these diseases in the jaw and facial region and to use the special cellular plasticity for regenerative medical approaches.

### **Oral medicine**

Chronic inflammatory diseases, such as inflammatory bowel disease, scleroderma or multiple sclerosis, are associated with a disturbed immune reaction. Due to the increasing incidence of the diseases, their examination is becoming increasingly important, especially with regard to interdisciplinary cooperation. Current scientific studies show a clear association between chronic inflammatory diseases and the presence of periodontitis. However, their mutual influence with a possible correlation of disease relapses to specific germ expressions has scarcely been studied. In the future, characteristic inflammatory mediators will be investigated to demonstrate a possible link between the oral biofilm and the inflammatory responses of systemic diseases.

## **Biomedical technology**

The research area biomedical technology comprises research projects on hard and soft tissue regeneration, healing processes of dental implants, and laser applications.

One research focus is on the modulation and optimization of peri-implant tissue in the context of chewing functional rehabilitation using implant-supported dentures. This refers to the preclinical and clinical investigation of new techniques and materials for the regeneration of jaw defects and the long-term stability of hard and soft tissue after jaw augmentation as well as the regeneration of peri-implant soft tissue and its influence on the health of peri-implant structures. The use of pluripotent stem cells from umbilical cord tissue in combination with tMP to optimize the supply of peri-implant hard tissue is currently being evaluated in a third-party funded study.

Furthermore, we investigate the temporal course of reperfusion and vascularization of free mucosal grafts and collagen matrices in the context of guided soft tissue regeneration.

In cooperation with the Bavarian Laser Center (BLC), tissue-specific laser surgery is also being investigated. The focus here is on the protection of specific tissue through non-contact tissue differentiation in soft and hard tissue surgery. In cooperation with the BLC, we are working on the design of a sensor and process control concept that regulates laser ablation tissue-selectively.

# Teaching

The Department of Oral and Cranio-Maxillofacial Surgery participates in the curricular teaching of Medicine and Dentistry with compulsory and optional subjects. A two-day extracurricular elective "Implantology ilect" was developed for dentistry students. Here it is possible to implant plastic models and pig jaws freehand and navigated. In addition, sinus lift techniques and periimplantitis therapies are implemented.

The optional subject "Skills Lab Facial Surgery" was designed for students of medicine. In this course, students learn the basics of local flaps on a pig model. In addition, theoretical and practical knowledge of microsurgical techniques is imparted.

The (post-) curricular teaching of dentistry also includes digital courses, which were conceived in cooperation with the Department of Hand Plastic Surgery and the Department of Oral and Maxillofacial Surgery of the Klinikum rechts der Isar in Munich. The course "eReconstruction", sponsored by the Virtual University of Bavaria (VHB), enables interested participants to learn aspects of plastic-reconstructive surgery free of charge. In cooperation with other (dental) medical disciplines of UK Erlangen and the Ludwig-Maximilians-University in Munich, the VHB has approved an extension of the range of services to include radiological and oral surgical curricula. For students of medicine, there is also the possibility of taking clinical traineeships as well as the elective subject "Oral and Maxillofacial Surgery" in the practical year.

Furthermore, (dental) medical and scientific doctorates are supervised.

#### **Selected publications**

Kesting MR, Koerdt S, Rommel N, Mücke T, Wolff KD, Nobis CP, Ringel F, Frohwitter G. Classification of orbital exenteration and reconstruction. J Craniomaxillofac Surg, 2017. 45(4): 467-473

Weber M, Wehrhan F, Baran C, Agaimy A, Büttner-Herold M, Preidl R, Neukam FW, Ries J. PD-L1 expression in tumor tissue and peripheral blood of patients with oral squamous cell carcinoma. Oncotarget, 2017. 8(68): 112584-112597

Buchbender M, Neukam FW, Lutz R, Schmitt CM. Treatment of enucleated odontogenic jaw cysts: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018. 125(5): 399-406

Frohwitter G, Rau A, Kesting MR, Fichter A. Microvascular reconstruction in the vessel depleted neck - A systematic review. J Craniomaxillofac Surg, 2018. 46(9): 1652-1658

Lutz R, Schmitt CM, Buchbender M, Neukam FW. Diagnosis, avoidance and management of complications of implant-based treatments. Eur J Oral Implantol, 2018. 11: S21-S25

Wehrhan F, Büttner-Herold M, Distel L, Ries J, Moebius P, Preidl R, Geppert C, Neukam FW, Kesting MR, Weber M. Galectin 3 expression in regional lymph nodes and lymph node metastases of oral squamous cell carcinomas. BMC Cancer, 2018. 18(1): 823

### International cooperations

Dr. E. Felszeghy, EARC (kft), Semmelweis University, Budapest: Hungary

Prof. Dr. Dr. E. Nkenke, Medical University, Vienna: Austria

# **Department of Orthodontics and Orofacial Orthopedics**

Chair of Dental, Oral, and Maxillofacial Medicine - especially Orofacial Orthopedics

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#### Contact

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### **Research focus**

- MRI in orthodontic diagnosis
- Material scientific examinations of orthodontic materials
- Quality of life of mothers of children with cleft lip and/or palate
- Identification of genetic risk variants by molecular genetics
- Mechanisms of dental brace-induced immune tolerance against nickelions

# **Structure of the Department**

Professorship: 1

- Personnel: 26 • Doctors (of Medicine): 10
- Scientist: 1
- Graduate students: 3

#### **Clinical focus areas**

- Treatment of newborn babies with cleft lip and/or palate
- Orthodontic treatment of cleft lip and/or palate
- Orthodontic treatment of dysgnathia / malformations of the upper and/or lower jaw
- Orthodontic treatment of craniofacial anomalies and syndromes
- Orthodontic treatment of tooth displacement
- Orthodontic treatment of tooth agenesis (hypo- or oligodontia)
- Evidence-based orthodontics

## Research

Research of the Department of Orthodontics and Orofacial Orthopedics includes the implementation of three-dimensional diagnosis in orthodontics. Other research areas are material scientific examinations of orthodontic materials and the quality of life of mothers of children with cleft lip and/or palate (CL/P). Besides this, we are currently building up a molecular genetics laboratory to identify genetic causes for many of our patients' conditions: CL/P, craniofacial dysgnathia, tooth agenesis (hypo- or oligodontia) as well as molar incisor hypomineralization and periodontitis.

## **MRI** in orthodontic diagnosis

Our department has focused on the application of three-dimensional diagnosis in orthodontics for several years. The conventional technique, computer tomography (CT), has become a well-established gold standard. In spite of excellent accuracy and image quality, each new CT scan exposes patients to radiation. In contrast, magnetic resonance imaging (MRI) allows a three-dimensional, radiation-free medical imaging. Therefore, we are collaborating with the Fraunhofer Institute for Integrated Circuits IIS in Würzburg and the Institute of Radiology of UK Erlangen to develop new MRI sequences with ultra-short echo times in order to enable imaging of hard tissue like teeth and bones. 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 3Dimaging and the evaluation of MRI as an alternative imaging technique to CBCT (cone beam computed tomograph), MSCT (multi slice computed tomograph), and industrial MSCT. Moreover, we develop methods of analysis to enable the use of established two-dimensional cephalometric analysis in three-dimensional MRI data sets. The long-term aim of this project is to replace the routine orthodontic X-ray imaging with radiation-free MRI.



Representation of the newly developed cephalometric analysis in three-dimensional MRI data set

# Material scientific examinations of orthodontic material

Further research fields are material scientific examinations of orthodontic materials, their biocompatibility, and the development of antibacterial material for orthodontic applications in collaboration with the Technical University of Munich. In the long term, by using these materials as bonding material for brackets we want to reduce number and size of demineralized areas after removal of fixed multibracket appliances, thus minimizing risk of caries for patients.

# Quality of life of mothers of children with cleft lip and/or palate

We want to assess the quality of life of mothers having a baby with CL/P. The aim of this study with 12 participating university hospitals is the prospective evaluation of mothers' quality of life, their sense of coherence, and social support after birth of a baby with CL/P. In order to measure changes in quality of life we collect data at three specific time points during the first year – resembling a period of enormous mental stress for parents. Mothers of healthy children are interviewed as controls. Collected data serve to analyze the course of treatment and possible deficits and to estimate the care situation of affected mothers.



Assessing quality of life of mothers of children with CL/P

## Identification of genetic risk variants by molecular genetics

In order to identify risk factors for CL/P, we examine DNA samples from a broad range of patients and, if applicable, their relatives and compare them to data from control groups. In cooperation with the Institutes of Human Genetics of the university hospital of Bonn and of UK Erlangen, we perform next generation sequencing analyses enabling us to analyze large regions of DNA up to whole genomes. Our aim is always to pinpoint (possibly inherited) changes in the patient's DNA sequence that lead to the manifestation of the disease. Chromosomal regions identified in this way serve to find and characterize responsible genes. Those genes are examined in detail with regard to their biological function and how it might cause the cleft. Using the described molecular genetic methods, we also seek to identify relevant genetic loci for craniofacial dysgnathia, tooth agenesis (hypo- or oligodontia) and in future for molar incisor hypomineralization.

In further molecular genetic analyses, we seek to identify gene variants contributing to formation and progression of periodontitis. Although the impact of a genetic component is estimably 33 - 50 %, only a few risk variants have been identified up to now. In order to identify unknown genetic variants causing a higher risk for periodontitis, we perform expression quantitative trait locus (eQTL) analyses. By this innovative method, we can identify changes in the transcriptome of immune cells stimulated with periodontal virulence factors and attribute them to certain gene variants. With the same technique, we investigate on genetic factors influencing atherosclerosis and allergies against metals. For these comprehensive analyses, we cooperate with the Institute of Human Genetics and the Institute of Medical Microbiology, Immunology and Parasitology of the university hospital of Bonn and with the Department of Cardiology, Angiology and Pneumonology of the university hospital of Heidelberg and Center of Human Genetics of the university hospital of Marburg.

At best, our molecular genetic analyses lead to new diagnostic possibilities that could direct appropriate therapeutic measures in the sense of personalized medicine. The acquired knowledge might also help to develop new medication and preventive measures.

# Mechanisms of dental brace-induced immune tolerance against nickelions

In a cell biological project we focus on the fact that small amounts of nickel ions released from dental braces can desensitize the immune system. Thus, they may exert a protective effect against the development of nickel allergies. We want to elucidate the molecular mechanisms how dendritic cells as well as fibroblasts of the gingiva may contribute to immune tolerance. This might proof useful for fighting allergies in general.

# Teaching

The Chair of Dental, Oral, and Maxillofacial Medicine – especially Orofacial Orthopedics is engaged in dental medicine. Within the scope of orthodontic analysis and treatment, the curriculum comprises comprehensive clinically based material. Skills lab work enables the students to collect and evaluate diagnostic data and to control the clinical application of orthodontic devices.

In addition, MD and PhD theses are supervised, and residents are further trained to become specialized orthodontists according to the Bavarian Curriculum.

#### **Selected publications**

Ludwig KU et al. Imputation of orofacial clefting data identifies novel risk loci and sheds light on the genetic background of cleft lip  $\pm$  cleft palate and cleft palate only. Hum Mol Genet. 2017; 26:829-842

Papageorgiou SN, Kutschera E, Memmert S, Gölz L, Jäger A, Bourauel C, Eliades T. Effectiveness of early orthopaedic treatment with headgear: a systematic review and metaanalysis. Eur J Orthod. 2017; 39:176-187

Detterbeck A, Hofmeister M, Haddad D, Weber D, Schmid M, Hölzing A, Zabler S, Hofmann E, Hiller KH, Jakob P, Engel J, Hiller J, Hirschfelder U. Determination of the mesiodistal tooth width via 3D imaging techniques with and without ionizing radiation: CBCT, MSCT, and µCT versus MRI. Eur J Orthod. 2017;39(3):310-319

Grozdinska A, Hofmann E, Schmid M, Hirschfelder U. Prevalence of temporomandibular disorders in patients with Hashimoto thyroiditis. J Orofac Orthop. 2018;79(4):277-288

Böhmer AC, Gölz L, Kreusch T, Kramer FJ, Pötzsch B, Nöthen MM, Jäger A, Mangold E, Knapp M, Ludwig KU. Investigation of dominant and recessive inheritance models in genome-wide association studies data of nonsyndromic cleft lip with or without cleft palate. Birth defects research. 2018; 110:336-341

Hofmann E, Detterbeck A, Chepura T, Kirschneck C, Schmid M, Hirschfelder U. Oculoauriculovertebral spectrum and maxillary sinus volumes: CT-based comparative evaluation. J Orofac Orthop. 2018 Jul;79(4): 259-266

# **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 three dimensional imaging

### **Structure of the Department**

Professorships: 2

Personnel: 49

- Doctors (of Medicine): 17
- Scientists: 12 (thereof funded externally: 0)
- Graduate students: 10

## **Clinical focus areas**

- Implant prosthetics
- · Fixed and removable prosthetic
- Diagnosis and treatment of temporomandibu-
- lar 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: Dr. R. Matta, Dr. C. Motel

Due to the lack of suitable metrological methods, it has so far been possible only to a very limited extent and in individual cases with very complex experimental set-ups to represent and quantitatively determine biomechanical influences in the oral cavity. A large number of theories on a wide variety of questions have so far neither been clearly confirmed nor refuted scientifically. The aim of the research area is to optimize a renewed, non-contact 3D optical deformation measurement system for clinical in vivo application on patients in order to enable guantitative measurements of biomechanical influences in the oral cavity in real time in future studies and to initiate innovative questions through in vitro investigations.

In ongoing and completed *in vitro* investigations in the fields of material science and biomechanics, the previously existing system has proven its worth. In addition, the first *in vivo* pilot studies on force-correlated tooth movements have demonstrated a corresponding clinical application.

An innovation introduced in the reporting period was the investigation of deformations of implants, superstructures, and bone under simulated chewing force, which allows dynamic changes on surfaces to be represented with high precision. For this purpose, the current version of the ARAMIS system from GOM GmbH, which is innovative in dental research, was purchased and already established through its presentation at a specialist congress. The first goal here was to demonstrate the advantages in the field of dental biomechanics over the conventional measuring methods currently used in this field, such as strain gauges. This method opens up a wide range of scientific applications for the future.

# 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 digital dentistry

# Pls: Dr. R. Matta, Dr. C. Motel

There is currently a change in technology in the field of dental impression taking. Digital impressions are becoming more established and their indication has been expanded to include multiunit bridges, extensive implant restorations and bite registration as a result of constant technological progress from single-tooth crowns.

This research area evaluates the accuracy of digital impressions taken by intraoral scanners also in comparison with conventional methods. This involves investigating which scan protocols, i.e. which sequence of work steps, can lead to the best possible digital imaging of the oral situation. In addition, various parameters of digital impression taking are considered, such as the geometry of the scan bodies required for digital implant impression taking and the various intraoral scanners available on the market, in order to assess the quality and reproducibility of this technology.



Illustration of 3 D deviation of CBCT in comparison to optical reference scan

# **CAD/CAM** research laboratories

PI: Dr. R. Matta, Dr. L. Wolf

Industrial CAD/CAM manufacturing technologies have gained significant market share in producing dental restorations in recent years, primarily due to standardized product quality and precision as well as economic processing routine in dental laboratories. To achieve high quality and precision, product aligned process routes are a mandatory prerequisite. The research group focuses on segmenting CAD/CAM processes and assessment of the impact on the overall quality. In addition to recently developed methodologies for 3D-display and analysis of microgaps in conventional dental restorations, new protocols are in development for a clinical assessment of fit of implant retained superstructures. The research laboratories are equipped with state-of-the-art industrial non-contact scanners and necessary analytical software programs. As high strength oxide ceramics are applied more frequently as framework materials in dentistry, several research projects assess the clinical application and factors influencing long-term success.



Comparison of the accuracy of CAD/CAM implant template to virtual planning

## **Prosthodontics and implant therapy based on three dimensional imaging** PI: Dr. R. Matta, Dr. A. Seidel

The three dimensional (3D) imaging becomes more and more important for the modern implant and prosthodontic therapy plan. This includes the Computer Tomography (CT), the Cone Bean Computer Tomography (CBCT), and the intraoral digital impression.

The focus is on the 3D accuracy of the X-ray imaging. In addition, the impact of different dental implant materials on the appearance of artifacts in the 3D virtual model is investigated. In this context a new method for the 3D 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 3D transfer of oral structures in "virtual" illustrations.



A new optical 3D measurement technology for biomechanical implant deformation

# Teaching

The main focus of traditional prosthodontic education has shifted from a technically oriented towards an interdisciplinary treatment approach. Prophylaxis and biology are in the focus as well as minimally invasive treatment concepts. Clinically relevant topics are introduced into the preclinical curriculum, focusing on biologic interactions and material properties. While theoretical knowledge remains integral part of dental education, manual manufacture of dental restoration will be taught only exemplarily. Two new extra-curricular courses have been introduced. Using these elective courses theoretical principles of digital dentistry as well as its forward-looking treatment options were taught for students of clinical prosthetic courses. Doctoral projects are offered at the Chair of Dental Prosthetics within the various research areas and supervised by the scientific staff.

## Selected publications

Matta RE, Bergauer B, Adler W, Wichmann M, Nickenig HJ. The impact of the fabrication method on the three-dimensional accuracy of an implant surgery template. J Craniomaxillofac Surg. 2017 Jun;45(6):804-808

Matta RE, Adler W, Wichmann M, Heckmann SM. Accuracy of impression scanning compared with stone casts of implant impressions. J Prosthet Dent. 2017 Apr;117(4):507-512

März K, Adler W, Matta RE, Wolf L, Wichmann M, Bergauer B. Can different occlusal positions instantaneously impact spine and body posture?: A pilot study using rasterstereography for a three-dimensional evaluation. J Orofac Orthop. 2017 May;78(3):221-232

Nkenke E, Vairaktaris E, Schaller HG, Perisanidis C, Eitner S. Influence of gender of the teaching staff on students' acceptance of a virtual implant planning course. J Craniomaxillofac Surg. 2017 May;45(5):614-619

Stelzle F, Riemann M, Klein A, Oetter N, Rohde M, Maier A, Eitner S, Neukam FW, Knipfer C. Long-term Outcome of Speech Intelligibility in Maxillary Dental Rehabilitation with Full Dentures: A Prospective Study Using Automatic Speech Quantification. Int J Prosthodont. 2017 Sep/Oct;30(5):419-425

Seidel A, Bergauer B, Lell M, Buder T, von Wilmowsky C, Dach E1, Wichmann M, Matta RE. Does formalin fixation influence MSCT/CBCT accuracy? Surg Radiol Anat. 2018 Jan;40(1):31-37

# **Institute of General Practice**

# **Chair of General Practice**

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## **Research focus**

- ACE Adverse Cascade Effects
- ICF International Classification of Functioning, Disability, and Health
- ICE Ideas, Concerns, Expectations
- GAP Good doctor patient communication
- WirtMed
- Model Practice MVZ Eckental
- Medical decision-making in general practiceDevelopment of classifications to describe the
- content of primary care
- BeLa (Beste Landpartie) for general practice
- Competence center vocational training for general practice Bavaria (KWAB)

# Structure of the Institute

Institute of General Practice: Professorship: 1 Personnel: 20 • Doctors (of Medicine): 8 • Scientists: 8 • (thereof funded externally: 6) • Graduate students: 15 MVZ Eckental: Personnel: 10 • Physicians (general practitioners): 4

### **Clinical focus area**

General practice in the medical care center (MVZ) Eckental

# Research

The Institute of General Practice focuses on health services research. All scientific activities come together in the research network PRO PRICARE (compare own report). Against the background of limited financial resources in an aging society and the lack of general practicioners (GP) trainees especially in the country side, the focus lies on how to detect medical under- and overuse and how to subsequently reduce it. Together with other chairs and institutes of FAU and UK Erlangen, we have established a long-term cooperation network for health services research. Also part of the network are several practice networks of Northern Bavaria, the Association of Statutory Health Insurance Physicians Bavaria (KVB) and the GWQ ServicePlus AG (representing health insurance funds).

# ACE – Adverse Cascade Effects

Clinical pathways of patients with thyroid disorders are analyzed in order to describe possible cascade effects leading from overdiagnosis to overtreatment. Therefore, three studies are conducted:

- Routine data analysis: Comparison of different patient groups with regard to morbidity, use of medical services and costs.
- Analysis of medical records and qualitative interviews: Tracing of individual clinical pathways.
- Multi Criteria Decision Analysis: Exploration of underlying motives and attitudes that influence the decision-making process of patients and doctors.

## ICF – International Classification of Functioning, Disability, and Health

Development of an ICF core set to identify the functional health of elderly patients. A systematic review, an expert survey, and qualitative interviews with elderly patients are conducted as well as an assessment of functional health of the patients. The intention is that by focusing on functional health of whole persons instead of pathologies of single organ systems, a meaningful framework to discriminate between necessary and unnecessary medical procedures can be provided.

## ICE – Ideas, Concerns, Expectations

Actively asking for ICE includes the patients otherwise mostly hidden agenda into the consultation. The aim of this project is to examine whether an improved patient-centered communication according to the ICE technique can reduce unnecessary diagnostic and therapeutic procedures for patients with acute uncomplicated back pain. Qualitative and quantitative studies are conducted alongside a cluster-randomized controlled trial in order to examine the effect of patient centeredness in general practice on medical overuse in consultations.

# GAP – Good Doctor –

# Patient Communication

The GAP study provides doctors and patients with acute back pain alike with the online portal

"tala-med", an electronic information system providing the latest scientific evidence that is simple to navigate and easily understood. The information given can support joint decisionmaking in diagnostics and therapy. The quality of the consultation when using the online portal – in comparison to routine consultations – is examined in a prospective, multicenter, clusterrandomized parallel group design. Funding: Federal Ministry of Health

## WirtMed

WirtMed aims at developing and testing new procedures intended to support the Association of Statutory Health Insurance Physicians and the statutory health insurances to analyze and control future quality and cost-effectiveness of drug prescribing in ambulatory care. Five sub-studies are conducted in order to examine and control different aspects of prescribing quality. Two substudies are carried out by the Institute of General Practice in cooperation with the consortium leader Department for General Practice of the Philipps University Marburg (Prof. Dr. N. Donner-Banzhoff).

Funding: Federal Ministry of Health

### Model Practice MVZ Eckental

The shortage of general practitioners especially in rural areas combined with an aging population calls for solution approaches to ensure long-term high-level primary care. This project aims at clinical governance as a within practice bottom-up approach to harmonize work processes. The focus lies in the exploration of the capacities of a given electronic health record (MediStar) to extend its use as the central tool for reflective practice and clinical governance. The aim is to develop and use meaningful checklist to be used as clinical guidelines, documentation, and data capture at the same time. Furthermore, multiprofessional case reviews for geriatric patients with special need for intensified care including non-medical care aspects are tested.

Funding: Bavarian State Ministry for Health and Care

# Medical decision-making in general practice

The family doctor is frequently confronted with unspecific symptoms, illness patterns in early stages and consequential diagnostic uncertainty. Taking these particularities into account, we examine influential factors of medical decision-making. Our qualitative and quantitative studies focus on the influence of ambiguity tolerance on the part of the doctors, the assessment of clinical symptoms among selected diagnosis as well as the consideration of scientific evidence in the decision-making process. Furthermore, treatment data are analyzed in cooperation with the KVB.

# Development of classifications to describe the content of primary care

Since 2006, Prof. Dr. T. Kühlein is a member of the WONCA International Classification Committee (WICC). Furthermore, he has been a member of the Executive Committee since 2012 and is head of the latter since 2016. The WICC is occupied, among other things, with the actualization and further development of the International Classification of Primary Care (ICPC). WONCA is the international organization for general practitioners. Since October 2014, Prof. Dr. T. Kühlein is the delegate of WONCA to the "Family of International Classifications Council" of WHO. Joint research and development projects are conducted in cooperation with the universities of Gent (Belgium) and Nijmegen (The Netherlands) on the coding of ICE and concerning the use of the ICF in primary care.

# BeLa (Beste Landpartie) for general practice

Due to a lack of young GPs, primary care especially in rural areas is in jeopardy. BeLa is a strategy to secure the recruitment of GP trainees by teaching students the advantages of a rural career track. The BeLa program examines whether financial and contentual support of students during the clinical part of the studies combined with a practical training in rural areas enhances the willingness to a subsequent vocational training and settlement these regions. Individual and motivational factors for a settlement in rural areas are identified in a qualitative process evaluation.

# Competence center vocational training for general practice Bavaria (KWAB)

The offers issued by the competence center aim at improving the contentual and didactical quality of vocational training in general practice to secure high quality primary care in Bavaria. Additionally, the undertaken measures will be reviewed and evaluated with regard to their effect. Under the umbrella of the competence center, seminars that accompany vocational training are offered regularly for future general practitioners. Furthermore, an experienced GP mentor is assigned to every young colleague in training. The competence center additionally offers Train-the-Trainer seminars for doctors that are licensed for vocational training in order to strengthen their didactic competence and hence optimize the quality of vocational training in practices. The Institute of General Practice has taken on the lead and coordination of the KWAB.

# Teaching

The Institute of General Practice engages in curricular teaching in the studies of medicine. Next to the GP-specific elective courses "Anamnesis training", "Smart decision-making in clinical everyday life" and "Problem-oriented learning from clinical cases", two interprofessional teaching projects deserve to be highlighted specifically: the elective course "Doctor and entrepreneur" and the "Anamnesis groups of the Faculty of Medicine of the FAU".

The elective "Doctor and entrepreneur" offers a simulation game for the settlement as a selfemployed physician. This offer aims directly at preventing the fears of medical trainees regarding the non-medical responsibilities of a settled doctor. The Institute, as patron, supports the student initiative "Anamnesis groups of the Faculty of Medicine of the FAU" (contents: training of anamnesis according to the bio-psycho-social model; improvement of patient-oriented consultation skills; handling of topics like subjective illness theories; experience of transference and countertransference: development of external and internal reflection: promotion of team communicative skills in interprofessional small groups). In 2016, the project was awarded the Deutsche Balintpreis of the Deutsche Balint-Gesellschaft e.V (DBG).

Bachelor's and Master's theses as well as medical doctorates are supervised.

### **Selected publications**

Alber K, Kuehlein T, Schedlbauer A, Schaffer S. Medical overuse and quaternary prevention in primary care - A qualitative study with general practitioners. BMC Fam Pract 2017; 18(1): 99

Hueber S, Kuehlein T, Gerlach R, Tauscher M, Schedlbauer A. "What they see is what you get": Prescribing antibiotics for respiratory tract infections in primary care: Do high prescribers diagnose differently? An analysis of German routine data. PLoS ONE 2017; 12(12): e0188521

Schrans D, Boeckxstaens P, De Sutter A, Willems S, Avonts D, Christiaens T, Matthys J, Kühlein T. Is it possible to register the ideas, concerns and expectations behind the reason for encounter as a means of classifying patient preferences with ICPC-2? Prim Health Care Res Dev 2018; 19(1): 1-6

Frank L, Hueber S, Kühlein T, Schedlbauer A, Roos M. Evidence and practice: How do primary care physicians evaluate screening interventions? A questionnaire study. Z Evid Fortbild Qual Gesundhwes 2018 Sep;135-136:1-9 Ludwig K, Machnitzke C, Kühlein T, Roos M. Barriers to practicing General Practice in rural areas - Results of a qualitative pre-post-survey about medical students during their final clinical year. GMS | Med Educ 2018; 35(4): Doc50

Muche-Borowski C, Abiry D, Wagner HO, Barzel A, Lühmann D, Egidi G, Kühlein T, Scherer M. Protection against the overuse and underuse of health care - methodological considerations for establishing prioritization criteria and recommendations in general practice. BMC Health Serv Res 2018; 18(1): 768

### International cooperations

Prof. Dr. J. de Maeseneer, Department of Family Medicine and Primary Health Care, Ghent University, Ghent: Belgium Dr. I. Heath. London: UK

Prof. Dr. G. Stucki, Department of Health Sciences and Health Policy, University of Lucerne, Luzern: Switzerland

Prof. Dr. J. Brodersen, Centre of Research & Education in General Practice, Department of Public Health, University of Copenhagen: Denmark

# Institute of Radiology

# Chair of Diagnostic and Interventional Radiology

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## **Research focus**

- Optimization of radiation dose and image quality in computed tomography
- 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 Chair**

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

# Special structural feature

Four locations (departments of Internal Medicine, Surgery, Gynecology and Obstetrics, Pediatrics and Adolescent Medicine)

# Research

Scientific focus of the Institute of Radiology is clinical and translational research. Within different study groups and research projects, the clinical impact of various imaging procedures or novel technical developments is evaluated. Furthermore, the Imaging Science Institute (ISI; compare own report) is operated in cooperation with Siemens Healthcare to integrate new developments in diagnostic imaging and novel ITsolutions into the clinical routine and the academic research. Finally, experimental and preclinical 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. Uder

CT is the major contributor to overall medical x-ray exposition. Radiation induced DNA-doublestrand-breaks (DSB) can be detected by immunofluorescence microscopy. Recent studies have shown a strong correlation between DSB levels and the dose deposed 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 guality. 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).

# Interventional radiology

PI: PD 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, of endovascular therapies in dysfunction of av-fistulas, 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**

PD Dr. W. Wüst, PD Dr. M. May, Dr. C. Treutlein, Dr. R. Heiss, Dr. J. Roth, Prof. Dr. M. Uder One of the main limitations of cardiac MRI are long examination times. Especially for older, ill patients an examination with multiple breathholds is very demanding. In the last couple of years, real time sequences were developed to speed up the examination time. Focus of studies in children and adults is the reproducibility and comparability to the standard sequence. Real time imaging not only shortens examination times, but also gives the opportunity to examine patients with arrhythmia to improve image quality compared to the standard sequence. Another development in the last couple of years are sequences for quantitatively characterization of cardiac tissue. One of the main drawbacks of this new technique is that published values are highly dependent on scanner and sequence type, thus leading to low comparability. Up to now, published values cannot be compared to each other and further studies are mandatory to increase the clinical acceptance of this new technique.

# Breast imaging and gynecological radiology

PI: Prof. Dr. R. Schulz-Wendtland, Prof. Dr. E. Wenkel, Prof. Dr. R. Janka, Prof. Dr. F. Laun, Dr. S. Ohlmeyer

In this group, new methods for digital mammography are developed in cooperation with different medical systems manufacturers. Based on substantial experimental and clinical studies, the 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 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 the 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

The joint project Clinical Data Intelligence of the Federal Ministry of Economics and Technology was successfully completed. By linking the contents from the electronic patient file and the gene analysis, possible changes in the diagnosis determination and/or image interpretation and the influence on the therapy management were examined. The working group optimized the automation of structured data extraction and anonymization for the large volumes of data that were required. The development of intelligent medical databases will be continued. Further research on modern algorithms, such as deep learning in connection with pattern recognition from radiological images, will be conducted. New approaches for direct integration of modalities (e.g. computed tomography) are being piloted.

# Experimental radiology and small animal imaging

PI: Prof. Dr. T. Bäuerle, Dr. C. Gillmann, Dr. S. Ellmann

Focus of this research group is the establishment and optimization of innovative multimodal imaging techniques (MRI, CT, PET, SPECT, ultrasound, and optical imaging), particularly within interdisciplinary research consortia (e.g. projects within DFG funded programs). Thereby information on the molecular, functional, and morphologic level are acquired noninvasively and correlated with the underlying pathology or pathophysiology. In cooperation with the Chair of Pattern Recognition, we apply automatic seqmentation solutions to determine quantitative image parameters. These parameters are integrated in machine learning algorithms for increasing diagnostic accuracy within larger collectives (radiomics). Examples include the investigation of experimental bone metastases, murine inflammation models (arthritis, asthma, and colitis). Major aim is the translation of these methods into clinical application, e.g. the discrimination of unclear breast and prostate lesions.

## Musculoskeletal imaging research

PI: Prof. Dr. F. Roemer, Prof. Dr. T. Bäuerle, PD Dr. T. Bayer, Dr. R. Heiss

The focus of this group is the characterization of osteoarthritis by MRI. One of the major research interests is the application of such MRIbased imaging tools 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. Another research focus is the development of compositional measurement methods for the assessment of cartilage, subchondral bone, and synovium at ultra-high field MRI (7T). A close collaboration with the Department of Radiology at Boston University School of Medicine is ongoing and has enabled active involvement in the largest on-going epidemiologic osteoarthritis studies including the Multicenter Osteoarthritis Study (MOST) and the Osteoarthritis Initiative (OAI), both with several thousand participants that are being followed over many years. The Institute is a 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

The focus of this group is on the development of new image acquisition, image reconstruction, and post-processing techniques for MRI. These techniques are evaluated in close collaboration by physicists and clinicians. The aim is to provide improved clinical radiological diagnostics. Among others, techniques are developed to acquire in vivo images of the sodium (23Na)and potassium (39K)-distribution. These nuclei play an important role in many physiological processes. For example, the 23Na- and 39Kconcentrations 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. In addition, high-gradient methods (e.g. dedicated breast gradients, G > 1 T/m) are being developed in a DFG-funded project to determine tissue microstructure. In order to enable a quantitative evaluation, suitable validation and reference objects, so-called phantoms, are also being developed. There are numerous national (e.g. German ultra-high field imaging (GUFI) network, DKFZ Heidelberg, MDC Berlin) and international collaborations (including Harvard Medical School, Boston, and Institut Myologie, Paris). In addition, various projects involve a very close cooperation with Siemens Healthineers.

# Teaching

Besides the standard lectures and practical courses, innovative clinically orientated courses are regularly offered including interactive discussions of clinical cases. In these courses the

students are taught a much more analytic and clinical rather than a systematic approach towards the interpretation of radiologic images. A new online course was established for students to prepare effectively for the state examination. Students of the degree program Medicine can always perform clinical electives or internships at our Institute. Students striving for a doctor's degree are supervised closely when writing their experimental or clinical thesis. Furthermore, the Institute of Radiology participates in degree programs Medical Process Management and Molecular Medicine (Faculty of Medicine) as well as Medical Technology (Faculty of Engineering). In addition, a joint seminar "Physics in Medicine" is offered in cooperation with the Department of Physics (Faculty of Sciences).

#### **Selected publications**

Czegley C, Gillmann C, Seyler L, Schauer C, Naschberger E, Uder M, Schett G, Bäuerle T, Hoffmann M. A chronic enthesitis model with inflammation an new bone formation characterized by multimodal imaging. Dis Model Mech. 2018 Aug 30;11(9). pii: dmm03404

Gast LV, Gerhalter T, Hensel B, Uder M, Nagel AM. Double quantum filtered 23 Na MRI with magic angle excitation of human skeletal muscle in the presence of B0 and B1 inhomogeneities. NMR Biomed. 2018 31(12):e4010

Heiss R, Wiesmueller M, Treutlein C, Seuss H, Uder M, May M, Wuest W. Cardiac T2 star mapping: standardized inline analysis of long and short axis at three identical 1.5 T MRI scanners. Int J Cardiovasc Imaging. 2018 Nov 21

Regus S, Lang W, Heinz M, Rother U, Meyer A, Almási-Sperling V, Uder M, Schmid A. Time-extended local rtPA infiltration for acutely thrombosed hemodialysis fistulas. Hemodial Int. 2018 22:31-36

Roemer FW, Kwoh CK, Fujii T, Hannon MJ, Boudreau RM, Hunter DJ, Eckstein F, John MR, Guermazi A. From Early Radiographic Knee Osteoarthritis to Joint Arthroplasty: Determinants of Structural Progression and Symptoms. Arthritis Care Res (Hoboken). 2018;70:1778-1786

Schellhaas B, Hammon M, Strobel D, Pfeifer L, Kielisch C, Goertz RS, Cavallaro A, Janka R, Neurath MF, Uder M, Seuss H. Interobserver and intermodality agreement of standardized algorithms for non-invasive diagnosis of hepatocellular carcinoma in high-risk patients: CEUS-LI-RADS versus MRI-LI-RADS. Eur Radiol. 2018 28:4254-4264

#### International cooperations

Prof. A. Bogdanov, PhD, University of Massachusetts, Worcester: USA

Prof. S. Trattnig, MD, Universitätsklinikum Wien, Vienna: Austria

Prof. A. Guermazi, MD, PhD, Boston University School of Medicine, Boston: USA

Prof. Y. Rathi, PhD, Harvard Medical School, Boston: USA

Prof. J. Titze, MD, Duke National University, Singapore: Singapore

# Institute of Radiology

# Division of Neuroradiology

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## **Head of Division**

Prof. Dr. med. Arnd Dörfler

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## **Research focus**

- 7 Tesla high-field-neuroimaging
- Multiple sclerosis
- Glaucoma
- Parkinson's disease and multisystem atrophy
- Epileptic seizures
- Preoperative diagnosis of pituitary adenomas
- Clinical and experimental validation of flatpanel volume CT
- Multimodal imaging of cerebrovascular diseases
- Preoperative multimodal imaging of epilepsy
- Functional and metabolic MR-imaging
- Holistic assessment of optical tract in glaucoma patients using diffusion tensor imaging
- Simulation of hemodynamics and fluid dynamics in cerebral aneurysms

# **Structure of the Division**

Professorship: 1

Personnel: 46

- Doctors (of Medicine): 16
- Scientists: 7 (thereof funded externally: 7)
- Graduate students: 3

### **Clinical focus areas**

- Diagnostic and interventional neuroradiology
- Multimodal diagnostics in cerebrovascular diseases, brain tumors, and epilepsy
- Functional and metabolic neuroimaging
- Spinal pain management

## 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 highfield MRI with 3 and 7 Tesla field strength are performed. In addition, there are several thirdparty research collaborations.

# 7 Tesla high-field neuroimaging

As part of a research collaboration with Siemens Healthineers, various scientific research projects are being carried out in close cooperation with the Department of Radiology and the Department of Neurology to validate and optimize clinical ultrahigh-field MRI.

## **Multiple sclerosis**

In patients with multiple sclerosis (MS), 7 Tesla imaging will be used to validate reproducible, independent, and sensitive imaging markers that will allow clinical trials of progressive MS to be completed in less time and with fewer resources, and that can be promptly brought into clinical routine for follow-up and therapy monitoring. Using ultra-high-field MRI, surrogate parameters (QSM, CEST, myelin-water imaging, Na-imaging, K-imaging) will be validated in multiple sclerosis patients in correlation to the clinical course (outcome measures). The Naand K-measurements are funded by the German MS Society. There is also an industry grant from Novartis AG.

### Glaucoma

The aim is to detect pathological protein deposits in the brain tissue in patients with pseudoexfoliatoin glaucoma (PEXG), using high-field molecular CEST MRI, to measure the effect of these proteins on neuronal and axonal integrity and resulting cell death by means of Na-imaging, and to measure the damage along the intracranial visual pathway by diffusion tensor imaging. Molecular CEST and Na-MRI signatures as well as structural DTI patterns will be used to characterize PEX glaucoma subtypes. Imaging markers will be correlated with ophthalmologic measurements and location of damage to the visual pathway in a hollistic approach.

# Parkinson's disease and multisystem atrophy

Idiopathic Parkinson's syndrome (IPS) can be differentiated from atypical Parkinson syndromes. The atypical Parkinson syndromes are characterized by a rapidly progressive course and a worse prognosis. Clinically, reliable imaging diagnostics for the early detection and differentiation of these entities is desirable. Hereby, ultrahigh-field MRI with high-resolution morphological sequences and new image contrasts for the direct visualization of the substantia nigra can improve early differential diagnosis. Additionally, QSM (quantitative susceptibility mapping) will be evaluated in patients with IPS and atypical parkinsonian syndromes compared with age-matched control subjects as functional surrogate parameters for early diagnosis and differentiation.

## **Epileptic seizures**

In close cooperation with the Epilepsy Center, multimodal diagnostics using 3 and 7 Tesla high field MRI (morphological high field MRI, functional MRI, MR spectroscopy, diffusion tensor imaging, MR volumetry and voxel-based morphometry) correlated to physiological parameters (EEG, MEG, WADA-Test, SPECT, PET) will be evaluated in the pre-surgical localization diagnostics of epileptogenic brain areas.

# Preoperative diagnosis of pituitary adenomas

In cooperation with the Department of Neurosurgery, we develop and validate high-resolution morphological and functional sequences for the preoperative delineation of micro- and macroadenomas of the pituitary gland in correlation to intraoperative findings. The aim is the exact preoperative delineation of the tumor spread in the cavernous sinus, as well as the relationship of the tumor to cranial nerves and vessels and improved detection of very small adenomas by dynamic T1-weighted flooding imaging.

## 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 cooperation with Siemens Healthineers and the Pattern Recognition Lab, we further evaluate intravenous and intraarterial flatpanel volume CT, angiographic techniques, and postprocessing algorithms in cerebrovascular disease. Hereby, a focus is set on the optimized visualization of cerebral microimplants, such as stents, coils, clips, new perfusion techniques, and advanced 3D visualization 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 diffusionweighted imaging, diffusion tensor imaging, susceptibility-weighted imaging, arterial spin labeling, and contrast-enhanced angiographic imaging, we evaluate the individual indication for acute stroke therapies, such as intravenous thrombolysis, intraarterial thrombectomy, and/ or other neuroprotective therapies. Hereby, a main focus is set on CT- and MR-derived patient selection for mechanical thrombectomy. Another clinical and scientific focus is the evaluation and validation of mechanical devices for mechanical thrombectomy in acute cerebral stroke.

# 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 to medical treatment. Hereby, a major focus is on correlation of highresolution 3T and 7T morphologic and functional MR imaging (MR spectroscopy, diffusion tensor imaging, functional MRI, perfusion- and diffusion-weighted MRI, MR volumetry/voxelbased morphometry) 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 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, DTI can be used to distinguish between different forms of glaucoma that require diverse treatment.

# 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 (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- and longterm strategy is to develop and clinically implement an automated software-platform that can be used within the endovascular 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.

In addition to the training of medical students in accordance with ÄAppO, the Division of Neuroradiology also conducts courses for the degree program in Medical Technology (Biological and Technical Vision) and the Chair for Pattern Recognition. In addition, the Division of Neuroradiology offers the lecture "Clinical Neuroimaging" since 2014.

Together with the Institute of Diagnostic Radiology, the education of physician spezialized in Diagnostic Radiology is carried out. For neuroradiology, there is full training authorization.

### Selected publications

Huhn K, Mennecke A, Linz P, Tschunko F, Kästle N, Nagel AM, Uder M, Dörfler A, Linker RA, Engelhorn T. (23)Na MRI reveals persistent sodium accumulation in tumefactive MS lesions. J Neurol Sci. 2017 Aug 15;379:163-166

Stadlbauer A, Zimmermann M, Kitzwögerer M, Oberndorfer S, Rössler K, Dörfler A, Buchfelder M, Heinz G. MR Imaging-derived Oxygen Metabolism and Neovascularization Characterization for Grading and IDH Gene Mutation Detection of Gliomas. Radiology. 2017 Jun;283(3):799-809

Mennecke A, Svergun S, Scholz B, Royalty K, Dörfler A, Struffert T. Evaluation of a metal artifact reduction algorithm applied to post-interventional flat detector CT in comparison to pre-treatment CT in patients with acute subarachnoid haemorrhage. Eur Radiol. 2017 Jan;27(1):88-96 Hoelter P, Lang S, Weibart M, Schmidt MA, Kott FX, Engelhorn T, Essig T, Kloska S, Dörfler A. Prospective intraindividual comparison of gadoterate and gadobutrol for cervical and intracranial contrast-enhanced magnetic resonance angiography. Neuroradiology. 2017 Dec;59(12): 1233-1239

Stadlbauer A, Zimmermann M, Doerfler A, Oberndorfer S, Buchfelder M, Coras R, Kitzwögerer M, Roessler K. Intratumoral heterogeneity of oxygen metabolism and neovascularization uncovers 2 survival-relevant subgroups of IDH1 wild-type glioblastoma. Neuro Oncol. 2018 Oct 9;20(11): 1536-1546

Schmidt MA, Knott M, Heidemann R, Michelson G, Kober T, Dörfler A, Engelhorn T. Investigation of lateral geniculate nucleus volume and diffusion tensor imaging in patients with normal tension glaucoma using 7 tesla magnetic resonance imaging. PLoS One. 2018 Jun 7;13(6):e0198830

#### International cooperations

Prof. C. Strother, Department of Radiology, University of Wisconsin, Madison: USA

Prof. Dr. A. Valavanis, Klinik für Neuroradiologie, Universitäts-Spital, Zurich: Switzerland

Prof. Dr. M. 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

## **Program representative**

Prof. Dr. Christoph Ostgathe

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# **Figures and structure**

In the winter term 2017/2018, 2,566 students were enrolled in the degree program Medicine (among them 182 students in the 1<sup>st</sup> term) and in the summer term 2018, 2,595 students studied medicine at the FAU (1<sup>st</sup> term: 182 students). In the academic year 2017/2018, 59.3% of the enrolled students were female. The percentage of women studying Medicine increased as compared to the academic year of 2016/2017 by 0.3%.

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) or having completed previous vocational training. 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 of Students 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 the teaching awards are financed by the achievement-oriented funds allocation (LOM). 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 euros, respectively. For the degree programs Dentistry, Molecular Medicine, and Medical Process Management, the best instructors receive 5,000 euros each. Instructors in the preclinical 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 euros. 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 40 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.

# SimPatiK

## (Simulated Patients in Hospital)

The simulation hospital where the students can train with simulated patients has opened in October 2018. The trainings of medical students can be carried out in seven rooms, decorated as patients' rooms with integrated one-way mirrors. With the help of simulated patients it is possible to introduce the courses for communicative skills in clinical settings as a teaching method.

According to their given roles the simulated patients are able to simulate various diseases from different areas of medicine as well as feelings, pains, and anxieties accompanying those diseases. Depending on the specific learning goals and competence areas the simulated patients can play their roles in different clinical setting. The realistic simulated communication training described above, especially covering burdensome issues, makes safe practicing of clinical history interviews and consultations possible which adds tremendous value to the safety of real patients. Moreover it is usually not possible to get a feedback from the real patients in clinical daily practice. Simulated patients are trained to give feedback from the patient perspective. The learning situation can be reflected upon in seminar groups with teachers, peers, and simulated patients. The structured feedback in the reflection phase is content as well as related social communicative behavior, which fosters the improvement of the skills.

The specially trained simulated patients are able to repeat their standard roles within examination situations. There are first experiences of their employment for the Objective Structured Clinical Examinations (OSCE), for the state examinations, as well as for team trainings in the collaborative healthcare provision.

The many years of experience with the simulated patients have proven that the training situation is perceived as being especially authentic. Currently ten departments of the Faculty of Medicine use simulated patients and the demand is rising.

### **Medical State Examination**

In 2017 the Medicine students in Erlangen ranked the fifth palace in Germany and the first place in Bavaria in the First State Medical Examination (first part of the physician exam). In the Second State Medical Examination, the students have reached the fourth place in Bavaria and the tenth place in the general ranking of Germany. In 2018, the students in Erlangen have topped their results in the First State Medical Examination by achieving the third place in German ranking and the remarkable first place in the Bavarian one. In the Second State Medical Examination the students in Erlangen finished eighth in the general German ranking and third in Bavaria.

# Dentistry

#### **Program representative**

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 guite considerable, given the extensive role played by practical training, as compared to what is the case with students taught in Medicine. New licensing regulations for the practice of Dentistry have been formulated, but are not likely to go into effect for a foreseeable future. The fact that new licensing regulations to practice Medicine are already in effect has resulted in a clear separation of the training provided in Dentistry from the training provided in Medicine.

As in the preclinical/theoretical phase of the degree program Medicine, the calculation of admission figures for the departments of dentistry is based on a ratio of students to clinical academic teaching staff. These parameters are considerably less favorable for dentistry students than for medical students (for instance, in terms of the amount of supervision and support provided to students during clinical internships where they are required to treat patients, there is an average ratio of six students per academic staff member in the departments of dentistry as opposed to somewhere between three and six students per academic staff member in the degree program Medicine; academic credit factors for internships are 0.3 for dentistry students as opposed to 0.5 for medical students).

The number of students admitted by the university has been constant for the last years, there is no increase resulting from lawsuits. Under the conditions offered by LOM, a performance-based funding scheme, finances for teaching the curriculum for the degree program Dentistry have improved. Under this scheme

the financing of staff positions, whether academic or non-academic (the latter also essential to ensure a good training environment), can be guaranteed on a long-term basis. Teaching evaluation is part and parcel of the training program at the departments of dentistry. The results are used in the process of updating and restructuring our curriculum with a view of achieving steady improvement in the quality of teaching. The departments of dentistry are equipped with high-quality technical systems in sufficient numbers so that they have no trouble satisfying the demands and needs that arise in connection with dentistry training. National and international quality comparisons show that our standards are very good. All the necessary prerequisites are given for our students to receive modern, clinically oriented training in the field of dentistry.

# **Molecular Medicine**

## **Program representative**

Prof. Dr. rer. nat. Anja Bosserhoff

## Coordination

Dr. rer. nat. Simone Reiprich

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## Aims and structure

The consecutive bachelor/master degree program Molecular Medicine combines subjects of experimental medicine with approaches and questions 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 improvements in diagnosis and therapy.

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 independently pursue research in medical and related fields.

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. A degree program coordinator who is responsible for the students ensures specialist counseling. 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 ensures that students are actively involved in decision-making and further development of the study programs.

## Bachelor's degree program Molecular Medicine

Each winter semester, 37 new students are chosen from among 800 - 1,000 applicants. The B.Sc. degree program spans six semesters in which a solid education in all basic disciplines of molecular medicine is achieved. Preclinical and theoretical institutes mainly teach the core curriculum in Molecular Medicine. 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 laboratory work. The degree program concludes with a 2-months experimental thesis.

### Master's degree 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's 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 courses link theoretical concepts with extensive laboratory practice, analysis, and discussion of current and classical research publications. The master degree program ends with an experimental thesis of six months. A mobility window in the third semester gives students an opportunity to gain laboratory experience abroad or in an industry context.

The curriculum of the M.Sc. degree program was updated significantly as of winter semester 2016/2017. The working language (including examinations) was switched to English, taking into account that English is the lingua franca in biomedical science. This opens the program for gualified international applicants.

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.

### Perspectives

The master degree program Molecular Medicine offers the opportunity to pursue a highquality 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. A variety of occupational fields in industry, private laboratory, and public institutions is available to the graduates. 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. Graduated Molecular Medicine students 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.



Graduates of Molecular Medicine 2017 (Photo: C. Stolt, FAU)



Bachelor graduates of Molecular Medicine 2018 (Photo: C. Warter, FAU)



The first graduates (2018) of the international master degree program Molecular Medicine (Photo: C. Warter, FAU)

# Medical Process Management

#### **Speaker**

Prof. Dr. med. Dr. h.c. Jürgen Schüttler

## **Program representative**

Prof. Dr. med. Harald Mang, MHBA

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## Aims 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 ETCS 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 connects medicine and healthcare to business process management and information technology. Strengthening patientorientation, 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. Within the reporting period, 120 students, applied annually for admission to MPM (80% female). In both years half of the applicants were admitted after passing the qualification assessment exam. 60% of the students who were admitted finally accepted the university place. This means that the student cohort of the tenth year contains 45 students, whereas the the cohort of eleventh year comprises 41 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's 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 FAU. 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's 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.



Graduate students 2017



Graduate students 2018 with Dean and program representative (photo: FAU/C. Warter)

# Logopedics

### **Program representative**

Prof. Dr. med. Dr. h.c. Heinrich Iro

## Coordination

Sabine Degenkolb-Weyers, MA

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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 further developed. 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 end of the model period is expected in 2021.





Graduates of 2017 and 2018, resp. (photos: private)

# **Center for Clinical Studies (CCS Erlangen)**

### **Managing director**

Dr. med. Bernd Gebhardt, MBA

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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 tasks and duties of the sponsor in clinical studies
- 3. Administration of the insurance for participants in clinical studies
- 4. Organization of educational events on all aspects of clinical studies

Since its inception, CCS participated in about 550 clinical research projects of members of the Faculty of Medicine and of UK Erlangen. These projects comprise several multinational clinical studies in Europe as well as several 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.

CCS is an associated member of both, the KKS-Netzwerk e.V., the association of the German university clinical study centers, and the Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V. (TMF), the umbrella organization for networked medical research in Germany.

# **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 of UK Erlangen. CCS evaluates the feasibility of the research project from an economic and organizational perspective as well as its compliance with 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 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 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 of UK Erlangen. This comprises obtaining insurance offers and accompanying the project until its conclusion.

# Education

At the request of the Faculty of Medicine, CCS in collaboration with the Chair of Clinical Pharmacology and Clinical Toxicology has currently conducted more than 50 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 often have a major impact on the feasibility and timely recruitment of clinical studies. Currently more than 1,000 physicians from UK Erlangen and the associated academic teaching hospitals have attended the courses.

# Comprehensive Cancer Center Erlangen-EMN

#### Director

Prof. Dr. med. Matthias W. Beckmann

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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, it runs a free tumor consultancy service for patients and their relatives.

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 CCC ER-EMN, there is a total of 22 certified organ cancer centers, 13 focal points, and 26 interdisciplinary tumor conferences that 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".

Patients suspected to have a complex oncological syndrome or with advanced/metastatic solid cancers are presented in the cross-regional molecular tumor board and can be tested with a comprehensive cancer-/genpanel. The results improve clinical decision making of innovative therapies.

The information brochure "Side by Side" of the CCC Erlangen-EMN offers relevant information on diagnosis, therapy, and other cancer related topics.

### Aims of 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) 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<sup>™</sup> and the data warehouse tool Cognos<sup>™</sup>. Supplementary to these IT systems, there are commercial IT solutions for cancer registry, trial management, and biobanking. Physicians and patients can soon search the CCCwebsite to get information about ongoing clinical trials. Clinical trials are important for innovation and the treatment of cancer patients. Clinical trials of all phases are conducted at the CCC Erlangen-EMN.

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Graphic: CCC/nandodesign.de

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-FMN.

## 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.

CCCC Comprehensive Cancer Center Erlangen-EMN Europäische Metropolregion Nürnberg

# German Center Immunotherapy (DZI)

### **Speakers**

Prof. Dr. med. Markus F. Neurath Prof. Dr. med. Georg Schett

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# Aims and structure

The German Center Immunotherapy (DZI) pursues three central tasks:

- 1. The development and application of targeted immunotherapies
- The establishment of new diagnostic procedures for disease detection and therapy monitoring
- 3. The use of advanced digital health technologies

By combining these three synergistic fields of activity, the DZI aims to enable individually targeted immunotherapy for cancer patients and patients with chronic inflammatory diseases.

## Research

The development of the DZI is based on the long-standing research focus of the Faculty of Medicine of the FAU in the field of immune research in inflammatory and cancer diseases. Based on the pioneering work of Prof. Dr. A. Kussmaul, the first describer of panarteriitis nodosa, and Nobel Prize winner Prof. Dr. Dr. h.c. H. zur Hausen, the pioneer of vaccine development against cervical cancer, an intensive interest in translational immunology and immunotherapy has emerged in Erlangen, which was continued by Erlangen scientists Prof. Dr. M. Röllinghoff, Prof. Dr. B. Fleckenstein and Porf. Dr. Dr. h.c. J. Kalden.

Based on this preliminary work, the DZI is sustainably expanding its clinical and scientific research work in the field of immunotherapy for inflammation and cancer. Here the main interest of the DZI lies in the development of new diagnostic and immunotherapy procedures for chronic inflammatory and neoplastic diseases. This development is also reflected in numerous acquisitions by research alliances in Erlangen as well as outstanding publications. These include, for example, work on the establishment of immune imaging and non-invasive diagnostic procedures for inflammatory and cancer diseases as well as the discovery of genetic changes, key signaling pathways, and new immune therapies for chronic inflammations and oncological diseases. In addition, DZI scientists conduct groundbreaking early clinical trials and regulatory studies in inflammation and cancer medicine.



The Dean, Prof. Dr. h.c. J. Schüttler, Prof. Dr. Dr. h.c. H. zur Hausen, both speakers (Prof. Dr. G. Schett, Prof. Dr. M.F. Neurath), the President of FAU, Prof. Dr. J. Hornegger and the Medical Director, Prof. Dr. Dr. h.c. H. Iro, at the ribbon-cutting ceremony. (from left to right; photo: M. Rabenstein/UK Erlangen)





# Interdisciplinary Center for Clinical Research (IZKF)

#### Chairman

Prof. Dr. med. André Reis

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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. 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. Members of the Faculty of Sciences may participate as co-applicants in project proposals.

The IZKF is financed by the state grant for teaching and research of the Faculty of Medicine and a contribution from the FAU.

#### **Research grants**

Every three years, IZKF offers single and joint research grants in all research areas of the Faculty of Medicine. Prerequisites for a successful application to the IZKF include an active publication record, own external funding, an interdisciplinary approach, and relevant preliminary work.

If project leaders apply for external funding by the end of the funding period, an extension for another six months additionally to the regular 30 months' duration is provided.

In the funding period from 2016 – 2019, 28 of 31 projects (90%) already received a funding extension. 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 crucial when evaluating IZKF's performance in advancing clinically oriented research at the Faculty of Medicine. Furthermore, scientific diplomas, patents, scientific prizes, and offers of professorships are relevant parameters. In 2017, 58 funded projects altogether published 75 original articles with a cumulative impact factor (IF) of 620.577; moreover 26 articles had an impact factor of over 10.

### **Career development**

The IZKF research groups offer over a period of up to six years attractive career development opportunities for outstanding young scientists with a training in medicine or natural sciences in one of the Faculties' main research fields. 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) is engaged in the field "Physics and Medicine". Both junior research groups are highly regarded cooperation partners for scientific projects and actively participate in the teaching and training of young scientists.

The annually tendered starting grant is aimed at young postdoctoral scientists (maximum 35 years) from the entire Faculty of Medicine without previous significant external funding. Over a funding period of 2.5 years, applicants are to submit their first application to an external funding organization. In order to enable physicians to better reconcile their research activities with clinical requirements, IZKF offers positions for laboratory rotations.

The newly established Clinician Scientist Program of the IZKF was announced for the first time in 2018. The program is aimed at physicians who are interested in science, have completed their doctorate during their specialist medical training, and who also aim for a structured scientific qualification program. Parallel to the IZKF application, a lateral entry into the program is possible with a leave of absence from a research association or a clinic. In addition to the advanced module for physicians with thirdparty funding, a basic module for younger physicians with a completed doctorate is also offered.

Some laboratory rotations (over a period of six months full-time or twelve months part-time) can also be filled outside the starting grant and the Clinician Scientist Program. They can be applied for on an ongoing basis and are aimed at clinically active physicians who need time off from their clinical obligations to carry out their own research projects.

To support experimental medical doctoral theses, the IZKF provides up to 18 scholarships per year for eight months for MD students. All doctoral students of the IZKF attend the GK of the IZKF that participates in the graduate school Life®FAU (compare own report).

#### Start-up support (ELAN)

ELAN supports young scientists (maximum 38 years) from the entire Faculty of Medicine for a maximum period of twelve months. The aim of ELAN is to prepare scientific projects for a successful external funding application (start-up projects), to develop new innovative ideas (pilot projects) or act as interim funding if temporary gaps arise. The application is possible on an ongoing basis. From 2019 onwards, the instrument of bridging projects will also be available. This program is aimed at advanced scientists with no basic material or personnel resources beyond their own position who finance their research predominantly through third-party funding. In cases where the respective institution is not in a position to do so, the projects should enable a temporary bridging of a precarious situation (e.g. rejected application for third-party funding) with the aim of ensuring the continuity of research by experienced, independently researching scientists with a good prospect of timely acquisition of new external third-party fundina.

## Core facilities and supporting activities

Core facilities or units are centralized platforms offering access to these cost-intensive modern methods and technologies to a broad user spectrum. IZKF offers an initial funding of core facilities for one or two funding periods. The supporting activities include the Visiting Professor Program and an international scientific meeting. In addition, central funds for participating in scientific meetings, publication charges and particularly cost-intensive experiments (High Tech Pool) provide additional support for funded projects.



Center for Clinical Research Erlangen

# **Preclinical Experimental Animal Center (PETZ)** at the Franz-Penzoldt-Center (FPZ)

### Speaker

(scientific and managing director) Prof. Dr. med. Stephan von Hörsten

**Contact** Dr. med. vet. Susanne Schwarz

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## Services 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.

PETZ 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. PETZ provides state-of-the-art phenotyping services for neurobiological, hematological, neuroendocrine, and immunological characterization of mice and rats. Already as early as the time of project application, the team of 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.



# **Mission and research**

The superior goal of PETZ is the continuous implementation of the principles of reduction and refinement being part of the 3R's 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 the PETZ is providing 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 end of 2018, a variety of different research projects representing over 92 working groups are realized in the PETZ. These researchers originate from 43 institutes, chairs, or departments. Most of these working groups belong to the Faculty of Medicine.



# Teaching

PETZ is a source of lectures, seminars, and practical courses on animal experimentation and ethics. The team organizes gualifying professional development courses in laboratory animal science (e.g. courses according to FELASA B criteria), offers the opportunity to learn animal experimental techniques and functions as a training company (Ausbildungsbetrieb) for the recognized occupation requiring formal training "laboratory animal technician", which is certified by the chamber of industry and commerce (IHK). The Center is a competent venue for surgical trainings in students' education as well as in the professional development of experienced practitioners. It places a priority on being a family friendly institution and implements the principles of gender equality in its processes and management to help its staff achieve a work lifebalance.

# **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. 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 the 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. 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 H. Leutheuser.

# Research

ZiMT acts in close interaction with Medical Valley EMN which was assigned as a German cluster of excellence in medical engineering in 2010. 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 8th European Union Research Program Horizon2020, the European Institute of Innovation and Technology (EIT) has extended its focus to "Together for healthy lives in Europe". 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 and UK Erlangen have established themselves as core partners of EIT Health and are 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.

## Entrepreneurship

Entrepreneurship and innovation are fundamental aspects of local and economic environments, especially in the sphere of medical technology and healthcare engineering. From this perspective, ZiMT serves companies as key contact in the FAU community and nationwide., ZiMT's responsibility is to support promising ideas from our partners and tailor cooperation between industrial and research players. The common goal will be to establish scientifically innovative products that meet real requirements of the market and to develop a strong innovative force in the Medical Valley. By means of multiple activities like startup consulting and hosting the EIT Health MedTech Bootcamp, ZiMT encourages networking of international partners and entrepreneurs at FAU. Simultaneously, ZiMT supports the ongoing innovation process in the fields of MedTech and Digital Health on a regional and national base, but also transnational.

### **Grant consulting**

The ZiMT office assists in the development of complex proposals that may represent a multidepartmental and inter-institutional collaboration. We also consult individually with faculty and postdocs at FAU and other Bavarian universities, and enterprises and startups who are writing grant proposals for external funding.

# 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 high numbers of applications from the very beginning and have a steady enrollment of about 800 students, establishing itself as one of the largest degree programs at the Faculty of Engineering. The consistently high number 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. Another outstanding feature about the Medical Engineering degree program is the high percentage of female students (50%).

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 B.Sc. degree program of Medical Engineering. The M.Sc. degree program Medical Engineering 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 M.Sc. in "Health & Medical Data Analytics", funded by EIT Health, will be offered beginning in the winter semester 2019/2020 and will support additional education in entrepreneurship with the possibility of studying abroad for one semester.

ZiMT offers separate lectures and seminars and therefore provides an early interfaculty exchange for students. Offers like the Innovation Research Laboratory (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.



# **Digital Health Innovation Platform (d.hip)**

#### Chairman of the executive board

Prof. Dr.-Ing. Erich Reinhardt

## Contact

Tobias Zobel

## Address

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## Aims and structure

Erlangen and Nuremberg are unique due to their academic and industrial environment. In the field of medical technology, the high density of clinical institutions, university and non-university research institutions and companies (from small start-ups to multinational corporations) provide ideal basic conditions for new and advanced product developments. In particular, digitization in the healthcare sector is one of the topics that the region is primarily involved in. It is also one of the biggest economic growth drivers: Experts estimate the global market volume for digital healthcare solutions to be over US\$ 230 billion by 2020, as compared with US\$ 135.9 billion in 2017 (source: Statista). The goal of the Digital Health Innovation Platform (d.hip) is to profit from this growth and jointly become the innovation leader for digital applications in order to optimize health care.

The partners Siemens Healthineers, UK Erlangen, FAU, and Medical Valley EMN have joined forces in the cooperation network d.hip to implement outstanding research projects in the field of digitization of the health sector over the next three years.

The Digital Health Innovation Platform was launched in spring of 2018. Since September, the new space has been in use in the former Siemens Healthineers showroom, which with over 500m<sup>2</sup> offers enough space for project teams, start-ups, and events. A maker space is also available for the production of small prototypes.

Since the initial call for projects in June 2018, the first projects have almost been completed. Representatives of the d.hip partners have submitted various innovative project ideas, for example to improve the care of Parkinson's patients, to optimize breast cancer research, or to improve the therapy of infectious patients using digital solutions. From all the submitted projects the best projects were selected and implemented in the d.hip Lablaboratory as well as directly at the partners' facilities. There are currently four calls per year to which applications can be submitted together with other d.hip partners.

d.hip is complemented by a scientific program, recruiting professorships in key technology areas and international graduate students for projects in Erlangen.

# Research

The d.hip research projects deal with future fields such as "Digital Health Twin & Family", precision medicine, hospital management, or new services for home care, in order to make the opportunities of digitization usable for every citizen.

In order to take advantage of the high numbers of experts from the region, a focus was defined for d.hip projects - the Digital Health Twin & Family. This topic revolves around the most holistic possible digital collection of patient data of various kinds. Processing this data will enable new diagnoses and therapy indications. These data refer, for example, to genomes, medical images, cardiovascular systems, connections between the functions of individual organs or simple information from patient letters. By individually comparing the data of a patient with this reference database, it is possible to respond more individually to the patients' needs based on identified parallels with documented clinical patterns or other anomalies.

Within the framework of the d.hip projects, employees from all d.hip partner institutions can submit their ideas to jointly advance the Digital Health Twin.

DIGITAL HEALTH

# **Emil-Fischer-Center (EFC)**

#### Speaker

Prof. Dr. rer. nat. Heinrich Sticht

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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 Faculties of Medicine and of Sciences, respectively. The EFC includes the full and associate professors from the following chairs:

- Biochemistry and Pathobiochemistry
- Biochemistry and Molecular Medicine
- Pharmacology and Toxicology
- Clinical Pharmacology and Clinical Toxicology (all Faculty of Medicine)
- Pharmaceutical Chemistry
- Pharmaceutical Technology
- Food Chemistry
- Bioinorganic Chemistry (all Faculty of Sciences)

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. The GK 1910 "Medicinal chemistry of selective GPCR ligands", whose second funding period was approved in 2018, represents a major joint initiative in the reporting period. Several EFC working groups are also involved in GK 2162 "Neurodevelopment and Vulnerability of the Central Nervous System "(compare own report). In the reporting period, more than 130 publications were produced that explicitly mention EFC as a participating institution.

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)", which was established shortly after foundation of the EFC. In addition, EFC provides the platform for the EFS lecture series. Instrumental equipment at the EFC comprises mass spectrometers, NMR-spectrometers, a CDspectrometer, various electrophysiological setups, and a bioinformatics computer cluster.



# **Erlangen Center for Infection Research (ECI)**

#### Speaker

Prof. Dr. rer. nat. Sven Krappmann (Faculty of Medicine)

## **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. ECI is a consortium of more than 30 professors and lecturers and their research groups that 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 FAU and UK Erlangen. 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, 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.

The organizational structure of the ECI comprises an executive board (Prof. Dr. S. Krappmann (MF, speaker), Prof. Dr. A. Burkovski (NF, deputy speaker)) and a planning team, consisting of the board together with five university lecturers (Prof. Dr. A. Bozec (MF), PD. Dr. A. Lührmann (MF), Dr. M. Petter (MF), Prof. Dr. K. Überla (MF), and Prof. Dr. S. Wirtz (MF)) and the members' assembly.

### Research

According to its central tasks and aims, 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 two ongoing collaborative research centers (SFB 1181, SFB/TRR 130), several research training groups (GK 1660, GK within SFB 1181) at the FAU as well as in the application for two further research training groups (GK 2504/1: "Novel antiviral approaches: from small molecules to immune intervention" [designated speaker: Prof. Dr. K. Überla; succesfull evaluation of the full proposal on December 10, 2018]; GK 2559/1: "ImmunoMicroTope: Microenvironmental, metabolic, and microbial signals regulating immune cell-pathogen interactions" [designated speaker: Prof. Dr. C. Bogdan; ful application in preparation]). 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 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" or "Integrated Immunology", but also the invitation of national and international infectious disease researchers for guest lectures.

#### Selected lectures

10.1.2019 Prof. Dr. F. Wagenlehner, Universitätsklinikum Giessen und Marburg GmbH, Justus-Liebig Universität Giessen

Urinary tract infections with multi-resistant pathogens: Therapeutic alternatives

23.11.2018 Prof. Dr. E.Schnettler, Molecular Entomology, Bernhard-Nocht-Institute for Tropical Medicine, Hamburg Arbovirus-mosquito interaction

15.10.2018 Dr. Yi. Kai Chan, Department of Genetics, Harvard Medical School and Wyss Institute for Biologically Inspired Engineering Harvard University, Boston: USA Engineering the innate immune response to viruses

9.7.2018 Prof. S. Kent, Department of Microbiology and Immunology, Peter Doherty Institute, University of Melbourne: Australia

Immunity to HIV – role of ADCC

22.6.2018 Prof. R. Sarid, The Mina and Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Ramat-Gan: Israel

Insights into the biology of KSHV

19.3.2018 Prof. B. R. Cullen, Department of Molecular Genetics and Microbiology, Duke University, Durham: USA Viral epitranscriptomics 24.11.2017 Prof. Dr. B. Horsthemke, Institut für Humangenetik, Universitätsklinikum Essen

Whole genome bisulfite sequencing in human monocytes and macrophages: The role of allele-specific and celltypespecific DNA methylation

20.10.2017 Dr. K. Sutter, Institut für Virologie, Universitätsklinikum Essen

Individual antiviral and immunomodulatory properties of IFNalpha subtypes during retroviral infections

18.7.2017 Prof. B. Linz, University of Georgia, Center for Vaccine and Immunology College of Veterinary Medicine, Athens, Georgia: USA

Evolution of Bordetella: From environmental bacteria to human pathogens

5.7.2017 Prof. Dr. Dr. A. Sing, Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit (LGL)

Diphtherie – ein Fall fürs Museum? Aktuelles zur Diphtherie in Deutschland



# **Imaging Science Institute (ISI)**

#### **Speakers**

Prof. Dr. med. Michael Uder Dr. med. Patrick Amarteifio (Siemens Healthcare)

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## Aims and structure

The Imaging Science Institute (ISI) was founded in 2005 as a cooperation project between Siemens Healthcare and the Institute of Radiology. 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-theart 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 45,000 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
- Medtron
- 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 improved 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 Leading Edge Cluster Medical Valley EMN connects ISI to a strong regional network. Main research focus are:

## **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" (clinical data intelligence) 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 the foundation of ISI in 2005, more than 25,000 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 wellbeing until very old age. At an advanced age, 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 are 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. These gadgets are also intended to document the amount of fluid consumed and thus to reduce caregiver burden. Newly developed products are tested in pilot studies with residents and nursing staff and adapted according to the feedback received. Recruitment and comprehensive phenotyping of an enable cohort of older people at the IBA will allow future comparisons with younger age-groups that were assessed in Freising using identical methods. Within the European joint project MaNuEL (Malnutrition in the Elderly), modifiable determinants of malnutrition in older persons were examined 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. Analyses of the worldwide "nutrition Day" project focused on the topic of dysphagia in nursing homes and the nutritional situation of affected residents.

# **Physical activity**

Targeted interventions to improve physical functioning, capacity, and performance as well as measures to promote physical activity can significantly improve and support (functional) mobility, the maintenance of independence, and social participation in life. In addition to controlling bodily functions, the aim of appropriate interventions is to increase adherence to lifelong physical activity and to expand the possibilities of physical activity in the respective settings. Behavioral exercise therapy leads to improved functional capacity, improved pain management, and improved workability in pain patients in rehabilitation. The participation of older people in exercise programs leads to increased physical functional (such as strength and balance), improves cognitive functions, reduces the risk of falling and the risk of dementia. Important aspects for sustained changes in physical activity behavior concern e.g. the affective attitude to physical activity and furthermore fundamental questions about the structural and process quality of exercise therapy. Physical activity promotion and even exercise therapy interventions can - for various indications - also be carried out successfully by the use of new media and the internet. A further research focus is motor control in persons with neurological diseases (e.g. Parkinson's disease), in movement or gait disorders after surgical interventions or after (sports) injuries. Beyond the individual level, the organizational or political level plays a central role in promoting physical activity of older people. The aim is, among other things, to create capacities (e.g. personnel development, distribution of resources, environmental conditions) and to improve the cross-organizational and cross-sector networking of organizations from the fields of sport, health, and social affairs in order to be able to expand and optimize the opportunities for physical ability to older people. Structured planning processes and a better networking of science, practice, and politics are important means for this. The recently published "National Recommendations for Physical Activity and Physical Activity Promotion" have an important influence on health and sports policy. Of particular interest for research into ageing are opportunities and obstacles in integrating evidence-based, structured exercise programs for the prevention of dementia into the practice of prevention providers, with particular attention being paid to target groups that are difficult to reach (e.g. socially disadvantaged older people and physically inactive people).

## **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 on the possibilities of assistive technology for supporting mobility and independent living in later life.

# Teaching

The majority of the ICA-members is engaged in the interdisciplinary course offerings of the master's degree program in gerontology. Some courses are realized in close cooperation with the associated ICA-members, 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 ICA-members at the Faculty of Medicine. Furthermore, 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 and Public Health (IZPH)

#### Speaker

Prof. Dr. med. Hans Drexler

### Contact

Prof. Dr. med. Peter Kolominsky-Rabas, MBA Managing Director

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# Aims and structure

In societies with demographic shift and budget constraints, the greatest challenges in health care – especially for the German Health Care System – are the efficient provision of health care services, quality improvement, and cost reduction. Solving those socially important challenges requires multi-professional outcomes research.

The Interdisciplinary Center for Health Technology Assessment and Public Health (IZPH) of the FAU is the first thematically inter-professional German research platform on health outcomes research across the faculties of the FAU. It was founded in 2001 and systematically merges scientific insights from the three Faculties of Medicine, of Engineering, and of Business, Economics, and Law, respectively. Central aims of the IZPH are the scientific-oriented and evidence-based political consulting using population and registry data as well as an analysis of health care under everyday conditions ("realworld evidence").

### Research

## Outcomes research/ health services research

Every day, there are about 890 new diagnoses of dementia and about 590 new diagnoses of stroke in Germany. Those numbers are vividly illustrating the huge importance of both widespread diseases, dementia and stroke, in health politics and their consequences for the social security system in Germany. Populationbased registries for the purpose of outcomes research of dementia and stroke are therefore the scientific focus of the IZPH, according to the slogan 'you can only manage what you measure'. The Erlangen Stroke Registry (ESPro) is an ongoing, population-based registry, including patients with stroke and vascular dementia. Founded in 1994, ESPro is one of the oldest and most comprehensive population-based registries in the EU, involving 8,800 documented cases and 1,500 follow-up examinations per year. Based upon its sustainable data collection, ESPro provides population-based, representative, epidemiological data (incidence, time course, and long-term survival rates), data according to the course of the disease (risk factors, cognitive function, and complications), data according to the utilization of care services as well as health economic data (patterns of care, use of health care services, costs of illness). ESPro is part of the Federal Health Monitoring (Gesundheitsberichterstattung (GBE)) and is evaluated and continuously funded by the German Federal Government since 2010.

The Bavarian Dementia Survey (BayDem) is a multi-center, longitudinal study at three different Bavarian sites. Participants are people with dementia defined by ICD-10 and their informal caregivers. Data was collected by standardized face-to-face interviews in cooperation with local actors.

Funding: Bavarian Ministry of Health and Care

#### Health technology assessment

In Germany, a growing number of people are injured or die due to dangerous implanted medical devices and prostheses. In 2017 alone, in total 14,000 injuries, deaths, and other problems related to medical devices were reported. Usually, the recall of medical devices or announcements of security warnings are left to the manufacturers themselves instead of being carried out by public authorities. Since 2010, there are about 1,000 recalls per year and three per day on average, initiated by manufacturers. In the same time, there were only six recalls mandated by public authorities. Implant registries are therefore required in order to secure sustainably and effectively citizens of defective medical devices, in particular dangerous implants and prostheses. In cooperation with the leading edge cluster Medical Valley EMN, IZPH is analyzing the requirements regarding the structure and content of implant registries in order to secure the safety of citizens. Concepts of quality assurance, transparency of data, public reporting and aspects of an independent funding of implant registries are prioritized. The work and publications of the IZPH regarding implant registries had an impact on the draft legislation 'Entwurf eines Gesetzes zur Errichtung eines Deutschen Implantateregisters (Implantateregister-Errichtungsgesetz – EDIR)' of the Federal Ministry of Health (BMG), published in January 2019.

#### **Health economics**

For the first time ever, the German health expenditures exceeded the threshold of 1 billion euros per day in 2017. According to Destatis, the health expenditures amounted to 374 billion euros in total for the year 2017, which accounts for a share of 11.3% of the gross domestic product. The high increase occurred in particular due to high health care costs for chronic diseases. In respect to the demographic development in Germany, associated with an ageing of the population, a further increase of health care costs in the area of age-related diseases is expected. On the one hand, IZPH is therefore focusing on cost-of-illness studies of widespread diseases with high public health relevance, such as dementia, stroke, and heart failure. In Germany, the annual costs of heart failure are about 23,000 euros, the lifetime costs are about 113,000 euros per patient. Those studies are fundamental in the context of health care planning for payers, service providers, and political decision makers. On the other hand, the IZPH is performing health economic evaluations of pharmacological and non-pharmacological treatments. Furthermore, novel methodological approaches are explored in order to make the benefits of innovative health technologies transparent. By doing this, IZPH facilitates a comprehensible and balanced reimbursement decision for the members of the conjoint self-administration (Gemeinsame Selbstverwaltung) in the German health care system (G-BA, GKV-Spitzenverband).

## Teaching

Interdisciplinary lectures are done by researchers of the IZPH. Thematically, those lectures include issues of Public Health, outcomes research, and health technology assessment in cross-sectional lecture rounds like "Q3-Gesundheitsökonomie, Gesundheitssystem, öffentliche Gesundheitspflege" and "Q10-Prävention und Gesundheitsförderung". A particular focus is on interdisciplinary lectures for students of the master's degree program Medical Process Management.

Frequent tutorials for young scientists ("Young Researchers Tutorials") as well as the supervision of Master's theses, MD, and PhD theses are completing the field of activity.

# Interdisciplinary Center of Ophthalmic Preventive Medicine and Imaging (IZPI)

#### **Speakers**

Prof. Dr. med. Georg Michelson Prof. Dr.-Ing. Bernhard Schmauss

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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 of 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, 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 technolo
  - gies 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 of Engineering cooperate within third-party funded projects of the Leading Edge Cluster "Medical Valley EMN e.V." and the School of Advanced Optical Technologies "SAOT" (compare own reports).

VR-Amblyopia Trainer Pl: Prof. Dr. G. Michelson, W. Mehringer, Prof. Dr. B. Eskofier A telemedically controlled dichoptic visual-motoric perceptive learning system for amblyopia therapy by means of Virtual Reality (VR) called VR-AMBLYOPIE TRAINER is developed. This VRsupported system uses a new binocular therapy concept to improve the visual acuity of amblyopic children and adolescents. Through a telemedical, ophthalmologic connection, the integration of the new therapy concept into the regular medical operation takes place.



### **Implicit Perimetry**

PI: Prof. Dr. G. Michelson, H. Hähnlein, J. Martschinke, Prof. Dr.-Ing. M. Stamminger

The Implicit Perimetry project is a Next-Generation HomeCare application to improve glaucoma treatment. The cross-institutional network structure enables HomeCare applications and Big Data applications. In implicit VR perimetry, the view of the saccade to the light stimulus shown is evaluated as the reaction to the light stimulus. The patient no longer has to press a button and stare rigidly into the center for more than 15 minutes. Implicit VR perimetry no longer requires a controller. The saccades are conscious or unconscious, fast, jerky eye movements between fixations, they last about 20 - 100 ms and occur about 200 ms after the stimulus. A HMD (Head Mounted Display) allows the use of VR techniques. Implicit VR perimetry is an excellent basis for use in telemedicine and home care.



#### Integrated diagnostic and e-Assistance system for patients with age-related macular degeneration (AMD)

Talkingeyes & More togetherwith IZPI is part of the BMBF project "Interactive Systems in Virtual and Real Spaces - Innovative Technologies for a Healthy Life" (IDeA). The project runs from 2019-2022. The keywords for this network are eye diseases, VR/AR, eye tracking, multi-user, telemedicine, human-machine interaction, assistive technologies. In this project, the Institute of Computer Science (Faculty of Engineering), Max-Planck-Institute for Biological Cybernetic (Tübingen), the Institute of Ophthalmology (university of Tübingen, IFA-UT), the International Center for Ethics in the Sciences and Humanities (university of Tübingen, IZEW), Blickshift GmbH, NMY GmbH and Talkingeyes & More GmbH at the Medical Valley Center cooperate. The network coordinator is Prof. Dr. A. Schmidt, Human-Centered Ubiquitous Media Group, Department of Computer Science of the Ludwig-Maximilians-Universität in Munich.

The goal of IZPI and Talkingeyes & More GmbH is the development of AR/VR-based optometry and telemedical multi-user applications. In particular,

- (1) Standardized methods for the investigation of visual function in AMD
- (2) User interfaces for multi-user functions and(3) Quality assurance of software and hardware
- development are to be developed.

In particular, HomeCare-based methods for visual function testing (TV monitor-, HTC VIVEand SmartPhone-supported VR-based variants), a digital Amsler Grid, a VR system for testing a 30° visual field, a VR system for testing binocular fusion at different viewing directions and a VR system for testing contrast sensitivity will be developed and validated.

# Teaching

IZPI researchers give lectures within several interdisciplinary frameworks of the Faculties of Medicine and of 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 "Bioological and Technical Vision" and "Medical Applications of Photonics".

# Leading Edge Cluster Medical Valley EMN

Speaker

Prof. Dr.-Ing. Erich R. Reinhardt

#### Deputy Speaker and Contact Faculty of Medicine

Prof. Dr. med. Dr. h.c. Jürgen Schüttler

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# **Aims and structure**

The Medical Valley European Metropolitan Region Nuremberg (EMN) is a leading international cluster in medical technology. Here, there are not only highly specialized leading international research institutions, but also many emerging companies. They work closely with world-renowned health research facilities in the cluster in order to find solutions to the challenges of healthcare of today and tomorrow.

The cluster is so outstanding that it was nominated as national Cluster of Excellence by the BMBF in 2010. Since 2007 Medical Valley EMN e. V. operates as a uniting cluster management organization. It currently has more than 200 members from industrial, science, healthcare, network, and political sectors. The key tasks of cluster management are the development, coordination, and marketing of the cluster. We measure our success by asking these fundamental questions:

Are we able to stimulate new ideas, projects, and foundations?

Do we obtain R&D (research and development) funding for innovative projects?

Do our services catalyze the innovation of ideas? Do our activities promote the cross-sectoral and transdisciplinary exchange of knowledge?

Do we strengthen exchange in the cluster and improve cultural cooperation?

Do we promote creative minds?

Do we support the internationalization of our partners?

Our services help the commercialization of the ideas of our members. Our offerings include funding-procurement and consulting, foundation support, identification and exchange of clinical partners, regulatory approval and reimbursement, strategic needs assessment and health economics evaluation, open innovation as well as international market access. To provide comprehensive support, we incorporate established specialists and experts within the cluster through the "One-Stop-Shop" principle. Our current specifically-selected activities include the operation of innovation centers in Erlangen and Forchheim, the coordination of the Bavarian Cluster Medical Technology (in cooperation with Forum MedTech Pharma), the conducting of the Medical Valley Awards (prize for research teams in pre-foundation phases), and the coordination of the platform "Digital medicalHealth" within the Center for Digitalization Bavaria. Since 2010 Medical Valley has acquired more than 150 million euros R&D grants for its partners.

# Research

Following you will find three examples of currently running projects with the Faculty of Medicine:

## digiDEM (sponsored by the Bavarian State Ministry of Health and Care)

The objective of digiDEM is derived from the Bavarian Dementia Strategy formulated in 2013. The aim of the Bavarian Dementia Strategy is to use innovative approaches and solutions, among other things, to bring about a change in awareness of how to deal with the disease and to create framework conditions that enable people with dementia (PwD) to live in the midst of our society and preserve their dignity in all phases. Based on the Bavarian Dementia Strategy of the Bavarian State Government and the recommendations of the Enquête Commission of the Bavarian Parliament, digi-DEM has the following goals:

- Establishment of a digital dementia register for the citizens of Bavaria with extensive data collection in all seven government districts of Bavaria
- Establishment of a digital dementia guide PwD and their nursing relatives
- Provision of digital services for PwD and cognitive disabilities
- Establishment of a digital support platform for voluntary engagement in the supervision of PwD
- Establishment of a digital participation platform for citizens in Bavaria

# d.hip (Digital Health Innovation Platform)

d.hip (compare own report) is a strategic partnership of FAU, UK Erlangen, Siemens Healthineers, and Medical Valley EMN e.V. to start outstanding research projects in future fields such as precision medicine, hospital management, or new services for home care. The overall subject matter is the joint vision "Digital Health Twin". In addition to projects, a d.hip lab was created, which offers over 500m<sup>2</sup> of space for project teams, workshops, and conference rooms. The d.hip program is rounded up by a scientific program that will lead to junior professorships in key technology areas and attract international doctoral students to Erlangen for projects.



Kick-off meeting of d.hip on April 2018 with high-ranking representatives of all d.hip-partners

### **Medical Valley Award**

Two teams with the members from the Faculty of Medicine were awarded in the last round. Each team received 500,000 euros for the next two years. Their topics were:

- Miniaturized, intra-urethral, energy-autonomous closure system for incontinence patients to improve their quality of life (6 million patients in Germany, about 350 million euro for incontinence material annually; Institute of Pathology)
- A sensor-based step (gait) analysis and algorithms for tumble risk detection purposes (Department of Neurology)



# Ludwig Demling Center for Molecular Imaging

#### Speaker

Prof. Dr. med. Markus F. Neurath

### Contact

Prof. Dr. med. Raja Atreya

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## Aims and structure

The aim of the project "Molecular endoscopic imaging at interfaces in inflammatory and neoplastic diseases", initially funded by the Emerging Fields Initiative (EFI), is to improve the detection of disease-specific changes in the tissue of patients with inflammatory or neoplastic disease entities.

Innovative imaging techniques will enable a more precise assessment of the mucosa. The techniques used include multispectral optoacoustic tomography (MSOT), functional magnetic resonance imaging (fMRI), the latest generation of endoscopic devices, and in particular endoscopic detection of the cellular molecular signature of the examined tissue. The improved detection of tissue alterations by means of identification and visualization of molecular target structures represents a pioneering field of medicine. By using interdisciplinary synergetic effects between different departments of UK Erlangen as well as theoretical and basic scientific institutes, innovative methods for molecular endoscopic imaging of inflammatory or neoplastic diseases have been established. In the process, findings from basic research regarding the immunopathogenesis of disease entities were incorporated and the resulting molecular signature of the cells was clinically used for the in vivo imaging of disease-specific changes. In memory of Prof. Dr. Ludwig Demling, former holder of the Chair of Internal Medicine and Director of the Department of Medicine, the corresponding clinical studies have been carried out mainly at the "Ludwig Demling Center for Molecular Imaging", named after him.

The aim of the Center is to clinically translate innovative translational research approaches into molecular imaging procedures and thereby create improved diagnostic and therapeutic algorithms for the lasting benefit of the patient.

## Research

An improved detection of lesions by means of identification and visualization of molecular target structures represents a future-oriented field within medicine. This structure-building approach has already been successfully implemented in a phase I study in Crohn's disease patients. A GMP-compliant, fluorescence-labelled anti-TNF antibody (in cooperation with the GMP-unit of the hospital pharmacy at UK Erlangen) was locally applied to the intestinal mucosa of the patients in order to enable detection and quantification of membrane TNF (mTNF)positive mucosal cells in vivo by means of endoscopic confocal laser endomicroscopy (CLE). The subsequent data evaluation showed a significant correlation between the clinical efficacy of subsequent anti-TNF therapy in Crohn's disease patients and the number of mTNF-positive intestinal cells detected by CLE. Subsequently, for the first time an approval was obtained to conduct a clinical study of molecular imaging with fluorescence-labelled anti-TNF antibodies in ulcerative colitis patients. Within the ongoing study, the expression of the molecular target structure mTNF in mucosal cells before and during anti-TNF therapy will be investigated endoscopically in vivo. To our knowledge, there is worldwide no ongoing comparable study on the prediction of response to therapy by molecular imaging. This approach could enable a novel, personalized therapeutic approach.

Patients with intestinal inflammation require optimized endoscopic care to determine the severity and extent of inflammation. In this context, the Ludwig Demling Center is conducting numerous studies with the latest generation of endoscopes. In addition to the endoscopic procedures mentioned above, sonography represents another important examination procedure for determining disease activity in patients with inflammatory bowel disease (IBD). For the first time, a new method was established for IBD patients. MSOT is the basis of this new and promising procedure for the non-invasive diagnosis of gastrointestinal diseases. The technique is based on the observation that the absorption of light leads to thermoelastic expansions of excited molecules, which can be registered as ultrasonic waves (photoacoustic effect). In addition, the use of excitation light with different wavelengths allows a targeted excitation and detection of certain molecules with characteristic absorption spectra (e.g. hemoglobin, melanin, etc.) and thus molecular imaging in biological tissue without additional staining methods. In current studies, experience with the use of MSOT for the assessment of gastrointestinal inflammation has been gained for the first time and a connection with endoscopic inflammatory activity has been demonstrated. In addition to these studies, pain perception before and after biological therapy is investigated by functional magnetic resonance imaging (fMRI) of the brain in cooperation with the Institute of Experimental and Clinical Pharmacology and Toxicology and the Divsion of Neuroradiology. The application of the blood-oxygen level-dependent (BOLD) fMRI study allows the visualization of pain perception in different brain areas after abdominal compression of the patients.

## Teaching

A further objective of the Ludwig Demling Center for Molecular Imaging is to disseminate the contents of this technology in courses. Furthermore, the endoscopic application of this procedure in the relevant endoscopic departments is passed on to medical staff by experienced endoscopists in practical HandsOn courses.

The L. Demling Center for Molecular Imaging has been organizing an international congress every two years since 2014 and awards a "Ludwig Demling Medal" for outstanding endoscopic achievements in memory of Prof. Dr. Ludwig Demling. In the meantime, this event has established itself as a high-quality continuing medical education event that is well recognized by national and international endoscopic experts.



Presentation of the Ludwig Demling Medal 2018 (from left to right): Prof. Dr. J. Siebler\*, Prof. Dr. M. Götz (University Hospital Tübingen), Prof. Dr. A. Dechene (Klinikum Nuremberg), Prof. Dr. C. Ell (Sana Klinikum Offenbach), Prof. J. Bergmann (university of Amsterdam; awardee 2018), Prof. Dr. M.F Neurath\*, Prof. Dr. R. Atreya\*. (Photo: UK Erlangen; \*Department of Medicine 1)

# **Medical Immunology Campus Erlangen**

#### **Speaker**

Prof. Dr. med. Christian Bogdan

## Scientific coordinator

Dr. rer. nat. Sonja Pötzsch

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# 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 of 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" and in the elite master program "Integrated Immunology", and coordinates the participation in competitive federal funding initiatives. Three times a year, the Campus publishes a newsletter, which reports on exciting publications, honors, and awards of the Campus' almost 100 members and also introduces new members.

## Research

The researchers of the Medical Immunology Campus Erlangen 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, diagnosis, and therapy of autoimmune, inflammatory, malignant, and infectious diseases are developed.

During the reporting period, the scientists of the Campus succeeded in setting up a new immunological SFB together with an integrated GK which in its first phase will be funded by the DFG from Juli 2018 until June 2022 (TRR 241 "Immune-epithelial communication in inflammatory bowel disease", compareown report). In addition, we hope for the approval of the GK 2504/1 "Novel antiviral approaches: From small molecules to immune intervention" (designated speaker: Prof. Dr. K. Überla), which was positively evaluated in December 2018, as well as for the success of two further GK initiatives, which are currently in the stage of preparing the full proposal (GK 2559/1 "Immunomicrotope: Microenvironmental, metabolic, and microbial signals regulating immune cell-pathogen interventions", designated speaker: Prof. Dr. C. Bogdan) or waiting for the decision on the preproposal (GK "Molekulare Stimulatoren und Kontrolleure der adaptiven Immunantwort", designated speaker: Prof. Dr. H.-M. Jäck).

# 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. In the winter term 2018/2019, a new elite master program on "Integrated Immunology" started, which is jointly run by the department of Biology and the Faculty of Medicine and financed by the Elite Network Bavaria. 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. Prof. Tak Wah Mak, Director of the Campbell Family Institute for Breast Cancer Research (Toronto, Canada) and Prof. Bruce Walker, Director of the Ragon Institute of MGH, MIT and Harvard, Boston, USA, delivered the Joachim Kalden Lecture on September 11, 2017 and December 10, 2018, respectively.

#### Lectures

In September 2017, scientists of the Campus organized the 47<sup>th</sup> Annual meeting of the German Society of Immunology (DGfl) in the Heinrich-Ladeshall in Erlangen with more than 1.000 participants from 27 countries. In 2017 und 2018, the Medical Immunology Campus Erlangen invited 54 national and international scientists to give a lecture with the guest seminar series of the Campus. The following compilation is a selection of the complete list which can be viewed on the homepage of the Campus. 10.1.2017 Prof. A. Alimonti, Institute of Oncology Research, Bellinzona: Switzerland

Reprogramming the tumor immune response for "prosenescence" therapy for cancer

30.5.2017 Prof. A. Zippelius, Department of Biomedicine, University Hospital Basel: Switzerland

Cancer Immunotherapy: Strategies for personalization and combination approaches

13.6.2017 PD Dr. S. Autenrieth, university hospital Tübingen

Modulation of dendritic cells by bacterial pathogens

17.10.2017 Prof. M. Sieweke, Centre d'Immunologie de Marseille Luminy: France

Stem cell like mechanisms of macrophage self renewal 7.11.2017 Prof. D. Finke, Universitäts-Kinderspital Basel:

Switzerland

License to operate - new insights into the regulation of ILC immune functions

14.11.2017 Prof. M. Dalod, Centre d'Immunologie de Marseille Luminy: France

Deciphering how immune responses against infections or cancer are shaped by the cell types and states of mononuclear phagocytes

5.12.2017 Prof. S. Jung, Weizmann Institute of Science, Rehovot: Israel

Macrophage strategies in gut and brain

23.1.2018 Prof. B. Ludewig, Institut für Immunbiologie, Kantonspital St. Gallen: Switzerland

Stromal cell – Innate lymphoid cell interaction

21.2.2018 K. van Gisbergen, PhD, Department of Hematopoiesis, Amsterdam: The Netherlands

Hobit as a tool to study the differentiation of tissue-resident memory T cells

21.3.2018 T. Weinkopff, PhD, Department of Microbiology & Immunology, University of Arkansas for Medical Sciences: USA

The Role of Vascular Remodeling during Leishmania Infection

17.4.2018 Dr. A. Triantafyllopoulou, Department of Rheumatology and Clinical Immunology, Charité Berlin DNA damage signals instruct macrophage differentiation in granulomatous diseases

24.4.2018, Prof. N. Gagliani, General, Visceral and Thoracic Surgery Department, UKE Hamburg-Eppendorf

T cell functional heterogeneity and tissue-resident memory cells: Understanding immune homeostasis and its underlying mechanisms

15.5.2018 Prof. W. Kastenmüller, Institute of Experimental Immunology (IEI), University of Würzburg Concepts of T cell activation from a spatiotemporal per-

spective

12.6.2018 Prof. S. Vermeire, Department of Gastroenterology, university hospital Leuven: Belgium Novel therapeutic opportunities in IBD and where to place them

them 3.7.2018 Prof. A. van Spriel, Department of Tumor Immunology, University of Nijmegen: The Netherlands

Tetraspanins: molecular organizers of the immune cell surface



# Medical Technology Test and Application Center (METEAN) of the Fraunhofer Institute for Integrated Circuits IIS

## Speakers and contact

Matthias Struck, Fraunhofer IIS Prof. Dr. med. Jochen Klucken, Division of Molecular Neurology

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# Aims and structure

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.

# Research

## Validation of wearables

### PI: Dr. N. Lang

Within a contract research project with an international sports association, we are currently validating five commercial wearables regarding usability and data quality. As reference system we are using wireless BIOPAC systems. The aim is an adequate use of wearables for training optimization in professional sports.

## Affective sensing

## PI: Dr. N. Lang

METEAN is currently in the planning phase for a study measuring and analyzing human stress, based on a multimodal system. Main goals are the development of a standardized stress data base as well as the detection of individual human stress parameters. Target markets are medical, automotive, human machine interfaces and robotics.

# Sensor based gait analysis for Parkinson patients

# PI: Prof. Dr. J. Klucken

The overall goal is to combine the medical knowledge and technical innovations in the field of gait analysis for Parkinson patients in order to improve diagnosis and therapy. In a current study the gait of Parkinson patients is acquired in METEAN and the data are analyzed.

## **EIT Health project MoveIT**

PI: Prof. Dr. J. Klucken

Parkinson's disease (PD) is a chronic movement disorder characterized by progressive gait impairment, leading to reduced mobility, poor quality of life, and frequent falls. MovelT improves healthcare for patients via wearable gait and fall sensors enabled as healthcare products by an innovative digital health pathway (DHP). The DHP defines the clinical application of these new technologies for multidisciplinary healthcare using stratified patient cohorts and care networks targeting gait and falls in PD.

# IT-infrastructures and medical data communication

# PI: C. Weigand

A close cooperation with the mobile health laboratory of Fraunhofer IIS is planned. The mobile health lab develops infrastructures for medical applications in order to improve communication between physicians, therapists, and patients.



The image illustrates the MovelT server structure that serves patients, physicians, and researchers as means of communication via a standard web browser

# ETechPatho (Enabling Technologies for Digital Pathology)

#### PI: Dr. M. Benz

In cooperation with the Institute of Pathology, Fraunhofer IIS develops supporting analysis methods for the diagnosis of adeno carcinoma in tissue sections of the colon. These are methods to differentiate different types of tissue or quantify tumor buds automatically. The requirements for those methods are conceived in close cooperation between Fraunhofer IIS and the Institute of Pathology. In addition to that, tissue sections are prepared, digitized, and annotated. New approaches with respect to adaption and explainability of these quantification methods based on deep neural networks are also under current investigation.

# iSTIX / Diglmmun

PI: V. Bruns

Within this project a low cost scanning solution for microscopy ("iSTIX") to digitize histopathologic samples is developed, which can also be used in small and medium-sized pathology departments. This platform is also used in the joint project "DigImmun" for the quantification of the tumor micro environment in the context of immune therapies of gastroesophageal tumors together with the Institute of Pathology as well as Definiens AG. Thus, the goal is to integrated Al-based quantification algorithms in the iSTIX platform. On the other hand workflows for the annotation, visualization, and connectivity e.g. for research and teaching or telepathology with cloud-based platforms shall be realized. Thus, it is planned to evaluate the platform in the environment of the Institute of Pathology and the Division of Nephropathology and to develop and integrate new relevant assisting functionality to support clinical workflows.

# 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 a junior research group of the IZKF of the Faculty of Medicine. Additionally, laboratory 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 group 2 of the IZKF Dr. P. Ceppi
- Clinical research groups
- Prof. Dr. A. Bozec (Department of Medicine 3 Rheumatology and Immunology)
- Prof. Dr. B. Winner (Division of Stem Cell Biology)
- Prof. Dr. J. Winkler
- (Division of Molecular Neurology)
- Prof. Dr. Dr. h.c. R. Horch
- (Department of Plastic and Hand Surgery)
- Prof. Dr. G. Krönke (Department of Medicine
- 3 Rheumatology and Immunology)

- Prof. Dr. K. Gelse (Department of Trauma Surgery Orthopedic Surgery)
- Prof. Dr. L. Gölz (Department of Orthodontics and Orofacial Orthopedics)
- PD Dr. I. Cicha (Department of Otorhinolaryngology – Head and Neck Surgery)

# **Research and teaching**

The main research topics at the NFZ comprise different aspects of molecular pathology, including tumor biology, immunology, neurobiology, and genetics.

The 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.


### **Optical Imaging Centre Erlangen (OICE)**

#### Speaker

Prof. Dr. Vahid Sandoghdar

#### **Contact Faculty of Medicine**

Prof. Dr. med. Markus F. Neurath

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#### Aims and structure

OICE is a central institute of the FAU. It delivers a platform for light-based microscopy, is involved in the development of new optical methods, and delivers education for researchers of every background and experience level.

OICE's Board of Members currently consists of more than 30 PIs from the Faculties of Medicine, of Sciences, and of Engineering, respectively, the UK Erlangen, the Max-Planck Institute for the Science of Light and the Fraunhofer Institute IIS. From within the Board of Members, a Steering Committee is elected for a bi-annual period. The Steering Committee, consisting of about ten members, itself elects its speaker for a two year period. The Committee conducts the scientific direction and development according to the request of the Board of Members. Further, the Steering Committee supports and supervises the head of OICE.

Dr. R. Palmisano is the assigned permanent head of OICE. He is responsible and in charge of the daily operation, supervising the administration and scientific staff, and the day-to-day performance.

Latest state-of-the-art microscopes from a variety of commercial suppliers are based at OICE for the use by researchers. The resolution of this microscopes ranges from 20 nm up to millimeters. This allows imaging of smallest intra-cellular structures within cells into organoids and tissue and ranges up to whole organ imaging of small mammalian animals and *in vivo* imaging in small mammalian animals.

OICE aims to identify new technologies and methods within the frame of light-based microscopy. Identified potential technologies are advertised by performing seminars or workshops or by invited speakers within the range of the FAU. Subsequently, a user based evaluation is performed and if the outcome is positive, OICE will coordinate the acquisition of such hardware and make it available to the researchers. Further OICE will then provide training, education, and access for the researchers from FAU, UK Erlangen, and additional institutes. This service is delivered by the Core Facility Unit (CFU) of OICE. In the meanwhile OICE supports more than 150 researchers from within the above mentioned entities per year.

#### Research

Within its Exploratory Research Unit (ERU), OICE is involved in research to optimize optical technologies, in the development of new methods, and in particular in the development of post image processing of imaging derived data sets, both qualitative and quantitatively. In this respect OICE cooperates with the Departments of Physics and Mathematics, the Max-Planck Institute for the Science of Light, UK Erlangen, the Fraunhofer Institute for Integrated Circuits (Department Smart Sensing and Electronics) as well as a number of international co-operations, such as for example Institute Pasteur, Paris; Kennedy Institute of Rheumatology, Oxford; Howard Hughes Medical Institute Janelia, Washington DC.



Dr. P. Tripal, member of staff at OICE, while imaging a sample with the super-resolution 2D/3D STED micro-scope, delivering a lateral resolution down to 20 nm

#### Teaching

OICE has no formal education and teaching obligations, but delivers more than 40 lectures, seminars, and practical workshops per year within its Educational Training Unit (ETU). They are open to all researchers from the FAU, UK Erlangen, and adjacent institutes. Topics of seminars reach out from methods or technologies to use of software, such as ImageJ/Fiji, OMERO, Matlab e.g. Practical courses cover hands-on workshop starting from basic fluorescence imaging or advanced laser microscopy imaging turning into specialized technologies or methods, for example super resolution microscopy (3D-STED / RESOLFT / STORM e.g.), intra-vital microscopy (Single / Multiphoton excitation), spinning disc laser scanning microscopy, Light-Sheet microscopy and more.



Light-Sheet microscopy hands-on workshop, conducted by OICE with attendees from UK Erlangen, the Faculty of Medicine, and the Faculty of Sciences



### **Translational Research Center (TRC)**

#### **Speakers**

Prof. Dr. rer. nat. Michael Stürzl Prof. Dr. med. Kerstin U. Amann

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#### Aims and structure

In 2014 the Translational Research Center (TRC) was inaugurated at the Faculty of Medicine with an exemplary concept and infrastructure. 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. 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 2019, all existing C modules will be filled with research units from the Departments of Medicine 3 and 4, the Department of Surgery, the Institute of Radiology and the Institute of Nuclear Medicine. 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 2018, the staff of the TRC consisted of 179 employees from 14 different nations.

#### Research

The TRC assembles research groups of the Departments of Internal Medicine, Nuclear Medicine, Surgery, the Division of Transfusion Medicine and Hemostaseology, and of the Institutes of Pathology and Radiology 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, the identification of novel therapeutic targets in inflammatory bowel disease, the development of new strategies for immunization, certain aspects of tumor and transplantation immunology, the mechanisms of immunomodulation of angiogenesis and immune evasion of tumor cells, as well as 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 research strategies.

The high research quality of the TRC is documented by (among others) six research articles published in 2017/18 under the first and last authorship of TRC members in internationally high-ranking journals, such as Leukemia, Nature Medicine, Nature Immunology, Gastroenterology, PNAS, and Gut.



### SFB 1181: Checkpoints for Resolution of Inflammation

#### Speaker

Prof. Dr. med. Georg Schett

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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. It aims to investigate the molecular mechanisms involved in the resolution of inflammation. The DFG supports the SFB with more than 13 million euro within four years. It 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 in 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:

- A) The switch from pro- to anti-inflammatory cytokine response
- B) The blockade of pro-inflammatory lymphocyte activation
- C) Fostering of tissue remodeling by cell death and tissue repair mechanisms

#### Research

In the first funding period of the SFB 1181, we were able to define several new molecular and cellular pathways that counter-balance inflammation and orchestrate resolution in diseasespecific manner. Based on the findings we were able to re-conceptualize the molecular and cellular map of resolution of inflammation in general. Furthermore, we could define new pathways of resolution with disease- or organ-specific activities. Examples include the role of IL-9 as resolution factor in the joints and IL-27 in the lungs as well as type 3 interferons (IL-28) as factor that fosters chronicity of inflammation in the gut. Break-through discoveries have been made in all three sections of the SFB.

In section A ("Innate Immune Mechanisms"), a break-through discovery was the identification of IL-9 as a master control cytokine of resolution of arthritis. Furthermore, in arthritis we also discovered pro-resolving functions of the TH2 cytokines IL-4/IL-13 and IL-5 which otherwise are involved in the pathogenesis of asthma. Our observations clearly indicate that the TH2-eosinophil axis exerts immunoregulatory effects in arthritis, thereby providing molecular evidence for Paul Ehrlich's concept of the eosinophil driven aurora of inflammation. In accordance with this concept, helminthic infection has been shown to inhibit autoimmunity, and type-2 innate lymphoid cells were identified as exerting pro-resolving and disease-controlling properties in murine and human arthritis. In section B ("Lymphocyte Activation and Function", two T cell-related factors have been identified that control resistance to resolution of inflammation in colitis: IL-23 receptor expression on intestinal T cells allowed to bypass resolution of inflammation elicited by TNF antagonists, whereas IL-7 receptor expression on intestinal T cells prevented resolution of colitis in graft-versus-host disease by activating the transcription factor BATF. Furthermore, it was recognized that cytokine-mediated regulation of antibody glycosylation and selective Fc-receptor binding are mechanisms that permit chronic inflammation rather than resolution. Finally, the cytokine-based mechanisms that regulate the pro-inflammatory or pro-resolving properties of antibodies have been meticulously analyzed during the first funding period, which led to the discovery that IL-23 is a key signal fostering antibody pathogenicity and chronicity of inflammation.

In section C ("Cell death and Tissue Response") new insights into neutrophil death and neutrophil extracellular trap (NET) formation in degrading cytokines and thereby mitigating inflammatory responses were obtained. While NETs are effective in limiting inflammatory responses, aggregated NET formation can also lead to detrimental congestion of endoluminal structures. Several new insights of the first funding period pertain to factors of the intestinal epithelial homeostasis, such as cytokines IL-28, IL-33, and IL-36 as well as intracellular enzyme caspase-8, controlling resolution of inflammation. Factors that are decisive for the perpetuation versus resolution of inflammation and have a strong impact on epithelial homeostasis are the cytokines IL-28, IL-33, and IL-36 as well as intracellular enzyme caspase-8. Furthermore, very recent findings obtained within the consortium have defined a homeostatic macrophage membrane-like surface structure in the joints, which share some of the molecular features of epithelial cells, i.e. the expression of tight junctions. Such structures control inflammatory responses in the joints by providing an immune-barrier function. With respect to resident tissue responses in conjunction with inflammation, the transcription factor PU.1 was found to act as master control switch of resident tissue activation. In addition, upstream of PU.1, SHP2, and STAT3 function as important checkpoints for tissue fibrosis. Data of the consortium furthermore showed that IL-36 signaling is linked to tissue fibrogenesis in the gut. Finally, arginase 1 (considered to be a marker of pro-resolving M2 macrophages) turned out to be dispensable or even detrimental for tissue repair in colitis. In addition to these key mechanistic findings in resolution of inflammation, several important technical innovations in the preclinical and clinical non-invasive imaging of the dynamics of inflammation arose from the SFB 1181. Furthermore, technical advances have been achieved in the three-dimensional molecular imaging of organs after "clearing" and making them accessible to lightsheet fluorescent microscopy.

The 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 200 publications since the foundation of 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 GK 1181 (compare own report) is affiliated to the SFB 1181.



Map of resolution with key mechanisms (bright grey squares), cells (blue squares), and molecules (dark grey squares) AAM, alternatively-activated macrophage; ILC, innate lymphoid cells; IL, interleukin; LPX, lipoxin; MF, macrophages; PMN, polymorphonuclear neutrophils; TGF, transforming growth factor; FASL, TRAIL, tumor necrosis factor related apoptosis inducing ligand; FASL, Fas ligand; ROS, reactive oxygen species



### Priority Program 1468: Osteoimmunology – IMMUNOBONE – A Program to Unravel the Mutual Interactions between the Immune System and Bone

#### Speaker

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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) was a priority program that was 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 was positively evaluated for a second funding period for additional three years with a total volume of 7.1 million euro. The interdisciplinary consortium consisted of 20 groups of 15 different research institutions of osteologic orthopedics, rheumatology, and immunology.

#### Research

At the time of the initial application, osteoimmunology was a newly discovered field of research between immunology and bone biology. This field was stimulated in particular by the discovery of RANKL (receptor activator of NF-κB ligand). With the establishment of the SPP 1468, this field has expanded significantly, revealing new mechanisms in the mutual regulation of bone and immune system. The main interest was the regulation of bone mass and architecture by immune system and inflammation as well as the characterization of bone and bone marrow as an organ necessary for differentiation and survival of immune cells. The extensive results obtained in SPP 1468 show that the immune and skeletal systems interact closely at several levels.

An important aspect of osteoimmunology is the regulation of the skeletal system by cytokines. Among other things, new findings on previously unknown biological functions of RANKL in the context of breast cancer, osteopetrosis, and diabetes mellitus could be defined. Furthermore, new insights were gained into how cytokines, which play a central role in psoriasis, affect bone. These results provide new explanations for immunological bone changes in psoriasis that have direct clinical relevance as IL-17 inhibition is already being used to treat psoriasis. A new role of the IL-23/IL-17 cytokine axis in the transition from autoimmunity to inflammation was also defined. In this context, completely new mechanisms of control of the skeletal system by autoimmunity emerged. Already within the first funding period, a link between autoantibody production and bone resorption was discovered within the framework of a "bedside-tobench approach". It was shown that human autoantibodies against citrullinated proteins found in most patients with arthritis are strong inducers of bone resorbing osteoclasts and cause bone loss. These findings provided new insights into bone resorption in rheumatoid arthritis. In the second funding period, the understanding of the role of these antibodies within the skeletal system was further developed and deepened by the discovery of Fc receptor-mediated regulation of osteoclasts and antibody glycosylation. Within the framework of the SPP 1468, new mechanisms of the regulation of bone formation could be identified in addition to immune regulators of osteoclasts. Thus, it could be shown that the nuclear receptor PPAR $\beta/\delta$  from the group of peroxisome proliferator-activated receptors (PPARs) contributes to osteogenesis by regulating the RANKL expression of osteoblasts and thus represents an innovative approach for the development of new bone-building osteoporosis drugs. Furthermore, excessive bone formation in connection with arthritis was an area of research in SPP 1468. Within this program, the role of Wnt proteins and their antagonists in pathological bone formation in arthritis was investigated during both funding periods. Within the consortium, new groundbreaking discoveries on the regulation of bone and inflammation by glucocorticoids were made, which form the basis for the development of cortisone drugs with low side effects, in particular preparations that take into account the single molecule function of glucocorticoid receptors. These findings play a central role, especially for inflammatory diseases such as arthritis, where inflammation and bone loss occur side by side.

In the field of clinical research, the consortium was able to develop methods that made it possible to visualize immune bone interaction in patients with inflammatory diseases using highresolution imaging techniques (high-resolution quantitative computed tomography). The data from these studies enabled a better understanding of the effects of inflammation and autoimmunity on bone homeostasis. On the one hand, they showed the effects of the therapeutic application of cytokine inhibitors on bone architecture and early changes in bone architecture in patients with autoimmunity who have not yet developed inflammatory disease.

Ultimately, SPP 1468 was able to present numerous new molecular mechanisms for how changes in the bone marrow affect immunohomeostasis and how these affect human diseases. SPP 1468 has also made a major contribution to the more accurate description of macrophage and osteoclast differentiation by cytokines.

#### Teaching

The heads of the research groups were 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.



# TRR 221: Modulation of graft-versus-host- and graft-versus-leukemia-immune responses after allogeneic stem cell transplantation

#### Speaker

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#### Aims and structure

In the SFB TRR 221 scientists of the universities and university hospitals in Regensburg, Erlangen, and Würzburg search for innovative immunotherapeutic methods to significantly improve allogeneic hematopoietic stem-cell transplantation (allo-HSCT). The SFB/Transregio 221 has been funded by the DFG for four years (2018 – 2021) with a funding volume of 14 million euros.

Within TRR 221, innovative immune modulation strategies will be investigated to separate graft-versus-host disease (GvHD) from graft-versus-leukemia/lymphoma (GvL) effects in order to enhance the safety and efficacy of allo-HSCT in the future. Briefly, the projects in area A (six subprojects) explore T cell redirection tools for the augmentation of hematopoiesis-specific GvL activity, and examine the reactivation of silenced GvL responses by checkpoint inhibition and through enhanced metabolic "fitness" of donor immune cells. The projects in area B (13 subprojects) investigate cell signaling pathways and immune regulatory/suppressive cells and networks including regulatory T cells, mesenchymal stromal cells and dendritic cells to prevent and/or treat acute and chronic GvHD. They also study the modulation of GvHD-promoting co-factors such as tissue inflammation, microbiome alterations, epithelial and endothelial damage for effective prophylaxis and therapy of severe GvHD. Promising strategies in GvL projects will be evaluated with respect to their influence on GvHD (and vice versa) and all participating institutions support translational studies evolving from the projects if considered sufficiently robust for clinical testing.

TRR 221 also has an integrated GK.

#### Research

Allo-HSCT is the standard of care for physically fit patients with high-risk hematologic malignancies and severe stem cell disorders. Around half a million transplantations have been performed to date and approximately 28 million voluntary stem cell donors are currently registered world-wide. The curative potential of allo-HSCT is based on the replacement of the patient s hematopoiesis by hematopoietic stem cells derived from a healthy donor and the immunologic eradication of residual patient hematopoietic cells by co-transplanted lymphocytes. This graft-versus-hematopoiesis reaction is mainly mediated by alloreactive donor T cells and affects also malignant hematopoietic cells, thereby evoking potent GvL effects. Although allo-HSCT offers a unique chance to rescue patients with otherwise incurable hematologic malignancies, still around one guarter of allo-HSCT recipients develop disease relapse or progress after transplantation. Thus, there is an urgent need to better understand and ultimately strengthen GvL responses to prevent tumor escape. However, GvL-promoting strategies carry the inherent risk of inducing GvHD, where donor T cells attack and damage nonhematopoietic tissues. The efficient prevention and treatment of severe GvHD is a pivotal prerequisite to benefit from allo-HSCT and its potent GvL effects. Hence, the elucidation of basic mechanisms in tissue-directed graft-versus-host responses is essential to reduce the high treatment-related morbidity and mortality in allo-HSCT. GvHD-free allo-HSCT is then an ideal immunotherapy platform to boost GvL responses for the cure of patients, including those with residual disease or relapse after transplantation. Within TRR 221, innovative immune modulation strategies will be investigated to separate GvHD from GvL effects in order to enhance the safety and efficacy of allo-HSCT in the future. Strengthening GvL responses without induction of severe GvHD is essential to decrease the relapse rate after allo-HSCT, especially if disease burden at transplant is high and/or the patient is unable to tolerate full intensity conditioning therapy. Improved GvL immune reactivity can be achieved by targeting of hematopoiesis-re-

stricted MiHAs, over-expressed leukemia antigens and "permissive" HLA mismatch antigens under certain conditions. Hence, several projects focus on the exploration of newly identified HLA class II MiHA presentation pathways as well as the re-targeting of GvL effector T cells using novel T cell modification techniques. On the contrary, avoidance of GvHD is key for successful allo-HSCT. Several projects therefore tackle the GvHD problem from different angles with the aim to develop innovative complementary or synergistic strategies.

All projects will be supported by service projects providing a centralized pathology unit in Regensburg for standardized consensus diagnosis and grading of experimental and human GvHD as well as expertise in the generation and crossbreeding of genetically modified mice.

#### Teaching

The integrated GK provides structured training of MD and PhD students of TRR 221 within an interdisciplinary curriculum that combines basic sciences of various fields, such as medicine, hematology/oncology, (transplantation-) immunology, microbiology, virology, pathology, transfusion medicine, molecular and cellular biology, tissue engineering, (epi-)genetics, metabolomics/proteomics, and more translational aspects, such as diagnostic and therapeutic principles in allo-HSCT and cellular therapy, GMP and GCP topics and disease-oriented clinical research.

All students participate in pre-existing graduate programs of the local TRR 221 sites and the GK will avoid redundancy, but focus on allo-HSCTspecific training modules that broaden and deepen the students qualification.

G>H G>L sfb transregio 221

## TRR 241: Immune-Epithelial Communication in Inflammatory Bowel Diseases

#### Speaker

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#### Aims and structure

The SFB/Transregio 241 (TRR 241) started in July 2018 between UK Erlangen and Charité Berlin. In cooperation with Deutsches Rheuma-Forschungszentrum Berlin, Medizinischen Universität Innsbruck, and the Universitätsklinikum Kiel, physicians, immunologists, and biotechnologists focus on the research of the interplay between epithelial cells and intestinal immune cells. A better understanding of the underlying mechanisms in intestinal bowel disease (IBD) is of fundamental importance to evaluate new and efficient therapy strategies. A long-term goal of the TRR241 is to develop drugs that cure the causes of IBD without suppressing important functions of the immune system and its cells. Further on, diagnostic strategies are going to be developed that predict the efficiency of treatment strategies - this is an important goal with regard to an efficient alleviation of symptoms and the reduction of therapy costs.

#### Research

In total, the scientific program of the TRR 241 includes 22 projects (TP), 14 of them under supervision of Erlanger scientists, working at the Departments of Medicine 1 and Medicine 3, of Surgery, of Dermatology, and the Institute of Medical Biotechnology.

- Interferons (IFNs) promote non-apoptotic epithelial cell death, upregulation of mixed lineage kinase domain-like protein and loss of immune homeostasis. The central question of this TP A02 is if and by which pathways epithelial IFN-regulated necrosis contributes to intestinal inflammation.
- Central mediators of prototypical type 2 responses such as IL-33 are upregulated in the mucosa of patients with IBD, but how type 2 responses may drive pathological features of IBD or vitally contribute to the protective tissue response to damage still remains ill-de-

fined. The aim of this TP is to analyze how IL-33 production and signaling controls mutual interactions between the immune, stromal, and epithelial cell compartments.

- IFN-γ is an important pathogenesis factor in IBD with potent vascular-directed activities. The principal aim of this TP is to elucidate the molecular mechanisms by which the activation of vascular endothelial cells by IFN-γ impairs vascular barrier functions and disturbs the immune – epithelial cell crosstalk in the course of IBD pathogenesis.
- This TP aims on an improved understanding of the regulation of prenylation within intestinal epithelial cells (IECs) and its function in epithelial integrity in the context of IBD. It intends to translate the respective findings in innovative biomarker and therapy strategies in IBD.
- Induced intra-epithelial lymphocytes (iIELs) are widely distributed within the IEC layer. Preliminary data of the group demonstrated that selected deficiencies within the conventional DC (cDC1) compartment result in distinct iIEL pool alterations. Hence, employing cDC1-targeted mice as iIEL deficiency model systems, this TP focuses on studying the molecular mechanisms and functional consequences of the iIEL-IEC crosstalk during intestinal homeostasis and inflammation.
- Neutrophil extracellular traps (NETs) instigate plasmatic coagulation and form emergency barriers on mucosal wounds with antimicrobial, yet also strong cytotoxic properties. Preliminary data of this TP identified that NETs take part in guiding mucosal healing responses. Restituting epithelia protect themselves from NET-borne cytotoxic mediators. Therefore, the project focuses on these protective mechanisms used by specialized epithelial cells and envision future therapies directed at NET-epithelial dysfunctions to support mucosal healing in patients suffering from IBD.
- Neuropeptide release is controlled by transient receptor potential (TRP) channels. Preliminary data of this TP suggests a previously unknown role of extra-neuronal TRP channel expression in intestinal immune and epithelial cells as well, indicating a complex neuro-immune-epithelial signaling network in the gut. The central topic is to understand how enteric neurons via secretion of neuropeptides orchestrate intestinal homeostasis and how TRP activation regulates intestinal mucosal immunity and epithelial cell function in addition.
- Advanced label-free optical technologies, such as multiphoton microscopy and Raman spectroscopy, hold great potential for diagnostic

and characterization of mucosal inflammation *in vivo*. This TP will further develop advanced optical technologies for the *in vivo* evaluation of mucosal inflammation in human IBD.

- In this TP clinically approved antibodies will be tested that target cytokine signaling or integrin-based homing of immune cells in the gut for their potential to allow endoscopic molecular *in vivo* imaging in ulcerative colitis patients. Such *in vivo* mapping of relevant inflammatory signaling pathways may allow the selection of the ideally suited neutralizing antibody for subsequent therapy and will thus open new avenues for personalized medicine in ulcerative colitis.
- In this TP, a clinical phase-III-study was designed to test tDCS (transcranial direct current stimulation) on its analgesic effects in IBD-patients with chronic abdominal pain. fMRI scans will be performed in these patients in order to investigate changes in the central nervous system. With the help of this preclinical model, the effects of tDCS on the enteric nervous system, intestinal barrier, neurotransmitters, as well as perineural immune cells will be investigated.
- Adoptive transfer of regulatory T cells (Treg) has successfully been used in preclinical models of colitis *in vivo*, but their usage for treatment of patients with ulcerative colitis remains poorly studied. Gut homing and effects on the gut epithelium of these Treg are detrimental to suppress gut-specific inflammation. In this TP, the molecular mechanisms of mucosal trafficking and retention of Treg in ulcerative colitis will be further defined.
- Within the IBDome-TP, a web-based database will be developed that integrates Omics data obtained from IBD patients with clinical data.
- There is an additional central project Z that includes administrative and cooperative tasks as well as data management for analysis of collected data.

#### Teaching

During the first funding period of the TRR 241, integrated PhD and MD students are funded within the attached GK. All PhD and MD students are integrated in this GK of the TRR 241 (iRTG) and Life@FAU, respectively (compare own reports).



### **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 first funded for the nine month conceptual phase of the Medical Informatics Funding Scheme of the BMBF (August 2016 to April 2017). Based on its successful pilot projects and its compelling and visionary concept, it received continued funding with an amount of 37.3 million euro for the four-year implementation and networking phase (2018-2021). 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. In 2017 the BMBF announced an additional funding program for university hospitals which did primarily not receive funding for the implementation and networking phase to apply for admission in one of the four funded consortia. This led to the extension of consortium with two new university hospitals. MIRACUM: This are now ten universities with university hospitals (Dresden, Erlangen, Frankfurt, Freiburg, Gießen, Greifswald, Magdeburg, Mainz, Mannheim, and Marburg), two universities of Applied Sciences (Hochschule Mannheim and Technische Hochschule Mittelhessen), 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 establishes the Erlangen Data Integration Center and provides 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". Based on first successful MIRACUM analysis results, this concept was applied to initiate an early cross-consortial demonstrator study with research questions focusing on rare diseases and on comorbidities to illustrate early interoperability between the MI-I consortia.

In the four years to come, MIRACUM will focus on the following three use cases:

- Alerting in care IT support for patient recruitment
- From data to knowledge A predictive clinico-molecular knowledge tool

3. From knowledge to action – Support for molecular tumor boards

Based on the proven MIRACUM data integration center concept, all MIRACUM partners already joined early 2018 to apply for additional funding to establish a Nationwide Registry for Recurrent Urolithiasis of the Upper Urinary Tract (RECUR). This application receives funding starting in May 2019 and will for the first time also include a non-university hospital (Waldkrankenhaus Erlangen) in the network and also further increase the data sets included in the registry with patient generated data via a mobile app for patient recorded outcomes.

#### 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 current funding phase MIRACUM aims at establishing the cross-university part-time master degree 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 to define the 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 consortiums 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 osteoarthrosis (OA). Thereby, regulation of inflammation mediated by the adipose tissue might be a key factor affecting the joint-boneunit. 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 ioint inflammation and bone architecture. Diabetes is associated to severe osteoarthrosis 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 METHARTHROS 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 concerning 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-y 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 adiponectin 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. RA - 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 addition, it has been demonstrated that obesity has an overall negative effect on the efficacy of cytokine therapies TNFi and TOC, whereas this cannot be demonstrated for the cell-directed therapies RTX and ABA. The strength of the influence depends on the endpoint considered as well as on gender. The findings mentioned here represent only a small part of the more than 50 results already published by 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.



### BMBF network for health service research PRO PRI-CARE (Preventing Overdiagnosis in Primary Care)

#### Speaker

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#### Aims and structure

In the tender issued by the BMBF concerning the structural development of health service research the target was set to further strengthen cooperation networks. PRO PRICARE, funded by BMBF with 2.1 million euros for three years (2017 – 2020), engages in the development and practical implementation of measures to prevent over- and undersupply in health care. It consists of:

- Seven academic institutions of the FAU
- Four medical practice networks in Franconia with around 200 general practitioner (GP) and specialist practices
- The Bavarian Association of Statutory Health Insurance Physicians (KVB)
- Company health insurance carriers, represented by the GWQ ServicePlus AG

Medical overuse is defined as "care in the absence of a clear medical basis or when the benefits of therapy do not outweigh the risks". Distinctions between ageing, risk factors, early stages of illness, and the actual disease itself became more and more blurred. Advances in medical technology, spirit of medical entrepreneurship, and the cultural phenomenon of increasing occupation with health matters harbor the risk for an "inflation of disease". Patients that are affected by an impending risk of overtreatment as well as medical interventions with low or non-existing benefit need to be identified and the latter reduced. One of the main responsibilities of a family doctor is the prevention of mis- and overtreatment and medication, since they – as generalists and first and last contacts - are normally the entry point into the health system for most patients and provide long-term supervision of the patient's health.

#### Research

Within the scope of PRO PRICARE, three research projects conducted in the current funding phase:

### ICF (International Classification of Functioning, Disability and Health)

Development of a core set of the International Classification of Functioning, Disability and Health (ICF) for geriatric patients in primary care The medical focus traditionally lies on the illness rather than on the disease of the patients. Particularly among elderly people, this inevitably leads to overtreatment. A prioritization of medical measures is therefore unavoidable. The effect size of a given treatment on preservation or recovery of functionality of individual measures could be a criterion for distinguishing between beneficial and less beneficial ones. For this purpose, functionality needs to be describable. Generally, the ICF could be an adequate tool for that. However, the ICF is far too complex to be used in the fast-paced environments of GP practices. Therefore, the development of so-called ICF core sets is required. Our hypothesis is that with a concentration on functional health, a reduction of overtreatment, particularly among elderly people, is possible. Such core sets for geriatric patients in GP practices are developed in four subprojects following international standards.

Cooperation partners: Institute for Biomedicine of Aging, Interdisciplinary Center for Public Health (IZPH)

#### ICE (Ideas, Concerns, Expectations)

The focus of this study is the doctor-patient communication. Communication skills are an important tool that can prevent unnecessary medicine. Patients are coming into practices with subjective ideas about their illness and with their own concerns and expectations. These should be elicited and discussed in the GP consultation. It is examined whether patient-centered communication according to the ICE technique helps to reduce the application of unnecessary diagnostic procedures among patients with acute back pain. Furthermore, simple supporting tools for an improved communication in the daily practice are developed.

Cooperation partners: Department of Clinical Psychology and Psychotherapy (Faculty of Humanities, Social Sciences, and Theology), Chair of Health Management (Faculty of Business, Economics, and Law)

#### ACE (Adverse Cascade Effects)

Adverse Cascade Effects: Causes and routes of clinical pathways for patients with thyroid nodules

Cascades are "processes that proceed in a stepwise manner from an initiating event to a seemingly inevitable conclusion". One example is the treatment of people with thyroid nodules. Thyroid nodules can contain thyroid cancer. On the other hand, it is rather scarcely that people die from thyroid cancer. The frequency of thyroid carcinoma has increased sharply over the last decades without the same increase in mortality rates. Presumably, the cause for this lies in overdiagnosis. The detection of thyroid nodules in ultrasound images is commonly a trigger of cascade effects that can lead to unnecessary invasive treatment.

So far, there are no systematic analyses available to determine the frequency of occurrence, the driving forces, and the effects of this cascade. This project aims to fill this gap by analyzing the clinical pathways of patients with thyroid nodules.

Cooperation partners: Chair of Health Management, IZPH, Institute of Medical Informatics, Biometry and Epidemiology

Health insurance data are provided by the KVB and the GWQ.

#### Teaching

The Young Researcher Program is a fundamental part of the PRO PRICARE research network and pursues the following aims:

- Methodical and content-related training in the field of health service research
- Promotion of networking and interdisciplinary exchange

The program addresses doctoral candidates of the network and aims to strengthen the interdisciplinary exchange and networking. The trainees come from different institutes and centers of UK Erlangen and FAU. They are trained methodically and content-related to work in the field of health service research. Seven doctoral candidates are currently part of the program. A mentor is assigned to each participating doctoral candidate. Together they can discuss job strategies, career plans, as well as formal and informal aspects of the PhD thesis. The trainee receives additional feedback and suggestions at the annual meeting with the external scientific advisory board which consists of international experts in the field of health service research and oversupply. An annual retreat enables the trainee to present own research in a larger college.

Furthermore, an extensive seminar program is provided with subject-specific and interdisciplinary content in the field of health service research. The trainees receive input from an experienced lecturer in order to deepen the methodical and content-related knowledge in the fields of health economics, public health, geriatric medicine, psychology, and general medicine with regard to health service research, oversupply, and demographic change.

### Bavarian Research Network: Induced Pluripotent Stem Cells (ForIPS)

#### Speaker

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#### Aims and structure

The Bavarian Research Network ForIPS was funded by the Bavarian State Ministry of Education, Science, and the Arts from 2013 - 2017 with almost four million euros and had 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 was to establish a biobank for human induced pluripotent stem cells (IPSC) of PD 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 were obtained and reprogrammed to the stage of pluripotency. As a result, patient specific stem cells were generated and in the framework of ForIPS further differentiated to neurons. Using this technology, ForIPS was 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

ForIPS focused 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, and resting tremor. Throughout the disease course, in particular, however, in the premotor stage, nonmotor symptoms such as hyposmia, autonomic dysfunction, disturbed gut mobility, and cognitive deficits are observed. The goal of the ForIPS network was, 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 provided 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) were analyzing the genetic and epigenetic stability and alteration of IPSC and its cellular derivatives. The scientific questions of other projects were 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) was 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, was examined by Prof. Dr. M. Götz (LMU Munich). The inflammatory interplay between neuronal and glial cells was the major task the ForIPS project of Dr. I Prots and Prof. Dr. B. Winner (Division of Stem Cell Biology), whereas Prof. Dr. F. Edenhofer (JMU Würzburg) aimed at developing transgene-free reprogramming strategies and at studying agedependent processes in cell culture models of PD. Furthermore, in situ reprogramming strategies of pericytes and the differentiation of IPS to specific striatal interneurons were 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 was a high interaction within the research network; furthermore a long-lasting biobank of IPS with its cellular derivatives was established at UK Erlangen. Novel technologies in life sciences, such as the IPSC-technology, are positioned in our society and raise important ethical gues-

tions, which were 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 the administrative assistance of J. Burczyk-Schuster (Division of Molecular Neurology), was 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 were 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 as well as an international symposium and a public hearing with the topic "Human biobanking for stem cell research".

Bayerischer Forschungsverbund

### **EIT Health**

#### Speaker

Prof. Dr. med. Dr. h.c. Jürgen Schüttler (supervisory board member of the German co-location center)

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#### Aims and structure

Created in 2008, the European Institute of Innovation and Technology (EIT) is an EU initiative that promotes innovation and entrepreneurship across Europe. Since December 9, 2014, EIT Health has been one of six "Knowledge and Innovation Communities", through which the EIT strives to solve societal challenges and contribute to different areas of life.

EIT Health aims to increase the competitiveness of European businesses, improve the quality of life of EU citizens, and strengthen the sustainability of healthcare systems. The network supports entrepreneurial and innovation-oriented thinking and action in the areas of healthy living and active aging and thus fosters new opportunities and resources for Europe.

EIT Health consists of more than 50 core partners (top-tier universities, research institutions, and companies) from 14 EU countries. The headquarters of EIT Health are located in Munich; moreover, six country nodes, the so-called "Co-Location Centers" (CLC; UK/Ireland, Scandinavia, Spain, France, Germany/Switzerland, Belgium/Netherlands), have been formed. 92 associate partners and seven "InnoStars" regions in Wales, Portugal, Poland, Hungary, Italy, and Croatia are also part of the network. The FAU, UK Erlangen, the company Siemens Healthcare, and the Fraunhofer-Gesellschaft are full members, and Medical Valley EMN e.V. is an associate partner.

With its investor approach, EIT Health drives the interlocking of companies, research institutions, and universities, stimulating innovation and serving as a driving force behind new solutions for Europe. EIT Health offers its members 25% additional funding for ongoing or expiring projects in the pillars "Innovation projects" (development of new products, services, and pro-

cesses), "Accelerator" (services for young companies), and "Campus" (educational offers for entrepreneurial and innovation-friendly thinking and acting with students, researchers, and employees of the healthcare industry). All projects and programs contribute to the three major thematic objectives of EIT Health: promote healthy living, support active aging, and improve healthcare systems.

Several research projects from the Faculty of Medicine have been successfully financed from the EIT Health funding framework. A selection of currently funded research projects and collaborations with the Faculty of Medicine is presented below.

#### P3 Stroke

Together with Siemens Healthineers and other European partners (University of Leuven, University of Bordeaux, University of Coimbra), the Chair of Pattern Recognition (Prof. Dr. A. Maier, Faculty of Engineering) and the Division of Neuroradiology are developing an innovative hybrid device (angiography and MRI) that should enable a faster diagnosis and treatment, in particular for stroke patients, through combining different medical imaging procedures. The clinical evaluation and validation of this new method takes place under the leadership of the Division of Neuroradiology in close collaboration with the Department of Neurology, while the development of the software and the post-processing algorithms are the task of the Chair of Pattern Recognition.

#### STHLM3 – Individual Prostate Cancer Risk Score

The Department of Urology and Pediatric Urology is participating in a European project under the leadership of the prestigious Karolinska Institute in Stockholm, Sweden. In an international multicenter applied study, a new application for the assessment of individual prostate cancer risk, the STHLM3 Risk Score, is being introduced, tested, and further developed. The goal is to more accurately estimate the probability of the presence of an aggressive prostate cancer and thus be able to adjust the diagnostic measures accordingly.

#### MovelT

The EIT funded project "MovelT", under the leadership of the Divison of Molecular Neurology and in collaboration with the Chair of Machine Learning and Data Analytics (Prof. Dr. B. Eskofier, Faculty of Engineering) and other European partner universities and companies, works on research addressing telemedical gait and fall analysis for Parkinson's patients. With support from wearable "gait and fall sensors", which are fixed in the shoe and on the upper body, in combination with a digital healthcare service system, imminent falls from Parkinson's patients can be detected early and prevented with a warning. Currently, sensor-based movement analysis is being refined, tested, and validated for further studies and subsequent clinical application.

#### Vital@Home

Similar to MovelT (see above), Vital@Home maps out a digital care concept for Parkinson's patients with the involvement of the Division of Molecular Neurology and the Chair for Machine Learning and Data Analytics (Prof. Dr. B. Eskofier, Faculty of Engineering). The project, led by Philipps Research, Netherlands, aims to improve the quality of life of Parkinson's patients at home. The key points of the technology-assisted Well-Being@Home projects feature, among others, an IT-supported medication plan and a quality of life assessment and coaching tool, which are enabled through motion monitoring and a digital platform.



### 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

The GCKD-study has started in 2009 as the largest cooperation project in the field of nephrology in Germany. Up to that time, controlled clinical studies were rarer in this field than in other disciplines. Managed by FAU, scientists from the universities of Aachen, Berlin, Freiburg, Hannover, Heidelberg, Innsbruck, Jena, München, Regensburg, and Würzburg cooperated with about 150 licensed nephrologists in Germany to include 5,000 patients with chronic kidney disease (CKD) in this large, prospective, observational cohort study and to observe them over a period of up to ten years. In the meanwhile, GCKD has enrolled 5,217 patients with CKD. Thus, the study is the largest cohort study worldwide prospectively monitoring patients with CKD.

Using modern analytical approaches, GCKD aims at identifying new risk factors, diagnostic and therapeutic possibilities in order to better understand the factors underlying the progression of CKD to end progression of the loss of function of the kidneys and the prevent cardiovascular complications.

The GCKD Study was originally funded by the KfH Foundation of Preventive Medicine and by BMBF (2009 – 2015). In the meanwhile, it is supported by a number of collaborative projects with industry partners. The GCKD study is also actively contributing to international consortia, such as the "Chronic Kidney Disease Prognosis Consortium" and the EU-consortium Biomarker Enterprise to Attack Diabetic Kidney Disease.

#### Research

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 risk to loose kidney function and develop cardiovascular disease in the setting of renal disease is highly variable. Factors determining progression and complication rates are to a large extent unknown.

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 postpone or avoid onset of dialysis.



### Horizon 2020: CloSed

#### Speaker

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#### Aims and structure

Most critically ill children admitted to Pediatric 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 – Pediatric Committee's (EMA-PDCO) priority list of off-patent medicines for which further clinical development are urgently needed.

The project CloSed (Clondine for Sedation of Paediatric Patients in Pediatric Intensive Care Units) was 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 commenced in December 2013 and had a duration of five years. Overall the project was funded with 6 million euros of which 1,3 million euros were foreseen for UK Erlangen.

The CloSed consortium comprised ten European partners (five clinical centers, one nonprofit 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. The consortium brought 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 was 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 manufactured the study drug; the Center for Clinical Studies was responsible for all pharmacovigilance activities and provided guidance in various aspects for the conduct of a multicenter clinical trial.

#### Research

The heart of the project was 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 was conducted in line with the ethical requirements in the pediatric population, considering risk minimization for patients and avoiding unnecessary studies. There were 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
- Generate safety and efficacy data on clonidine in children and adolescents from birth to <18 years</li>
- 3. Use the project results to apply for a Pediatric Use Marketing Authorization (PUMA)
- Develop guidelines for sedation of critically ill newborns and children in PICU within the European Society of Pediatric Neonatal Intensive Care (ESPNIC)

The aim of our research was 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.

In November 2018 the EU funding period ended. All ongoing task and analysis of the clinical will be continued and finalized beyond the end of the official funding period.



### Horizon 2020: EuroHYP-1

#### Speaker

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#### Aims and structure

The EuroHYP-1 trial was a pan-European, open, randomized, phase III clinical trial which investigated the benefit of therapeutic cooling in adult patients with acute ischemic stroke. The trial was 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 was funded by the European Union from 2012 to July 2018 within the seventh framework program. 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 contributed substantially to the leadership of the trial. Overall 63 institutions and well-known neurovascular centers in 13 European countries were involved in this project.

EuroHYP-1 was supported by the "European Clinical Research Infrastructure Network (ECRIN)", the "Stroke Alliance for Europe (SAFE)", the "European Stroke Organization (ESO)", and the "European Stroke Network (ESN)".

#### Research

Following a recruitment period of 52 months, recruitment was closed in March 2018 after inclusion of 98 patients. 49 patients were randomized to therapeutic hypothermia versus 49 to standard treatment alone. Four patients were lost to follow-up. 31% of the 49 patients randomized to hypothermia achieved cooling to the extent defined in the study protocol and had a body temperature  $\leq$ 35.0°C for at least six hours during the active cooling period. The functional outcome after 91 days did not differ between the groups (odds ratio, 1.01; 95% confidence interval [CI], 0.48 to 2.13; p = 0.97). The number of patients with one or more serious adverse events was not different (relative

risk, 1.22; 95% Cl, 0.65 to 1.94; p = 0.52). Based on the analysis conducted, no safety concerns arose regarding hypothermia from Euro-HYP-1. The central imaging assessment of CT and MRI-Scans of the brain did not detect difference in infarct volume at 24 hours after randomization between patients allocated to hypothermia and the control group. Biomarker studies did not reveal a major effect of hypothermia on the levels of markers for brain barrier dysfunction or cardiac stress. However, levels of several inflammatory and immunity markers, such as IL-6, CRP or PCT, were elevated after 24 hours in the treatment group. At the same time, the observed reduction of glial fibrillary acid protein (GFAP) levels at 72 hours might constitute an indication of a favorable response in the brain with reduced brain damage in patients treated with hypothermia. Regarding quality of life, the EQ5D scores - including deceased patients with a value of zero - did not show a significant difference (relative risk 1.10 95%CI [-0.2213; 0.1375] p=0.64).

Apart from these results, EuroHYP-1 led to a harmonization of the heterogeneous approaches to therapeutic cooling in awake patients within a unique protocol across 63 institutions in 13 European countries. Expert recommendations on the prevention and treatment of shivering, which constitutes one major clinical challenge for the successful delivery of therapeutic hypothermia, were formulated based on an Euro-HYP-1 consensus in close collaboration with world leading hypothermia centers in the United States.

In summery the following important implications from the EuroHYP-1 study arise for future research:

(1) Compatibility of hypothermia with interventional stroke treatment and thrombectomy is essential.

(2) Prophylactic antibiotic treatment of infection and pneumonia has to be considered.

(3) For awake stroke patients, more balanced cooling strategies and a thorough, pre-emptive shivering control are warranted to improve feasibility.

(4) The target temperature for the mild hypothermia treatment in awake patients is feasible only in the 34.5 - 35.5 °C range rather than the originally targeted 34 - 35 °C.



### MelEVIR – Melanoma, Extracellular Vesicles, and Immune Response

#### Speaker

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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 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, 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 is funded from April 1, 2016 until September 30, 2019 with 1.6 million euro by the BMBF under the e:Bio initiative for Systems Biology.

#### Research

Experimental results indicate that macroscopic tumors can produce and load into the blood large amounts of extracellular vesicles (pEV). It is also known that the immune system can produce and secrete pEVs in response to stimulus. In the project we are exploring the hypothesis that the minimal residual disease (MRD), the small amount of disperse tumor cells, and micrometastases left after the tumor resection cannot be the unique origin of the high levels of pEV that are found in high risk patients. Rather, large amounts of pEV are also 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 MelEVIR we are developing, testing, and translating into clinical practice a computer modeling based diagnostic tool which uses the profiling of pEV and tumor samples.

Precisely:

1. We have collected and quantified samples for primary tumors and pEV from melanoma patients.

2. We have performed experiments to elucidate the role of pEV in the tumor-immunity interaction.

3. We are using these data to develop and characterize mathematical and computational models describing the tumor-immunity interaction and assessing the risk of tumor relapse in the patients.

The final aim is to integrate the predictive model into the clinical routine and in the electronic records of the patient.

In MelEVIR we have profiled the content of melanoma patient's pEV in miRNAs, chemokines, cytokines, and other soluble factors. Further, we have used Nanostring technology to profile the immunogenicity of melanoma patients' tumor samples.

As part of the project we have developed the Virtual Melanoma Cell, an online tool developed to facilitate the mining of high-throughput data by biomedical researchers. The tool relies in the use of computational modelling and network biology algorithms to analyze, compare, and visualize high-throughput data from melanoma samples.



A. Screenshot of the Virtual Melanoma Cell, the online platform for network biology-based analysis of melanoma high-throughput data

B. Functional analyses of miRNA contained in melanoma patient pEVs. Left: Heat map showing repression scores of miRNA targets based on the pEV miRNA expression fold changes and the biological evidence on the miRNA-target interactions (Red: Tumor bearing; Orange: High risk; Blue: Low risk) Right: The mapping of the gene repression scores in a network accounting for cell cycle regulation in melanoma

### Internationalization of the Faculty of Medicine

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#### **Basis**

The internationalization of the Faculty is integrated in the target agreement on the internationalization of universities between the Bavarian State Ministry of Education, Science, and the Arts and FAU. In 2013, the Faculty of Medicine defined its own activities concerning internationalization in a strategic paper, focusing on "research", "clinic", and "teaching" with the main focus on research.

#### Welcoming culture

Over the last years, the faculties have been supporting the work of FAU's Welcome Center concerning "welcoming culture". Together, they introduced networking events for scientists across all faculties, as e.g. the "Brown Bag Break" (BBB). In cooperation with the alumni management, the operational organization of BBB rotates through all faculties. So far, the Faculty of Medicine has successfully hosted twice the BBB in the Translational Research Center.

International students are supported by the mentoring program "MedBuddy" that helps settling in and gives orientation. The "Med-Buddy"-concept is "from students for students" and furthers the welcoming culture, the international exchange on a student's level and the cross-cultural competence of FAU's students.

#### **Studies**

The bilingual homepage of the Faculty of Medicine gives detailed information on internationalization for "incoming" and "outgoing" students ("Student Mobility").

The office of the Dean for Student Affairs (contact: N. Walther) supports students of FAU when it comes to the organization and validation of a stay abroad, e.g. as part of the final year clinical elective. These stays can be supported by e.g. ERASMUS or within the interdisciplinary network project TRENAL (compare own report). International students may do a placement in the Faculty's research institutions and departments.

Recently, the international Master degree program Molecular Medicine (compare own report) has started. Its teaching language is English (contact: Dr. S. Reiprich).

#### **Research cooperations**

The institutes, departments, and divisions of the Faculty of Medicine have worldwide research cooperations. On the occasion of this research report, all chairs belonging to the Faculty were interviewed. The result of these interviews is the basis for the cooperation maps that show where our scientists have existing research cooperations in Europe and worldwide. Transcontinental partnerships focus on Northern America (including USA) whereas the European ones are the strongest in Great Britain, France, the Netherlands, and Austria.

You will find more information on the mobility of scientists in the appendix of this research report ("International cooperations"). The list gives detailed information on the kind of mobility (incoming or outgoing), on the duration of the stay, the cooperating institutes, the project title, and funding sources.

### Recruitment of scientists and improvement of infrastructure

By recruiting measurements, as for example touting our faculty at the naturejobs career exposition in London (2017), initiated by the BMBF campaign "Research in Germany", several young researchers could be won for IZKF. We issued guidelines explaining the process operations concerning external inquiries by students or employees about working at UK Erlangen and at the Faculty of Medicine. These guidelines reduce organizational and language problems and help with recurring procedures concerning legal and formal questions.

On the Faculty's website, there is a glossary that was established in close collaboration with FAU's Language Service to advance the standardization of the English used by the administration organs and to facilitate paperwork for non-local people.



Cooperations of the Faculty of Medicine within Europe The width of the circles reflects the number of partnerships in the country in question. (Map: colourbox.de)

Many departments and divisions have established international working groups within the last years and are eager to engage international visiting physicians and guest scientists. They try to support these people as much as possible when questions or problems arise. In one-onone interviews, involved people confirmed that the international cooperations enrich the groups both, socially and scientifically.

#### **Funding and partnerships**

Within the period of the research report, we succeeded in raising several external funds and in establishing international partnerships. TRENAL (Translational Kidney Research; compare own report) is an example for an external funding: It is a themed partnership on kidney research, funded for five years (2015 – 2020) by the German Academic Exchange Service (DAAD). It comprises research as well as teaching; Partner institutions are Yale University, University College London, Charité Berlin, and the Max Planck Institute of the Science of Light. Erlangen's university medicine has many inter-

national ties in the field of medical engineering as e.g. partner of the leading edge cluster Medical Valley EMN, funded by BMBF from 2011 – 2015, and of the EU alliance EIT Health (compare own reports). EIT Health, for example, that supports universities, scientific organizations, and companies when it comes to network within Europe, funds several research cooperations and projects. Cooperating with Medical Valley EMN, we could successfully raise BMBF-funding for international innovation partnerships (2016 – 2017) with Massachusetts/Connecticut (USA), Rio Grande do Sul (Brazil), and Hong Kong (China) directly after the end of the funding of the excellence initiative.

#### **Summary and prospect**

The increasing number of projects basing on international networks and the intensive scientific mobility within the Faculty of Medicine indicate that the strategy concerning internationalization was successful. It was early that the Faculty of Medicine decided to continue its internationalization activities after the end of the official funding period (2013 – 2018). We will continue to recruit qualified scientists, e.g. by presenting on career fairs. Furthermore, we plan to do workshops with excellent international institutions, focusing on our core research areas, as e.g. the workshop at the Universidade de São Paulo (2019), which focuses on medical engineering. These activities shall help to build new research cooperations and to uphold existing ones.





International cooperations of the Faculty of Medicine The width of the arrows reflects the number of partnerships on the continent in question. (Map: colourbox.de)

## Thematic network: Translational kidney research – from physiology to clinical application (TRENAL)

#### Speaker

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#### **Contact Faculty of Medicine**

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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 is funded by the BMBF as one of the projects of the DAAD program line "Thematic Networks". This project allows nephrologists, physiologists, nephropathologists, and basic researchers to participate in translational research in nephrology. Clinical departments and institutes from FAU and the Max Planck Institute for the Science of Light cooperate with partners at Yale University, New Haven, at the University College London (UCL), and, since 2017, the Charité - Universitätsmedizin Berlin.

In 2018, funding was granted for another two years, 2019 and 2020, supporting the consolidation of the established networks between the four universities.

#### 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. Every year, physicians in training and students participated in the yearly Applied Renal Physiology Course at the UCL in London, which provides a comprehensive overview of up to date basic renal science and clinical applications. Furthermore, 16 TRENALfunded young scientists from Erlangen and Berlin attended the Kidney Week of the American Society of Nephrology in New Orleans (2017) and San Diego (2018). This most prestigious international meeting in the field of nephrology provided the participants with excellent opportunities to present their data, to discuss their research ideas, and to develop networks. Three of the participating TRENAL students were selected for the ASN STAR Award program.

#### Teaching

TRENAL places a strong emphasis on the career development of medical students and young researchers. The program for the international exchange of MD students in Erlangen and Berlin was further developed. It now consists of a one year fulltime research period, with six months spent in a research laboratory in Germany (Erlangen or Berlin), followed by a six months period in a research facility at Yale or UCL. This program is supported by the IZKF in Erlangen and the BIH (Berlin Institute of Health) in Berlin. In 2017 and 2018, 19 medical students were funded by TRENAL to participate in the program. Teaching is further supported by lectures of visiting scientists from the TRENAL partner universities.



TRENAL scholarship holders from Erlangen and Berlin in New Haven (Photo: MedFak/E. Schwartze)



### Clinical Research Unit 257: Molecular pathogenesis and optimized therapy of chronic inflammatory bowel disease (CEDER)

#### Speaker

Prof. Dr. med. Markus F. Neurath

#### Head

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#### **Aims and structure**

The Clinical Research Unit 257 "Molecular pathogenesis and optimized therapy of chronic inflammatory bowel disease (CEDER)" was established in 2012 by the DFG. The grant was concluded after the maximal funding period of six years in July 2018. The research focus was on the development and (pre-)clinical testing of novel diagnostic and therapeutic approaches for inflammatory bowel diseases (IBD). IBD include the two major forms Crohn's disease (CD) und ulcerative colitis (UC). Both disorders are characterized by episodes of inflammatory flares and periods of remission. IBD patients typically suffer from abdominal pain, diarrhea, anemia, weight loss, and fatigue. Additional to physicians, biologists, and biotechnologists from the Department of Medicine 1, physicians and biologists from the Departments of Medicine 3, of Surgery, of Dermatology and from the Division of Immune Modulation were included into the research program of the clinical research unit. Aim of the unit was to evaluate the crosstalk between immune cells and epithelial cells in the gut in order to develop new, innovative, and effective treatment strategies for the therapy of IBD patients.

Moreover, KFO 257 evaluated concepts of IBD pathogenesis in order to develop new diagnostic and therapeutic approaches for the clinical management of these diseases. This translational research approach was conducted in a close interaction between clinically and scientifically active IBD specialists and experienced basic scientists in Erlangen. Together, physicians and scientists worked in three research areas: A: Regulatory mechanisms of mucosal immune cells

- TP01: Cytokine mediated mechanisms in the immune-pathogenesis of IBD PI: Prof. Dr. C. Becker / PD Dr. S. Wirtz
- (Medicine 1)TP03: Functional analysis of the immune modulator sCD83 in the pathogenesis and therapy
- of IBD PI: Prof. Dr. A. Steinkasserer / PD Dr. M. Lech-
- mann (DIM)
- TP11: Neutrophil extracellular traps orchestrate the immune response in IBD
   PI: Prof. Dr. Dr. M. Herrmann / Dr. M. Leppkes (Medicine 3/Medicine 1)

B: Regulatory mechanisms of gut resident cells

• TP05: Immune regulation of angiogenesis in IBD

PI: Prof. Dr. M. Stürzl / Dr. M. Waldner (Surgery/Medicine 1)

- TP10: Neuropeptides and TRP receptors as effectors of immune cell activation in IBD PI: PD Dr. M. Engel (Medicine 1)
- TP12: Functional characterization of prenylated Rho proteins in the pathogenesis of IBD PI: Dr. I. Atreya (Medicine 1)

C: Therapy and prediction of therapy response

- TP07: Analysis of the molecular mode of action of cyclosporine A in IBD PI: PD Dr. B. Weigmann (Medicine 1)
- TP08: Characterization and expansion of regulatory T cells for cell-based therapy of IBD PI: Prof. Dr. M.F. Neurath / Dr. C. Bosch-Voskens (Medicine 1/Dermatology)
- TP13: *In vivo* endoscopic molecular imaging to predict therapeutic response to anti-adhesion molecule therapy in CD patients PI: Prof. Dr. R. Atreya (Medicine 1)
- TPZ: Central project to coordinate the scientific program of KFO 257
- PI: Prof. Dr. C. Becker (Medicine 1)

#### Research

One of the major problems during therapeutic treatment of IBD patients is that subgroups of patients do not respond to a given therapy for unknown reasons. Numerous achievements have been made during the funding with potential for future therapeutic improvements. The project TP13 focused on the improvement of the predictability of therapy response of biological therapies. By using a fluorescently labeled antibody against  $TNF\alpha$ , it was demonstrated

that patients with high numbers of mTNF expressing cells showed significantly higher response rates to subsequent anti-TNF therapy. Project TP08 successfully established a GMP conform method to greatly expand regulatory T cells isolated from the peripheral blood of UC patients. Based on this method, a study protocol for Treg treatment of UC patients was developed and submitted to the Paul Ehrlich Institute for approval. A clinical phase I trial using such expanded Treg will start once the protocol is approved. The clinical research unit was also successful on identifying novel molecular pathways involved in IBD pathogenesis. Accordingly, TP12 demonstrated for the first time that a posttranslational activation of a specific enzyme determines the maintenance of epithelial integrity and immune homeostasis in the gut. TP01 found an unexpected function of IL-33 as a regulator of epithelial barrier functions, which further on promotes the antimicrobial defense. The influence of IFNy on IBD pathogenesis was analyzed in the TP05. They demonstrated that  $\mathsf{IFN}\gamma$  is increased in IBD patients and had a direct influence on epithelial cells in IBD tissues. Project TP07 focused on the underlying signaling axis of Cyclosporine A that is already used for IBD treatment. It could be shown that Cyclosporine A modulated the production of inflammatory cytokines and the survival of T lymphocytes in UC patients.

In addition to the scientific achievements, the clinical research unit has been able to recruit and train highly motivated national and international doctoral candidates. It also promoted the careers of clinician scientists by enabling laboratory rotations for clinicians. Five projects were led by young physicians setting up or consolidating their own research groups.

#### 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)

### **Clinical 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 F. Neurath

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#### Aims and structure

Since July 2016, the DFG has been funding the research group on colorectal cancer with 3.5 million euros 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 micromilieu have a decisive influence on tumor growth. The cellular composition of this micromilieu 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 FOR 2438 are investigating the complex molecular and cellular interrelations in the micromilieu 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 VEFGR2 signaling in CD4+ T cells in the pathogenesis of colorectal cancer

Pl: 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
   Pl: 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

Pl: 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

Dr. rer. nat. Agnes Giniewski

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#### Aims and structure

The DFG has been supporting the collaborative research center Transregio 130 (TRR 130) "B cells: Immunity and Autoimmunity" since 2013. The intercity research consortium assembles B cell immunologists from the Faculties of Medicine and of Sciences at FAU (coordinating university) as well as the Albert-Ludwigs University Freiburg, Charité Berlin, Deutsches Rheuma-Forschungszentrum, the Universitätsmedizin Göttingen, and the university Ulm, 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 five participating locations, an integrated research training group "B cells and beyond" with a strong research and training program as well as mentoring and career development concept has been established within the TRR 130. Common retreats, laboratory rotations within the TRR 130 and the annual B cell winter school provide an ideal platform for an intensive exchange between principle investigators and doctoral students within and between the five 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 pathogenfighting antibodies. Scientists of the TRR 130 examine the mechanisms that control the activation of B cells and the production of antibodies. In particular, scientists of this consortium will elucidate in detail how B cell responses are triggered, how B cells learn to remember pathogens (the so-called immunological memory) and how plasma cells manage to produce high affinity antibodies for long periods of time. A second scientific topic of the TRR 130 is to understand how B cells with autoreactive antigen receptors are activated to produce autoantibodies that attack the body s own tissue. Autoantibodies can be involved in the pathogenesis of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus or multiple sclerosis. The scientists of this consortium aim at broadening the general knowledge of B cell and antibody-mediated autoimmune diseases with the long-term goal to develop new therapeutic strategies against these diseases.

#### Teaching

The training program of the GK within TRR 130 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 TRR 130. 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 TRR 130 investigators. A student exchange program allows optional visits in laboratories within the TRR 130 to broaden the range of methods of the PhD students, to foster exchange, and to promote cooperation between the participating locations. In addition there is also the possibility for external laboratory rotations. 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 GK 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 in network meetings with other GK and organize one session of the international TRR 130 symposium. To promote public awareness about the importance of immunological research, the PhD students belonging to the GK also participate in local public relations projects. Finally, the GK covers the costs to attend scientific congresses and the three immunology schools of the "Academy of Immunology" within the German Society for Immunology (DGfl).



### Integrated Research Training Group (iRTG) of the SFB/TRR 241: Immune-Epithelial Communication in Inflammatory Bowel Diseases

#### Coordinator

PD Dr. med. Imke Atreya, PhD

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#### Aims and structure

The integrated Research Training Group (iRTG) "Intestinal Inflammation – From Bench to Bedside" as part of the SFB/TRR 241 (compare own report) will be funded by the DFG for four years (2018 – 2022). Within the SFB/TRR 241 joint research consortium (FAU, Charité Berlin, DRFZ Berlin, CAU zu Kiel), the GK training program has the following specific aims:

- 1. Support network formation between MD and PhD doctoral candidates;
- 2. Improve the national and international visibility of young researchers
- 3. Provide a structured educational program to the doctoral candidates.

In particular, we intend to prepare the elected young researchers for a future scientific career at the interphase between clinical and biological research and support their gain of knowledge in the field of chronic inflammatory bowel diseases. Thus, by participating in the GK, the graduate students will be able to strongly improve their subject-specific, interdisciplinary, technical, and personal competences. In order to provide medical doctoral researchers with an excellent starting point for a future career as clinician scientist, the GK includes a two-yeartrack educational program for MD graduate students and offers excellent candidates the possibility to apply for an GK-granted medical doctoral researcher fellowship.

#### Research

Crohn's disease and ulcerative colitis, as the two main entities of inflammatory bowel diseases (IBD), are characterized by chronic relapsing inflammatory processes of the gastrointestinal tract and significantly impair the quality of life of affected patients. In order to improve already existing therapeutic strategies or identify innovative therapeutic target structures for an optimized clinical intervention of IBD, it will be elementary to further elucidate the complex pathogenesis of the disease on a cellular and molecular level. Based on recent scientific discoveries, two aspects emerged as particularly important factors for IBD pathogenesis and prognosis:

1. Integrity of the intestinal epithelium

2. Mucosa-infiltrating immune cells within the gut

In July 2018, the SFB/TRR 241 was implemented by the DFG in order to further investigate the complex interplay between intestinal epithelial cells and the surrounding immune cells, identify new therapeutic strategies and, overall, optimize the clinical management of IBD patients. The synergistic teamwork between clinical and basic research scientists from Berlin and Erlangen will be organized in three project areas:

- A Immune regulation of intestinal barrier functions
- B Epithelium as modifier of mucosal immunity and inflammation
- C Diagnostic and therapeutic intervention of IBD

#### Teaching

The GK includes several educational tools, which will support the doctoral candidates of the SFB/TRR 241 in successfully organizing their scientific project, achieving a high level of expertise in the field of IBD, forming transregional networks, and further developing their personal skills.

• Mentoring committee

The doctoral candidates will discuss their scientific progress together with the three members of their mentoring committee, which includes the direct supervisor plus two additional SFB/TRR 241 priniciple investigators. Both sites (Erlangen and Berlin) of the research consortium are represented within the individual mentoring committees.

- Coordinated scientific forum devoted to IBD Doctoral candidates from Erlangen and Berlin join a monthly webinar, which includes individual progress reports, method seminars and a journal club.
- SFB/TRR 241 retreat
   Once a year, doctoral researchers in Erlangen and Berlin will organize a two-day scientific retreat and discuss their scientific data together with invited external experts.
- Methodical internship
   In order to further develop technical skills of
   the doctoral researchers and to strengthen
   their network formation, the GK offers them
   the possibility to join a methodical internship
   in a laboratory of choice within the SFB/TRR
   241 consortium.
- Career and competence program Structured education in the field of biostatistical analyses Good Scientific Practice and interdisciplinary issues



### Integrated Research Training Group 1181: Checkpoints for Resolution of Inflammation

#### Speaker

Prof. Dr. rer. nat. Dr. med. habil. Martin Herrmann

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#### 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 (FOR 2886, TRR 241, TRR 221, GK 1160 (Erlangen), TRR 130 (Erlangen, Berlin, Freiburg, Göttingen), IRTG 914 (München), CiM/IMPRS (Münster)) already led to joint scientific symposia.

In February 2019, the GK 1181 consisted of 41 graduates (18 full members, 9 GK-supported medical stipends, 14 associated doctorates) and 10 alumni.

#### 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 be researched by the SFB 1181.

The SFB 1181 (Checkpoints for Resolution of Inflammation; compare own report) has been funded by the DFG since 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 turn the graduate students into 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 international guest speakers in the multi-facetted 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 the 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.



**Checkpoints for Resolution of Inflammation** 

### Research Training Group 1660: Key Signals of Adaptive Immune Response

#### Speaker

Prof. Dr. rer. nat. Hans-Martin Jäck

#### Coordination

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#### Aims and structure

Since October 2010, the DFG and Bavaria have been supporting the first doctoral Fast-Track program that was established at a German university.

To increase the attractiveness of our program and to recruit the best students, we have developed an innovative doctoral pilot program for undergraduates with a bachelor's degree which will lead to the Dr. rer. nat. in 4.5 years. The program also accepts nine doctoral students with a master's or diploma degree (associated graduates). In addition, we have developed a doctoral training program for six talented medical students. The doctoral students with a bachelor's degree will first pass through a 1.5-year training program where they will receive intensive training in immunology and related disciplines, participate in three research-oriented laboratory rotations (including one at an 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 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 euros for 4.5 years.

The program will end in autumn 2019, but a new initiative with similar structures and new training concepts, particularly in the training of medical doctoral students, has already been applied for. This follow-up program will hopefully be launched in 2020, following a positive decision by the DFG.

#### Research

Our research program focuses on the molecular analysis of three cell populations (dendritic cells, B cells, and T cells) which will contribute to our fundamental understanding of how the adaptive immune response works under physiologic as well as pathophysiologic conditions. The main research focus concentrates on the identification of intra- and extracellular signaling factors that control the activation as well as the interaction of these cell types. Beyond the molecular analysis of these three cell types in mouse model systems, the role of these signals in autoimmunity and inflammatory disease will be investigated.

To achieve this goal, we have recruited 20 research groups headed by internationally recognized experts in the field of the biology of dendritic cells, B cells, and T cells from nine institutes and clinical departments at the FAU. All supervisors have external funding and are experienced in graduate training.

#### Training

During their theses, the doctoral graduate and medical students will participate in the successfully tested core events and activities of the expired GK 592 and the first funding period of the GK 1660:

- 1. A bi-weekly doctoral regular meeting organized by the students
- Subject-specific as well as interdisciplinary workshops
- Research symposia and network meetings with members of other external training grants
- 4. External laboratory visits
- 5. 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 thesis advisory committee comprising three members. The final symposium is planned for 2019 in Bad Endorf, Bavaria. In a varied program, not only renowned guest speakers will present new research findings, but also the doctoral students will present their research work. Career lectures by alumni from the first cohort of doctoral students will round off the program.

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. med. 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 neuropsychiatric and -degenerative disorders.

In the GK 2162, eleven groups of the Faculties of Medicine and of Sciences combine forces to train a total of 48 PhD and MD students over the period of 4.5 years in the novel concept that neurodevelopment constitutes a major determinant for the individual's vulnerability to neuropsychiatric and -degenerative disease in later life.

The team is composed of basic and physicianneuroscientists with expertise in the areas of CNS (central nervous system) development, genetics of CNS disorders, and modeling of neuropsychiatric and –degenerative diseases. Project leaders of the GK 2162 are

- Prof. Dr. S. Kürten (Chair of Anatomy and Cell Biology)
- Prof. Dr. C. Alzheimer (Chair of Physiology and Pathophysiology)
- Prof. J.H. Brandstätter (Chair of Animal Physiology)
- Prof. Dr. M. Wegner (Chair of Biochemistry and Pathobiochemistry)
- Prof. Dr. J. Winkler (Division of Molecular Neurology)
- Prof. Dr. B. Winner (Division of Stem Cell Biology)
- Prof. Dr. J. Kornhuber (Chair of Psychiatry and Psychotherapy)
- Prof. Dr. A. Reis (Chair of Human Genetics)
- Prof. Dr. A. Fejtová (Professorship of Molecular Psychiatry)
- Prof. Dr. D.C. Lie (Professorship of Molecular Medicine with focus on Molecular Imaging).

#### Research

Development of the 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 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 block seminars 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. To promote that purpose, graduate students are encouraged to regularly invite experts in their field of research as guest speakers and to present their work at national and international conferences.

Many excellent speakers from all over the world joined our first international symposium "Neurodevelopment and CNS vulnerability", which took place in September 2018 in Erlangen. International leaders in the field of neuronal development und vulnerability, such as Prof. F. Gage (Salk Institute, USA), Prof. Dr. S. Jessberger (UZH, Zurich, Switzerland) or Prof. H. Song (University of Pennsylvania, USA) held lectures and gave the students valuable input during lively and interactive poster sessions.

A particular concern of 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's focus and develop their own scientific profiles.

Additionally, five 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.



Lively poster session at the first international GK 2162 symposium



Participants of the first international GK 2162 symposium

### **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 of 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 comentor. 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, 148 PhD students have enrolled in the program. Until February 2019, already 102 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 within the framework of the excellence initiative of the German federal and state governments to promote science and research at German universities. SAOT offers a structured, internationally oriented (working language: English) and interdisciplinary education program to graduate students. 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 diagnostics, therapy, and surgery techniques. Moreover, technical specifications are defined which will serve as the basis for future development and engineering of bio-optical sensors and apparatuses for medical applications.

To reach these objectives, the Clinical Photonics Laboratory (CPL) and a junior professorship for functional imaging in medicine (Prof. Dr. M. Waldner, Department of Medicine 1 – Gastroenterology, Pneumology, and Endocrinology; since 2018 W2 Professor for Functional Imaging in Medicine) 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. The most recent principal investigator to join SAOT for the topic "Optics in Medicine" is Prof. Dr. Dr. M. Kesting (Department of Oral and Cranio-Maxillofacial Surgery). To intensify the interdisciplinary and international collaborations, SAOT routinely organizes international workshops.

#### 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 graduate students 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 graduate students. At the end of this academy, they have to pass the entrance examination which covers all scientific topics of SAOT.



### Life@FAU: Graduate School of Life Sciences at FAU

### Chairperson of the steering committee

Prof. Dr. rer. nat. Christoph Becker

#### Coordination

Dr. Katrin Faber

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#### Aims and structure

The FAU Graduate School of Life Sciences (Life@FAU) supports interdisciplinary graduate programs in medicine and science at FAU. The graduate school is a platform for an interdisciplinary graduate program and belongs to the FAU Graduate Center (FAU-GC). It is funded equally by the Faculty of Medicine and the Department of Biology at the Faculty of Sciences. Within Life@FAU, further GK as well as further graduate programs could be involved. Graduate students are involved in the graduate school during their PhD thesis (Dr. rer. nat./Dr. rer. biol. hum./Dr. med./Dr. med. dent.) at the Faculty of Medicine or the Faculty of Sciences. The doctorate procedure is applied to the General Regulation of Doctoral Studies of the FAU and the corresponding faculty. The development of Life@FAU is supervised by a steering committee that decides on fundamental issues. The Steering Committee is made up of equal numbers of representatives from the Faculty of Medicine and the Department of Biology.

In order to be admitted to the Life@FAU program, candidates must be working on a doctoral project that addresses a medical, biological, or biophysical issue. The Steering Committee decides whether to admit candidates in each individual case.

Life@FAU offers a structured training program to graduate students at the FAU. It supports the academic exchange between the participating graduate students and the standardization of the graduate students' education at the Faculty of Medicine and the Faculty of Sciences. Furthermore, Life@FAU offers the participation to already existing training programs as well as to newly established training programs.

Research training groups and other individual programs are part of Life@FAU. The following GK participate in Life@FAU:

• GK SFB 1181

• GK 2162

- IZKF-Research Training Group
- KFO 257
- GK 1660
- SFB/TRR 130
- GK 1962
- SFB/TRR 225
- SFB/TRR 221
- SFB/TRR 241

The Life@FAU administrative office provides support to the chairperson and the steering committee and is first contact for the graduate students.

#### Teaching

The PhD students are supervised by a mentoring committee, consisting of three supervisors; at least one of the supervisors must be eligible for a doctorate and one supervisor should be part of a different department. Regular meetings of the mentoring committee and the doctoral candidate are to be carried out at least once a year until the PhD theses is submitted. For a successful completion of the program, a minimum of requirements is to be met by each member of Life@FAU:

- The doctoral candidates are required to complete a number of interdisciplinary training modules, for instance the training module Good Scientific Practice, scientific writing, communication, and practical courses for training in laboratory methods.
- Furthermore, the active participation in the monthly Jour Fixe is mandatory. These seminars are organized by the doctoral candidates; they are responsible for defining the subject matter of the meetings. The subject should be based on relevant training modules and can take the form of a journal club, progress reports, presentations by guest speakers and other educational matters.
- Participants of Life@FAU are required to attend locally organized guest speaker seminars. Graduate students are free to choose the seminars they wish to attend from the local program of guest speaker seminars.
- Life@FAU offers the opportunity to talk or present a poster at an international symposium.
- Moreover, Life@FAU offers the graduate students to attend the internal annual retreat. During the retreat the graduate students have the opportunity to present and discuss their research results.

A record of study is used to document the achievements of each candidate. The record of study and compliance with training module re-

quirements will be reviewed during meetings with the supervision committee.

When a candidate has acquired their doctorate and completed all training modules, they will be issued with a certificate confirming successful participation in the program.



### **Emerging Fields Initiative: BIG-THERA**

#### Speaker

Prof. Dr. rer. nat. Diana Dudziak

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#### **Aims and structure**

Breast cancer is the leading cause of cancer death in women, the second most common cancer worldwide, and the fifth most common cause of cancer-related deaths. The development and progression of breast cancer is a dynamic biological and evolutionary process. It involves a composite organ system, with transcriptome shaped by gene aberrations, epigenetic changes, the cellular biological context, and environmental influences. Breast cancer growth and response to treatment has a number of characteristics that are specific to the individual patient, for example the response of the immune system and the interaction with the neighboring tissue. The overall complexity of breast cancer is the main cause for the current, unsatisfying understanding of its development and the patient's therapy response. Although recent precision medicine approaches, including genomic characterization and immunotherapies, have shown clear improvements with regard to prognosis, the right treatment of this disease remains a serious challenge.

The vision of the BIG-THERA team is to improve individualized breast cancer diagnostics and therapy, with the ultimate goal of extending the life expectancy of those patients. Therefore, the team aims to:

- Improve methods for non-invasive early diagnosis and therapy follow-up based on magnetic resonance (MR) imaging
- Elucidate the interplay between the immune system and cancer growth to segregate immunologically distinct breast cancer subtypes for immunotherapy design
- Create new strategies for immunophenotyping of tumors using nanomedicine-based techniques
- Resolve ethical challenges associated with the new advancements in breast cancer research
- Optimize therapeutic decisions using Big Data and approaches, which rely on the information acquired through OMICs studies, imaging as well as modeling *in vitro*, *in vivo*, and *in silico*.

The BIG-THERA team consists of ten different scientists, covering almost the entire spectrum of FAU's scientific focus. Six members belong to the Faculty of Medicine (Prof. Dr. C. Alexiou, Prof. Dr. T. Bäuerle, Prof. Dr. M.W. Beckmann, Prof. Dr. D. Dudziak, Prof. Dr. P. Fasching, Prof. Dr. M. Uder), two members are part of the Faculty of Sciences, and the two other members of the interdisciplinary team belong to the Faculty of Engineering (Prof. Dr. F. Nimmerjahn, Prof. Dr. A.-S. Smith), resp. Faculty of Humanities, Social Sciences, and Theology (Prof. Dr. P. Dabrock). The BIG-THERA initiative has been funded by EFI for three years with 900,000 euros.

#### Research

Over the last two decades, the understanding of breast cancer changed from identifying groups of patients with an unfavorable prognosis, prompting a treatment with toxic chemotherapy, to the understanding that breast cancer consists of different molecular subgroups. Overall, the prognosis of tumor patients is much better when primary tumors display already an antitumor immune signature, most importantly the presence of cytotoxic CD8+ T cells. However, until today, the therapeutic responses in breast cancer patients are not as predictable as in some other cancer types. Thus, the early stratification of patients according to the efficacy of certain therapies is an essential clinical need.

Therefore, the main goal of BIG-THERA is to deepen our understanding of the interplay between the immune response and breast cancer by generating an analysis platform improving the diagnostics and prognostics for the disease. Within the funding period, BIG-THERA wants to provide proof of principles for each of these work packages. To achieve our aims, we defined six work packages for our interdisciplinary team to combine our scientific expertise:

**WP1** – Imaging as a tool for stratification, diagnostics, and prognostics in breast cancer

**WP2** – OMICs analysis and immunological imaging

**WP3** – Development of model systems for studies of breast cancer *in vitro* and *in vivo* 

**WP4** – Increase of lymphocyte content in the tumor

**WP5** – Identification and analysis of the ethical challenges within BIG-THERA

**WP6** – Big Data analysis and modeling BIG-THERA integrates various scientific disciplines to combine clinical, immunological, cellular, imaging, and mathematical datasets. Most importantly, the consortium has developed and is fur-

ther developing predictive theoretical models for prognosis of therapy success in the treatment of breast cancer (neo-adjuvant chemotherapeutic and immunotherapeutic approaches) with the ambitious aim to diagnose tumor immune cell infiltration via non-invasive medicine. These models incorporate breast cancer image data derived from MRI, ultrasound, and mammography with transcriptomics data under consideration of histopathological and immunomonitoring data. Physician-oriented, BIG-THERA has started to launch their models in direct translation into the clinical routine, thereby allowing for a better stratification of breast cancer based on machine learning and digital health processes. Beside these points, one other characteristic in BIG-THERA is the establishment of a new preclinical model system for direct testing of new therapeutic approaches and image technology (e.g. 7T MRI) as well as predictive theoretical models for reconstituted tissue growth. The preclinical mouse model together with common breast cancer mouse models allow for the integration of nanomedicine based approaches for the directed trafficking of immune cells into the tumor. The newly founded DZI (compare own report) will incorporate these methods for cancer treatment applications. From the beginning, BIG-THERA has incorporated a characteristic, which is not applied in common proposals - the ethical evaluation and discussion of data derived from different procedures generating Big Data and thereby data, which could not have been derived from single methods. The discussion of these ethical guestions is very important in digital health oriented projects, as BIG-THERA, and considers data collection, storage, and dissemination on the wellbeing of the individual and the society.

#### Teaching

The members of the BIG-THERA team teach students of Medicine, Dentistry, Molecular Medicine, integrated immunology, integrated life sciences, and cell and molecular biology, physics, and informatics. The team meets for monthly seminars and organizes practical training courses for Bachelor's, Master's, MD, and PhD students involved in BIG-THERA.

### **Emerging Fields Initiative: CYDER**

#### Speaker

Prof. Dr. rer. nat. Felix B. Engel

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#### Aims and structure

CYDER was 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.I. Shankland (University of Washington School of Medicine)). CYDER was funded from 1.1.2015 to 31.12.2017 by the Emerging Fields Initiative (EFI) with 1,25 million euros.

#### 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 is 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 was to better understand the effects of cell cycle activation in such diverse processes as cancer, regeneration, and chronic organ failure. Ultimately, CYDER strived 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 cycleassociated diseases. In addition, CYDER had the goal of supporting the internationalization efforts of the FAU and of promoting junior scientists.

The CYDER consortium

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.

CYDER contributed to 37 original publications as well as eight reviews published in international journals, such as Cell, Cell Research, Blood, and Elife as well as Nature Medicine, Gut, Journal of Clinical Investigation, and Kidney International.

Highlights of our research results are for example: 1) 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.

2) Structural centrosome aberrations are frequently observed in early stage carcinomas, but their role in malignant transformation is poorly understood. Our data show that when Nineinlike protein (Nlp) was overexpressed to levels resembling those seen in human tumors, it formed striking centrosome-related bodies (CRBs), which sequestered Ninein and affected the kinetics of microtubule (MT) nucleation and release. In turn, the profound reorganization of the MT cytoskeleton resulted in mislocalization of several adhesion and junction proteins as well as the tumor suppressor Scribble, resulting in the disruption of epithelial polarity and cell-cell interactions. Remarkably, cells harboring Nlp-CRBs displayed an enhanced proliferative response to epidermal growth factor. These results demonstrate that structural centrosome aberrations cause not only the disruption of epithelial polarity, but also favor overproliferation, two phenotypes typically associated with human carcinomas.

3) Chromosomal translocations fuse the N-terminus of the histone methyl transferase MLL with a variety of different fusion partners. These events replace the enzymatic activity of MLL with the function of the respective fusion partner creating highly potent leukemogenic fusionproteins that cause a particularly aggressive subtype of acute leukemia. The CYDER consortium succeeded in clarifying how the frequent MLL fusion partner ENL creates aberrant chromatin states and therefore ectopic gene-expression by recruiting the polymerase-associated-factor PAF1. This perturbation of normal gene expression patterns eventually transforms hematopoietic cells.

4) 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.

5) 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.

#### Teaching

Seminars for all consortium members and for interested students and researchers of FAU took place monthly. In addition, CYDER regularly organized symposia and scientific presentations with invited speakers (for details see homepage).

Members of the consortium supervised 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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#### **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 the maximum duration of four years with a total amount of 660,000 euros. 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, politics, and literature studies. The project focuses on the following aspects:

### 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 interdisciplinary analyzed and questioned about their concrete possibilities of measures, which should be operationalized on different levels of healthcare. 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.

#### 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.

### Human rights for patients in vulnerable situations

Starting with various kinds of vulnerability - inherent, situational, and pathogenic -, different groups of patients whose situations are characterized 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.

### 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 lifewordy based values?

In that context a new award on "Human Rights and Ethics in Medicine for the Elderly" was established with funding by the Kraft Foundation (Munich).

Large-scale projects in close contact with the project "Human Rights in Healthcare" are:

- Bavarian dementia-survey "BayDem" (Bavarian Ministry of Health and Care)
- "MRSA in End-of-Life Care" (BMBF) palliative care
- Graduate school "OptiDem" Optimizing Strategies for Dementia (Carstens Foundation; until autumn 2018)
- New graduate school "Human Rights and Ethics in Medicine for the Elderly" (Kraft Foundation; since summer 2018)

#### Teaching

The project leaders of all three faculties involved supervise Master's, MD, and PhD theses. Two habilitations had been finished during the project.

In November 2017 the international public conference "Human Rights for Persons with Dementia" that took place in Nuremberg was organized by the project team.



### **Emerging Fields Initiative: MoJo 3D**

#### Speaker

Prof. Dr. med. Kolja Gelse

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#### Aims and structure

Due to the demographic ageing, degenerative joint diseases, such as osteoarthritis, will gain more and more importance. With currently more than nine million patients suffering from osteoarthritis, the economic and social burden is enormous. To date, artificial joint replacement represents the golden standard with more than 233.000 total knee arthroplasties and 187.000 total hip arthroplasties being implanted per year in Germany. In this respect, it has to be considered that the implantation of artificial joints is always a non-reversible operation that not only removes the destroyed cartilage, but also healthy bone substance. In particular, the subchondral bone, which itself represents a biomechanically valuable structure, is lost by artificial joint replacement. Furthermore, from an anatomical and biomechanical point of view, a complete joint function can never reconstituted by an artificial implant. However, the most important disadvantage of artificial joints is their limited survival rate. Wear, but also infections contribute to loosening of the implants, which require complex revision operations that generate resulting costs of 550 million euros per year in Germany.

The project "MoJo 3D – Modular Composite Joint 3D" has been funded by the Emerging Fields Initiative (EFI) for three years (2017 – 2019) with a volume of 440.000 euros. The research project is performed in close cooperation with Dr. T. Fey (Department of Materials Science; Institute of Glass and Ceramics, Faculty of Engineering) and Prof. Dr. G. Krönke (Department of Medicine 3).

#### Research

The aim of the EFI project "MoJo-3D" is the development of an innovative biological joint implant for the reconstruction of the articular joint surface. The concept is based on the preservation of the valuable subchondral bone plate by replacing only the overlying destroyed articular

cartilage. In contrast to established methods for cartilage repair, which are only suited for small circumscribed cartilage defects with intact surrounding cartilage, this concept aims to replace even large destroyed joint surfaces (osteoarthritis) by preservation of the subchondral bone.

This novel and innovative research project is based on modular polymer-ceramic-composites combined with cell-therapy. Ceramic buildingblocks are connected by polymer structures and anchored to the underlying bone by special anchoring modules. The modular composition allows the use of various materials (monolithic, hierachical, bi-phasical) and various geometrical forms. Furthermore, the entire spectrum of proper materials is available, which include bioinert-nonresorbable to bioactive-resorbable materials. The free spaces and holes between the building blocks can be filled by stem cells or cultivated chondrocytes. The forming cartilage matrix is supposed to contribute to a biological joint surface structure. In order to increase the resilience, a layer of collagen or polymers is applied onto the modular lattice structure, which itself can adopt any contour and contributes to a low-friction surface.

The modular fabrication of the lattice constructs, based on ceramic-polymer-composites, is performed in reproducable patterns and the three-dimensional flexible constructs can be applied on any surface contours of articular joints. This also includes the use of various materials, including aluminium-oxide, hydroxyapatite, tricalcium-phosphate, bi-phasic calciumphosphate, and bioglas.

For stable fixation onto the bone, special anchoring modules are integrated within the modular lattice construct and provide stable bonding to the subchondral bone. The anchoring concepts with various pin geometries were tested using reference material (Sawbone) and bovine bone explants. Biomechanical measurements demonstrated excellent stability with pull-out forces that biomechanically exceeded the horizontal shear forces and vertical tension loads that occur within the joints.

For the low-friction surface layer, polylactic-acid (PLA) proved to be better suited than collagen due to its superior strength, since the otherwise high difference in material strength from surface layer to the ceramic building blocks would result in excessive adverse peak loads.

Cell-culture experiments demonstrated that all cell types investigated (chondrocytes, BMSCs, periosteal cells) well adhere to the various building-block materials and PLA-scaffolds and, furthermore, the cells proliferate and form an extracellular matrix. Constructs of ceramic building blocks were biomechanical stably applied to joint explants using the integrated pins. The cellular repopulation of these explant-constructs was achieved by dynamic cell culture conditions (Spinner flasks). A homogeneous three-dimensional cellular distribution within the free spaces and holes and direct interaction with the building blocks could be improved by suspending the cells within a collagen gel. The chondrogenic differentiation of the applied cells with formation of a cartilaginous matrix was achieved by stimulation wiht TGF-ß or BMP-2.

Parts of the work have been published in various scientific journals.

### **Emerging Fields Initiative: Moves**

#### Speaker

Prof. Dr. med. Jürgen Winkler

#### **Scientific coordinator**

Prof. Dr. med. Jochen Klucken

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#### Aims and structure

The overall goal of the project was 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 spatiotemporal gait parameters that objectively support the clinical work-up by identifying PDand 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 were: Divisions of Molecular Neurology (Prof. Dr. J. Winkler, Prof. Dr. J. Klucken) and of Trauma Surgery (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 Theoloqy).

This project was funded 2014 – 2017 by the Emerging Fields Initiative of FAU with a total of 1,060,000 euros.

#### Research

Motor symptoms in PD were assessed during a randomized, controlled treadmill intervention study. Patients were stratified into an experimental 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 meters 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.

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 results of these highly interdisciplinary studies were presented in multiple international journal publications and conference contributions and have led beneath other fundings to a successful application of an IMI / H2020 followup project (Mobilise-D).

#### Teaching

The multidisciplinary team offered different students and researchers from the Faculties of Medicine, of Engineering, and of Humanities, Social Sciences, and Theology 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 Medical Engineering degree program, but also medical students, sport scientists, Master and doctoral 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 euros 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 Virgina (USA). After moving to UK Erlangen in 2006, he started as clinical fellow at the Department of 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 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. Meanwhile, Prof. Dr. G. Krönke was able to acquire additional funding by Industry (e.g. Novartis and Agios) and the German Research Foundation (e.g. the Research Unit 2886 "PANDORA") to pursue his research on autoimmunity and inflammation.

#### 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 erythematodes. Insights into underlying mechanisms should foster novel therapeutic approaches for the treatment of such diseases.

In this ERC-funded project, the team of Prof. Dr. G. Krönke was able to dissect the molecular mechanisms underlying the clearance of dying cells by macrophages. These insights provide not only valuable information about the pathogenesis of autoimmune diseases, but additionally help to define novel targets for anti-tumor therapies.

#### Teaching

Prof Dr. G. Krönke is engaged in teaching medical students, students of Molecular Medicine, and students of the Master program "Integrated Immunology".

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



Photo: Erich Malter

## From CARs to TRUCKs: Induction of a concerted anti-tumor immune response by engineered T cells

#### Speaker

Prof. Dr. med. Andreas Mackensen

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#### Aims and structure

In the consortium "From CARs to TRUCKs", scientists from Erlangen, Frankfurt, Hannover, Köln, Münster, Tübingen, and Würzburg collaborate to apply genetically modified immune cells for the treatment of tumors. The consortium addresses the generation of genetically modified T cells with tumor-specificity.

Four big subprojects cover the development of this cell therapy from bench to bedside. Hereby TRUCK stands for "T cells redirected for universal cytokine killing". These 4<sup>th</sup> generation CARs, which contain an extra domain for inducible cytokine secretion besides signaling and costimulatory domains were engineered by a member of this consortium. By this targeted cytokine secretion, not only the adaptive immunity, but also additionally the innate immunity becomes activated.

The projects are investigated in cooperating institutes all over Germany. The project has been supported by "Deutsche Krebshilfe" for three years (2016 – 2019) with 2.5 million euros. The long term aim is to translate this novel T cell engineering technology into clinical application for the treatment of solid tumors.

#### Research

Adoptive cell therapy with engineered T cells that interact with tumor cells via chimeric antigen receptors (CARs) has shown impressive clinical success in CD19-positive B cell lymphomas. Recently, two CD19 CAR products have even obtained marketing authorization in Germany. A central aim is to extend CAR therapy to solid tumors as these are more difficult to target because of the heterogenous expression of target antigens and the inhibitory effects of tumor stroma.

This project aims at developing T cells expressing not only a CAR specific for a tumor-associated antigen, but also a CAR-inducible transgene which encodes for an immune-activating molecule. These TRUCKs respond to interaction with their target by secretion of a cytokine. The advantage of this approach is to activate innate immunity and to induce locally restricted secondary adaptive immune responses against antigen-negative tumor cell variants.

The consortium works on different projects:

- Optimization of gene vectors for increased safety and effective expression of transgenes One important factor for increasing safety is the addition of a so-called suicide-gene enabling the shutdown of the cells.
- Preclinical validation of efficacy and safety of these cells in a mouse model Cells will be injected into a humanized mouse model to investigate the efficacy against tumor cells. The elimination of solid tumors, infiltrating immune cells, but also systemic effects of the cytokine will be analyzed. The effect onto tumor cells can be visualized by bioluminescence.
- Establishment of the procedures for clinicalgrade TRUCK vector design and cell manufacturing, aiming at the preparation of a clinical trial

For the manufacturing of cell products for patients, materials must be of high quality (GMP-grade/clinical-grade). The production must be up-scaled to obtain a sufficient high cell number for a patient. The preparation of so-called standardized operating procedures (SOPs) and the validation of the manufacturing process are obligatory for the application for a manufacturing authorization.

4. Exploration of alternative immune-activating cytokines and modulators of immune-inhibitory checkpoints in tumor tissues for manipulation of the tumor microenvironment and the increase of the efficacy of the T cells.

The Department of Medicine 5 owns a GMP (Good manufacturing Practice) laboratory where the clinical-grade manufacturing of CAR/TRUCK T cells was successfully established.



Photo: Department of Medicine 5

#### Teaching

The heads of the clinical research groups are involved in the traditional teaching program (lecturers, seminars, practica) covering all subjects in the field of Medicine and Molecular Medicine and the PhD and MD program for basic and translational research.

### **Cord-Michael Becker-Prize**

#### Speaker

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

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Dean's office of the Faculty of Medicine Krankenhausstr. 12 91054 Erlangen Phone: +49 9131 8524638 Fax: +49 9131 8522224 molmed-info@fau.de 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 euros. It is awarded to graduates of any of the 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.

#### Awardees of 2017 and 2018

In 2017, Dr. S. Koren-Hauer was awarded with the Cord-Michael Becker-Prize for her thesis entitled "Effects of PIK3CA mutations on mammary cell fate and cancer". Dr. S. Koren-Hauer studied Molecular Medicine at FAU. After her studies, she pursued a doctoral thesis at the Friedrich Miescher Institute for Biomedical Research at the University of Basel. Her results are significant in the field of tumor biology and breast cancer. She could show that the frequent mutations analyzed by her are causative for tumor heterogeneity and that the cell of tumor origin is decisive for malignancy. Reducing tumor heterogeneity may be beneficial for therapy and outcome of the patient.

In 2018, Dr. D. Hotter was honored with the Cord-Michael Becker-Prize. He received the award for his doctoral thesis "Modulation of viral gene expression and antiviral immune response by primate lentiviral proteins Vpu, Vpr and Nef". Dr. D. Hotter studied Molecular Medicine at the University of Ulm and continued

with a doctoral thesis at the Institute for Molecular Virology of the university hospital Ulm. His results yield fundamental insights into the mechanisms of the immune deficiency virus HIV to escape from the innate immune response. His work helps to develop new therapies that are based on better immune control of HIV and aim for a reduction of the detrimental chronic activation of the immune system.



The awardee 2017, Dr. S. Koren-Hauer, with Prof. Dr. B. Fleckenstein of the Research Foundation of Medicine (Photo: C. Stolt, FAU)



Cord-Michael Becker-Prize 2018

(from left to right): Prof. Dr. B. Fleckenstein, Prof. Dr. W.G. Daniel (Research Foundation of Medicine), Prof. Dr. F. Kirchhoff (thesis supervisor of the awardee), Dr. D. Hotter (Cord-Michael Becker-awardee 2018), Prof. Dr. Dr. h.c. J. Schüttler (Dean), Prof. Dr. C.M. Becker (guest of honor) (Photo: C. Warter, FAU)
## 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 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 prize committee consists of the professors of the research committee 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 euros and a certificate.

#### **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 plague 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.



Jakob Herz (1816-1871), around 1850, StadtAE V.A.b.3

In 2018, the Faculty of Medicine elected Prof. Laurence Zitvogel, MD, PhD, for the Jakob-Herz-Prize. Prof. L. Zitvogel from Paris is widely recognized for being a pioneer in the field of oncology and for her innovative achievements in the field of cancer immunotherapy. In the focus of her research is the influence of the immune system on the genesis and treatment of cancer.

Prof. L. Zitvogel is scientific directress at the Gustave Roussy Cancer Center in Villejuif, France, and professor of immunobiology at the University of Paris XI Medical School. She was convinced that killing cancer cells cannot be the only treatment option for cancer. This conviction finally led to the concept of immunogenic cell death. She could prove that the classical cancer treatment (chemotherapy, radiotherapy) only is effective against cancer (at least in parts) with the help of the immune system. Not only, but also thanks to her successful research, classical cancer treatment has expanded by two new fields, i.e. targeted therapy and immunooncology.

Prof. L. Zitvogel's current research is divided into three main areas. First, she is studying different modes of action of immune checkpoint inhibitors and looking for predictors of response to immune-modulation. Second, Prof. L. Zitvogel is trying to characterize how the gut microbiome plays a part in cancer immune-surveillance. Finally, she is working to identify the molecular mechanisms behind immunogenic cell death, a form of cancer cell death that triggers the activation of T-cells towards the remaining cancer cells.

Prof. L. Zitvogel has published more than 452 papers, quite a few of them in high ranking journals, such as "Nature Reviews Immunology", "Science", and "Nature Medicine". She has been awarded several prizes.



Prof. Dr. Dr. h.c. J. Schüttler, Dean, and the awardee, Prof. Dr. L. Zitvogel

# Promoting equality of women and gender research

## Women's representative, Faculty of Medicine

Prof. Dr. med. Kerstin Amann

## Deputies

Prof. Dr. rer. nat. Ursula Schlötzer-Schrehardt Prof. Dr. (TR) Yesim Erim

## Address

Office of the Women's Representative of the Faculty of Medicine Divison 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

## **Function and structure**

The women's representative of the Faculty of Medicine serves the academic staff of FAU and UK Erlangen. In October 2007, the Executive Board of FAU and the Faculty of Medicine concluded the first target agreements for increasing the proportion of women in academia, thus strengthening the position of the faculty's women's representative. On February 5, 2018, the third target agreement was signed, including these goals to be achieved by 2022:

- Increase in the number of women with 'Habilitation' from 20.7% (2015) to 30% (2022)
- Increase in the number of female W2 professors from 14.6% (2016) to 20% (2022)
- Increase in the number of female W3 professors from 3.7% (2012-2016) to 10% (2022)
- Increase in the number of female senior physicians from 20% (2015) to 30% (2022).

### **Gender mainstreaming**

In addition to systematic headhunting, FAU aims to increase the proportion of female professors by means of gender-sensitive appointment procedures. This entails making appointment processes more transparent and ensuring that, next to the woman's representative, one additional female expert is part of each appointment committee. Furthermore, a member of the Senate of FAU monitors the appointment process in order to achieve a systematic and consistent consideration of gender aspects.

#### **Mentoring program ARIADNEmed**

Program coordinator: Dr. M. Zirngibl The ARIADNEmed mentoring program, aimed at young female researchers in the postdoctoral and postgraduate phases, started in October 2008 as part of the target agreements for increasing the proportion of women in academia. The core component of the program is individual mentoring/coaching of young female scientists by experienced female and male professors, focusing on strategic questions regarding career development and leading to the concrete decisions. In addition, ARIADNEmed offers a highquality seminar program on relevant career topics, such as funding, work-life balance, publishing or coaching for appointment processes. A program round lasts for 18 months. In July 2018, the sixth round ended and the seventh round, with 21 young female scientists from FAU's Faculty of Medicine and/or UK Erlangen, commenced

#### **Gender lectures**

Every term, the women's representative organizes "Gender Lectures" featuring one or two female speakers who may serve as role models, motivating young female researchers to pursue an academic career themselves. Each lecture consists of a 30 – 40-minute talk, followed by a discussion.

#### **Travel grants and scholarships**

Talented postdoctoral researchers can apply for financial support to attend scientific conferences. The travel grant may be applied for once a year, with a maximum of three times overall – under the condition that applicants actively participate in the conference in question, e.g., via a talk or a poster contribution.

#### Protected research period for female postdocs

Since 2018, female physicians who care for children or other relatives can go on paid leave to fully dedicate themselves to their 'Habilitation' process. The exemption can be granted either for two to three months (100%) or four to six months (50%). The Faculty of Medicine's women's representative decides on the applications.

### Office for work and family at UK Erlangen

The office, staffed with one part-time official, began its work in September 2018. Its task is to facilitate the compatibility of science, career, and family and to promote equal opportunities for young female scientists. To this end, the office develops specific measures and provides advisory services. Moreover, in cooperation with FAU's Office of Equality and Diversity, it advises DFG-funded research networks on the use of gender equality funds, from the application phase to the conception and implementation of concrete measures (gender consulting).

### **Public relations**

In October 2016, the faculty women's representative's own website was launched. Interested parties may here find detailed information, e.g., on funding opportunities, contacts, and topics, such as sexual harassment at the workplace.



# Johannes and Frieda Marohn-Foundation

## Head of the scientific board

Prof. Dr. med. Christian Alzheimer

## Contact

Vasiliki Ikonomidou Johannes and Frieda Marohn-Foundation – Office Universitätsstraße 19 91054 Erlangen Phone: +49 9131 8526955 Fax: +49 9131 8526928 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 cooperation 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 2017 - 2018)

Financial year	Budget	Number of accepted applications
2017	242,262.23 Euro	5 (129,845.25 Euro)
2018	238,303.11 Euro	4 (104,905.00 Euro)

## Finalized projects (Time of funding 2017 – 2018)

Number of projects	Number of publications	Continued funding by other foundations*
5	6	1





Frieda Marohn

Johannes Marohn

## **Research Foundation of Medicine**

#### Speaker

Prof. Dr. med. Werner G. Daniel

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Research Foundation of Medicine at the UK Erlangen Östliche Stadtmauerstraße 30a 91054 Erlangen Phone: +49 9131 8540555 Fax: +49 9131 8533182 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 euros 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, including the bestowal of research awards
- 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 euros 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 euros 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 Rudolf-Wöhrl-Hörsaal and Ernst-Freiberger-sen.-Hör saal). 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. Until the end of 2018, the Research Foundation of Medicine was able to distribute approximately 4.9 million euros for various projects. This high amount became possible also by a "Matching-Funds" concept, established by the UK Erlangen in 2011. The UK Erlangen increases all financial supports given by the Research Foundation of Medicine by additional money out of the clinic income that is subject to income tax. The "Matching-Funds" program has also stimulated the willingness of donators for funding immensely. This concept is successfully practiced in other countries, as e. g. USA and 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.

- The "Erlanger Medizinische Bürgervorlesung", a series of 12 – 14 lectures on up-to-date medical topics, was initiated in 2007 and addresses each term interested citizens. During the last 20 terms, it 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 fifth 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 2018, Prof. Dr. L. Zitvogel, Institut Gustave Roussy, Villejuif, and Professorship for Immunology and Biology, Université Paris Sud, 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 2016, the prize was given to Dr. L. T. Jae, PhD (Marburg,

Cambridge/USA, Utrecht), in 2017 to Dr. S. Koren-Hauer, PhD (FAU, Basel); both prizes were handed out in 2017.

• The Cord-Michael Becker-Prize 2018 was awarded to Dr. D. Hotter (Ulm).

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 2017, Dr. K. Sofia Friedlein (Department of Neurosurgery) and Dr. E. Eberhard (Institute of Physiology and Pathophysiology), and in 2018, Dr. N. Oetter (Department of Oral and Cranio-Maxillofacial Surgery) and Dr. J. Dieckow (Chair of Functional and Clinical Anatomy) were awarded this prize for their outstanding theses.

On November 30, 2017, the Research Foundation of Medicine celebrated the tenth anniversary in the Orangerie in Erlangen. The ceremony was attended by a large number of participants, including the Bavarian Minister of the Interior, for Sport, and Integration, J. Herrmann, representatives of FAU, UK Erlangen and in particular many supporters, sponsors, and friends of the Research Foundation of Medicine. An anniversary publication describes the development and achievements of the foundation during the first ten years in details.



Tenth anniversary of the Research Foundation of Medicine (from left to right) Prof. Dr. Dr. h. c. H. Iro (Medical Director), Prof. Dr. W. G. Daniel (Chairman of the Executive Board of the Research Foundation of Medicine), J. Herrmann (Bavarian Minister of State), Prof. Dr. B. Fleckenstein (Chairman of the Board of Trustees of the Research Foundation of Medicine), Prof. Dr. J. Hornegger (President of FAU)

## Further foundations for research support

In addition to before mentioned possibilities, 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 the 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. In 2018, L. Zeitler was honored by the Luise-Prell prize. M. Dahlmanns received the Fritz and Maria Hofmann prize. Both awardees were honored for their excellent graduation in the degree program Molecular Medicine.
- The Thiersch Prize is awarded annually for the best and most concise postdoctoral qualification (Habilitation). In 2017, Dr. T. Gramberg (Institute of Clinical and Molecular Virology) was awarded with the Thiersch-Preis for his outstanding habilitation thesis on "Die Rolle von SAMHD1 als Restriktionsfaktor der retroviralen Infektion". In 2018, Dr. C. Günther (Department of Medicine 1) was awarded the Thiersch Prize for her habilitation thesis on "Molecular regulation of programmed cell death in inflammatory diseases".
- The Staedtler Prize, provided by the Staedtler-Foundation, honors outstanding doctoral theses. In 2018, Dr. I.N. Schellinger received the prize for her dissertation thesis. 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 Institute of Clinical Microbiology, Immunology, and Hygiene Wasserturmstraße 3 – 5 91054 Erlangen Phone: +49 9131 8522551 Fax: +49 9131 8522573 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 200th birthday in a ceremony at the castle of the FAU. In the year of the 200th birthday of the PMSE, the Medical Society, which had separated from the PMSE in 1958 after the 150th birthday celebration of the Societas physico-medica Erlangensis, merged again with the PMSE.

As of February 7, 2019, the Society has 324 members inside and outside Germany, with 15 of them being honorary and corresponding members. Once per year the Society holds a members assembly upon invitation by the council.

Each year, 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 2018, twelve volumes of reports were published, each of them consisting of up to four single issues. Besides 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.

#### Lectures

12.12.2018 Prof. Dr. V. Zaburdaev, Department of Biology and Max-Planck-Zentrum für Physik und Medizin, FAU Mechanical Forces as Drivers of Bacterial Motility and Formation of Microcolonies

9.5.2018 Prof. A. W. Friedrich, Medical Microbiology and Infection Prevention, University Medical Center Groningen: The Netherlands

Interventional diagnostic stewardship for the prevention of antimicrobial resistance

4.10.2017 Prof. M. Radisic, University of Toronto, Toronto General Research Institute: Canada Towards organs-on-a-plate and injectable tissues



## International mobility of scientists

## **Visiting Scientists\***

## **Department of Anesthesiology**

 Project title: Neuropathic pain mechanisms PI: Prof. Dr. K. Zimmermann Dr. Ricardo Kusuda from the Department of Pharmacology, University of São Paulo, Brazil (11/2016 – 10/2017)

### **Department of Medicine 1 –** Gastroenterology, Pneumology, and Endocrinology

Project title: Gata 4

Funding: Humboldt-Foundation

- PI: Prof. Dr. M.F. Neurath / Prof. Dr. C. Becker Dr. Jay Patankar from the University of British Columbia, Vancouver, Canada (09/2016 – 08/2018)
- · Project title: The regulation and pathophysiological role of epithelial cell death in the gut Funding: CSC scholarship
- PI: Prof. Dr. M.F. Neurath / Prof. Dr. C. Becker Yuqiang Yu, PhD student from Jilin University, Changchun, China (10/2015 - 10/2019)

## **Department of Medicine 3 – Rheumatology and Immunology**

- Project title: New targets in fibrotic diseases Funding: DAAD scholarship for PhD PI: Prof. Dr. J. Distler / Dr. A. Ramming Mahmad Housni, PhD student from Damascus, Syria (since 10/2017)
- Project title: Rolle von RORalpha in Arthritiden Funding: amongst others BMBF Pl: Prof. Dr. J. Distler
- Rosebeth Kagwiria, PhD student from Kenya (01/2014 02/2018)
- · Project title: Innate Lymphoid Cells new players in Psoriatic Arthritis Funding: scholarship PARTNER Fellowship Pl: Dr. A. Ramming Dr. Maria Gabriella Raimondo from Milano,
- Italy (since 07/2017)
- Project title: Hyperuricemia and gout Funding: Articulum fellowship PI: Prof. Dr. Dr. M. Herrmann Dr. Lenka Petru from Prague, Czech Republic
- (04/2017 03/2018) · Project title: Effect of obesity on rheumatoid
- arthritis development Funding: scholarship Rheumatology Department of Renji Hospital Shanghai
- PI: Prof. Dr. A. Bozec Dr. Song Rui, PhD student from the Rheumatology Department, Renji Hospital Shanghai, China (06/2017 – 06/2020)
- Project title: Role of AP-1 transcription factor in macrophage responses during infection Funding: scholarship Rheumatology Depart-ment of Renji Hospital Shanghai PI: Prof. Dr. Á. Bozec

Cao Shan, PhD student from the Rheumatology Department, Renji Hospital Shanghai, China (06/2017 – 06/2020)

 Project title: Resolution of rheumatoid arthritis inflammation by allergic responses Funding: scholarship Jingmen Second People Hospital PI: Prof. Dr. A. Bozec

Liu Mengdan, PhD student from Jingmen Second People Hospital, Jingmen, China (06/2017 – 06/2020)

- · Project title: Disease-related processes of psoriatic arthritis
  - Funding: scholarship PARTNER fellowship PI: Prof. Dr. G. Schett
- Dr. Maria Sokolova from Moskow, Russia (05/2018 – 04/2019)
- Project title: Die spontane Differenzierung von mesenchymalen Stammzellen Funding: Humboldt scholarship
- PI: Prof. Dr. G. Schett
- Dr. Koshiro Sonomoto from Fukuoka, Japan (04/2017 - 09/2019)
- Project title: Influence of hypoxia in gut epithelial cells on rheumatoid arthritis initiation Funding: scholarship Jingmen Second People Hospital

PI: Prof. Dr. A. Bozec

Jinming Wen, PhD student from Jingmen Second People Hospital, Jingmen, China (06/ 2017 - 06/2020)

## **Department of Medicine 5 –** Hematology and Oncology

- Project title: Characterization of tumor cell dormancy after treatment with Moxetumomab pasudotox
  - Funding: intramural funding of the University of Rome
  - PI: Dr. F. Müller

Dr. Elisabetta Anselmi, University of Rome "Sapienza", Italy (09/2018 - 03/2019)

## Institute of Anatomy - Chair of **Functional and Clinical Anatomy**

• Project title: Untersuchungen zu den ableitenden Tränenwegen des Menschen Funding: Humboldt fellowship PI: Prof. Dr. F. Paulsen

Dr. Mohammad Javed Ali from L.V. Prasad Eye Institute, Hyderabad, India (since 2015)

• Project title: Distribution of goblet cells at the mouse ocular surface Funding: Khon Kean University

PI: Prof. Dr. F. Paulsen

Dr. Nichapa Phunchago from Khon Kaen University, Khon Kaen, Thailand (since 2018)

## **Institute of Human Genetics**

• Project title: Analyse der molekularen Grundlagen von Glioblastomen mittels Transkriptom- und Pathwayanalysen PI: Prof. Dr. A. Reis Didem Seven, PhD student from Istanbul Uni-

versity, Istanbul, Turkey (10/2017 - 09/2018)

- Project title: Genomic Search and Candidate Analysis in Costa Rican Families affected with Charcot-Marie-Tooth (CMT) Disease PI: Prof. Dr. A. Reis Prof. Alejandro Leal from Universidad de Costa Rica, San José, Costa Rica (11/2016 02/2017) · Project title: Identifikation von Genen für au-
- tosómal rezessive Entwicklungsstörungen PI: Prof. Dr. A. Reis

Esen Gümüslü, Student from Kocaeli University, Izmit/Kocaeli, Turkey (09/2018 – 01/2019)

## Institute of Neuropathology

• Project title: Molecular and histopathological studies on focal cortical dysplasia

Funding: SPRINT (FAU and FAPESP) PI: Prof. Dr. I. Blümcke

Jose Eduardo Peixoto-Santos, PhD, Department of Neurology, UNICAMP, Campinas, Brazil (06/2017 – 06/2018)

 Project title: European Epilepsy Brain Bank Funding: University of Mexico PI: Prof. Dr. I. Blümcke

Jesus Cienfuegos Meza, MD, General Hospital, Ministry of Health, Medical Specialty Program, National Autonomous University of Mexico (UNAM) (09/2017 - 11/2017)

## Institute of Physiology and Pathophysiology

 Project title: Aufklärung lichtunabhängiger abdomineller Schmerzattacken bei hepatischen Porphyrieerkrankungen: Rolle der TRP-Kanäle und der Häm-Vorstufen

Funding: Visiting Professor-Program of FAU PI: Prof. Dr. P. Reeh

Prof. Alexandru Babes from the University of Bucharest, Romania (07/2017 – 09/2017)

• Project title: Einfluss von alpha-Adrenozeptor-Agónisten auf die Durchblutung der Hirnhäute and Interaction of sympathetic efferents with with meningeal nociceptors - a possible pathophysiological correlate of stress-induced susceptibility for headache

Funding: Alexander von Humboldt-Foundation

PI: Prof. Dr. K. Meßlinger

Dr. Mária Dux from the Institute of Physiology, University Szeged, Hungary (06/2017) 07/2017 and 06/2018 – 07/2018)

### Nikolaus-Fiebiger-Center for Molecular Medicine Chair of Experimental Medicine I

• Project title: Generation of a genome-wide map of ZEB1-dependent changes in chromatin status

PI: Prof. Dr. T. Brabletz / Dr. F. Ferrazzi Giulia Graziano, student from the Università di Padova, Italy (10/2018 – 02/2019)

## FAU Scientists going abroad\*

## Department of Medicine 4 – **Nephrology and Hypertension**

• Project title: Genetische Ursachen des nephrotischen Syndroms

Funding: DFG PI: Dr. F. Hildebrand

Dr. Tilman Jobst-Schwan at Boston Children's Hospital, USA (03/2015 - 07/2018)

## Institute for Biomedicine of Aging

- Project title: Die Beziehung zwischen oralem Gesundheitsstatus und der Entstehung von Mangelernährung im Alter – Sekundärdatenanalysen der Longitudinal Aging Study Amsterdam (LASA)
- Funding: DFG research fellowship

PI: Dr. E. Kiesswetter Dr. E. Kiesswetter at the Vrije Universiteit Amsterdam, Department of Health Sciences, Netherlands (12/2017 - 05/2018)

\*Duration of stay at least three months

## Selection of honors and prizes

## 2017

Federal Cross of Merit on the Bond (Bundesverdienstkreuz am Bande) Prof. Dr. Reinhold Eckstein Division of Transfusion Medicine and Hemostaseology

Honorary member of the Austrian x-ray society (ÖRG) Prof. Dr. Willi A. Kalender Institute of Medical Physics

Honorary doctorate of the University of Medicine and Pharmacy Craiova, Romania Prof. Dr. Horia Sirbu Division of Thoracic Surgery

Franz-Oehlecker-Medal Prof. Dr. Reinhold Eckstein Division of Transfusion Medicine and Hemostaseology

m4-Award (BioM) Prof. Dr. Anja Boßerhoff, Prof. Dr. C. Hellerbrand Institute of Biochemistry

**Exploration Grant of the Boehringer-Ingelheim-Foundation** Dr. Andrea Thoma-Kreß

Institute of Clinical and Molecular Virology

German study award (Körber foundation) Dr. Jan Suckau Department of Plastic and Hand Surgery

Hufeland award Dr. Julia Berendt Division of Palliative Medicine

Renate-Wittern-Sterzel award Prof. Dr. Michael Stürzl Department of Surgery

Transplant-Registry-Early-Career-Award PD Dr. Christian Heim Department of Cardiac Surgery

Herbert Lewin research award Dr. Jessica Tannenbaum Institute of the History of Medicine and Medical Ethics

Jörg-Vollmar award Dr. Ulrich Rother Department of Surgery

**Stephen-Bayne-Mid-Career-Award Prof. Dr. Ulrich Lohbauer** Department of Operative Dentistry and Periodontology Dr.-John-P.-Bilezikian-ISCD-Global-Leadership-Award Prof. Dr. Klaus Engelke Institute of Medical Physics

Lung Cancer Young Investigator Award der International Association for the Study of Lung Cancer (IASLC) Dr. Paolo Ceppi Nikolaus-Fiebiger-Center of Molecular Medicine (NFZ), IZKF Junior Research Group 1

## **2018**

Cross of Merit on the Bond (Verdienstkreuz am Bande) Prof. Dr. Hans Drexler Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine

**Bavarian Order of Merit Prof. Dr. Dr. h.c. Werner Hohenberger** Department of Surgery

Honorary member of the British Institute of Radiology Prof. Dr. Stephan Achenbach Department of Medicine 2 – Cardiology and Angiology

Honorary doctorate of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania Prof. Dr. Max-Josef Hilz Department of Neurology

Langener Science Award Prof. Dr. Gerhard Krönke Department of Medicine 3 – Rheumatology and Immunology

German Cancer Award Prof. Dr. Thomas Brabletz Chair of Experimental Medicine I

Dr. Willmar Schwabe award PD Dr. Matthias Engel Department of Medicine 1 – Gastroenterology, Pneumology, and Endocrinology

Franz-Köhler award (Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie, DGTHG) PD Dr. André Rüffer Division of Pediatric Cardiac Surgery

Theo and Friedl Schöller prize Prof. Dr. Elmar Gräßel Department of Psychiatry and Psychotherapy

Advancement award palliative medicine (Deutsche Gesellschaft für Palliativmedizin, DGP) Prof. Dr. Christoph Ostgathe / Prof. Dr. Cornel Sieber Division of Palliative Medicine / Institute for Biomedicine of Aging

Prize of the Rolf-and-Hubertine-Schiffbauer-Foundation Prof. Dr. Dorothee Volkert Institute for Biomedicine of Aging

Research award on Glaucoma (German Opthalmological Society) Dr. Bettina Hohberger Department of Ophthalmology Science Award of the German Society of Plastic, Reconstructive, and Aesthetical Surgery PD Dr. Anja Miriam Boos Department of Plastic and Hand Surgery

Georg-Haas award (Verband Deutsche Nierenzentren e.V.) Dr. Sebastian Röder Division of Nephropathology

Dermato Oncology Junior Scientist Award Bianca Simon Department of Dermatology

Junior prize (Deutsche Gesellschaft für Muskelkranke e.V.) Dr. Matthias Türk Department of Neurology

Otto-Westphal dissertation prize (Deutsche Gesellschaft für Immunologie, DGfl) Dr. René Pfeifle Department of Medicine 3 – Rheumatology and Immunology

Researcher award (Norddeutsche Suchtforschungsverbundes, NSF) Prof. Dr. Christian P. Müller Department of Psychiatry and Psychotherapy

Advancement award of the Rolf-and-Hubertine-Schiffbauer-Foundation Dr. Katrin Singler Institute for Biomedicine of Aging

Cultural award Bavaria Dr. Nicole Goerig Department of Radiation Oncology

Otfrid-Foerster-Medal (Deutsche Gesellschaft für Epileptologie, DGfE) Prof. Dr. Hermann Stefan Emeritus of the Department of Neurology

Young Investigator Award of the Transplantation Society PD Dr. Christian Heim

Department of Cardiac Surgery

Carla Boetes Young Investigator Award PD Dr. Matthias Dietzel Institute of Radiology

Shimon Gatt Award Dr. Lyubov Kalinichenko Department of Psychiatry and Psychotherapy

## Doctorates theses, habilitations\*, board and additional qualifications

#### **Institute of Anatomy** Chair of Anatomy and Cell Biology

#### Doctorate theses 2017

Jeßberger, Carmen, Dr. med.: Untersuchung eines circadianen Rhythmus der Neurotransmitter NO und VIP in intrinsischen choroidalen Neuronen der Hühnerchoroidea

Safi, Sami Alexander, Dr. med.: Myelinated axons in the auricular branch of the human vagus nerve

Traub, Simone, Dr. med.: Verlaufsanatomie des Nervus saphenus in Bezug auf die transsartoriale Nervenblockade

Zimmermann, Jan, Dr. med. dent.: Homer1 (VesL-1) in the rat esophagus: focus on myenteric plexus and neuromuscular junction

#### Doctorate theses 2018

Beck, Josefa, Dr. med.: Immunhistochemischer Nachweis von FRMD6 in den Hirnnerven der Ratte, des Frosches und des Menschen

Koch, Christian, Dr. med.: Epithelial cell types and their proposed roles in maintaining the mucosal barrier in human chagasic-megacolonic mucosa

Muck, Paul, Dr. med. dent .: Qualitative und quantitative Untersuchung des Agrin-LRP4-MuSK Signalwegs im Ösophagus und im Skelettmuskel der Ratte

Tischler, Georg, Dr. med.: Immunhistochemische Darstellung MHC-II exprimierender Zellen und deren topographischer Assoziation mit dem enterischen Nervensystem und vaskulären Strukturen der Tunica muscularis propria der Ratte

Zinsser-Krys, Jillena, Dr. med.: Immunhistochemische Bestimmung der Co-Lokalisation von Neurotransmittern und -peptiden in Serotoninpositiven enterischen Nervenfasern an motorischen Endplatten im Mäuseösophagus

## **Institute of Anatomy**

Chair of Functional and Clinical Anatomy

#### Doctorate theses 2017

Abrar, Daniel, Dr. med.: Charakterisierung einer Meibomdrüsen-Epithelzelllinie zur Untersuchung der Meibomdrüsen-Dysfunktion

Altersberger, Valerian, Dr. med.: Die Bedeutung der Melanocortinrezeptoren im Rahmen der Meibomdrüsendysfunktion

Dieckow, Julia, Dr. med.: Die Chemokinrezeptoren CXCR4 und CXCR7 vermitteln TFF3-induzierte Zellmigration unabhängig vom ERK1/2-Signalweg

Frömmling, Paul, Dr. med.: Der Effekt von Somatostatin auf die korneale Wundheilung Schröder, Henrik, Dr. rer. biol. hum.: Etablierung zweier Expressionssysteme für SFTA3 in Escherichia coli und humanen embryonalen Nierenzelllinie HEK 293T

Sheats, Michelle, Dr. med.: Die Surfactant Proteine A,B, C und D des menschlichen Larynx

#### Doctorate theses 2018

Beckenbauer, Eva, Dr. med. dent.: Untersuchungen zur Psoriasin-abhängigen Angiogenese in humanen Korneaepithelzellen

Siber-Hoogeboom, Regina, Dr. med. dent .: Obstruktive Schlafapnoe und Rhonchopathie sind mit einer Runterregulierung von Trefoil Faktor Family 3 (TFF3) assoziiert - Hinweise für eine Veränderung in der oralen Mukuszusammensetzuna

#### Habilitation 2018

Hammer, Christian Manfred, PD Dr. rer. nat.: Neuartige Femtosekundenlaser-Applikationen in der cornealen Chirurgie

Garreis, Fabian, PD Dr. rer. nat.: Bedeutung antimikrobieller Peptide und Temperatur-sensitiver TRP Kanäle an der Augenoberfläche und im Tränensystem

## Institute of Biochemistry -**Emil-Fischer-Center**

Chair of Biochemistry and Molecular Medicine

## Doctorate theses 2017

Hannappel, Christian, Dr. med.: Charakterisierung der α-Synuclein Oligomerisation in Synucleinopathien

#### Doctorate theses 2018

Barth, Anna, Dr. med.: Identifikation MIA inhibierender Medikamente und Peptide

Hildenstein, Frank, Dr. med.: ATP-Rezeptoren auf Mesangiumzellen der Ratten-Niere: funktionelle Identifikation und Charakterisierung

Mittnacht, Sebastian, Dr. med.: Effekt von N-Ethylglycin und N-N-Dimethylglycin auf die Glycintransporter GlyT1/GlyT2 und die Glycinrezeptoren a1-3

Schmid, Kathrin, Dr. med.: Die Rolle des Clusters miR-302-367 in der Entstehung und Progression des malignen Melanoms

Süß, Thomas, Dr. med.: Der Einfluss von miR-188-5p und miR-30a auf die Expression von Oberflächenmolekülen bei Rheumatoider Arthritis und Osteoarthritis

von Wittgenstein, Julia, Dr. rer. nat.: Characterization of sox11 as a novel activity-dependent gene with dentate gyrus-specific expression

## Institute of Biochemistry -**Emil-Fischer-Center**

Chair of Biochemistry and Pathobiochemistry

#### Doctorate theses 2017

Kravic, Bojana, Dr. rer. nat.: In murine skeletal muscles ablation of Erbin is associated with impaired NMJs and the loss of CK2 beta with impaired mitophagy

Muth, Katharina, Dr. rer. nat.: Analysis of oligodendrocyte progenitor cell differentiation following genetically manipulated expression of Sox transcription factors in Mus musculus

#### Doctorate theses 2018

Turnescu-Uzat, Tanja, Dr. rer. nat.: The role of Sox8 and Sox10 in myelin maintenance and expression of the myelin gene Mog in the mouse central nervous system

#### Institute of Biochemistry -**Emil-Fischer-Center**

**Professorship of Bioinformatics** 

#### Doctorate theses 2017

Socher, Eileen, Dr. rer. nat.: Computerbasierte Analyse von pH-induzierten Effekten auf die Proteinstruktur

#### Doctorate theses 2018

Kahler, Anna, Dr. rer. nat.: Intrinsische Flexibilität und Strukturelle Stabilität von Proteinen Sandmann, Achim, Dr. rer. nat.: Moleküldynamik-Simulationen zur Untersuchung lokaler Deformation von DNA in Protein-DNA-Komplexen

#### Institute of Physiology and Pathophysiology Chair of Physiology

#### Doctorate theses 2017

Achterberg, Anne, Dr. med.: Die Bedeutung von Activin bei Alkoholtrinkverhalten

Bolsinger, Julia, Dr. med.: Ernährungswissenschaftliche Studien zu Pathogenese, Klinik und Prävention von Typ 2 Diabetes und Metabolischem Syndrom in der Nilratte (Arvicanthis niloticus)

Denner, Ann Catherine, Dr. med. dent.: Untersuchung des TRPA1-Rezeptorkanals in der Dura mater von Nagetieren bezüglich seiner Rolle in der meningealen Nozizeption und Kopfschmerzentstehung

Groß, Norbert, Dr. med.: Systemische Desensitivierung von TRPA1 durch Capsazepin und Senföl – eine neue Strategie gegen Schmerz und Entzündung

Heßler, Sabine, Dr. rer. nat.: Einfluss von BACE1 auf die KCNQ-Kanäle

Koch, Angelika, Dr. med.: Vergleich von 3T und 1,5T bei der funktionellen Bildgebung somatosensorischer und motorischer Reize

Will, Christine, Dr. med. dent.: Änderung des Gefäßdurchmessers am Hirnstamm als indirektes Maß der trigeminalen Aktivität

#### **Doctorate theses 2018**

Brauner, Jan, Dr. med.: Das Antipsychotikum Risperidon inhibiert spannungsgesteuerte Natriumkanäle bei klinisch wirksamen Konzentrationen Hartmann, Stephanie, Dr. rer. nat.: beta-Secretase BACE1 regulates expression and function of voltage-dependent K+ channel Kv3.4 in the hippocampus

Nagler, Lorenz, Dr. med.: Mikroneurographische Untersuchung der axonalen Eigenschaften von humanen C-Nervenfasern unter Lacosamid-Einfluss

Schmidt, Jakob, Dr. med.: Wirkung des Anti-CGRP-Spiegelmers NOX-L41 auf die neuronale Aktivität im Nucleus spinalis n. trigemini der Ratte

## Habilitation 2018

Hoffman (geb. Diskin), Tal, PD Dr. rer. biol. hum.: Sensory transduktion and transformation in peripheral nerve fibers and their endings

Kichko, Tetyana, PD Dr. rer. nat.: Mechanismen sensorischer Irritation und neurogener Entzündung in der Trachea

<sup>\*</sup> Postdoctoral qualification showing ability to lecture and do research at professorial level

#### Institute of Cellular and Molecular Physiology Chair of Physiology (Systems Physiology)

Doctorate theses 2017

**Niklas, Christian,** Dr. med.: Wirkung von Prostaglandin E2 und Arachidonsäure auf den transepithelialen Ionentransport renaler Sammelrohrepithelzellen

#### Doctorate theses 2018

Göhl, Kristina, Dr. med.: Funktionelle Charakterisierung der Liddle-Mutation P642A in der alpha-Untereinheit des epithelialen Natriumkanals (ENaC)

**Krappitz, Annabel**, Dr. med.: Identifizierung spezifischer Proteaseschnittstellen in der γ-Untereinheit des humanen epithelialen Natriumkanals (ENaC) mit funktioneller Bedeutung für dessen Regulation

Wallner, Sandra, Dr. med.: Untersuchungen zu funktionell relevanten Motiven am N-Terminus der d-Untereinheit des epithelialen Natriumkanals (ENaC)

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

#### Doctorate theses 2017

**Braun, Michael,** Dr. med.: Berufskrankheit 5103 – Hautkrebs durch natürliche UV-Strahlung. Erfahrungen mit der Begutachtung: Auswertung der Gutachten aus den Jahren 2010-2015

**Clarner, Annika Christine,** Dr. rer. biol. hum.: Laienbasierte Akutversorgung nach Arbeitsunfällen. Untersuchung zur Evidenz von Erstbetreuungssystemen – als psychische Ersthilfe – im öffentlichen Personennahverkehr

Körber, Michael, Dr. med.: Subjektive Arbeitsbelastung, Arbeitszufriedenheit, Work-Life-Balance von Ärzten und Pflegekräften eines Kommunalklinikums im ländlichen Raum im Vergleich zu einem großstädtischen Universitätsklinikum

Munker, Šven, Dr. med. dent.: Die Platin- und Rhodiumexposition der deutschen Allgemeinbevölkerung – Urinlevel und beeinflussende Faktoren

Wacker, Michaela, Dr. med.: TEWL & Corneometrie vs. HEROS – Aussagekraft biophysikalischer Methoden im Feldversuch im Vergleich zu Ergebnissen eines quantitativen Hautscores in Bezug auf die Früherkennung des Handekzems

#### Doctorate theses 2018

**Bernet, Franziska,** Dr. med.: HEROS vs. Polarisationsspektroskopie – Vergleich zweier Methoden zur Früherkennung und Dokumentation des Handekzems

**Brandt, Adrian,** Dr. med.: Checkliste versus Mitarbeiterbefragung – Gibt es einen Goldstandard für die Gefährdungsbeurteilung psychischer Belastungen? – Pilotprojekt an einem Universitätsklinikum

Kladt, Carolin, Dr. med.: Evaluation der Reliabilität des Permeabilitätskoeffizienten (Kp) für die Bestimmung der Hautpenetrationshöhe von chemischen Stoffen auf der Basis von Flynn s Datenbank

#### Additional qualification 2018

Pink, Mario, Dr.: Expert chemist for toxicology

#### **Institute for Biomedicine of Aging** Chair of Internal Medicine (Geriatrics)

#### Doctorate theses 2017

Schülein, Samuel, Dr. rer. biol. hum.: Auswirkung eines Rollators auf Gangparameter stationärer geriatrischer Patienten

**Christner, Sara,** Dr. med.: Screening von Mangelernährung bei Patienten in der stationären Geriatrie

Grosch, Ella, Dr. med.: Ernährungszustand bei geriatrischen Tagesklinik-Patienten – Prävalenz, Vergleich unterschiedlicher Screening-Verfahren und mögliche Ursachen von Mangelernährung Jurga-Freytag, Malgorzata, Dr. med.: Das Phänomen der Harninkontinenz in einer Population geriatrischer Rehabilitationspatienten unter Berücksichtigung der Begleitmorbiditäten, der Funktionsdefizite und des Verlaufs

**Kronawitter, Vera,** Dr. med.: Die Clinical Frailty Scale bei älteren Patienten mit arterieller Hypertonie

Wiedenmann, Katharina Jutta Erika, Dr. med.: Gesundheitssituation pflegebedürftiger Senioren und Seniorinnen in Privathaushalten

#### Doctorate theses 2018

Berchtold, Sarah, Dr. med.: Der Einfluss von Medikamenten auf das Sturzrisiko bei Menschen mit geistiger Behinderung

Forster, Christian, Dr. med.: Die diabetische Neuroosteoarthropathie (DNOAP) – Vergleich der Aussagekraft der verschiedenen diagnostischen Verfahren zur Erfassung der Charcot-Arthropathie

Streicher, Melanie, Dr. rer. biol. hum.: Nutritional situation and nutritional support in nursing homes – Results from the nutritionDay project

### Institute of Clinical and Molecular Virology

Chair of Clinical Virology

## Doctorate theses 2017

Fuchs, Sebastian, Dr. rer. nat.: AAV-mediated antibody gene transfer for the prevention of immunodeficiency virus infection in rhesus monkevs

**Groß, Christine**, Dr. rer. nat.: Effects of the viral Tax protein on cell-to-cell transmission of Human T-cell leukemia virus type 1 (HTLV-1)

Schilling, Eva-Maria, Dr. rer. nat.: Funktionsmechanismus der de-SUMOylierung durch das Regulatorprotein IE1 des humanen Cytomegalovirus

#### Doctorate theses 2018

Boscheinen, Jan, Dr. med.: Herstellung einer Herpes Simplex Typ 1 (HSV-1) basierten Tumorvakzine

Friedrich, Melanie, Dr. rer. nat.: Die Rolle des Ubiquitin-Proteasom-Systems in den späten Prozessen der HIV-1 Replikation

**Reichel, Anna**, Dr. rer. nat.: Role of the chromatin remodeling factor SPOC1 for human cytomegalovirus replication

#### Habilitation 2018

**Temchura, Vladimir Viktor**, PD Dr. (RUS): Nanoparticle-based antiviral vaccines: from rational design to preclinical evaluation

#### Institute of Clinical and Molecular Virology

**Division of Experimental Therapeutics** 

#### Doctorate theses 2017

Becker, Andreas Michael, Dr. rer. nat.: Influence of glutaminyl cyclases on pyroglutamateamyloid beta formation in transgenic mouse models

#### Institute of Clinical Microbiology,

## Immunology, and Hygiene

Chair of Microbiology and Immunology of Infection

#### Doctorate theses 2017

Leitherer, Sabine, Dr. rer. nat.: Biochemical and functional characterization of two tyrosine phosphatases expressed by the intracellular parasite Leishmania major

asite Leishmania major **Mischke, Thomas,** Dr. med.: Wirkung eines neuen synthetischen TLR9-Agonisten auf myeloische Immunzellen und auf die Aktivierung von NK-Zellen in der experimentellen Leishmaniose

#### Doctorate theses 2018

**Paduch, Katrin,** Dr. rer. nat.: Funktion und epigenetische Regulation der Arginase-1 in Makrophagen *in vitro* und während der Leishmania major Infektion *in vivo* 

**Sossau, Daniel**, Dr. med.: Role of host cell- and parasite-derived arginase in murine Leishmania mexicana infections

Werner, Markus, Dr. med.: Mikrobielle Resistenz von xenogenen Kollagen-Membranen

#### Habilitation 2017

Valenza, Giuseppe, PD Dr. med.: Molekulare Epidemiologie multiresistenter Bakterien

#### Institute of Clinical Microbiology,

Immunology, and Hygiene Division of Infection Biology

## Doctorate theses 2017

Willebrand, Ralf, Dr. rer. nat.: Activation of Eosinophils-cytokine release and survival signals

## Institute of Experimental and

**Clinical Pharmacology and Toxicology** Chair of Pharmacology and Toxicology

#### Doctorate theses 2017

Schirdewahn, Christoph, Dr. med.: Elektrophysiologische Untersuchungen zum Einfluss der Proteinkinase A auf die cAMP abhängige Aktivierung von HCN-Kanälen in Spinalganglienzellen der Maus

#### Doctorate theses 2018

Höfler, Daniel, Dr. med.: Untersuchungen zur cAMP-abhängigen Modulation von HCN2-Kanälen bei inflammatorischem und neuropathischem Schmerz Jamra, Sina, Dr. rer. nat.: Die Rolle der Proteinkinase A in linksventrikulärer Herzhypertrophie

#### Habilitation 2017

Heindl-Erdmann, Cornelia Bettina Ulrike, PD Dr. rer. nat.: Untersuchung schmerzrelevanter Mechanismen durch elektrophysiologische Analysen und funktionelle magnetresonanztomographische Bildgebung an Mäusen

## Institute of Experimental and

#### **Clinical Pharmacology and Toxicology** Chair of Clinical Pharmacology and

Clinical Toxicology

#### Doctorate theses 2017

**Bujok, Krystyna,** Dr. med.: Die Bedeutung des Prostaglandintransporters OATP2A1 für die durch Prostaglandin E2-vermittelte zelluläre Signaltransduktion

Gilde, Astrid, Dr. med.: Untersuchungen zur Inhibition von intestinalen, hepatischen und renalen Arzneistofftransportern durch Lenalidomid Gläser, Hartmut, Dr. med.: Organic Anion Transporting Polypeptides und der Organic Anion Transporter 1 beeinflussen die zelluläre Aufnahme des Flavonoids Quercetin

**Pontones, Constanza,** Dr. med.: Die Wechselwirkung zwischen Trimethoprim und Metformin – Pharmakokinetik, Pharmakodynamik und Bezug zu endogenen Markern für Interaktionen an Arzneistofftransportern

Schächtele, Simone, Dr. rer. nat.: Arzneimitteltherapiesicherheit in einer großen geriatrischen Kohorte: Untersuchungen zu QT-Intervall verlängernden Arzneimitteln

#### Doctorate theses 2018

Hacker, Kristina, Dr. rer. nat.: Funktions- und Inhibitionsuntersuchungen zu den von SLC22A1, SLC22A2 und SLC6A4 kodierten Transportproteinen OCT1, OCT2 und SERT

#### Institute of Human Genetics Chair of Human Genetics

#### Doctorate theses 2017

Ehrlicher, Maria, Dr. rer. nat.: Identifizierung genetischer Risikofaktoren bei Psoriasisarthritis Ismeier, Kathrin, Dr. med.: Identifizierung und Analyse des SETDB1-Gens als Kandidatengen für mentale Retardierung

mentale Retardierung Stanek, Eva-Maria, Dr. med.: Identifizierung von Genen für Mentale Retardierung durch Targeted Next Generation Sequencing

#### Doctorate theses 2018

**Grüner, Johanna**, Dr. med.: RHOBTB2 – Charakterisierung eines neuen Kandidatengens für eine Epileptische Enzephalopathie

Lukassen, Sören, Dr. rer. nat.: The contribution of transposable elements to meiotic sex chromosome inactivation (MSCI) and their detection in whole exome sequencing data

Maler, Bettina, Dr. med.: Etablierung einer Spoc1-"knockout"-Mauslinie

Scheller, Ute, Dr. med.: Transkriptionelle Charakterisierung des Kandidatengens EDC3 für mentale Retardierung

Tawamie, Hasan, Dr. rer. nat.: Identification and characterization of candidate genes in individuals with autosomal recessive intellectual disability

Zahnleiter, Diana, Dr. rer. nat.: Identifikation und Charakterisierung genetischer Faktoren für idiopathischen Kleinwuchs

#### **Board qualification 2018**

Wiesener, Antje, Dr. med.: Humangenetik

#### **Institute of Human Genetics** Division of Stem Cell Biology

Doctorate theses 2018

**Stoll, Svenja**, Dr. med.: Einfluss des NMDA-Signalwegs und von alpha-Synuklein Oligomeren auf die adulte hippocampale Neurogenese

## Institute of Medical Informatics, Biometry, and Epidemiology

Chair of Medical Biometry and Epidemiology

## Doctorate theses 2017

Schneider, Lisa, Dr. med. dent.: Die Rolle der Kindergärten beim kindlichen Sonnenschutz: Empirische Ergebnisse einer Befragung in der Stadt Erlangen und im umgebenden Landkreis Erlangen-Höchstadt

#### Doctorate theses 2018

Müller, Katharina, Dr. med.: Hautkrebsprävention an bayerischen Kindergärten: ein Vergleich der Regionen Erlangen und Fürth

#### Habilitation 2017

Adler, Werner, PD Dr. rer. biol. hum.: Anwendung und Optimierung von baumbasierten Klassifikationsensembles in der Medizin Habilitation 2018

**Hofner, Benjamin**, PD Dr. rer. nat.: Boosting methods for complex biological and biomedical applications

Mayr, Andreas, PD Dr. rer. biol. hum.: Erweiterung der gradientenbasierten Boostingmethode in der biomedizinischen Forschung

#### Institute of Medical Informatics, Biometry, and Epidemiology Chair of Medical Informatics

## Doctorate theses 2017

Zunner, Christian, Dr. med.: Abbildung lokaler Laborwertbezeichnungen auf die internationale Standard-Klassifikation LOINC: Durchführung und Evaluation

#### Doctorate theses 2018

Fehd, Caroline, Dr. rer. biol. hum.: Erzeugung von wissenschaftlichen Mehrwert durch Weiterverwendung anästhesiologischer Daten aus Narkodata (Datenanalyse und -auswertung) Hinderer, Marc, Dr. rer. biol. hum.: IT-gestützte Entscheidungsprozesse Molekularer Tumorboards in deutschen Universitätsklinika – Unterstützungsmöglichkeiten und elementare Herausforderungen

#### Habilitation 2018

Sedlmayr, Martin, PD Dr. rer. nat.: Big Data Infrastrukturen für die medizinische Forschung und Versorgung

#### Institute of Medical Physics Chair of Medical Physics

#### Doctorate theses 2017

Aklan, Bassim, Dr. rer. biol. hum.: Integrated PET/MR Hybrid Imaging: Simulation and Evaluation of Modified System Hardware Design and Reconstruction Software

Gerner, Bastian, Dr. rer. biol. hum.: Quantitative Computertomographie des distalen Unterarms

Schwab, Andreas, Dr. rer. biol. hum.: Streustrahlungsartefaktreduktion in der Brust-Computertomografie

Töpfer, Thomas, Dr. rer. biol. hum.: Quantifizierung von Knochenerosionen bei rheumatoider Arthritis in hochauflösenden CT-Bildern Witke, Andreas, Dr. rer. biol. hum.: Einfluss unterschiedlicher Kraft-Trainingsprogramme auf leistungsphysiologische und gesundheitsrelevante muskuläre und kardiale Größen bei untrainierten Männern im mittleren Lebensalter. Eine randomisierte kontrollierte Interventionsstudie mit modernen, bildgebenden Verfahren. Die PUSH-Studie

#### Doctorate theses 2018

**Grimm, Alexandra,** Dr. rer. biol. hum.: Quantitative Techniken der Magnetresonanztomographie und -spektroskopie zur Messung von muskulärem Fett

Jiang, Zhenzhen, Dr. rer. biol. hum.: Implementierung und Evaluation von 3D Rekonstruktions-Algorithmen für Dedizierte Brust CT Teschler, Marc, Dr. rer. biol. hum.: Ganzkörper-Elektromyostimulation – Möglichkeit, Chancen und Risiken der neuen Trainingstechnologie

#### Habilitation 2017

**Schmidt, Bernhard,** PD Dr. rer. biol. hum.: Dose Reduction for Computed Tomography

## Institute of Neuropathology

Chair of Neuropathology

## Doctorate theses 2017

Miermeister, Christian, Dr. med.: Spezifikation histologischer Kriterien für die Diagnose atypischer Hypophysenadenome basierend auf Daten aus dem deutschen Register für Hypophysentumoren

Schurr, Johannes, Dr. med.: Milde kortikale Entwicklungsstörung mit oligodendroglialer Hyperplasie in Frontallappenepilepsie: Eine neue klinisch-pathologische Entität

#### Doctorate theses 2018

Schult, David, Dr. med.: Identifikation neuer diagnostischer Marker und potentieller Therapiestrategien bei Hypophysentumoren

#### Institute of Pathology

Chair of General Pathology and Pathological Anatomy

#### Doctorate theses 2017

Barthelmeß, Sarah, Dr. med.: Solitäre fibröse Tumoren und Hämangioperizytome mit verschiedenen Varianten der NAB2-STAT6 Genfusion sind jeweils durch typische Histomorphologie sowie charakteristische klinisch-pathologische Merkmale gekennzeichnet **Braumandl, Karin**, Dr. med.: Untersuchungen zu ß-Catenin hinsichtlich des Mutationsstatus, sowie klinisch-pathologischer Eigenschaften in aggressiver Fibromatose (Desmoid-Tumor)

Ernst, Susanne, Dr. med.: Kliniko-pathologische Charakterisierung der Prostatastanzen unter besonderer Berücksichtigung des Gleason-Grades Forster, Stefan, Dr. med.: Die Rolle der Deathassociated Protein Kinase in Zellmigration und Verankerungs-unabhängigem Wachstum von Darmkrebszellen

Kapsner, Lorenz, Dr. med.: Vergleich verschiedener Methoden zur Erstellung von Libraries für die Next-Generation-Sequenzierung

Koschemann, Victoria, Dr. med.: MED12 Mutationsstatus als diagnostischer Marker zur Differenzierung glattmuskulärer Tumore

Schloßbauer, Mathias, Dr. med.: Evaluation des Regressionsgradings nach Dworak in Kombination mit möglichen prognostischen Faktoren bei Lebermetastasen des kolorektalen Karzinoms

Wachter, Peter, Dr. med.: Immunhistochemische Charakterisierung molekularer Subtypen des mammaeren Morbus Paget

#### Doctorate theses 2018

**Dorsch, Melissa**, Dr. med.: The role of DAPK in M1/M2 macrophages and for their interplay with colorectal tumor cells

Döhla, Manuel, Dr. med.: Über den Charakter der epithelialen Inflammation bei Achalasie Erben, Pia Barbara, Dr. med.: Die prognostische Bedeutung der nukleären und zytoplasmatischen Karyopherin Alpha2-Expression in einem Kollektiv radio(chemo)therapierter Plattenep-

ithelkarzinome des Kopf-Hals-Bereichs Hoja, Benjamin, Dr. med.: Assoziation eines Polymorphismus im Genlocus 11q13.3 mit der Expression des Kandidatengens CCND1 in Nierenzellkarzinomen unter Berücksichtigung der klinisch-pathologischen Parameter

Kumm, Niklas, Dr. med.: Massive Parallelsequenzierung unterschiedlich erstellter DNA-Bibliotheken Gastrointestinaler Stromatumore und Systemischer Mastozytosen zur Detektion niederfrequenter Mutationen in KIT und PDGFRA

#### Habilitation 2017

Stöhr, Christine, PD Dr. rer. nat.: Molekulare Pathologie der histologischen Typen des Nierenzellkarzinoms

**Bertz, Simone Yongsu,** PD Dr. med.: Histomorphologische und molekulare Untersuchungen beim Harnblasenkarzinom: Prognostische und prädiktive Faktoren

#### **Board qualification 2018**

Geppert, Carol, Dr. med.: Pathology

Additional qualification 2018

Geppert, Carol, Dr. med.: Cytology (MiAc)

#### Institute of Pathology Division of Nephropathology

#### Doctorate theses 2017

Haslinger, Stefan, Dr. med.: Altersbedingte glomeruläre Veränderungen bei hereditärer reduzierter Nephronenzahl am Beispiel der heterozygoten GDNF (+/-)-Maus

**Olmes, Gregor,** Dr. med.: CD163 positive M2clike Makrophagen dominieren in Nierenbiopsien von Patienten mit Lupusnephritis Wörnle, Christoph, Dr. med.: Thrombospondin als prognostischer Faktor in der Nierentransplantation

#### Doctorate theses 2018

**Bibl, Katharina**, Dr. med.: Pathomechanismen der kardialen Angiogenese bei chronischer Niereninsuffizienz

Hagen, Manuel, Dr. med.: Die Reaktivierung des Zellzyklus sensibilisiert Podozyten für Folgeschäden

**Röder, Sebastian**, Dr. med.: CD44 de novo Expression in Parietalen Epithelzellen wird durch ERK-Aktivierung vermittelt und führt zu Matrixakkumulation und erhöhter Zellmigration in Fokal Segmentaler Glomerulosklerose

Röscher, Laura Alina, Dr. med.: Renale Komplementaktivierung in der Pathogenese der arteriellen Hypertonie

#### Habilitation 2018

**Bockmeyer, Clemens Luitpold,** PD Dr. med.: microRNAs, ADAMTS13 und thrombotische Mikroangiopathie: Glomeruläre Genexpressionsanalysen

#### **Board qualification 2018**

Pfister, Frederik, PhD: Pathology

#### **Institute of the History of Medicine and Medical Ethics** Chair of the History of Medicine

#### Doctorate theses 2017

**Braun, Isabel,** Dr. med. dent.: Andreas Pratje (1892 – 1963). Anatomie und Rassenkunde in Erlangen

Hirschmann, Eva, Dr. med.: Geschichte der Anorexia nervosa

#### Institute of the History of Medicine and Medical Ethics Professorship for Medical Ethics

Doctorate theses 2017

**Braun, Birgit**, Dr. phil.: Friedrich Meggendorfer: Person und Ethik eines Psychiaters im Nationalsozialismus

Lehner, Anna, Dr. med.: Medizin und Menschenrechte; Forschung an Gefängnisinsassen nach 1945

#### Habilitation 2017

Reis, Andreas Alois, PD Dr. med.: Ethische Fragen bei der Erforschung, Prävention und Behandlung von Infektionskrankheiten. Analysen im Kontext der Weltgesundheitsorganisation

#### Habilitation 2018

Schmidhuber, Martina, PD Dr. phil. fac. theol.: Ethische und theoretische Aspekte der Alzheimer-Demenz

#### Nikolaus-Fiebiger-Center of Molecular Medicine

Chair of Experimental Medicine I (Molecular Pathogenesis Research)

#### Habilitation 2017

Stemmler, Marc, PD Dr. rer. nat.: Molekulare Aspekte der epithelial-mesenchymalen Transition (EMT) während der Embyonalentwicklung und bei der Krebsentstehung

## Nikolaus-Fiebiger-Center of Molecular Medicine

Chair of Experimental Medicine II (Molecular Oncology)

#### Doctorate theses 2017

Ntourmas, Senem, Dr. rer. nat.: Topologische und funktionelle Charakterisierung des Amer1 Proteins im Kontext des Wnt- und Hippo Signalwegs

#### Doctorate theses 2018

Jalal, Kowcee, Dr. rer. nat.: Functional characterization of PGAM5 in the Wnt/B-Catenin signalling pathway

Lasierra Losada, María, Dr. rer. nat.: Analysis of the role of Zeb1 during pancreas organogenesis and homeostasis

**Ruh**, **Manuel**, Dr. rer. nat.: The role and regulation of the EMT-transcription factor ZEB1 in osteosarcoma tumor progression

#### Habilitation 2018

**Brabletz**, **Simone**, PD Dr. rer. nat.: The role of ZEB1/miR-200 in the progression of epithelial tumors

#### **Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH** Chair of Orthopedics and Orthopedic Surgery

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#### Doctorate theses 2017

**Burow, Mareike,** Dr. med.: Perioperative Komplikationen bei Wirbelsäulenoperationen bei Patienten mit Muskeldystrophie Duchenne und Spinaler Muskelatrophie

**Gothner, Tilman,** Dr. med.: Der Stand der Radiostereometrischen Analyse (RSA) außerhalb der Hüft- und Kniegelenkendoprothetik

#### Doctorate theses 2018

**Dussa, Chakravarthy,** Dr. med.: Behandlung von schweren Spitzknickfüßen bei Zerebralparese mittels Navikulektomie kombiniert mit Mittelfußarthrodese

**Eibl, Thomas,** Dr. med.: Die Eclipse<sup>™</sup>- und die Affinis<sup>®</sup> Short-Schulterprothese – ein Vergleich zweier schaftfreier Schulterprothesensysteme mit unterschiedlichen humeralen Verankerungskonzepten

Hüttmeyer, Miriam, Dr. med.: Aktueller Wissensstand der Radiostereoanalyse in der Hüftendoprothetik

Klein, Malina, Dr. med.: Auswirkungen verschiedener Röntgenprojektionen einer metallischen tibialen Knie-Endoprothesen-Komponente auf die Validität von Modell-basierten RSA-Phantomexperimenten

Wanivenhaus, Fabian, Dr. med.: Präklinische Reliabilitätsermittlung eines markerbasierten RSA (Röntgen-Stereophotogrammetrische-Analyse)-Messaufbaus in medial-lateraler Projektion anhand der Femurkomponente der BPK-S Integration Ceramic BIOLOX®delta Knieendoprothese am Sawbone-Modell

#### Habilitation 2017

Fujak, Albert Mieczyslaus, PD Dr. med.: Orthopädisches Management bei Patienten mit neuromuskulären Erkrankungen mit besonderer Berücksichtigung der Spinalen Muskelatrophien (SMA)

#### **Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH** Division of Orthopedic Rheumatology

#### Doctorate theses 2017

Kupfer-Pishkova, Olga, Dr. med.: Auswirkungen des DRG-Systems auf die stationäre Rehabilitation nach Hüft- und Kniegelenkersatz Naus, Rainer Philipp, Dr. med.: Funktionsgewinn nach bikondylärer Knie-TEP im 2. Halbjahr: Unterschiede zwischen rheumatoider Arthritis und Gonarthrose

Schauer, Alexander, Dr. med.: Einfluss von Insulin und Dexamethason auf den L-Typ Ca2+ Strom von isolierten Kardiomyozyten der Ratte

#### Doctorate theses 2018

Friedrich, Christopher, Dr. med.: Synergismus von Steroid- und Peptidhormonen bei der Regulation des L-Typ Ca2+-Stroms in linksventrikulären Kardiomyozyten der Ratte

Westphal, Elisa, Dr. med.: Abweichungen plantarer Kraftverhältnisse in der dynamischen Pedobarographie – Die Rolle von Innenschuhmesssystemen und ortsbasierter Messplattformen als beeinflussende Faktoren

#### **Board qualification 2017**

Weiß, Julian, Dr. med.: Orthopedics and Accident Surgery

Wittmann, Mareike, Dr. med.: Orthopedics and Accident Surgery

#### **Department of Anesthesiology** Chair of Anesthesiology

#### Doctorate theses 2017

Aust, Christian, Dr. med.: Auswirkungen der Allgemeinanästhesie auf die kognitiven Funktionen bei Patienten mit vorbestehendem milden Defizit – Pilotstudie zur Erfassung der Inzidenz und möglicher Einflussfaktoren

**Fröhlich, Katharina Maria,** Dr. med.: Retrospektive Analyse der analgetischen Effizienz von Hydromorphon-TCI-PCA und Morphin-PCA in der frühen postoperativen Schmerztherapie kardiochirurgischer Patienten

Hoffmann, Melanie, Dr. med.: Anatomische Lokalisation der Stimmlippen im Verhältnis zur Halswirbelsäule – ein neuer prädiktiver Faktor für schwierige Intubation?

Hüttl, Matthias Stephan, Dr. med.: Entwicklung eines Inhaltsclusters und Blended-Learning-Curriculums zum Notfallmanagement für Zahnmediziner

**Kroker, Lisa,** Dr. med.: Posttranslationale Modifikation spannungsabhängiger Natriumkanäle durch den reaktiven Glykolysemetaboliten Methylglyoxal

Maier, Jan-Niklas, Dr. med.: Der intravenöse Zugang in der Verantwortung des Rettungsfachpersonals: Einstellungen – Leistungen – Schwierigkeiten

Maiwald, Thomas, Dr. med.: Outcome der AED-Anwendung im Rettungsdienst – eine retrospektive Erhebung aus einem AED-Programm Stubner, Benedikt, Dr. med.: Vergleich der Effektivität von drei unterschiedlichen Verfahren zur Präoxygenierung und postoperativen Sauerstofftherapie nach Extubation bei Patienten mit bariatrischen Operationen Weith, Thomas, Dr. med.: Konzeption und Entwicklung eines medizinischen Casereport-Portals "OrphanCases" in Angliederung an das Projekt OrphanAnesthesia

#### Doctorate theses 2018

Berlin, Sabrina, Dr. med.: Messung von Propofol in der Atemluft – Erste klinische Erprobung eines neuen elektrochemischen Sensors

**Bögler, Felix,** Dr. med.: Der Stellenwert der nicht-invasiven beat-to-beat Blutdruckmessung mittels des ClearSight-Systems (Edwards Lifescience) bezüglich Schlagvolumen und Herzzeitvolumen

**Eger, Stephanie,** Dr. med.: Vesikel-abhängige TRPM8-Kanalexpression steigert die Kaltsensitivität kutaner C-Fasern im murinen Haut-Nervenpräparat

Gräbner, Tina, Dr. med.: Pharmakokinetische Modellbildung der gemessenen Gesamtkonzentrationen von Hydromorphon in den ersten 24 Stunden nach kardiochirurgischem Eingriff mit Herz-Lungenmaschine

Kienle, Florian, Dr. med.: Pilotstudie zum Einfluss digitaler Visualisierungssysteme auf Narkoseführung, Hämodynamik und Prozesszeiten im operativen Routinebetrieb

Kilian, Melanie, Dr. med.: Detektion von Vitalparametern mit nicht-linearer Schwingkreistechnologie: Evaluation eines nichtinvasiven Sensorsystems im porcinen Reanimationsmodell

Peter, Julian, Dr. med.: Pharmakodynamische Modellbildung von Hydromorphon während postoperativer Schmerztherapie nach kardiochirurgischen Eingriffen

**Vollenbruch, Vera,** Dr. med.: Evaluation of a method converting venous values of acid-base and oxygenation status to arterial values in patients undergoing an abdominal, heart or neurosurgery

#### Habilitation 2017

**Prottengeier, Johannes Joachim**, PD Dr. med.: Beiträge zur Prozessoptimierung: Operational Research in präklinischer Notfallmedizin und Interhospitaltransfer

**St. Pierre, Michael,** PD Dr. med.: Human Factors in der Anästhesiologie – Simulationsbasierte Strategien zur Stärkung der Patientensicherheit

#### Habilitation 2018

**Castellanos, Alvaro Ixchel**, PD Dr. med.: Auswirkungen und Mehrwert durch EDV im Intensivmedizinischen Umfeld – klinisch, organisatorisch und finanziell

**Eisenried, Andreas,** PD Dr. med.: Nozizeption und erweitertes physiologisches Monitoring im perioperativen Kontext

#### **Board qualification 2017**

Gold, Andreas, Dr. med.: Anesthesiology Moritz, Andreas, Dr. med.: Anesthesiology Staedtler, Sven, Dr. med.: Anesthesiology Sturm, Tanja, Dr. med.: Anesthesiology Wiernik, Michael, Dr. med.: Anesthesiology

#### **Board qualification 2018**

Huberth, Sandra, Dr. med.: Anesthesiology Kienle, Florian, Dr. med.: Anesthesiology Lange, Leonie, Dr. med.: Anesthesiology Meißner, Stephan, Dr. med.: Anesthesiology Nowak, Katharina, Dr. med.: Anesthesiology Schmitt, Kimberly, Dr. med.: Anesthesiology

#### Additional qualification 2017

Wehrfritz, Andreas, Dr. med.: Palliative Medicine

#### Additional qualification 2018

Kränzlein, Diana, Dr. med.: Intensive Care Medicine

Nefzger, Tobias, Dr. med.: Intensive Care Medicine

**Prottengeier, Johannes,** PD Dr. med.: Intensive Care Medicine

Rhode, Doris, Dr. med.: Special Pain Therapy Weller, Konrad, Dr. med.: Special Pain Therapy

## Department of Anesthesiology

Division of Molecular Pneumology

#### Doctorate theses 2017

**Bergauer, Annika**, Dr. med.: Die Rolle von IFNa und IFN- $\alpha$  während der Immunantwort auf virale Atemwegsinfektionen bei Vorschulkindern mit Asthma bronchiale

#### Doctorate theses 2018

Balabko, Liubov, Dr. med.: Erhöhte Expression der Th17-IL-6R/pSTAT3/BATF/RorcT-Achse in der Tumor-Region des Adenokarzinoms im Vergleich mit Plattenepithelkarzinom der Lunge Bielor, Carina, Dr. med.: Die Rolle von TGF-beta bei der Regulierung von Rhinovirus-induzierten Immunantworten bei allergischem Asthma

**Eisenhut, Felix,** Dr. med.: FAM13A fördert das Wachstum von nicht-kleinzelligem Lungenkrebs (NSCLC) und kontrolliert Tumorzellproliferation und -überleben

Hentschke, Isabell, Dr. med.: Die Rolle von IFNß und IL-33/ST2 in der Immunantwort auf Bakterien des Respirationstraktes bei Kindern mit Asthma bronchiale

#### **Department of Anesthesiology** Division of Palliative Medicine

#### Doctorate theses 2017

Bartz, Lena, Dr. med.: Subkutane Medikamentengabe in der Palliativmedizin

**Heß, Stephanie**, Dr. med.: Entwicklung der Patienten mit Nichttumorerkrankungen in der Spezialisierten stationären Palliativversorgung in Deutschland – eine Analyse über die Zeit (2002-2011)

Klosa, Philipp, Dr. med.: The EAPC framework on palliative sedation and clinical practice-a questionnaire-based survey in Germany

Weigel, Susanne, Dr. med.: Hornhautspende in der Palliativmedizin – Auswirkung eines standardisierten Vorgehens

#### Doctorate theses 2018

**Berendt, Julia**, Dr. rer. biol. hum.: Comprehensive Cancer Center (CCC) in Deutschland: Empirische Untersuchung zur Integration der Palliativmedizin und Entwicklung einer Best Practice Strategie

#### Additional qualification 2017

Hoyer, Evelyn, Dr. med.: Palliative Medicine Müller, Marietta: Palliative Medicine Steigleder, Tobias, Dr. med.: Palliative Medicine

## Additional qualification 2018

Gold, Andreas, Dr. med.: Palliative Medicine

#### **Department of Cardiac Surgery** Chair of Cardiac Surgery

#### Doctorate theses 2018

**Friedl, Sven,** Dr. rer. biol. hum.: Methoden der digitalen Bildverarbeitung zur Bewegungsanalyse nativer Herzklappen und Bioprothesen anhand von Hochgeschwindigkeitsvideoaufnahmen

Li, Chang, Dr. med.: Isolierung und Charakterisierung adulter mesenchymaler Stroma-/ Stammzellen aus humanem Thymusgewebe und deren potentielle therapeutische Möglichkeiten

### Habilitation 2017

Heim, Christian Michael, PD Dr. med.: Experimentelle Studien zur chronischen Abstoßung nach thorakaler Organtransplantation

## **Department of Cardiac Surgery**

Division of Pediatric Cardiac Surgery

### Doctorate theses 2018

Schrüfer, Philipp, Dr. med.: Konotrunkale Defekte – Unterschiedliche Genexpression im Aortengewebe von Neugeborenen Speth, Marlene, Dr. med.: Pädiatrische extrakorporale Unterstützungssysteme mit einer Diagonalpumpe der dritten Generation

#### **Department of Dermatology**

Chair of Skin and Veneral Diseases

#### Doctorate theses 2017

**Baur, Rebecca**, Dr. med.: Die Rolle von Notch-Rezeptoren und ADAM-Metalloproteasen in der Pathogenese der Psoriasis

Fendt, Christin, Dr. med. dent.: Typ IV-Sensibilisierung auf patienten-eigene Handschuhe im Kollektiv der Hautklinik Universitätsklinikum Erlangen von 2002-2011

Mahlberg, Ulrike, Dr. med.: Subjektive und objektive Parameter in der Beeinflussung der Lebensqualität bei Patienten mit Vitiligo Moreira, Alvaro, Dr. med.: Eosinophilie als potentieller Biomarker für Melanom

#### Doctorate theses 2018

**Matejko**, **Maria**, Dr. med.: The impact of alitretinoin on epicutaneous patch test results in patients with hand eczema

**Reimer, Katharina**, Dr. med.: Characterization of Immune Cell Subsets in a Novel Murine Model of Human Trisomy 21

#### **Board qualification 2017**

**Bosch-Voskens, Caroline**, Dr.: Dermatological and Venereal Diseases

Köceroglu, Mehmet Ikbal: Anesthesiology

**Kersting, Florina**, Dr. med.: Dermatological and Venereal Diseases

#### Board qualification 2018

Lienert, Anne-Marie, Dr. med.: Dermatological and Venereal Diseases

**Böhm, Olga,** Dr. med.: Dermatological and Venereal Diseases

Heppt, Franz, Dr. med.: Dermatological and Venereal Diseases

Zeller, Stephanie, Dr. med.: Dermatological and Venereal Diseases

## Department of Medicine 1 – Gastroenterology, Pneumology, and Endocrinology

Chair of Internal Medicine I

### Doctorate theses 2017

Abendroth, Benjamin, Dr. rer. biol. hum.: Untersuchung zur Rolle Batf-abhängiger T-Zellen in der Pathogenese der intestinalen Graft-versus-Host-Erkrankung

**Ebert, Thomas,** Dr. med.: Einleitung einer druckkonstanten CPAP-Therapie mittels Auto-Titration versus manueller Titration – Randomisierte Studie zu Effektivität und Langzeitcompliance

Hirschmann, Simon, Dr. med.: Sicherheit und Wirksamkeit intravenöser Cyclophamid-Stoßtherapie bei Patienten mit therapierefraktärem Morbus Crohn

Hofmann, Eva, Dr. med.: Akute beatmungspflichtige respiratorische Insuffizienz internistischer Intensivpatienten – Patientencharakteristika, Ätiologie, Prognose

Migliarina, Vera, Dr. med.: Ursachen, Diagnostik, Behandlungs- und biographischer Verlauf der Hypophysenvorderlappeninsuffizienz in einer Endokrinologischen Sprechstunde

**Orlemann, Till,** Dr. med.: Der Einfluss von körperlichem Training in Form von Ganzkörper-Elektromuskelstimulation und Ernährungstherapie bei mangelernährten Patienten mit maligner Grunderkrankung in kurativer oder palliativer Behandlungssituation

**Rösch, Lara,** Dr. med.: Stellenwert der Leberelastometrie (Acoustic Radiation Force Impulse) während antiviraler Tripeltherapie bei chronischer Hepatitis C

Schiemer, Jonas, Dr. med.: Die Rolle von Batf3 in der pulmonalen Manifestation eines transplantablen Tumors

Schuster, Susanne, Dr. rer. biol. hum.: GeriQ-ED Quality Indicators for Geriatric Emergency Care – Entwicklung von Qualitätsindikatoren für die Versorgung von geriatrischen Notfallpatienten

Volmer, Stefan, Dr. med.: Molekulare Charakterisierung einer T-Zell-assoziierten Signatur beim nicht-kleinzelligen Lungenkarzinom

Hahn, Anna, Dr. med.: Endoskopische Therapie intestinaler Stenosen bei Morbus Crohn: Erfolg und Prognose

Keim, Victor Johannes, Dr. med.: Klinische Anwendung des Diagnose-Scores der International Autoimmune Hepatitis Group in der Diagnostik der unklaren Hepatopathie. Eine retrospektive Analyse

#### Doctorate theses 2018

**Carstensen, Antje,** Dr. med.: Charakterisierung des Immunzellinfiltrats bei gastrointestinal vermittelten Allergien und relevanten Differentialdiagnosen mithilfe von immunhistochemischen Nachweisverfahren der Diaminoxidase, CD117 und MBP

Haziri, Drilon, Dr. med.: Transplantation des fäkalen Mikrobioms und deren Einfluss auf die Klinik und paraklinischen Parameter bei Patienten mit Clostridium-difficile-Infektion

**Heyn, Sabrina**, Dr. med.: Spektrum und Krankheitsverlauf biliärer Neoplasien am Universitätsklinikum Erlangen im Zeitraum von 1990 bis 2014

Junker, Rebecca, Dr. med.: Die Prävalenzbestimmung von Hepatitis C in einem definierten Patientenkollektiv mittels eines Schnelltestverfahrens

Kästner, Robert, Dr. med.: Einsatz insulinotropher Antidiabetika bei älteren Patienten – Effektivität, Einflussfaktoren, Patientenwissen

Koch, Julia, Dr. med.: Prospektive Untersuchung von Patienten mit Chronisch Entzündlichen Darmerkrankungen mittels B-Bild-Darmsonographie zur Beurteilung des Stellenwertes der Darmsonographie

Krischke, Eugenia, Dr. med.: Intestinales IgE, Nahrungsmittelelimination und Veränderungen klinischer Parameter anhand der Rom III Kriterien und der Schweregradskalierung bei Reizdarmpatienten

Lang, Elisabeth, Dr. med.: Etablierung eines krankenhauseigenen Systems zur Ernährungsüberwachung für pädiatrische Patienten mit einer malignen Erkrankung

Müller, Stephanie, Dr. med.: ELGE – ESI und Leitsymptom getriggertes 10 Minuten EKG zur STEMI Identifizierung in der ZNA

**Paulus, Susanne**, Dr. med.: Neutrophil Extracellular Traps in der Pathogenese der chronischentzündlichen Darmerkrankungen

Schindlbeck, Andrea, Dr. med.: Einfluss von körperlichem Training in Form von Ganzkörper-Elektromyostimulation und individueller Ernährungstherapie auf Patientinnen mit maligner gynäkologischer Grunderkrankung – eine kontrollierte Pilotstudie

Schink, Kristin, Dr. rer. biol. hum.: Einfluss einer therapiebegleitenden kombinierten Bewegungs- und Ernährungsintervention bei Krebspatienten

Vasilakis, Thomas, Dr. med.: Immunohistochemische Expression von Diaminooxidase am oberen Gastrointestinaltrakt bei gastrointestinal vermittelten Allergien

Wilk, Florian, Dr. med.: Kennzahlen und Qualitätsindikatoren einer Zentralen Notaufnahme

#### Habilitation 2017

**Günther, Claudia,** PD Dr. rer. nat.: Molecular regulation of programmed cell death in inflammatory diseases

#### Habilitation 2018

Albrecht, Heinz, PD Dr. med.: Innovative endoskopische Diagnostik und Therapie bei malignen und entzündlichen Erkrankungen des Gastrointestinaltraktes Atreya, Imke, PD Dr. med, PhD: Signaltransduktion in Immunzellen bei Darmentzündung und Darmtumorgenese

Pfeifer, Lukas Johannes, PD Dr. med.: Klinische Bedeutung der ARFI-Elastographie in der Diagnostik der Leberzirrhose

Rath, Timo, PD Dr. med.: Immunologische Mechanismen der Pathognese von Darmentzündungen und Lebererkrankungen

**Zirlik, Sabine,** PD Dr. med.: Färbetechniken bzw. bildgebende Verfahren an respiratorischen Materialien in und ex vivo

## Board qualification 2017

Hirschmann, Simon, Dr. med.: Internal Medicine

Hofmann, Eva Maria: Internal Medicine

Jungbauer, Stefan: Internal Medicine Lindner-Hagel, Annette: Internal Medicine

Merola, Elettra: Internal Medicine Pfeifer, Lukas, PD Dr. med.: Internal Medicine

Rath, Timo, Prof. Dr. med.: Internal Medicine

#### **Board qualification 2018**

Engel, Matthias, PD Dr.: Gastroenterology Geppert, Annika, Dr. med.: Internal Medicine Koch, Franz: Internal Medicine Müller, Lisa, Dr. med.: Internal Medicine Schellhaas, Barbara, Dr. med.: Internal Medicine

#### Department of Medicine 2 – Cardiology and Angiology Chair of Internal Medicine II

#### Doctorate theses 2017

Kopp, Sebastian, Dr. med.: Vergleichende *ex-vivo*-Untersuchung koronarer atherosklerotischer Plaques mittels 64-Zeilen-Spiral-Computertomographie, Optischer Kohärenz-Tomographie und histomorphologischer Analyse

Luther, Kirsten, Dr. med. dent.: Quantifizierung des epikardialen Fettvolumens mittels kardialer Computertomographie: Vergleich von Protokollen mit unterschiedlicher Röhrenspannung Pecher, Stefan, Dr. med.: Physiologische Einflussfaktoren auf das Leistungspotenzial von Athleten – eine sportmedizinische Analyse von nordischen Kombinierern

Schmidkonz, Christian, Dr. med.: Interobservervariabilitäten der CT-Angiographie für die Bestimmung der Dimensionen des Aortenannulus vor kathetergestütztem Aortenklappenersatz (TAVI)

Wiedemann, Ricarda, Dr. med.: Vergleich der intrakoronaren versus intravenösen Applikation von Adenosin zur Messung der myokardialen fraktionellen Flussreserve

#### Doctorate theses 2018

Atzinger, Armin, Dr. med.: Zusammenhang zwischen mittels kardialer Computertomographie nachgewiesenem Ausmaß der koronaren Artherosklerose und kardiovaskulären Ereignissen in der Langzeit-Nachbeobachtung

Biburger, Lukas, Dr. med.: Computertomographie-basierte Bestimmung des Projektionswinkels für die kathetergestützte Aortenklappen-Implantation: Einfluss auf Kontrastmittelmenge, Strahlenexposition und Interventionsdauer **Brünkmann, Christina Ilse,** Dr. med.: Evaluation der diagnostischen Genauigkeit eines ultraportablen Echokardiographiegerätes im klinischen Routinealltag

**Deser, Maximilian,** Dr. med.: Prognostic value of coronary computed tomography angiography and coronary calcium in the long-term follow-up of patients with suspected coronary artery disease

**Feher, Marcel**, Dr. med.: Randomisierter Vergleich systolischer und diastolischer CT-Datensätze zur Planung der kathetergestützten Aortenklappenimplantation: Eine prospektive Outcome Studie

Gaßmann, Hendrik, Dr. med.: Einflüsse von hochintensivem Intervalltraining und moderatem Ausdauertraining im heimischen Umfeld bei Herzinsuffizienz auf die Endothelfunktion, kardiopulmonale Leistungsfähigkeit und inflammatorische Marker (EndoHEART)

Kallert, Lisa, Dr. med.: Randomisierter Vergleich periprozeduraler Komplikationsraten von transradialer und transfemoraler Koronarangiographie und -intervention bei Patienten über 75 Jahre

Mahjour, Shahin, Dr. med.: Angiografische Beobachtung des Restenoseverhaltens von Drug-Eluting-Stents der ersten Generation

**Plank, Pia Maria**, Dr. med.: Predictors of Technical Failure in Transradial Coronary Angiography and Intervention

Schmid, Jasmin, Dr. med.: Evaluation von Koronarstents mittels Niedrigdosis Dual-Source Computertomographie und Iterativer Rekonstruktion

Zimmer, Thomas, Dr. med.: Ausschluss von Koronarstenosen mittels koronarer CT-Angiographie: Einfluss koronarer Kalzifizierungen

#### Habilitation 2018

Schlundt, Christian, PD Dr. med.: Bildgebung und physiologische Messungen zur Unterstützung kardialer Interventionen

Raaz-Schrauder, Dorette, PD Dr. med.: Biomarker bei der Pathogenese der Koronaren Herzerkrankung

**Arnold, Martin**, PD Dr. med.: Optimierung der periprozeduralen Verfahren für den kathetergestützen Aortenklappenersatz

#### **Board qualification 2018**

**Bal**, **Zeynap**, Dr. med.: Internal Medicine and Cardiology

Bittner, Daniel, Dr. med.: Internal Medicine and Cardiology

Lindemann, Hannes, Dr. med.: Internal Medicine and Cardiology

Schmid, Jasmin, Dr. med.: Internal Medicine and Cardiology

#### Additional qualification 2018

Arnold, Martin, Dr. med.: Intensive Care Medicine

#### Department of Medicine 3 – Rheumatology and Immunology Chair of Internal Medicine III

#### Doctorate theses 2017

**Chen, Guangliang**, Dr. med.: High fat diet increases melanoma cell growth in the bone mar-

row niche by inducing osteopontin and interleukin 6

**Del Vecchio, Tina,** Dr. med.: Zunahme antifibrotischer Effekte und verbesserte Substanzverträglichkeit durch kombinierte Hemmung der Morphogen-Signalwege

Pitkowski, Jana, Dr. med.: Die Hemmung von HSP90 hemmt den TGFß Signalweg und reduziert Fibrose in experimentellen Modellen

Sendlbeck, Melanie, Dr. med.: Vergleich von drei häufig verwendeten Schmerzskalen bei Patienten mit rheumatoider Arthritis und deren Rolle bei der Messung von Veränderungen im Schmerzempfinden

Simon, Dominic, Dr. med.: The role of galectin-3 in bone homeostasis

Standfest, Kathrin, Dr. med.: Analyse des Einflusses einer begleitenden Therapie mit synthetischen disease Modifying Antirheumatic Drugs und einer Vortherapie mit biologischen Disease Modifying Antirheumatic Drugs auf die Wirksamkeit von Tocilizumab bei Patienten mit rheumatoider Arthritis

**Stoll, Andrej,** Dr. med.: Identifizierung HLA-C restringierter, HIV-1 spezifischer CTL Epitope mittels Peptid induzierter Hochregulierung der HLA-C Expression

#### Doctorate theses 2018

**Baumann, Julian**, Dr. med.: Analyse von JAK-STAT-Signalwegen bei Patienten mit rheumatischen Erkrankungen und bei Patienten mit HIV1-Infektion

Kraus, Sebastian, Dr. med.: Longitudinale Vergleichsanalyse der Reparatur struktureller Knochenschädigungen bei Patienten mit rheumatoider Arthritis unter Therapie mit TNF- oder IL-6 Rezeptorinhibitoren

Krieter, Manuel, Dr. med.: Charakterisierung subklinischer Veränderungen in artikulären Strukturen bei Risikopatienten für die Entwicklung einer rheumatoiden Arthritis mittels Magnetresonanztomographie und hochauflösender peripherer quantitativer Computertomographie **Reichert, Helena**, Dr. med.: Interaktion morphogener Signalwege in der Entstehung fibrotischer Erkrankungen

**Renner, Peter,** Dr. med.: Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients (Review)

Seuffert, Fritz, Dr. med.: Untersuchungen zum Einfluss des Knorpelproteins Ucma auf den klinischen Verlauf der seruminduzierten Arthritis bei Mäusen

**Simon, David,** Dr. med.: Analyse periartikulärer Knochenveränderungen bei Patienten mit kutaner Psoriasis ohne Psoriasis-Arthritis

**Vogel, Kristin,** Dr. med.: Die diagnostische Güte der [18F]-FDG-PET/CT zur Ursachenfindung von Fieber unklarer Genese und Entzündung unklarer Genese

von Pickardt, Gero, Dr. med.: Innate Lymphoid Cells und Interleukin-17 in der Pathogenese Rheumatischer Erkrankungen

#### Habilitation 2017

Hoffmann, Markus, PD Dr. rer. nat.: Molekulare Mechanismen zur Entstehung von Autoimmunerkrankungen Rech, Hans Jürgen, PD Dr. med.: Neue Diagnostik und neue Therapien in der Rheumatologie - Früherkennung, Prädiktion, Remission und Verlauf bei entzündlich rheumatologischen Erkrankungen

#### Habilitation 2018

Bozec, Aline, Prof. Dr. rer. nat.: Organ cross-talk controlled by transcription factors, nutrients and cytonkines during bone homeostasis and diseases

## **Board qualification 2018**

Araujo, Elizabeth: Internal Medicine and Rheumatology

Ramming, Ándreas, Dr. med.: : Internal Medicine and Rheumatology

## Additional qualification 2017

Harrer, Ellen, Dr. med.: Infectiology Krönke, Gerhard, Prof. Dr. med.: Infectiology Wacker, Jochen, Dr. med.: Infectiology

#### **Department of Medicine 3 – Rheumatology and Immunology** Division of Molecular Immunology

#### Doctorate theses 2018

Daum, Patrick, Dr. rer. nat.: Beteiligung der Mikroprozessorkomplex-Untereinheit DGCR8 an der adaptiven Immunantwort und Keimzentrumsreaktion

Meinzinger, Julia, Dr. rer. nat.: Rolle der microRNA-148a in der Plasmazelldifferenzierung Pracht, Katharina, Dr. rer. nat.: Funktion der miR-148a in reifen Plasmazellen

Rokvic, Ljiljana, Dr. rer. nat.: Analysis of impact of hyperosmolality on development, activation and differentiation of B lymphoid cells

Winkelmann, Rebecca, Dr. med.: KLF2 - Ein negativer Regulator der klonalen Prä-B-Zell Expansion und der B-Zell Aktivierung

#### **Department of Medicine 4** -**Nephrology and Hypertension** Chair of Internal Medicine IV

## Doctorate theses 2017

Dörfelt, Kathrin, Dr. med.: 23Natrium-Magnetresonanztomographie zur nicht-invasiven Bestimmung von Natrium-Akkumulationen in Muskulatur und Haut bei Dialysepatienten

Karl, Annalena, Dr. med.: Hinterwurzelganglienneurone mit Afferenzen aus der Niere von Ratten – Veränderte Empfindlichkeit im Modell des sekundären Bluthochdrucks

Kozinski, Claudia, Dr. med.: Funktionelle Veränderungen der renalen Hämodynamik bei Prädiabetikern während eines hyperglykämischen Clamp-Tests im Vergleich zu gesunden Probanden

Moye, Brigitte, Dr. med.: Einfluss des Spenderalters auf die Ergebnisse der Nierentransplantation - Ergebnisse aus der frühen Phase des Eurotransplant Senior Program

Ranzenbacher, Anna-Lisa, Dr. med.: CMV- und HSV-Reaktivierung bei kritisch kranken Patienten. Prävalenz und Diagnostik

## Doctorate theses 2018

Beckmann, Sophie, Dr. med.: Evaluation der Nierentransplantationen im Eurotransplant Senior Programm in den Jahren 2008-2013 am Transplantationszentrum Erlangen-Nürnberg

Boemke-Zelch, Franziska, Dr. med.: Die Auswirkung der SGLT2-Transporter Inhibition durch Dapagliflozin auf den Natriumgehalt des Gewebes im menschlichen Körper

John, Lukas, Dr. med.: SLC26A6 and Coatomer Subunit Delta - Association and Consequences for Regulation of Oxalate Transport

Keller, Mirjam, Dr. med.: Effekte von Linagliptin auf die renale Endothelfunktion bei Patienten mit Diabetes mellitus Typ 2

Kurzhagen, Johanna, Dr. med.: Urin Elektrolyte - Vergleich der 24h - Sammelurinuntersuchung mit Spontanurinproben bei chronisch nierenkranken Patienten im Rahmen der GCKD -Studie

Müller, Simon, Dr. med.: Funktionelle Bedeutung von Keratinen in humanen primären Tubulusepithelzellen

Schellinger, Isabel Nahal, Dr. med.: Einfluss von HIF-stabilisierenden Interventionen auf die gestörte Ischämie-induzierte Angiogenese bei Niereninsuffizienz

Seitz, David, Dr. med.: Kontrolle von Bluthochdruck bei erwachsenen Patienten mit chronischer Nierenerkrankung in Deutschland - Eine Querschnittsanalyse anhand der "German Chronic Kidney Disease"-Studienkohorte

Tzinis, Nadja, Dr. med. dent.: Bedeutung von ASIC für Neurone der Hinterhornganglien mit renalen und nicht-renalen Axonen

#### Habilitation 2017

Schödel, Johannes, PD Dr. med.: Determinanten, Repertoire und Konsequenzen der DNA-Bindung von Hypoxie-induzierbaren Transkriptionsfaktoren

Buchholz, Björn, PD Dr. med.: Proliferationsund sekretionsabhängige Mechanismen des Zystenwachstums bei der autosomal dominanten polyzystischen Nierenerkrankung ADPKD

#### **Board qualification 2017**

Buchholz, Björn, Dr. med.: Internal Medicine

and Nephrology Dienemann, Thomas, Dr. med.: Internal

Striepe, Kristina, Dr. med.: Internal Medicine Weidemann, Charlotte, Dr. med.: Internal Medicine

#### **Board qualification 2018**

Bosch, Agnes, Dr. med.: Internal Medicine Dieterle, Anne, Dr. med.: Internal Medicine Müller-Deile, Janina, Dr. med.: Internal Medicine and Nephrology Rüdel, Benjamin, Dr. med.: Internal Medicine

#### Additional qualification 2018

Dienemann, Thomas, Dr. med.: Intensive care medicine

## **Department of Medicine 5 –**

Hematology and Oncology Chair of Hematology and Oncology

#### Doctorate theses 2017

Bittrich, Max, Dr. med.: Anti-Tumor-Effekte von murinen Zytokin-stimulierten Natürlichen-Killer-Zellen

Bricks, Juliane, Dr. med.: Der Einfluss von oxidativem Stress auf das Immunsystem von Patienten mit chronisch lymphatischer Leukämie unter besonderer Beachtung des T-Zellkompartiments

Busse, Marika, Dr. rer. biol. hum.: Arzneimitteltherapiesicherheit (AMTS) in der Onkologie: Systematische Analyse des Medikationsprozesses von Patienten unter medikamentöser Tumortherapie

Haimerl, Maria, Dr. med. dent.: Bestimmung der unreifen Thrombozyten mit Sysmex XE-5000 und Abbott CD-Sapphire bei hämatoonkologischen Patienten

Vasova, Ingrid, Dr. med.: Allogene Stammzellersttransplantation bei hämatologischen Neoplasien: Einflussfaktoren auf das Transplantationsergebnis und auf das Auftreten einer Graft-versus-Host Erkrankung

#### Doctorate theses 2018

Cybulska, Annalina, Dr. med.: Vergleich unreifer Thrombozyten zwischen Patienten mit Knochenmarksversagen und Patienten mit Immunthrombozytopenie mittels Sysmex XE-5000 und Abbott CD-Sapphire

Schmittlutz, Katrin, Dr. med.: Untersuchungen zur Immunpathogenese der intestinalen Graftversus-Host Erkrankung (GVHD)

Schreiner, Elisabeth, Dr. med.: Zusammenhang zwischen der Frequenz, mitotischen Aktivität und Differenzierung doppelt-negativer T-Zellen und der Entwicklung einer akuten Graft-versus-Host Disease nach allogener hämatopoetischer Stammzelltransplantation

### Habilitation 2018

Bruns, Heiko, PD Dr. rer. nat.: Funktion und Bedeutung von Tumor-assoziierten Makrophagen bei hochmalignen Lymphomen

#### Board qualification 2017

Brückl, Valeska, Dr. med.: Internal Medicine and Hematology and Oncology

#### **Board qualification 2018**

Bosch, Jacobus, Dr. med.: Internal Medicine and Hematology and Oncology Kremer, Anita, PD Dr. med.: Internal Medicine and Hematology and Oncology Waibel, Heidi, Dr. med.: Internal Medicine and Hematology and Oncology

#### Additional qualification 2018

Behzad, Ali, Dr. med.: Acupuncture

#### Department of Neurology Chair of Neurology

#### Doctorate theses 2017

Abel, Henning, Dr. med.: Effekte der intraventrikulären Fibrinolyse auf chronische Shuntabhängigkeit und Outcome nach aneurysmatischer Subarachnoidalblutung

Ammon, Fabian, Dr. med.: Nachweis zentraler Baroreflex-Funktionsstörung mittels Valsalva-Manöver bei Patienten mit stattgehabtem leichten Schädelhirntrauma

**Bogenreuther, Anna Christina**, Dr. med.: Charakteristika intrazerebraler Blutungen unter oralen Antikoagulanzien – Vergleich von Vitamin-K-Antagonisten und direkten oralen Antikoagulanzien

**Distler, Michael,** Dr. med.: Paradoxe Kinesien bei Patienten mit Idiopathischem Parkinson-Syndrom: die Erwartung zeitlicher Zwänge als kritischer Auslöser

**Durner, Gregor,** Dr. med.: 24/7 Live Stream Telemedicine Home Treatment Service for Parkinson's Disease Patients

**Gutjahr, Isabell**, Dr. med.: Neuroanatomische Korrelate von kardialen Rhythmusstörungen bei Patienten mit akutem ischämischen Schlaganfall – eine Voxel-basierte statistische Analyse

Karthaus, Anne, Dr. med.: Die Rolle der immunregulatorischen Moleküle TIM-3 und Galectin-9 in der Pathogenese entzündlicher Muskelerkrankungen

Katrissioti, Eleni, Dr. med.: SASBAG Spasticity after Stroke in Bavaria and Greece

Kopp, Markus, Dr. med.: Die prognostische Bedeutung elektrokardiographischer Early Repolarization-Muster, allgemeiner EKG-Veränderungen sowie der Herzfrequenzdynamik in der Akutphase zerebrovaskulärer Erkrankungen

Macha, Kosmas, Dr. med.: Frühzeitige Antikoagulation mit direkten oralen Antikoagulantien bei Patienten nach transitorischer ischämischer Attacke oder ischämischem Schlaganfall

Niederländer, Charlotte, Dr. ref. biol. hum.: Health Technology Assessment innovativer Medizintechnologien: Stellenwert von Implantatregistern für die systematische Bewertung von Medizinprodukten

**Sammet, Laura**, Dr. med.: Charakterisierung zirkulierender CD4+CD8+ doppelt positiver T Zellen bei Patienten mit Multipler Sklerose

Schwarzmann, Katharina, Dr. med.: Die differentiellen Auswirkungen produktiver und rezeptiver Kunstintervention auf die funktionellen Konnektivitäten des Default Mode Networks bei kognitiv unbeeinträchtigten Rentnern im Vergleich zu Personen der gleichen Altersgruppe mit subjektiv kognitiver Beeinträchtigung. Eine funktionelle MRT-Studie

Sembill, Jochen, Dr. med.: Die frühzeitige Therapielimitierung beim Schlaganfall: Häufigkeit, Modus und Einflussfaktoren

**Sprügel, Maximilian,** Dr. med.: Wahrnehmung des Faches Neurologie im Laufe des Medizinstudiums: Ergebnisse einer monozentrischen Untersuchung

**Strinitz**, Marc, Dr. med.: Fibrinolysis treatment for cerebral intraventricular hemorrhage: a temporal and spatial voxel-based analysis

Wang, Ruihao, Dr. med.: Bulbusdruckversuch induziert paradoxe, diskrete sympathische Aktivierung bei Patienten mit in der Vorgeschichte stattgehabtem mittelschweren oder schweren Schädelhirntrauma

Winder, Klemens, Dr. med.: Neuroanatomic Correlates of Female Sexual Dysfunction in Multiple Sclerosis

Zwirlein, Konstantin, Dr. med.: Effekte differentieller C-Faser Stimulation auf somatosensorische Antwortprofile

#### Doctorate theses 2018

Andres, Elisa, Dr. med.: Verhaltensänderungen bei Menschen mit geistiger Behinderung unter Perampanel

**de Rojas Leal, Carmen**, Dr. med.: Positive kardiovaskulär-autonome Effekte nach Beginn einer Fingolimod Therapie

Deutsch, Martina, Dr. med.: Sexuelle Dysfunktion als möglicher Auslöser depressiver Verstimmungen bei Patientinnen mit Multipler Sklerose Elsner, Ann-Catrin, Dr. rer. biol. hum.: Einfluss der Pharmazeutischen Betreuung auf die Adhärenz von Schlaganfallpatienten mit Vorhofflimmern in Bezug auf die medikamentöse sekundäre Schlaganfallprophylaxe mit direkten oralen Antikoagulantien – eine Pilotstudie

Hauck, Paulina, Dr. med.: Pharmakologische Blockade zeigt den Einfluss der sympathischen Modulation auf die Phasenbeziehung zwischen sinusuidalen Oszillationen des Blutdrucks und der zerebralen Blutflussgeschwindigkeit

Holländer, Christian, Dr. med.: Langzeitüberleben mit Duchenne-Muskeldystrophie am Beispiel eines Zentrums für Körperbehinderte: 50 Jahre interprofessionelle Förderung im Wichernhaus Altdorf

Kissel, Jan, Dr. med.: Der Einfluss von Natriumchlorid auf myeloide dendritische Zellen

Kugler, Johannes, Dr. med.: Sensitivität und Spezifität von GPBB bei Patienten mit Schlaganfallsymptomen

Liu, Mao, Dr. med.: Veränderte emotionale und autonome Verarbeitung olfaktorischer Reize bei Patienten nach stattgehabtem, leichtem Schädelhirntrauma

Lorenz, Katrin, Dr. med.: Troponin I-unabhängiger Outcomeprädiktor für intrakranielle Blutungen?

May, Lisa-Sophie, Dr. med.: CD133/Prominin-1 positive Membranpartikel im Liquor bei Patienten mit entzündlichen und degenerativen ZNS-Erkrankungen

**Milker, Antje**, Dr. med.: Intrazerebrale Blutungen unter Vitamin-K-Antagonisten: Charakteristika, Langzeitoutcome und prognostische Faktoren

Mondorf, Carolin, Dr. med.: Lipofuszin als Marker für ischämisch-induzierte Neurogenese

Müller, Tamara, Dr. med.: Vasospasmen-Detektion und Outcome-Prädiktion mittels Elektroenzephalographie bei Patienten mit Subarachnoidalblutung

**Ohnemus**, Tessa, Dr. med.: Effekte von Schlaganfallslokalisation und autonomer Dysregulation auf die Schlaganfall-assoziierte Hyperglykämie **Rötger, Caroline**, Dr. med. dent.: Effekte neuer Therapien sowie des Kv1.4 Knockouts auf die MOG-FAE der C57BI /6 Maus

Trini, Florian, Dr. med.: C-Nozizeptoren modulieren differentiell die Verarbeitung taktiler Reize in primären und sekundären somatosensorischen Kortizes – eine fMRI-Studie

Willfarth, Wolfgang, Dr. med.: Auswirkungen des perihämorrhagischen Hirnödems und weiterer Parameter auf das klinische Outcome nach intrazerebraler Blutung

#### Habilitation 2017

**Uhl, Martin,** PD Dr. med.: Immunmodulation beim Glioblastom

#### Habilitation 2018

Kuramatsu, Joji Benjamin, PD Dr. med.: Korrelation von klinischen Parametern und Therapiestrategien mit funktionellem Outcome nach intrakranieller Blutungen

#### **Board qualification 2017**

Giede-Jeppe, Antje, Dr. med. Dipl.-Mol. med.: Neurology

Kuramatsu, Joji, Dr. med.: Neurology Merkel, Jasmin, Dr. med.: Neurology Olmes, David, Dr. med.: Neurology Sauer, Eva-Maria, Dr. med.: Neurology

#### **Board qualification 2018**

Bobinger, Tobias, Dr. med.: Neurology Madzar, Dominik, Dr. med.: Neurology

#### Additional qualification 2018

Blinzler, Christian, Dr. med., MHBA: Medical Quality Management

Blinzler, Christian, Dr. med., MHBA: Intensive Care Medicine

**Breuer, Lorenz,** Dr. med.: Intensive Care Medicine

Kallmünzer, Bernd, PD Dr. med.: Intensive Care Medicine

Möbius, Cornelia, Dr. med.: Intensive Care Medicine

**Uhl, Martin**, PD Dr. med.: Intensive Care Medicine

## **Department of Neurology**

#### Division of Molecular Neurology

#### Doctorate theses 2017

**Menges, Stefanie**, Dr. rer. nat.: The interplay of alpha-synuclein, oxidative stress and mitochondrial dysfunction in Parkinson s disease.

**Mrochen, Anne**, Dr. med.: Olfaktorisch assoziierte Anhedonie beim idiopathischen Parkinson-Syndrom

**Sommer, Annika**, Dr. rer. nat.: Modelling Neuroinflammation in sporadic Parkinson s disease

#### Doctorate theses 2018

**Goßler, Julia**, Dr. med.: Sensorbasierte Ganganalyse zur Beurteilung des Gangs und der posturalen Stabilität beim idiopathischen Parkinson-Syndrom: der Stellenwert im Vergleich zu klinischen Skalen, der Selbsteinschätzung des Patienten und der Posturographie

Langemann, Hanna, Dr. med.: Der Einfluss von a-Synuclein und Alter auf die hippokampale Neurogenese in einem transgenen Parkinson-Maus-Modell

**Minakaki, Georgia**, Dr. rer. nat.: The functional link between autophagy, exosomes and the transcellular spread of alpha synuclein in Parkinson' s disease

Süß, Patrick, Dr. med.: Resilienz hippocampaler Struktur und Funktion im Kontext chronischer peripherer Entzündung

#### **Department of Neurosurgery** Chair of Neurosurgery

#### Doctorate theses 2017

**Bittermann, Philipp,** Dr. med.: Abweichende Level von PRG3 verstärken die Onkogenese in glialen Hirntumoren **Ghoochani, Ali,** Dr. rer. biol. hum.: Untersuchungen zum Hirntumormikromillieu: Angiogenese, Mikroglia und medikamentöse Therapien

Hatipoglu Majernik, Gökce, Dr. med.: Effekte von Tyrosinkinase-Inhibitoren bei primären und sekundären intrakraniellen Tumoren – eine *in vitro* Studie

Hofmann, Andrea, Dr. med.: Aktuelle Bedeutung von Neuronavigation und intraoperativer MRT-Bildgebung für epilepsiechirurgische Eingriffe: Die Erlanger Serie mit 415 Patienten

Kellermann, Isabel, Dr. med.: Evaluation von S100B in Serum und Liquor bei Patienten mit Subarachnoidalblutung und Schädel-Hirn-Trauma

Krawagna, Maximilian, Dr. med.: Erfahrungen mit der intraoperativen Indocyaningrün-Videoangiographie nach intrakraniellem Aneurysma Clipping

Wimmer, Cornelia, Dr. med.: Neuronavigation und intraoperative MRT-Bildgebung für epilepsiechirurgische Eingriffe bei Gangliogliomen

#### Doctorate theses 2017

Heinzelmann, Denise, Dr. med.: Risikofaktoren für multiple intrakranielle Aneurysmen

Kurucz, Peter, Dr. med.: Endoskopische Zugangswege zu den Zisternen der hinteren Schädelgrube durch die retrosigmoidale Schlüssellochkraniotomie: Eine anatomische Studie Sehm, Tina, Dr. rer. biol. hum.: New Methods and Approaches for the Therapy of Malignant Gliomas

#### Habilitation 2017

**Sommer, Björn,** PD Dr. med.: Evaluation der intraoperativen MRT-Bildgebung und funktionellen Neuronavigation im Bereich der Epilepsiechirurgie

**Brandner, Sebastian,** PD Dr. med.: Charakterisierung der Verteilung cerebraler Proteine im Liquorsystem

#### **Board** qualification 2017

Bozhkov, Yavor, Dr. med.: Neurosurgery

#### Additional qualification 2018

Brandner, Sebastian, PD Dr. med.: Intensive Care Medicine

#### **Department of Nuclear Medicine** Chair of Clinical Nuclear Medicine

#### Doctorate theses 2017

Welz, Friedrich, Dr. med.: Absolute SPECT/CT-Quantifizierung der zerebralen 99mTc-HMPAO-Aufnahme bei Patienten mit neurokognitiven Erkrankungen

Wiesmüller, Marco, Dr. med.: Comparison of lesion detection and quantitation of tracer uptake between PET from a simultaneously acquiring whole-body PET/MR hybrid scanner and PET from PET/CT

#### Doctorate theses 2018

Sachs, Julia, Dr. med. dent.: Einflussfaktoren auf das Ergebnis der Radioiodtherapie bei benignen Schilddrüsenerkrankungen **Stotski, Natalia,** Dr. med. dent.: SPECT/CT Quantifizierung der Konzentration von Tc-99m-Dicarboxy-Propan-Diphosphat (DPD) in Metastasen bösartiger Tumoren

#### Habilitation 2018

Maschauer, Simone, PD Dr. rer. nat.: Entwicklung von neuen 18F-fluorglycosylierten Radiotracern für die Molekulare Bildgebung

#### **Board qualification 2017**

**Schneller, Angelika,** Dr. med.: Nuclear Medicine

Erdinger, Matthias, Dr.med.: Nuclear Medicine

#### Board qualification 2018

Shafae, Shahid: Nuclear Medicine

## Department of Obstetrics and Gynecology

## Chair of Obstetrics and Gynecology

#### Doctorate theses 2017

Amann, Manuela, Dr. med.: Einfluss von genetischen Varianten im Brain derived neurotrophic factor (BDNF)-Gen im Zusammenhang mit depressiven Veränderungen nach der Schwangerschaft

**Domínguez Martín, Silvia,** Dr. med.: Humanes Seminalplasma und sein Effekt auf die Kontraktilität der Uterusmuskulatur am Modell des extrakorporal perfundierten Schweineuterus

Hagenbeck, Carsten, Dr. med.: Assoziation zwischen computergestützt bestimmter mammographischer Dichte und dem Proliferationsmarker Ki-67 beim invasiven Mammakarzinom – Ergebnisse einer Fallstudie

Hönig, Annika, Dr. med.: Schwangerschaften nach VZO-Behandlung – eine Erfolgs- und Zufriedenheitsanalyse

Kellner, Dietlind-Sara, Dr. rer. biol. hum.: Prädiktoren der Therapie-Compliance bei postmenopausalen Patientinnen mit hormonrezeptorpositivem Mammakarzinom

Lewens, Johanna, Dr. med.: Vergleichende Expression und Lokalisation der HERV-Hüllgene in humanen Plazenten bei schweren Schwangerschaftskomplikationen

**Maktabi, Amina,** Dr. med.: Kryokonservierung von humanem ovariellem Gewebe zum Erhalt der Fertilität bei Patientinnen mit maligner Erkrankung – 15 Jahre klinische Erfahrung am Universitätsklinikum Erlangen

Nabieva, Naiba, Dr. med.: Muskuloskelettale Schmerzen bei Mammakarzinom-Patientinnen unter der Therapie mit dem Aromataseinhibitor Letrozol

Öhlschläger, Annelie, Dr. med.: Einfluss der mammographischen Dichte auf Tumorcharakteristika beim Mammakarzinom

**Oversohl, Nicola**, Dr. med.: Hat eine IVF/ICSI-Behandlung einen gesundheitsökonomischen Wert für die deutsche Gesellschaft?

**Reuter, Benoit**, Dr. med.: Genetische Polymorphismen im Aromatasegen (CYP19A1) und deren Assoziation mit dem Geburtsgewicht des Kindes

Thaler, Kerstin, Dr. med.: Bedeutung von zwei Single Nucleotid Polymorphismen im Aromatase-Gen (CYP19A1) für die Entstehung einer Mammakarzinomerkrankung – Eine Fall-Kontroll-Studie Wunderle, Marius, Dr. med.: Einfluss niedrig penetranter genetischer Risikofaktoren auf die Genexpression ausgewählter Risikogene in Tumoren von Patientinnen mit Mammakarzinom Zeuner, Rebecca, Dr. med.: Mammographische Dichte als Risikofaktor für Brustkrebs – Ergebnisse einer deutschen Fall-Kontroll-Studie

#### Doctorate theses 2018

Becker, Karina, Dr. med.: Risikofaktoren für Endometriose in einer deutschen Fall-Kontroll-Studie

**Blum, Simon**, Dr. med.: Epidemiologische Faktoren bei verschiedenen klinischen Formen der Endometriose. Eine Fall-Fall-Untersuchung

**Geisenhainer, Karolin**, Dr. med.: In-vitro-Untersuchungen zur pharmakologischen Wirkung von humanem Seminalplasma auf die Kontraktilität des extrakorporal perfundierten Schweineuterus

**Geyer, Thomas,** Dr. med.: Einsatz von Pertuzumab und Trastuzumab im Vergleich zu Trastuzumab-Monotherapie beim HER2–positiven Mammakarzinom – eine multizentrische Kohortenstudie

Halmen, Sonja, Dr. med.: Uterine Sarkome und Karzinosarkome – eine retrospektive Studie mit 143 Frauen

Pandey, Shikshya, Dr. med.: Epidemiologische Risikofaktoren für das Mammakarzinom und deren Assoziation mit molekularen Subtypen im postmenopausal Patientinnen mit hormonrezeptorpositivem Mammakarzinom – eine Fall-Fall Analyse

**Proske, Kim,** Dr. med.: Symptome und funktionelle Einschränkungen, Kurzzeit- und Langzeitkomplikationen sowie Schwangerschaftsraten nach operativer Sanierung einer Rektumendometriose

**Ruder, Lucia**, Dr. med.: Einflussfaktoren auf die kontraktile Wirkung von menschlichem Seminalplasma auf Schweineuteri

**Stelzl, Patrick,** Dr. med.: Soluble factors secreted by human endometrial stromal cells and their role in trophoblast migration

Turk, Greta, Dr. med.: Einfluss von Geburtsparametern auf das Wachstum und die Entwicklung des Körpergewichts von Kindern – eine Nachbeobachtungsstudie über zehn Jahre

#### Habilitation 2017

Häberle, Lothar, PD Dr. rer. nat.: Analyse hochdimensionaler Daten zur Ätiologie, Pathogenese und Prognose des Mammakarzinoms

#### Habilitation 2018

Wesselmann, Simone, PD Dr. med.: Qualitätssicherung und -verbesserung in der Onkologie: Verbindung zwischen Zertifizierung und Leitlinien

Hack, Carolin, PD Dr. med.: Integrative Medizin in der Behandlung von gynäkologisch-onkologischen Patientinnen

## Board qualification 2017

Schwenke, Eva, Dr.: Gynecology and Obstetrics

#### Board qualification 2018

**Bayer, Christian**, Dr.: Special Obstetrics and Perinatal Medicine

Gaß, Paul, Dr.: Gynecology and Obstetrics Hack, Carolin, PD Dr.: Gynecological Oncology Hackl, Janina, Dr.: Gynecological Endocrinology and Reproductive Medicine

Hildebrandt, Thomas, Dr.: Special Obstetrics and Perinatal Medicine

Jud, Sebastian, PD Dr.: Special Obstetrics and Perinatal Medicine

Koch, Martin, Dr.: Gynecological Oncology Rauh, Claudia, PD Dr.: Special Obstetrics and

Perinatal Medicine **Stumpfe, Florian**, Dr.: Gynecology and Obstetrics

#### Additional qualification 2017

Hackl, Janina, Dr.: Naturopathic Methods

#### Additional qualification 2018

Sell, Charlotte, Dr.: Drug-based tumor therapy Stahl, Olga, Dr.: Drug-based tumor therapy

#### **Department of Ophthalmology** Chair of Ophthalmology

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## Doctorate theses 2017

**Birner, Barbara**, Dr. med.: Melanindispersionssyndrom und -glaukom: Morphometrische Analyse des vorderen Augenabschnittes mittels SL-OCT

Brehmer, Katharina, Dr. med.: 25 Hertz Adaptation: Einfluss auf die Erholungszeit bei Glaukompatienten

Holbach, Benedict, Dr. med.: Semiautomatische morphometrische Analyse parapapillärer Autofluoreszenz in Augen mit und ohne glaukomatöse Optikusatrophie

**Queck, Susanne,** Dr. med.: Langzeitergebnisse nach Trabekulektomie mit intrakameraler Gabe von Bevacizumab im Vergleich zur Anwendung von Mitomycin C

Werner, Judith, Dr. med.: Vergleich der diagnostischen Wertigkeit morphometrischer Verfahren in der Glaukomdetektion aus der Augenklinik mit Poliklinik

#### Doctorate theses 2018

Aher, Avinash, Dr. rer. biol. hum.: Die Entwicklung elektrophysiologischer Techniken, um Sehbahnen und erkrankte Netzhaut funktionell zu charakterisieren

Akbaba, Yasemin, Dr. med.: Die "Bubble in the roll"-Technik unter Verwendung des Endoject DMEK-Injektors: Einfluss der Luftblase auf den Endothelzellverlust

Hadjiraftis, Savvakis, Dr. med.: Vergleich der digitalen Planimetrie und Laser-Scanning-Tomographie zur Quantifizierung der Glaukomprogression

Meixner, Eva, Dr. med.: Messung der retinalen Wall-to-Lumen Ratio mittels Adaptiver Optik: eine klinische Studie

**Roth, Jan-Peter,** Dr. med.: Molekularbiologische Identifizierung von Targetgenen des Enzyms Lysyloxidase-like 1 (LOXL1) in humanen Optikusastrozyten

Schlögl, Andreas, Dr. med.: Langzeitergebnisse nach Descemet Membrane Endothelial Keratoplasty Schoemann, Johannes, Dr. med.: Korrelation zwischen zerebralen Mikroinfarkten und der DTI-bestimmten Integrität der Sehstrahlung bei Patienten mit primärem Offenwinkelglaukom

von Marchtaler, Philipp, Dr. med.: Partneraugenvergleich von Luft und Schwefelhexafluoridgas als Tamponade bei der Descemet-Membran-Endothel-Keratoplastik

Wittmann, Barbara, Dr. med. dent.: Eyepass Glaukomimplantat bei medikamentös therapierefraktärem Offenwinkelglaukom

Wolz, Johannes, Dr. med.: Telemedizinische Untersuchung der Papilla nevi optici und der Retina bei Patienten nach kürzlich stattgefundenem Schlaganfall oder transitorischer ischämischer Attacke

#### Habilitation 2017

Huchzermeyer, Cord, PD Dr. med.: Sinnesphysiologie der inneren und äußeren Netzhaut, inklusive Glaukom

#### Habilitation 2018

Weller, Julia Marina, PD Dr. med.: Pathophysiologie des Hornhautendothels und Therapie mittels Descemet Membrane Endothelial Keratoplasty

#### **Board qualification 2017**

Akbaba, Yasemin, Dr. med.: Ophthalmology Köferl, Patricia, Dr. med.: Ophthalmology

#### **Board qualification 2018**

Menzel-Severing, Johannes, Dr. med.: Augenarzt

Hohberger, Bettina, Dr. med.: Augenarzt

## Department of Otorhinolaryngology -Head and Neck Surgery

Chair of Otorhinolaryngology

#### Doctorate theses 2017

Beck, Eva, Dr. med.: Biomechanische Simulation der Stimmlippenbewegung bei Kindern und Erwachsenen

**Dubrovskiy, Denis,** Dr.-Ing.: Bildverarbeitung bei endoskopischen Hochgeschwindigkeitsaufnahmen der Stimmlippenbewegungen

Garea Garcia, Larissa, Dr. med. dent.: Phonembasiertes Hörtraining im Störgeräusch

Hauken, Juliane, Dr. med. dent.: Starre und flexible Endoskopie: Auswirkung auf berechnete quantitative Stimmparameter

Jaeger, Doris, Dr. med.: Zeitverlauf der telemetrisch gemessenen, elektrisch evozierten Summenaktionsportale bei 101 Cochlea-Implantat Versorgungen

**Jalyzada, Kavan**, Dr. med.: Versorgung des Hebedefektes am Unterarm nach Hebung eines freien Radialistransplantats: Vakuum-Versiegelung versus konventioneller Verband

Kinateder, Charlotte, Dr. med.: Basiskompetenzen für Lese- und Rechtschreibleistungen und Prüfsystem für Schul- und Bildungsberatung für die Klassen 6-13 bei jugendlichen Sprachheilschülern

Klingbiel, Larissa, Dr. med. dent.: Ultraschallelastographie – Darstellung von Parotistumoren: jüngste Erfahrungen und Identifikation charakteristischer Muster Knör, Mareike, Dr. med.: Prävalenz von humanen Papillomaviren (HPV) in Nasen- und Antrochoanalpolypen und Assoziation mit klinischen Parametern

Liebscher, Tim, Dr. rer. biol. hum.: Elektrophysiologische Untersuchungen entlang der Hörbahn: Reizantworten des peripheren und zentralen Hörsystems bei Cochlea-Implantat-Trägern

Schilling, Achim, Dr. rer. nat.: On the estimation of sensory and perceptual thresholds: theoretical limitations and practical implications Schlücker, Luisa, Dr. med.: Sprachverstehen

und Lebensqualität bei Cochlea-Implantat-Trägern im höheren Lebensalter

Thümmler, Rebecca, Dr. med. dent.: Einfluss einer Hörgeräteversorgung auf das Einsilberverstehen und das subjektiv erlebte Alltagshören

Wagner, Jennifer, Dr. med.: Prä- und Postoperative Stimmanalyse nach Injektionslaryngoplastik

#### Doctorate theses 2018

Alberter, Katrin, Dr. med. dent.: Elektrisch evozierte Hirnrindenpotentiale bei Cochlea-Implantat-Trägern

Arbeiter, Mareike, Dr. med.: Eine Analyse des auditiven Feedbacks und der Phonation von Normalstimmen

**Birk, Veronika**, Dr.-Ing.: Automated experimental setup for phonation investigation in *ex vivo* larynges

Forster, Jan, Dr. med. dent.: Die Entstehung von Tinnitus bei Mongolischen Wüstenrennmäusen steht im Zusammenhang mit einer Synaptopathie an den inneren Haarsinneszellen der Cochlea

**Gollnast, Dominik**, Dr. med. dent.: Analyse audiometrischer Unterschiede von Patienten mit und ohne Tinnitus aus einer großen klinischen Datenbank

**Greiner**, **Nicole**, Dr. med.: Kinästhetisches und auditives Feedback bei der Phonation von Patienten mit funktioneller Dysphonie

**Günther, Vanessa**, Dr. med. dent.: Aktuelle Methoden zur Stimmlippenanalytik – Übersicht und Speziesvergleiche

Guth, Jan Philipp Christian, Dr. med.: Hirnstammaudiometrie bei Stimulation mit einem Knochenschallleitungs-Implantat am Tiermodell: Messetablierung und vergleichende Latenzmessung bei der Mongolischen Wüstenrennmaus (Meriones unguiculatus)

Hochgesand, Julia, Dr. med. dent.: Komplikationen nach Cochlea-Implantat-Versorgung bei Erwachsenen

Krauß, Patrick, Dr. rer. nat.: Stochastic Resonance as a Putative Cause of Subjective Tinnitus Maul, Corinna, Dr. med. dent.: Aktuelle Therapiekonzepte in der Behandlung des Tinnitus

Meyer, Kristina, Dr. med. dent.: Nasenrekonstruktion durch Stirnlappentechnik an der HNO-

Klinik der Universität Erlangen-Nürnberg in den Jahren 2002 bis 2009 Ramadan, Amr, Dr. med.: Die Altersstimme: Ein

Review

**Richters, Malte,** Dr. med. dent.: Objektiver und Subjektiver Hörgewinn der Cochlea-Implantat-Versorgung

Semmler, Marion, Dr.-Ing.: Endoscopic laserbased 3D imaging for *in vivo* examination of human phonation

#### Habilitation 2018

Traxdorf, Maximilian, PD Dr. med.: Neuartige pathophysiologische, diagnostische und therapeutische Ansätze in der Schlafmedizin Kniesburges, Stefan, PD Dr.-Ing.: Multimodale Analyse der physikalischen Mechanismen der menschlichen Phonation

#### **Board qualification 2017**

Kißlinger, Franziska Maria, Dr. med.: Otorhinolaryngology

Schapher, Mirco, Dr. med.: Otorhinolaryngology

Stützer, Tobias, Dr. med.: Otorhinolaryngology Treutlein, Eric, Dr. med.: Otorhinolaryngology

#### **Board qualification 2018**

Wolf, Elke, Dr. med.: Otorhinolaryngology

#### Additional qualification 2017

Bauer, Judith, Dr. med.: Quality certificate Somnology Treutlein, Eric, Dr. med.: Quality certificate

Somnology

#### Additional qualification 2018

Haferkamp, Jens, Dr. med.: Quality certificate Somnology

## Department of Pediatric and Adolescent Medicine

Chair of Pediatrics

#### Doctorate theses 2017

Bannier, Sara, Dr. med.: Kapillarisierung und angiogenetische Faktoren in Herz und Nieren nach intrauteriner Wachstumsrestriktion (IUGR) Frey, Daniel, Dr. med.: Hypoxia Potentiates LPS-Mediated Cytotoxicity of BV2 Microglial Cells In Vitro by Synergistic Effects on Glial Cytokine and Nitric Oxide System

Hébert, Steven, Dr. med.: Praktische Umsetzung einer spezialisierten ambulanten pädiatrischen Palliativversorgung im Medical Valley der Europäischen Metropolregion Nürnberg

Kharboutli, Soraya, Dr. med.: Metabolische Signatur der Zöliakie im Kindesalter – Massenspektrometrische Untersuchungen im Serum

**Leonhardt, Carl-Stephan,** Dr. med.: Identifizierung des RNA Recognition Elements der RNA-bindenden Proteine der RBPMS-Familie sowie ihrer mRNA-Zielstrukturen im Transkriptom

Maderer, Carmen, Dr. med.: Etablierung einer routinetauglichen PCR – Methode zur Charakterisierung genomischer Bruchpunkte bei Patienten mit alveolärem Rhabdomyosarkom mit PAX3/FKHR bzw. PAX7/FKHR – Translokation

Mühlberger, Theresa, Dr. med.: Effekte von akuter systemischer Hypoxie und rekombinantem Erythropoietin auf apoptotische und inflammatorische Effektorkaskaden im unreifen Gehirn der Maus

Offenmüller, Sonja, Dr. med.: Identifizierung neuer Risiko-Loci für die pädiatrische akute lymphoblastische Leukämie mittels der Anwendung eines Panels Krebs-assoziierter genetischer Polymorphismen **Pauli, Mara,** Dr. med.: Ototoxizität nach Cisplatintherapie bei Osteosarkompatienten – Vergleich der Klassifikationen Brock, Chang, SIOP und Münsteraner

Penger, Theresa, Dr. med.: Kinder und Jugendliche mit Morbus Basedow in der endokrinologischen Ambulanz der Kinder- und Jugendklinik des Universitätsklinikums Erlangen

**Rückert, Franziska**, Dr. med.: Membranoproliferative Glomerulonephritis-Krankheitsverlauf und Therapie pädiatrischer Patienten

Schirl, Christian, Dr. med.: Vergleich der Genexpression von Adrenomedullin, Endothelin-1, endothelialer NO (Stickstoffmonoxid)-Synthetase, induzierbarer NO-Synthetase, 11B-Hydroxysteroiddehydrogenase Typ 1 und Adiponectin in subkutanem, omentalem und mesenterialem Fettgewebe von Kindern und Erwachsenen

Schmidt, Martina, Dr. med.: Entwicklungsneurologische Ergebnisse im Kleinkindalter ehemals Früh- und Reifgeborenen der Geburtsjahrgänge 2008-2011 mit neonatalen zerebralen Anfällen Stumpf, Isabel, Dr. med.: Untersuchungen zur Körperzusammensetzung bei mangelgeborenen Kindern (Small-for-Gestational Age, SGA) unter Therapie mit rekombinantem humanen Wachstumshormon (rhGH)

Weiß, Susanne, Dr. med.: Determination of Thrombin Activatable Fibrinolysis Inhibitor (TAFI) activity by Liquid Chromatography/ Electrospray lonization Mass Spectrometry and its potential role in Hemophilia

Wölfel, Michael, Dr. med.: Umfrage zur Lebenssituation von jungen Frauen mit Ullrich-Turner-Syndrom nach einer Wachstumshormontherapie im Kindesalter

#### Doctorate theses 2018

Bartunik, Hannah, Dr. med.: Charakterisierung des Tumorsuppressorproteins GKN2 in der humanen Plazenta

Fiedlschuster, Andrea Doris, Dr. med.: Spätfolgen nach allogener Stammzelltransplantation – Daten aus einem kinderonkologischen Zentrum Görlitz, Katharina, Dr. med.: Genomische BCR-ABL1-Bruchpunkte bei kindlichen Leukämien

Hartjen, Sebastian, Dr. med.: Alpha 8 Integrin: Expression in Trophoblasten von Mensch, Ratte und Maus

Hellberg, Julia, Dr. med.: Zirkulierende Tumor-DNA als Biomarker zur Quantifizierung des Tumorvolumens und des Therapieansprechen beim Ewing-Sarkom

Hess, Johannes, Dr. med.: Fehlgeburten in Familien mit einem Kind mit klassischem Adrenogenitalen Syndrom mit 21-Hydroxylasedefekt

**Keck, Franziska**, Dr. med.: Adrenarche bei Mädchen mit Ullrich-Turner-Syndrom unter Wachstumshormontherapie

Öttl, Paul, Dr. med.: Untersuchungen zur Adhärenz von kleinwüchsigen Kindern bei der Therapie mit humanem Wachstumshormon

**Polczer, Brigitte-Karin**, Dr. med.: Jugendliche nach dem Ende der Wachstumshormontherapie bei einem in der Kindheit diagnostizierten Wachstumshormon-Mangel

Schön, Sabine, Dr. med.: Pubertät und Gonadenfunktion bei überlebenden Jungen nach einer Tumortherapie im Kindesalter Schulze, Nadja, Dr. med.: Kinder und Jugendliche mit nicht-klassischem adrenogenitalen Syndrom mit 21-Hydroxylase-Defekt – Ergebnisse einer multizentrischen Studie in Bayern und Baden-Württemberg

Steinki, Katja, Dr. med.: Pubertät und Gonadenfunktion bei überlebenden Mädchen und jungen Frauen nach einer Krebstherapie im Kindesalter

Waltschew, Fabian, Dr. med.: Revisionen und Komplikationen der permanenten Herzschrittmachertherapie bei Kindern und Jugendlichen mit angeborenem Herzfehler. Eine multizentrische Analyse des Kompetenznetzes Angeborene Herzfehler Berlin

Weber, Marie, Dr. med.: Günstiges Outcome pädiatrischer kolorektaler Karzinome bei nachgewiesenem genetischen Tumorsyndrom Wünsche, Anna Stephanie, Dr. med.: Nicht-invasive vorgeburtliche Diagnose der hypohidrotischen ektodermalen Dysplasie durch sonografische Darstellung der Zahnanlagen

#### Habilitation 2017

**Tzschoppe, Anja**, PD Dr. med.: Mechanismen der perinatalen Programmierung – Die Rolle plazentarer Marker für die postnatale Entwicklung

#### Habilitation 2018

Marek, Ines, PD Dr. med.: Bedeutung des Mesangiumzell-spezifischen Integrins alpha8 beta1 für die Homöostase im Glomerulus der Niere

#### Board qualification 2017

**Bauer, Stefanie**, Dr. med.: Pediatric and Juvenile Medicine

Lubig, Julia, Dr. med.: Pediatric and Juvenile Medicine

Plattner, Erika, Dr. med.: Pediatric and Juvenile Medicine

**Rechenauer, Tobias,** Dr. med.: Pediatric and Juvenile Medicine

**Steif, Benedikt,** Dr. med.: Pediatric and Juvenile Medicine

Zierk, Jakob, Dr. med.: Pediatric and Juvenile Medicine

#### **Board qualification 2018**

Albrecht, Andrea, Dr. med.: Pediatric and Juvenile Medicine

Fahlbusch, Fabian, Dr. med.: Neonatology

Moosmann, Julia, Dr. med.: Pediatric and Juvenile Medicine

**Osinski, Daniela**, Dr. med.: Pediatric and Juvenile Medicine

**Ruppel, Renate,** Dr. med.: Pediatric and Juvenile Medicine

Stenger, Nico: Pediatric and Juvenile Medicine

#### Additional qualification 2017

Götze, Thomas: Pediatric Gastroenterology

## **Department of Pediatric and**

Adolescent Medicine Division of Pediatric Cardiology

#### Doctorate theses 2017

**Löwe, Julia**, Dr. med.: Hypertonieprävalenz und antihypertensive Therapie bei Patienten mit korrigierter Coarctatio aortae

#### Doctorate theses 2018

**Stenger, Anna,** Dr. med.: Nutzen der dreidimensionalen Rotationsangiografie bei aortalen katheterbasierten Interventionen in der Kinderkardiologie

#### **Board qualification 2017**

Kunz, Barbara: Pediatric and Juvenile Medicine Rubarth, Kai: Pediatric and Juvenile Medicine

#### **Board qualification 2018**

**Berzel, Simon**, Dr. med.: Pediatric Cardiology **Böcker**, **Dorothée**, Dr. med.: Pediatric and Juvenile Medicine

Schmidt, Thomas: Pediatric Cardiology Schöber, Martin, Dr. med.: Pediatric Cardiology

Steif, Angela: Pediatric Cardiology Weigelt, Annika, Dr. med.: Pediatric Cardiology

#### Additional qualification 2018

Habash, Sheeraz: Special training Pacemaker Prießmann, Helga, Dr. med.: Special training Pacemaker

## Department of Plastic and Hand Surgery

Chair of Plastic Surgery and Hand Surgery

#### Doctorate theses 2017

Bertram, Martin, Dr. med.: Der Einsatz dermaler Gewebematrix als Hüllgewebe um Silikonimplantate zur Prävention der Kapselfibrose Sessler, Christine, Dr. med.: SB431542 – selektiver Inhibitor der TGFbeta1-abhängigen profibrotischen Proteinexpression – Eine molekularbiologische Studie an Dupuytren'schen Fibroblasten

#### Doctorate theses 2018

**Sterzinger, Sebastian,** Dr. med.: Die Rolle der plastisch-rekonstruktiven Chirurgie in der interdisziplinären chirurgischen Behandlung von Weichteilsarkomen – eine retrospektive Studie 2004 – 2014

#### Habilitation 2017

Boos, Anja Miriam, PD Dr. med.: Angiogenes und Stammzellen in der regenerativen Medizin – von *in vitro* Versuchen zum Großtierexperiment

#### Additional qualification 2017

Boos, Anja Miriam, PD Dr. med.: Hand Surgery Schmitz, Marweh, Dr. med.: Hygiene Officer

#### Additional qualification 2018

Ludolph, Ingo, Dr. med.: Hand Surgery

#### **Department of Psychiatry and Psychotherapy** Chair of Psychiatry and Psychotherapy

#### Doctorate theses 2017

**Bouna-Pyrrou, Polyxeni,** Dr. med.: Internet gaming disorder, social network disorder and laterality: handedness relates to pathological use of social networks

Dorscht, Lisa, Dr. rer. biol. hum.: Welche Patienten kommen in die multimodale Schmerztherapie? – Multifaktorielle Analyse der Versorgungswege chronischer Schmerzpatienten Garbers, Lilli, Dr. med. dent.: Erfassung der Häufigkeit und klinische Charakterisierung des obstruktiven Schlafapnoesyndroms bei in psychiatrischer Behandlung befindlichen Patienten Gieseler, Christin, Dr. med.: Pilotstudie zur Untersuchung der Auswirkung eines operativen Eingriffs auf die kognitive Leistungsfähigkeit bei älteren Menschen

Haiberger, Ilka, Dr. med.: Genexpression von DNMT-1, -3a und -3b, MBD2, CREB, HERP und Alpha-Synuclein während des frühen Alkoholentzugs

Hansbauer, Maximilian, Dr. med.: CB1 und CB2 Rezeptorexpression und Promotormethylierung bei Patienten mit Cannabisabhängigkeit Helldörfer, Eva, Dr. med.: Die Rolle der sauren Sphingomyelinase bei der Etablierung von Alkoholtrinkverhalten im Mausmodell

Katona, Mirjam, Dr. med.: Predictors of healthrelated quality of life in stroke patients after neurological inpatient rehabilitation: a prospective study

**Meinzer, Stefan**, Dr. rer. biol. hum.: Translating the determination of subjective customer perceptions from the healthcare sector to the service industry

Schmiedeberg, Anke, Dr. rer. biol. hum.: Validierungsstudie des Erlangen Test of Activities of daily living in Mild dementia or Mild cognitive Impairment (ETAM)

Schöpf, Isabella, Dr. med.: Die Rolle der alpha-CaMKII Autophosphorylierung im hippocampalen Gyrus dentatus bei den akuten zellulären Effekten von Alkohol und Kokain in der Maus

**Sommerer, Helen**, Dr. med.: Symptomkomplexspezifische Therapie der Schizophrenie mit Antipsychotika der zweiten Generation (Atypika): Eine Meta-Analyse

Steinhauser, Nicolas, Dr. med.: Geschlechterunterschiede in der kortikalen Repräsentation der gleichgeschlechtlichen Liebe – eine fMRI-Studie

Waltschew, Katharina, Dr. med.: Kognitive Effekte einer Serie akzelerierter repetitiver transkranieller Magnetstimulation (aTMS) bei Patienten mit bisher medikamentös therapieresistenter Depression

Weiland, Judith, Dr. med.: Orexin A Expression und Promotormethylierung bei Patienten mit Cannabisabhängigkeit

#### Doctorate theses 2018

Bauereiß, Anna, Dr. med.: Untersuchung der getrennten Exozytose der Alzheimer Proteine APP und BACE mittels Fluoreszenzmikroskopie Düsenberg, Michaela, Dr. med.: Nachweis von Oberflächen-Ceramid auf THP-1-Zellen mittels Durchflusszytometrie

Fischer, Christina, Dr. med.: Flashbackanalyse bei PTBS mit Verlust des Bewusstseins während des PTBS-verursachenden Traumas

Goschenhofer, Anna, Dr. med.: Verlauf von Homocystein während stationärer Entgiftung von Alkoholabhängigen Hasselbach, Franziska, Dr. med.: Depressivität und TNF- $\alpha$  bei chronischer Nierenerkrankung und nach Nierentransplantation

**Huber, Sabine**, Dr. rer. biol. hum.: Role of prenatal testosterone exposure in the development of alcohol addiction

Kalinichenko, Liubov, Dr. rer. biol. hum.: The role of acid sphingomyelinase in depression/ anxiety-induced alcohol addiction

Lehmeier, Stephanie, Dr. med.: Der Einfluss von Ethanolkonsum auf die Ceramidaseaktivität von Gewebe und Plasma im Rattenmodell

Neeser, Bianca, Dr. med.: Einfluss der Modulierung des Mikrotubulisystems auf die Beta-Amyloidsekretion

Siller, Teresa, Dr. med.: Exosomale microRNA-Expressionsprofile bei nierenkranken Patienten mit affektiven Störungen vor und nach Nierentransplantation – Eine klinisch-experimentelle Studie

**Straubmeier, Melanie,** Dr. rer. biol. hum.: Die Ergebnisse der Outcome Variablen von Menschen mit kognitiven Beeinträchtigungen im Rahmen einer cluster-randomisierten, multizentrischen, nicht-medikamentösen Interventionsstudie in der Tagespflege mit telefonischer Angehörigen-Kurzintervention

Taha, Lava, Dr. med.: Relative Häufigkeiten von Th17-, Th1- und regulatorischen T-Zellen unter mononukleären Zellen des peripheren Blutes bei der Alzheimer Krankheit

Weinbeer, Johannes, Dr. med.: Das IL1-System und Chemokin-Rezeptoren in der Pathophysiologie und Diagnostik der Alzheimer-Erkrankung

#### Habilitation 2017

Müller, Helge, PD Dr. med.: Einfluss von somatischen und Umweltfaktoren auf den Verlauf Psychischer, insbesonderer affektiver Störungen Amato, Davide, PD Dr. rer. nat.: Mechanism of antipsychotic action and failure

#### Habilitation 2018

**Spitzer, Philipp,** PD Dr. med.: Die Alzheimer-Erkrankung und das Immunsystem: Zusammenhänge und deren Implikation für Biomarker

#### Board qualification 2017

Müller, Elisabeth: Psychiatry and Psychotherapy

**Oberstein, Timo,** Dr. med.: Psychiatry and Psychotherapy

#### Board qualification 2018

**Bouna-Pyrrou**, **Polyxeni**, Dr. med.: Psychiatry and Psychotherapy

**Kustermann, Andreas,** Dr. med.: Psychiatry and Psychotherapy

**Rinck**, **Daniela**, Dr. med.: Psychiatry and Psychotherapy

Tektas, Ozan, Dr. med.: Psychiatry and Psychotherapy

Wagner, Claudia, Dr. med.: Psychiatry and Psychotherapy

#### Additional qualification 2018

Müller, Elisabeth: Primary Addiction Treatment Spitzer, Philipp, Dr. med.: CBASP

## Department of Psychiatry and Psychotherapy

Division of Child and Adolescent Mental Health

#### Doctorate theses 2017

Köhler-Jonas, Janna Nicola, Dr. rer. biol. hum.: Kinder mit einem früh operierten Ventrikelseptumdefekt: Entwicklungsstand und Verhalten im Einschulungsalter?

Krischke, Eva, Dr. med.: Die transkranielle Magnetstimulation als neurophysiologisches Verfahren zur Darstellung der veränderten Exzitabilität des motorischen Systems bei der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung – eine Metaanalyse

**Oschmann, Stephanie**, Dr. med. dent.: Visuelle Aufmerksamkeit von jugendlichen und erwachsenen Patientinnen mit Anorexia nervosa gegenüber emotionsauslösenden Stimuli und Nahrungsmittelbildern

#### Doctorate theses 2018

Fauck, Vanessa, Dr. med.: Joggen als virtuelle Realität bei PatientInnen mit Essstörung und Bewegungsdrang

Kremer, Anna-Lena, Dr. med.: Positive und negative psychosoziale Entwicklung und posttraumatische Reifung bei jungen Erwachsenen mit einer Krebserkrankung im Kindesalter, Typ-1-Diabetikern und gesunden Gleichaltrigen

**Kreß, Inge**, Dr. med.: Differential diagnoses of food related gastrointestinal symptoms in patients with anorexia nervosa and bulimia nervosa: A review of literature

**Neubert, Sina**, Dr. med.: Pränatale Alkoholexposition und körperliche Entwicklung von der Geburt bis zum Alter von sechs Jahren: Eine Untersuchung basierend auf Ethanolmetaboliten im Mekonium

**Reber, Sandra Therese,** Dr. med.: Koordinaten der Immunsuppressiva-Adhärenz bei Nierentransplantierten Patienten

Vogel, Anne, Dr. med.: Neuronale Verarbeitung von Körperbildstimuli bei Patientinnen mit Anorexia nervosa im Vergleich zu gesunden Probandinnen – eine fMRT-Studie

#### Board qualification 2017

**Bialecki, Diana,** Dr. med.: Pediatric and Juvenile Psychiatry and Psychotherapy

## Additional qualification 2017

Hader, Saskia: Child and Adolescent Psychotherapy

Hecker, Elke: Child and Adolescent Psychotherapy

## Department of Psychiatry and Psychotherapy

Division of Psychosomatics and Psychotherapy

## Doctorate theses 2017

Schaubschläger, Anke, Dr. med. dent.: Der Approach-Avoidance Task bei Patientinnen mit Anorexia nervosa: ein computerisiertes Verfahren zur Untersuchung assoziativer Prozesse

#### **Department of Radiation Oncology** Chair of Radiotherapy

## Doctorate theses 2017

Betz, Elena, Dr. med. dent.: Neoadjuvante Radiochemotherapie mit und ohne regionaler Tiefenhyperthermie des lokal fortgeschrittenen Rektumkarzinoms an der Strahlenklinik des Universitätsklinikums Erlangen von 2004 bis 2012 Ellmann, Anna, Dr. med.: Untersuchung der individuellen Strahlenempfindlichkeit bei Rektumkarzinompatienten und Patienten mit Verdacht auf erhöhte Strahlenempfindlichkeit mit Hilfe der 3-Farb-FiSH-Technik

Falk, Jens, Dr. med. dent.: Wechselwirkungen des Proteinkinaseinhibitors Vemurafenib im bestrahlten Gewebe

Fiebig, Nora, Dr. med.: Oxidativer Stress als Ursache der zytotoxischen Wirkung von Efavirenz auf Pankreaskarzinomzellen

Frömming, Désirée, Dr. med. dent.: Auswirkung niedrig- und hochdosierter ionisierender Strahlung auf gesunde primäre Hautfibroblasten

**Goerig, Nicole,** Dr. med.: Häufigkeit des Auftretens Cytomegalovirus-assoziierter Enzephalopathie im engen zeitlichen Zusammenhang mit der Bestrahlung des Gehirns

**Grabenbauer, Maximilian,** Dr. med. dent.: Wirkung von Vemurafenib und Dabrafenib in Kombination mit ionisierender Strahlung auf Fibroblasten und auf maligne Melanomzellen

**Griebl, Sebastian-Willibald**, Dr. med.: Additive Wirkung von Metformin auf die Radiochemotherapie mit Temozolomid in der Glioblastomzelllinie U251

**Gryc**, **Thomas**, Dr. med.: Interstitieller Brachytherapie-Boost bei Analkarzinompatienten mit unzureichendem Ansprechen auf die simultane Radiochemotherapie

Jeßberger, Jonas, Dr. med.: Combination of growth pattern and tumor regression identifies a high risk group in neoadjuvant treated rectal cancer patients

Körber, Verena, Dr. med.: Synergistische tumortoxische Effekte des nicht-nukleosidischen Reverse-Transkriptase-Inhibitors Efavirenz und ionisierender Strahlung bei Pankreaskarzinomzellen

Kötter, Bernhard, Dr. med.: Hypofraktionierte Bestrahlung steigert in vitro das immunogene Potential von Brustkrebszellen mit intakter Caspase-3 und niedriger Grundimmunogenität

Mayo, Theresa, Dr. med.: Untersuchung der Strahlenempfindlichkeit von Bronchialkarzinompatienten mit Hilfe der 3-Farb-FISH-Technik sowie des Einflusses von Strahlung auf die Anzahl der zirkulierenden Immunzellen

Mayr, Franz Xaver, Dr. med. dent.: Der Einfluss fraktionierter Bestrahlung auf Zelltod und immunogenes Potential von murinen kolorektalen CT26 Tumorzellen

Mielert, Theresa, Dr. med. dent.: Häufigkeit von Entzündungszellen im Blut von Rektumund Kopf-Hals-Karzinompatienten im Vergleich zu gesunden Personen und deren prognostische Bedeutung Nagl, Sandra, Dr. med.: Intraepithelial Distances between Inflammatory Cells are Prognostic Favourable in Anal Squamous Cell Carcinoma

**Posselt, Rebecca**, Dr. med.: Die räumliche Verteilung von FoxP3+ und CD8+ Tumor-infiltrierenden T-Zellen spiegelt deren funktionelle Aktivität wider

**Rath, Philipp,** Dr. med.: CT-Morphologie und Texturanalyse von Plattenepithelkarzinomen des Kopf-Hals-Bereichs

**Reif, Julian**, Dr. med.: Tumortoxischer Effekt und strahlensensibilisierende Wirkung des Nicht-nukleosidischen Reverse-Transkriptase-Inhibitors Efavirenz bei Rektumkarzinomzellen

**Ries, Johannes,** Dr. med. dent.: Bedeutung von Zell-in-Zell Strukturen und E-Cadherin Komplex für das Outcome von Anal- und Rektumkarzinomen

Schilling, Teresa, Dr. med.: Einfluss neoadjuvanter Radiochemotherapie auf die Lebensqualität bei Patienten mit Rektumkarzinom und Faktoren, die diese beeinflussen: Eine klinisch prospektive Längsschnittstudie

Schöniger, Alexander, Dr. med.: Apoptose und Nekrose durch Bestrahlung und Chemotherapie von Lymphozyten im Blut von Tumorpatienten und Kontrollprobanden

Seibold, Johannes, Dr. med. dent.: Organschonende Behandlung des Peniskarzinoms mittels interstitieller Pulsed-dose-rate-Brachytherapie Steffens, Rieke, Dr. med.: Das rezidivierte

Glioblastom: Wer erhält eine tumorspezifische Therapie und wie häufig kann es behandelt werden?

**Stolz, Irmela**, Dr. med.: Vergleich unterschiedlicher Boosttechniken in der Strahlentherapie des Mammakarzinoms bezüglich lokaler Kontrolle und Kosmetik

Stritzelberger, Jenny, Dr. med.: Untersuchung der Wirksamkeit von CCNU und Radiotherapie in einem Modell von erworbener Temozolomid-Resistenz bei der Glioblastomzelllinie U251

Wirsing, Anna, Dr. med.: Nicht-professionelle Phagozytose von Tumorzellen

#### Doctorate theses 2018

**Brandt, Tobias,** Dr. rer. biol. hum.: Quantifizierung von Organ- und Patientenbewegungen während der Strahlentherapie und Implementierung einer 4D-Dosisberechnung

Heidrich, Sarah, Dr. med.: Die Wirkung der B-RAF-Kinaseinhibitoren Vemurafenib und Dabrafenib und des Multikinaseinhibitors Pazopanib in Kombination mit Radiotherapie auf die Entwicklung einer Strahlendermatitis *in vivo* sowie der Einfluss dieser Medikamente auf immunregulatorische Zellen

Hoffmann, Christian, Dr. med.: Hirnvolumenreduktion nach Ganzhirnbestrahlung: Quantifizierung und prognostische Relevanz Meedt, Stefan, Dr. med.: Entwicklung einer Testbatterie zur neurokognitiven Funktionsprüfung im Rahmen der HIPPO-SPARE Studie Müller, Jan, Dr. med.: Funktionelle Ergebnisse und lokale Kontrolle nach stereotaktischer Radiotherapie beim Vestibularisschwannom Muth, Carolin, Dr. med.: *In vitro* und *ex vivo* Untersuchungen zum immunogenen Potential des Glioblastoms

Ott, Laura, Dr. med.: Prognostische Bedeutung von Cell-in-Cell (CIC) Strukturen bei Kopf-Halsund Magentumoren

**Prasetio**, **Heru**, Dr. rer. biol. hum.: Dose Reconstruction for Gimbal-Based Dynamic Tumor Tracking

Sakka, Mazen, Dr. med.: Dosisreduktion am Herzen durch tiefe Inspiration bei der Bestrahlung der linken Mamma. Ist die IMRT gegenüber der VMAT von Vorteil?

Schenker, Hannah, Dr. med.: Cell-in-Cell Structures are more potent Predictors of Outcome than Senescence and Apoptosis in Head and Neck Squamous Cell Carcinomas

Ultsch, Luisa, Dr. med.: Individuelle Strahlenempfindlichkeit verschiedener humaner Fibroblastenlinien unter besonderer Betrachtung der prämaturen Seneszenz und des BRAF-Inhibitors Vemurafenib

**Wozar, Fabian**, Dr. med.: Prognostische Bedeutung von Aktivierter Caspase 3 und MRE11 als Biomarker beim Rektumkarzinom

Ziegler, Angela, Dr. med. dent.: Darstellung der Lebensqualität und Überlebenszeitanalyse mittels Kaplan-Meier Kurven von Patienten mit Rektumkarzinom unter und nach neoadjuvanter Radiochemotherapie

#### Habilitation 2017

Frey, Benjamin, PD Dr.-Ing.: Immunmodulation durch ionisierende Strahlung

#### **Board qualification 2018**

Hecht, Markus, Dr. med.: Radiotherapy

#### **Department of Surgery** Chair of Surgery

#### Doctorate theses 2017

Boencke, Cora, Dr. med.: Multimodal Therapy of Extremity Soft Tissue Sarcomas after Unplanned Excision

Bohrer, Andreas, Dr. med.: Erhöhte O-GlcNAcylierung im Kaposi-Sarkom korreliert mit dem Warburg-Effekt

Brand, Verena, Dr. rer. nat.: The role of BMP9 signaling during tumor progression

**Brandt, Hannes,** Dr. med.: Der Einfluss der Leberresektion auf das intrahepatische Tumorwachstum

**Deeg, Johannes,** Dr. med.: Sonographische Evaluierung von Rindbandrupturen mit besonderem Fokus auf die A3 Ringbandruptur: Eine Kadaver-Studie

**Del Medico, Alexander**, Dr. med.: Stellenwert der antiviralen Therapie bei Lebertransplantation unter Hepatitis-B assoziierter Leberzirrhose, Langzeitergebnisse

**Grenz, Sandra**, Dr. rer. nat.: Differentielle Evaluierung des IFN-alpha- und IFN-gamma-dominierten Tumormikromilieus und dessen Einfluss auf die Prognose im Kolonkarzinom

**Gruber**, Elisa, Dr. med. dent.: Vaskuläre Malformationen – eine retrospektive Analyse von Patienten aus der Spezialsprechstunde für Gefäßmalformationen am Universitätsklinikum Erlangen Kiehlmann, Marcus Vishal, Dr. med.: Einfluss der Qualität der Chirurgie auf die Prognose von Patienten mit Rektumkarzinom nach neoadjuvanter Langzeitradiochemotherapie

Knüttel, Dagmar, Dr. med.: Versorgung von Narbenhernien mit Netz bei Patienten mit Immunsuppression nach Lebertransplantation

Krenz, Katrin, Dr. med. dent.: Veränderungen der Mikroperfusion in den Angiosomen des Fußes bei Patienten mit chronisch kritischer Beinischämie – O2C-gestützte Messungen während perkutaner transluminaler Angioplastie

Liebl, Andrea, Dr. rer. nat.: SPARCL1 as novel marker and regulator of endothelial cell quiescence and vessel homeostasis in colorectal carcinoma

Maier, Christiane, Dr. rer. nat.: Hemmung der Phosphodiesterase 4 (PDE4) reduziert experimentelle Hautfibrose durch Modulierung der Interleukin-6-Freisetzung aus M2 Makrophagen Meisel, Julia, Dr. med.: Biomechanische Evaluation einer neuen Operationsmethode zur Ringbandplastik

Müller, Christian, Dr. med.: Primary and recurrent sporadic desmoids: Prognostic factors influencing recurrence-free survival after complete gross resection

**Niebling, Norman,** Dr. med.: Der diagnostische Nutzen der systolischen Akzelerationszeit und des Wiederstandindex als nicht-invasive Maßnahme zur Erkennung von akuten und chronischen Transplantationsabstoßungen nach orthotoper Lebertransplantation

#### Doctorate theses 2018

**Brämswig, Simon Lukas,** Dr. med. dent.: Ergebnisse der intraoperativen Kontrollangiographie in der Karotischirurgie und deren Auswirkung auf den perioperativen Outcome

**Goller, Katja,** Dr. med. dent.: Kombinierter Therapieansatz zum Beinerhalt mittels arterieller Rekonstruktion/AV-Loop Anlage und freiem Gewebetransfer bei kritischer Ischämie der unteren Extremität

Hamel, Sajad, Dr. med.: Risikofaktoren zur postoperativen Rekurrensparese und postoperativen symptomatischen Hypocalcämie nach Schilddrüsenoperation in einem großen Patientenkollektiv

**Irollo, Elena**, Dr. rer. biol. hum.: Role of collagen-X in the metastasis of colorectal carcinoma **Kohl, Valerie**, Dr. med. dent.: Die ältesten Alten mit kolorektalem Karzinom: Behandlung, Komplikationen und Prognose

Kovacs, Martin, Dr. med.: Nabel- und mediane Narbenhernioplastik: eine retrospektive Kohortenstudie konventioneller versus laparoskopischer Netzversorgung in der Abteilung für Allgemein- und Viszeralchirurgie der Klinik Hallerwiese Nürnberg in den Jahren 2011 bis 2013

Murtadak, Vinay, Dr. rer. biol. hum.: *In vitro* analysis of the impact of Kaposi's sarcoma-associated herpes virus (KSHV) on experimentally induced necroptosis

Schinz, Katharina, Dr. med.: Einfluss des Arcus plantaris auf Majoramputation, Wundheilung und Überleben bei Patienten mit terminaler Niereninsuffizienz und kritischer Extremitätenischämie **Scholz**, **Julia**, Dr. med.: Die Rolle des intravaskulären Ultraschalls bei der Planung und der Implantation endovaskulärer Aortenstentprothesen

Schöngart, Elisabeth, Dr. med. dent.: Ergebnisse der arteriovenösen Loopanlage zum freien Gewebetransfer bei ausgeprägten Weichteildefekten

Suchowski, Karina, Dr. rer. nat.: Noninvasive Bioluminescence Imaging of AKT Kinase Activity in Cancer Xenografts: Correlation of the Kinase Activity with the Therapeutic Response to EGFR and PI3K Inhibitors

Wittmann, Theresa, Dr. med.: Maligne Melanome mit unbekanntem Primärtumor: Ein Vergleich mit malignen Melanomen der Haut

#### Habilitation 2017

**Britzen-Laurent, Nathalie,** PD Dr. rer. nat.: Molecular function of guanylate-binding protein-1 in the Th1 immune microenvironment of colorectal carcinoma

Regus, Susanne, PD Dr. med.: Komplikationsmanagement des Hämodialyseshunts

#### **Board qualification 2018**

**Elshafei, Moustafa:** Visceral Surgery **Brunner, Maximilian,** Dr. med.: Visceral Surgery

#### Additional qualification 2018

Weber, Georg, PD Dr. med.: Master of Health Business Administration (MHBA)

#### **Department of Surgery**

Division of Pediatric Surgery

#### Doctorate theses 2017

Amberg, Jana, Dr. med. dent.: Die operative Versorgungsrealität angeborener Brustwandfehlbildungen in der BRD – Eine systematische epidemiologische Analyse der Jahre 2005-2012 Simon, Kirsten, Dr. med.: Prävention und Therapie von Wundheilungsstörungen nach offenen Brustwandkorrekturen mit Hilfe der Unterdrucktherapie

Ambarsari, Yuletta Adny, Dr. med.: Systemic to Pulmonary Artery Shunting with Heparinbonded Grafts

**Bechtold, Caroline,** Dr. med.: Die Aortenbogenrekonstruktion beim Neugeborenen mit biventrikulärer Morphologie: Erhöhtes Risiko für die Entwicklung einer Rekoarktation bei der Verwendung von Autologem Perikard

Janssen, Carina, Dr. med.: Kardioprotektion bei Aortenbogenoperationen: Validierung der Beating-Heart-Methode

#### Doctorate theses 2018

**Grupp, Sina,** Dr. med.: Beidseitiger anterolateraler flail chest: Vergleichende Untersuchungen verschiedener Osteosynthesevarianten am menschlichen Leichenpräparat

Schmitt, Sonja, Dr. med.: Die Altersverteilung der Sternumfraktur in der Bundesrepublik Deutschland – eine epidemiologische Auswertung im Zeitraum 2005 bis 2012

#### Board qualification 2018

Syed, Julia, Dr.: Pediatric Surgery

#### **Department of Surgery** Division of Thoracic Surgery

Doctorate theses 2017

Dudek, Wojciech, Dr. med.: Zweiundvierzigjährige Erfahrung in der chirurgischen Behandlung des pulmonal metastasierten kolorektalen Karzinoms

#### Habilitation 2018

Schreiner, Waldemar, PD Dr. med.: Das lokal fortgeschrittene nicht-kleinzellige Lungenkarzinom: innovative chirurgische Therapieverfahren, Ergebnisse und prognostische Faktoren

#### **Department of Surgery**

Division of Transfusion Medicine and Hemostaseology

#### Doctorate theses 2017

Bosser, Markus, Dr. med.: Frei und intrazellulär zirkulierende Wachstumsfaktoren der Angiogenese vor und nach Resektion eines kolorektalen Karzinoms

Fischer, Johannes, Dr. med.: Die Ausstattung von Thrombozvten mit Wachstumsfaktoren der Angiogenese (VEGF, PDGF, TGFß) vor und nach großen Operationen

Heider, Stefan, Dr. med.: Multiparametrische in vitro Lymphozyten-Stimulation bei Gesunden Hohensee, Friederike, Dr. med.: Vergleich verschiedener Gefrierschutzlösungen zur Tiefkühlkonservierung von Stammzellen

Koch, Elisabeth, Dr. med. dent.: Der Einfluss einer Volumensubstitution mit 250 ml physiologischer Kochsalzlösung nach Plasmapherese auf Blutbildund Kreislaufparameter beim Blutspender

Zink, Ulrike, Dr. med.: Automatisierter Nachweis geringster Leukozytenkonzentrationen in Thrombozytenkonzentraten

#### Doctorate theses 2018

Biegel, Leonie, Dr. med.: Untersuchungen zur Korrelation zwischen etablierten Methoden zur Thrombozytenqualitätstestung (Hypotone Schockreaktion und "extent of shape change") und dem neuen ThromboLUX™

Damrah, Mohammed, Dr. med.: HNA-Genotypverteilung bei Menschen mit syrischer Herkunft Fischer, Sören, Dr. med. dent.: Analyse von 4882 klinischen Proben zur Optimierung eines Protein-S-Mangel-Screenings unter Berücksichtigung von Faktor-V-Leiden-Mutation

Gedeon, Robert, Dr. med. dent.: Retrospektive Analyse der Zellnachbildung bei Leukozytenapheresen gesunder Blutspender und Patienten mit Malignem Melanom Transfusionsmedizinische und Hämostaseologische Abteilung der Chirurgische Klinik mit Poliklinik

## Habilitation 2017

Strobel, Julian, PD Dr. med.: Oualitätsgesicherte Herstellung von Blut- und Stammzellkomponenten

## Additional qualification 2017

Dullinger, Katharina, Dr. med.: Hemostaseology

Kuta, Piotr, Dr. med.: Hemostaseology

#### Additional qualification 2018

Achenbach, Susanne, Dr. med.: Medical Quality Management

#### **Department of Trauma Surgery – Orthopedic Surgery** Chair of Trauma Surgery and Orthopedic Surgery

#### Doctorate theses 2017

Golditz, Tobias, Dr. med.: Chronische Instabi-lität im oberen Sprunggelenk als Risikofaktor einer Ostheoarthrose: Untersuchung mittels quantitativem T2-mapping

Koch, Peter, Dr. med.: Einfluss prozessierter Meniskus-Allografts auf die Progression von Arthrose im Schafsmodel

Syed, Julia, Dr. med.: Trichterbrustkorrektur -Historie und Innovation

Zingler, Christian, Dr. med.: Untersuchungen zur Zellmotilität von Chondrozyten in humanem adulten Gelenkknorpel

#### Doctorate theses 2018

Dorofeev, Anton, Dr. med.: Analyse der postoperativen Ergebnisse nach valgisierenden proximalen Tibiaumstellungsosteotomie: der Vergleich zwischen den navigierten zuklappenden und konventionellen aufklappenden Techniken

Höwener, Karin, Dr. med.: Prospektiv randomisierte Studie zur Untersuchung der Auswirkung mechanischer Kompression auf die Häufigkeit der Entstehung eines postoperativen Seroms/Hämatoms in der Hüftendoprothetik Söllner, Stefan, Dr. med.: Intraoperative Validierung des quantitativen T2-Mapping bei Patienten mit Knorpeldefekten im Kniegelenk

Witt, Ramona, Dr. med.: Mesenchymal stem cells and myoblast differentiation under HGF and IGF-1 stimulation for 3D skeletal muscle tissue engineering

#### Habilitation 2018

Mauerer, Andreas Georg, PD Dr. med.: Alternative Materialien zur Prophylaxe und Therapie von Komplikationen in der Knieprothetik Dickschas, Jörg, PD Dr. med.: Kniegelenknahe Osteotomien bei Pathologien des Femoropatellargelenkes

#### **Board qualification 2018**

Stapel, Philipp, Dr. med.: Orthopedics and Accident Surgery

#### Additional qualification 2017

Gelse, Kolja, Prof. Dr. med.: X-Ray Diagnosis skeletal system

#### Additional qualification 2018

Pachowsky, Milena, Dr. med.: Special Accident Surgery

#### **Department of Urology** Chair of Urology

#### Doctorate theses 2017

Agic, Dino, Dr. med.: Die ersten Da Vinci®-Prostatektomien der Urologischen Klinik des Universitätsklinikums Erlangen: eine retrospektive Auswertung

Pandey, Abhishek, Dr. med.: Mehrzeitige Harnröhrenplastik mit Skrotallappen und Mundschleimhaut nach erfolgloser Hypospadiekorrektur

Schöniger, Maximilian, Dr. med.: Immunhistochemische Analyse der Proteine Zink Finger 217, Myosin VI, ETS related gene und E-Cadherin bezüglich ihrer Eignung als prognostische Marker für das Prostatakarzinom Doctorate theses 2018

Zintl, Laura-Marie, Dr. med. dent.: Harnleiterstenosen nach Nierentransplantation

#### Additional qualification 2017

Kunath, Frank, PD Dr. med.: Drug based tumor therapy

Lieb, Verena, Dr. med.: Fellow of the European Board of Urology

#### Additional qualification 2018

Richterstetter, Mario, Dr. med.: Sexual Medicine (FECSM)

## **Department of Operative Dentistry**

and Peridontology Chair of Dental, Oral, and Maxillofacial Medicine - especially Operative Dentistry, Periodontology, and Pediatric Dentistry

#### Doctorate theses 2017

Beisig, Michael, Dr. med. dent.: Stand der digitalen Bildgebungsverfahren im Vergleich zum Zahnfilm

Ickerott, Jonas, Dr. med. dent.: Hall-Sensoren intergrierte Endometrie - ein innovatives Verfahren zur Bestimmung der Wurzelkanallänge Itze, Corinna, Dr. med. dent.: 3D meterological

observations on fractured dental composite surfaces – Fraktur von dentalen Kompositen: Welche Informationen können aus der 3D Oberflächenanalyse gewonnen werden?

Knoll, Nadja, Dr. med. dent.: Eindringtiefe des Wurzelkanalsealers AH Plus abhängig von verschiedenen Trocknungsmethoden des Wurzelkanals

Kraus, Stefanie, Dr. med. dent.: Der Einfluss von Bulk-Fill vs. konventioneller Komposite bei der Verwendung unterschiedlicher Etch-and-Rinse Adhäsive auf die Mikrozugefestigtkeit

Mellinghoff, Felix, Dr. med. dent.: Entwicklung bimanueller Fähigkeiten im zahnärztlichen Tätigkeitsbereich: Eine experimentelle Studie

Perez Tomas, Adrian, Dr. med. dent.: Einflussfaktoren von experimentellen Infiltrationsmaterialien auf die Festigkeit von Keramik

Rödel, Lena, Dr. med. dent.: Self-adhesive resin cements: pH-neutralization, hydrophilicity and hydroscopic expansion stress

Röhm, Philipp, Dr. med. dent.: Der Einfluss des Lagerungsmediums bei Langzeitlagerung auf die Frakurresistenz von Zähnen mit simuliertem nicht abgeschlossenem Wurzelwachstum

Schmunk, Alexandra, Dr. med. dent.: Randspaltverhalten neuer Komposite unter dem Einfluss von Schichttechnik und Kavitätengröße Tran-Vinh, Ylan Elisa, Dr. med. dent.: Einfluss der Politur auf die Festigkeit von zahnfarbenen

Restaurationsmaterialien Wendler Ernst, Michael, Dr. med. dent.: Characterization of Residual Stresses in Zirconia Veneered Bilayers for Dental Restorations

### Doctorate theses 2018

Harre, Sarah Johanna, Dr. med. dent.: Zu den Polymerisationseigenschaften von Bulk-Fill Materialien und konventionellen Kompositen

Hornung, Karola, Dr. med. dent.: Einfluss von verschiedenen Prophylaxepulver und -pasten auf die Oberflächenrauheit und den Materialabtrag bei Dentin und Schmelz

Hübner, Jérôme, Dr. med. dent.: Einflussfaktoren experimenteller Infiltrationsharze und Lösungsmittel auf den Kontaktwinkel

**Kreusch, Christine**, Dr. med. dent.: Apikale Dichtigkeit zweier Wurzelkanalsealer – Epiphany und Apexit Plus – unter Verwendung von vier Obturationstechniken

Lackmann, Helena, Dr. med. dent.: Effizienz und Gebrauch von Polymerisationsgeräten in ländlichen Zahnarztpraxen

Leithäuser, David, Dr. med. dent.: Dichtigkeitsuntersuchung von Wurzelkanalfüllungen in Abhängigkeit vom Alter der Zähne

Lindner, Robert, Dr. med. dent.: Quantitative Randspaltanalyse verschiedener Bulk-Fill Materialien vor und nach thermomechanischer Belastung

Loher, Claudia, Dr. med. dent.: Zusammenhang zwischen Korngröße und Alterung bei Zirkonoxidkeramiken

**Ludwig, Mira,** Dr. med. dent.: Bimanuelles Training für Zahnärzte: Eine experimentelle Studie

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Vetter, Nikola, Dr. med. dent.: Penetrationstiefen unterschiedlicher medikamentöser Einlagen in die Dentintubuli

#### Department of Oral and Cranio-Maxillofacial Surgery

Chair of Dental, Oral, and Maxillofacial Medicine – especially Oral and Maxillofacial Surgery

#### Doctorate theses 2017

**Broghammer, Sophie,** Dr. med. dent.: Gibt es einen histomorphologisch fassbaren Unterschied zwischen der fluoreszenzmarkierten Sequestrotomie und der Resektion nach klinischen Gesichtspunkten bei Medikamenten-assoziierten Kiefernekrosen? Eine histomorphologische Analyse des Knochenremodelin

**Dietrich, Eva-Maria**, Dr. med.: Retrospektive deskriptive Studie bezüglich der angewandten postoperativen medikamentösen Schmerztherapie in einer Mund-, Kiefer- und Gesichtschirurgischen Klinik im Zeitraum 2012-2015

**Gammel, Lisa,** Dr. med. dent.: Weichgewebsaugmentation zur Verdickung der peridentalen Gingiva – Autologes Bindegewebstransplantat versus porcine Kollagenmatrix (mucoderm<sup>®</sup>). Eine histologische und immunhistologische tierexperimentelle Vergleichsstudie

Goldschmidt, Sophia, Dr. med. dent.: Gibt es einen immunhistochemisch fassbaren Unterschied zwischen der Fluoreszenz-markierten Sequestrotomie und der Resektion nach klinischen Gesichtspunkten bei Medikamenten-assoziierten Kiefernekrosen? Eine immunhistochemische Analyse der Osteoklastenaktivität Hentschel, Andreas, Dr. med. dent.: Überleben und Patientenzufriedenheit von kurzen Implantaten innerhalb der ersten 2 Jahre in Funktion: eine retrospektive Kohortenstudie mit 694 Implantaten in 416 Patienten

Humann, Julia, Dr. med. dent.: Volumetrische Vermessung nach gingivaler Volumenaugmentation mittels einer porcinen Kollagenmatrix im Vergleich zum autologen Bindegewebe

Knipfer, Christian, Dr. med.: Raman Difference Spectroscopy: ein berührungsloser Ansatz zur optischen Biopsie für die Früherkennung von Tumoren der Mundhöhle

Konopka, Isabell, Dr. med. dent.: Vergleich des klinischen Verlaufs primärer oraler Plattenepithelkarzinome (OSCC) mit der Makrophagenpolarisierung im Tumor

Kruzolek, David, Dr. med. dent.: Etablierungsprozess für die klinische Anwendung der Computerassistierten Herstellung von Titangittern zur Orbitabodenrekonstruktion

Neumahr, Franziska, Dr. med. dent.: Bisphosphonat-assoziierte Osteonekrose des Kieferknochens – retrospektive Analyse des Patientengutes der Mund-Kiefer- und Gesichtschirurgischen Klinik am Universitätsklinikum Erlangen mit besonderer Betrachtung Implantat assoziierter Nekrosen

**Preidl, Raimund,** Dr. med. dent.: Bestimmung der Perfusion freier, mikrovaskulärer Transplantate mittels intraoperativer Fluoreszenzangiographie

Voit, Mizzi, Dr. med. dent.: Makrophagenpolarisation bei Bisphosphonat-assoziierten Kiefernekrosen – eine vergleichende immunhistochemische Analyse von humanem Knochengewebe

#### Doctorate theses 2018

Behrends, Tessa, Dr. med. dent.: Die Erstellung eines Klassifikationssystems für Kiefergelenkserkrankungen und seine Anwendung – Korrelieren magnetresonanztomographische Befunde mit den Schmerzintensitäten von Patienten mit craniomandibulären Dysfunktionen?

Gebrebrhan, Magda, Dr. med. dent.: Vergleichende Analyse der Makrophagen- und Osteoklasten Polarisation in der Bisphosphonatassoziierten Kiefernekrose und der Osteoradionekrose

**Gross, Christian**, Dr. med.: Osteoklasten-Profil der Medikamenten-assoziierten Osteonekrose des Kiefers nach Bisphosphonat-Therapie: Ein Vergleich mit der Osteoradionekrose und der Osteomyelitis – Eine immun-histochemische Analyse von humanen Proben

Hagen, Julia, Dr. med. dent.: Über die Passgenauigkeit anhand von 3D-Modellen vorgebogenen Rekonstruktionsplatten und deren Auswirkung auf die Kiefergelenksstellung

Kreißel, Sebastian, Dr. med. dent.: Kostenund Ertragsvergleich bei Zungenkarzinomen in Abhängigkeit der Behandlungsmethode (Mikrovaskuläre Deckung vs. lokal-plastische Defektdeckung)

Marsing, Lena, Dr. med. dent.: Die Makrophagenpolarisation in apikalen Granulomen, radikulären Zysten und follikulären Zysten

Oetter, Nicolai, Dr. med.: Etablierung und Validierung eines Klassifikations- und Scoring-Systems zur *in vivo* Diagnostik von Plattenepithelkarzinomen der Mundhöhle mittels Konfokaler Laserendomikroskopie

**Rohde, Maximilian**, Dr. med. dent.: Die Differenzierung oraler Hart- und Weichgebe mittels der LIBS-Technik – Ein Ausblick auf die gewebespezifische Laserchirurgie

Sander, Janina, Dr. med. dent.: Vergleichende Analyse der Makrophagenpolarisierung in kraniofazialen und extrakranialen Osteosarkomen Schwertner, Maximilian, Dr. med. dent.: Intraoperativ-zeitlicher Vergleich zwischen individuell vorgebogenen und nicht vorgebogenen Titangittern zur Orbitabodenrekonstruktion – eine prospektive Studie

Sparrer, Julius, Dr. med. dent.: Insertion oraler Implantate bei Diabetes mellitus Typ 2-Patienten – Eine retrospektive Erfolgsanalyse nach verlängerter Einheilzeit und unter verschiedenen Einflüssen

#### Habilitation 2017

Lutz, Rainer, PD Dr. med. Dr. med. dent.: Hartgewebsaugmentation und Osseointegration von biofunktionalisierten Implantaten

**Ries, Jutta Charlotte,** PD Dr. rer. nat.: Nutzung molekularbiologischer Marker zur diagnostischen Sicherung, Früherkennung und Prognoseeinschätzung des Plattenepithelkarzinoms der Mundhöhle

Schmitt, Christian Martin, PD Dr. med. dent.: Modulation periimplantärer Hart- und Weichgewebe

von Wilmowsky, Cornelius, PD Dr. med. Dr. med. dent.: Einheilung von Biomaterialien bei kompromittierter Wundheilung

### **Board qualification 2017**

Lutz, Rainer, PD Dr. med. Dr. med. dent.: Oromaxillofacial Surgery

von Wilmowsky, Cornelius, PD Dr. med. Dr. med. dent.: Oromaxillofacial Surgery

#### **Board qualification 2018**

von Wilmowsky, Cornelius, PD Dr. med. Dr. med. dent.: Oral Surgery

**Buchbender, Mayte,** Dr. med. dent.: Oral Surgery

### Additional qualification 2017

Schmitt, Christian, PD Dr. med. dent.: M.S. (International Master for Applied Scientific Dental/Medical Education and Research (iMasder))

#### Additional qualification 2018

Wehrhan, Falk, PD Dr. med. Dr. med. dent.: Master of Health and Business Administration (MHBA)

## Department of Orthodontics and Orofacial Orthopedics

Chair of Dental, Oral, and Maxillofacial Medicine – especially Orofacial Orthopedics

#### Doctorate theses 2017

**Demmrich, Friedrich Steffen Christian**, Dr. med. dent.: Untersuchung des Asymmetrieindex nach Katsumata et al. bei symmetrischen Patienten

Forschner, Marcus, Dr. med. dent.: Untersuchung der Haftkraft orthodontischer Befestigungselemente auf unterschiedlichen Restaurationsmaterialien unter Verwendung eines Universal-Primers (Monobond Plus®)

Hofbeck, Manuela, Dr. med. dent.: Asymmetrien des Mittelgesichts bei Anomalien des Okulo-Aurikulo-Vertebralen Spektrums (OAVS)

#### Doctorate theses 2018

Hofmeister, Michael, Dr. med. dent.: DVT, CT, Industrielle CT und MRT in der Kieferorthopädie - Ein Vergleich unterschiedlicher 3D-Bildgebungsverfahren für kieferorthopädische Fragestellungen

#### **Board qualification 2017**

Schütz, Katrin, Dr. med. Dr. med. dent.: Orthodontist

#### **Board qualification 2018**

Chepura, Taras, Dr. med. dent.: Orthodontist Grozdinska, Alina, Dr. med. dent.: Orthodontist

Klinker, Theodor, Dr. med. dent.: Orthodontist Meyer, Ksenija, Dr. med. dent.: Orthodontist Rupf-Köhler, Stephanie, Dr. med. dent.: Orthodontist

#### **Department of Prosthodontics**

Chair of Dental, Oral, and Maxillofacial Medicine - especially Prosthetic Dentistry

## Doctorate theses 2017

Enssle, Anne, Dr. med. dent.: Patienten mit einer Bisphosphonat-assozierten Kiefernekrose -Eine psychometrische Evaluation

Kreuzer, Meike, Dr. med. dent.: Vergleich von digitalen und herkömmlichen Abformungen anhand der dreidimensionalen Passung von Kronen und Brücken

Wolf, Linda, Dr. med. dent.: Die Deformation der Mandibula - eine dreidimensionale in-vivo-Studie

#### Doctorate theses 2018

Herbst, Alexandra, Dr. med. dent.: Analyse der Oberflächenveränderungen von verblendeten Zirkonoxid- und monolithischen Lithiumdisilikatkronen mit einem 3D-Weisslichtscanner

Kaiser, Matthias, Dr. med. dent.: Triple-Sense-Methode und orale Stereognose. Untersuchung zur Effektivität einer zahnärztlichen hypnotherapeutischen Kombinationstherapie zur Behandlung von starkem Würgereiz anhand einer klinischen Studie

Kitzinger, Julia, Dr. med. dent.: Klinische Evaluation der Kaukraft bei implantatprothetisch rehabilitierten Patienten nach chirurgischer Therapie oraler Tumoren

März, Karoline, Dr. med. dent.: Hat die Änderung der Okklusion einen unmittelbaren Einfluss auf die Körperhaltung und die Wirbelsäule? Pilotstudie einer dreidimensionalen Untersuchung mittels Rasterstereografie

Seidel, Anna, Dr. med. dent.: Der Einfluss von Formaldehydfixierung auf die Genauigkeit von dreidimensionalen CT- und DVT-Modellen eine Grundlagenarbeit für radiologische Studien Worch, Thomas, Dr. med. dent.: Stereognostische und psychometrische Evaluation von Patienten mit ausgeprägtem Würgereiz

#### **Institute of General Practice**

## Chair of General Practice

### Doctorate theses 2017

Alber, Kathrin, Dr. med.: Überversorgung und Quartäre Prävention in der Allgemeinmedizin -Eine qualitative Studie mit Hausärzten Nittritz, Christine, Dr. med.: Konsultationskompetenz als Element in der allgemeinmedizinischen Weiterbildung in Deutschland - eine qualitative Befragung

#### **Institute of Radiology** Chair of Diagnostic Radiology

## Doctorate theses 2017

Klempka, Anna, Dr. med.: Begleitverletzungen der skapholunären und lunotriguetralen Ligamente sowie des TFCC bei distalen, intraartikulären Radiusfrakturen. Diagnostik mittels CT-Arthrographie.

Reske, Stefan, Dr. med.: Ganzkörper-CT in der Schockraumversorgung vom Polytraumapatienten - Optimierung von Strahlenexposition, Bildqualität und Untersuchungszeit

Sandmair, Martin, Dr. med.: Semiautomatic segmentation of the kidney in magnetic resonance images using unimodal thresholding

Schmid, Andrea, Dr. med.: Bessere Bildqualität und niedrigere Strahlendosis im Kopf-Hals-CT: weiterentwickelte modellbasierte und Sinogram-gestützte iterative Rekonstruktion in Verbindung mit automatisierter Anpassung der Röhrenspannung

Schmieder, Raphael, Dr. med.: Vaskuläre Sicherheit und renale Effekte der endovaskulären Nierennervablation

Wild, Melanie, Dr. med.: Wirbelkörperfrakturen unklaren Ursprungs in CT-Untersuchungen bei Krebspatienten: Radiologisches Reporting und Wahrnehmung der Kliniker

Zeulner, Bernd, Dr. med.: Essstörungen und Sportsucht im Ausdauersport

#### Doctorate theses 2018

Brendel, Stephanie, Dr. med.: Iterative Rekonstruktion in der Computertomographie

Büstgens, Felix, Dr. med.: Stentimplantation zur Behandlung der malignen oberen Einflussstauung bei mediastinalen Raumforderungen

Dinzl, Veronika, Dr. med.: Practicability of Hygienic Wrapping of Touchscreen Operated Mobile Devices in a Clinical Setting

Hader, Christopher, Dr. med.: Selektives Venenblutsampling bei Hyperparathyreoidismus mit unklarer Nebenschilddrüsenlokalisation

Özdemir, Derya, Dr. med.: Kernspintomographische Untersuchung struktureller und funktioneller Anpassungserscheinungen des Herzens untrainierter Männer an ein hochintensives Krafttraining in einer randomisierten Longitudinalstudie

Schnaiter, Johannes, Dr. med.: Diagnostische Genauigkeit eines mittels paralleler Bildgebung beschleunigten Knie-MRT Protokolls in Korrelation zur Arthroskopie

#### Habilitation 2017

Rompel, Oliver, PD Dr. med.: Bildgebende Diagnostik der Thoraxorgane bei Kindern mit modernen CT- und MRT-Techniken

#### Habilitation 2018

Bayer, Thomas, PD Dr. med.: Diagnostik von Verletzungen im Klettersport mit der Magnetresonanztomographie Schmid, Axel, PD Dr. med.: Neue Verfahren in der Interventionsradiologie

## **Board qualification 2018**

Ellmann, Stefan, Dr. med.: Radiology Scharf, Michael, Dr. med.: Radiology Seuß, Hannes, Dr. med.: Radiology Sommer, Matthias, Dr. med.: Radiology

#### Institute of Radiology Division of Neuroradiology

#### Doctorate theses 2017

Hauer, Michael, Dr. med.: Evaluation der effektiven Patienten- und Untersucherdosis an einer modernen Flach-Detektor-Angiographieanlage Svergun, Stanislav, Dr. med.: Evaluation eines Algorithmus zur Metallartefaktreduktion in der Flachdetektor-C-Bogen-CT

#### Doctorate theses 2018

Eckert, Matthias, Dr. med.: Optimized flat-detector CT in stroke imaging: ready for first-line use? Flat-detector CT in stroke imaging

#### Board qualification 2017

Lang, Stefan, Dr. med.: Radiology

#### Board qualification 2018

Aghazadeh, Yashar, Dr. med.: Neuroradiology Kästle, Nicola, Dr. med.: Neuroradiology Mühlen, Iris, Dr. med.: Radiology Schmidt, Manuel, Dr. med.: Radiology

## **In Memoriam**

## 2017

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**Prof. Dr. Helmut Schmidt** Institute of Pathology and Anatomy

**Prof. Dr. Otto Paul Hornstein** Professor for Skin and Veneral Diseases

**Prof. Dr. Franz Gall** Emeritus of the Chair of Surgery

**Prof. Dr. Karl Theo Schricker** Division of Transfusional Medicine

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